Liver Cancer

Research Article

Liver Cancer 2024;13:193–202
DOI: 10.1159/000531820

Received: March 8, 2023
Accepted: June 27, 2023
Published online: July 7, 2023

Multicenter Phase II Trial of Lenvatinib plus Hepatic Intra-Arterial Infusion Chemotherapy with Cisplatin for Advanced Hepatocellular Carcinoma: LEOPARD

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Keywords
Hepatocellular carcinoma · Lenvatinib · Cisplatin · Hepatic arterial infusion chemotherapy · Systemic therapy

Abstract
Introduction: Hepatic arterial infusion chemotherapy (HAIC) with cisplatin and lenvatinib exhibits strong antitumor effects against advanced hepatocellular carcinoma (HCC). Higher antitumor activity is expected for the combination treatment. The aim of this trial was to evaluate the efficacy and safety of lenvatinib in combination with HAIC using cisplatin in patients with advanced HCC. ***Methods:*** In this multicenter, open-labeled, single-arm, phase II trial, patients with advanced HCC categorized as Child-Pugh class A with no prior history of systemic therapy were enrolled. Patients received lenvatinib plus HAIC with cisplatin (lenvatinib: 12 mg once daily for patients ≥60 kg, 8 mg once daily for patients <60 kg; HAIC with cisplatin: 65 mg/m^2, day 1, every 4–6 weeks, maximum of six cycles). The primary endpoint

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was the objective response rate (ORR) assessed using modified RECIST by the Independent Review Committee. The secondary endpoints were the ORR assessed using RECIST v1.1, progression-free survival, overall survival, and frequency of adverse events associated with the treatment. ***Results:*** A total of 36 patients were enrolled between September 2018 and March 2020. In the 34 evaluable patients, the ORR assessed by the Independent Review Committee using modified RECIST and RECIST v1.1 were 64.7% (95% confidence interval [CI]: 46.5–80.3%) and 45.7% (95% CI: 28.8–63.4%), respectively. The median progression-free survival and overall survival were 6.3 months (95% CI: 5.1–7.9 months) and 17.2 months (95% CI: 10.9 – not available, months), respectively. The main grade 3–4 adverse events were increased aspartate aminotransferase (34%), leukopenia (22%), increased alanine aminotransferase (19%), and hypertension (11%). ***Conclusion:*** Lenvatinib plus HAIC with cisplatin yielded a favorable ORR and overall survival and was well tolerated in patients with advanced HCC. Further evaluation of this regimen in a phase III trial is warranted.

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Introduction

Systemic therapy is one of the important treatment modalities for patients with advanced hepatocellular carcinoma (HCC) who are not indicated for treatment with hepatectomy, local ablative therapy, or transarterial chemoembolization (TACE) [1]. Many regimens, such as atezolizumab plus bevacizumab (Atezo+Bev), durvalumab plus tremelimumab (Durva+Treme), sorafenib, lenvatinib, regorafenib, cabozantinib, and ramucirumab, are currently accepted as standard treatments for patients with advanced HCC, and these treatments are applied in clinical practice in many countries [1–3].

Lenvatinib is a tyrosine kinase inhibitor that targets vascular endothelial growth factor receptor (VEGFR) 1–3, fibroblast growth factor receptor (FGFR) 1–4, platelet-derived growth factor receptor (PDGFR)-α, RET, and KIT. The phase III REFLECT trial evaluated lenvatinib as compared with sorafenib in the treatment of patients with advanced HCC [4]. The primary endpoint of non-inferiority in terms of overall survival of lenvatinib compared with sorafenib was met, and statistically significant and clinically meaningful improvements in the secondary endpoints of progression-free survival, time to progression, and objective response rate (ORR) were also observed in patients treated with first-line lenvatinib. On the basis of these results, lenvatinib has been acknowledged as a standard therapy for advanced HCC. However, Atezo+Bev [5] and Durva+Treme [6] have been demonstrated to yield significant survival benefit over sorafenib in advanced HCC patients. Therefore, lenvatinib is currently positioned as the first-line treatment option for patients in whom Atezo+Bev and Durva+Treme are contraindicated [7–9]. In a recent study, lenvatinib+pembrolizumab failed to demonstrate statistical superiority in overall survival and progression-free survival compared with lenvatinib plus placebo [10]. However, lenvatinib in combination with various other treatments, such as TACE [11, 12], is also under investigation because of the promising treatment outcomes of lenvatinib for advanced HCC.

Hepatic arterial infusion chemotherapy (HAIC) has not reached widespread acceptance as a standard treatment for HCC, but it is sometimes available for advanced HCC as an alternative treatment option for systemic therapy [1]. HAIC is associated with increased local concentrations of the anticancer agent in the tumor and reduced systemic distribution of the drug. A stronger antitumor effect and lower incidence of systemic adverse reactions are expected from the direct administration of an anticancer drug from the hepatic artery as compared with systemic therapy. HAIC regimens such as cisplatin [13–15], 5-fluorouracil plus cisplatin [16, 17], and 5-fluorouracil plus interferon [18] have high response rates and result in favorable overall survival. Among these regimens, HAIC with cisplatin can be easily administered because it does not require placement of the hepatic arterial infusion reservoir system as performed with the other two regimens. Additionally, preclinical research has shown that cisplatin exerts a synergistic anticancer effect with VEGF inhibitors in other cancer types [19–21], and HAIC with cisplatin plus sorafenib demonstrated prolonged overall survival as compared with sorafenib alone in patients with advanced HCC in our previous randomized phase II trial [14]. Therefore, to explore the potential high antitumor effects by the addition of lenvatinib, we conducted a phase II trial to evaluate the efficacy and safety of lenvatinib plus HAIC with cisplatin in patients with advanced HCC.

Materials and Methods

Study Design

This study consisted of two parts. The feasibility confirmation part was designed to evaluate the tolerability of the combination therapy of lenvatinib and HAIC with cisplatin in the first 6 patients among the patients with advanced HCC enrolled in the study, and

the phase II part was performed to examine the efficacy and safety of this combination regimen in patients with advanced HCC.

This trial was registered with Japan Registry of Clinical Trials (https://jrct.niph.go.jp/) (identification number jRCTs031180019). This trial was conducted with the approval of the National Cancer Center Hospital East Certified Review Board (CRB3180009), the permission of directors of each participating institution, and in accordance with the Declaration of Helsinki. Patient registration and data collection were managed by the LEOPARD data center. The integrity of the data was ensured through careful review by the staff of the data center, the principal investigator (M.I.), and the trial statistician (T.S.).

Patient Eligibility

The patient inclusion criteria were as follows: (1) histologically or clinically confirmed HCC (excluding mixed type), (2) hepatectomy, local ablative therapy (e.g., radiofrequency ablation), and TACE were not indicated, (3) no prior systemic therapy, (4) aged 20–80 years, (5) presence of intrahepatic tumors affecting prognosis irrespective of the presence of extrahepatic tumors, (6) presence of measurable lesions, (7) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, (8) adequate organ function (neutrophil count ≥1,500/mm^3, hemoglobin ≥8.5 g/dL, platelet count ≥75,000/mm^3, serum total bilirubin ≤2.0 mg/dL, serum albumin ≥2.8 g/dL, aspartate aminotransferase [AST] and alanine aminotransferase [ALT] ≤200 U/L, serum creatinine ≤1.2 mg/dL or creatinine clearance ≥60 mL/min, prothrombin time-international normalized ratio ≤2.3), (9) Child-Pugh score of 5–6 points, (10) blood pressure can be sufficiently controlled by three or fewer antihypertensive agents, (11) HAIC was technically feasible, (12) at least 4 weeks had passed since the end of the previous treatment, (13) expected survival for at least 12 weeks, and (14) written consent. In this protocol, clinically diagnosed HCC was defined as tumor stain on early phase and washout on late phase by contrast-enhanced CT or MRI.

The exclusion criteria were as follows: (1) history of treatment with lenvatinib or cisplatin (including use in TACE) for HCC, (2) moderate or massive ascites or pleural effusion, (3) 24 h urinary protein of 1 g or more if proteinuria was 2+ or more in the urinary protein qualitative test, (4) hepatic encephalopathy, (5) uncontrollable heart failure, angina, arrhythmia, and myocardial infarction within 6 months, (6) active double cancer, (7) severe mental disorder, (8) history of hypersensitivity to drugs containing iodine and contrast medium, (9) serious drug allergy, (10) history of gastrointestinal bleeding or active hemoptysis within 28 days or with hemorrhagic or thrombotic disease, (11) pregnant and lactating females or females of childbearing age unless using effective contraception, (12) difficulty in taking oral medications, (13) brain metastasis or subdural metastasis, (14) HIV positive, (15) complications with active infection requiring systemic treatment (excluding hepatitis virus), (16) pulmonary fibrosis or interstitial pneumonia, (17) blood transfusion, blood products, or hematopoietic factor such as granulocyte colony-stimulating factor within 14 days, and (18) the investigators judged the candidate as inappropriate for this study.

Protocol Treatment

The protocol treatment consisted of a combination therapy of lenvatinib and HAIC with cisplatin (up to six courses) and subsequent lenvatinib monotherapy. The lenvatinib and HAIC with cisplatin treatment for the combination therapy were started on the same day. Lenvatinib was taken at a dose of 12 mg once daily for patients with a body weight ≥60 kg or 8 mg once daily for patients with a body weight <60 kg. HAIC with cisplatin was administered at 65 mg/m^2 up to six courses every 4–6 weeks, considering cumulative dose of cisplatin. Cisplatin was administered over 20–40 min through a catheter inserted into the proper hepatic artery or the hepatic artery that feeds the tumor. Treatment continued until radiological or symptomatic tumor progression, unacceptable toxicity, or technical difficulty in repeating the HAIC.

The main criteria for suspending lenvatinib were as follows: (1) grade 3–4 leukocytopenia, neutropenia, or thrombocytopenia; (2) intolerable grade 2 or grade 3–4 non-hematological toxicity; (3) AST >200 U/L, or ALT >200 U/L; (4) grade 3 proteinuria; and (5) hypertension with systolic blood pressure ≥160 mm Hg and diastolic blood pressure ≥100 mm Hg despite maximum antihypertensive treatment. If the criteria were met, lenvatinib was suspended. After the recovery of the adverse events, administration was resumed with a dose reduction (starting with 8 mg once daily, followed by 4 mg once daily, and then 4 mg every other day).

The criteria for dose reduction of HAIC with cisplatin were as follows: (1) grade 4 leukocytopenia, neutropenia, thrombocytopenia, or thrombocytopenia requiring blood transfusion; (2) intolerable grade 2 or grade 3–4 non-hematological toxicities; (3) AST or ALT >400 U/L; and (4) creatinine >2.0 mg/dL. If the criteria were met, treatment was suspended; after recovery of these events, the cisplatin dose was reduced to 50 mg/m^2 (first time) and 35 mg/m^2 (second time). Patients who discontinued the study treatment were permitted to receive other anticancer treatment at the physician's discretion.

Tolerability Assessment

Dose-limiting toxicities (DLT) were evaluated in the first 6 patients enrolled in the study as the feasibility confirmation part of the study. The period of DLT evaluation was set as the time between the initiation of the first course and the initiation of the second course of study treatment. The following adverse events for which the causal relationship with study treatment could not be ruled out were defined as DLT: (1) febrile neutropenia, (2) grade 4 leukocytopenia or neutropenia lasting 7 days or longer, (3) grade 4 thrombocytopenia, (4) grade 3 or higher non-hematological toxicity (excluding hypertension, proteinuria, palmar-plantar erythrodysesthesia, γGTP, persistent loss of appetite/nausea/electrolyte abnormalities within 3 days, AST/ALT ≤400 U/L, Cr ≤2.0 mg/dL), (5) hypertension that could not be controlled even with maximum treatment, (6) adverse events of lenvatinib treatment that cannot be resumed for more than 4 weeks, and (7) the initiation criteria for the second course of intra-arterial cisplatin administration were not met even after 10 weeks from the initiation of the first course of cisplatin.

DLT was evaluated using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. If the number of patients with DLT was two or less, the combination therapy was judged to be tolerable, and the study moved to the phase II part. If 3 or more patients experienced DLT, the trial was to be discontinued. Supportive care for adverse events that may affect the evaluation of DLT was performed after confirming DLT.

Table 1. Patient characteristics

Characteristic	Patients, *n*	%
Age, years		
Median	68	
Range	23–78	
Sex		
Male	33	91.7
Female	3	8.3
ECOG performance status		
0	35	97.2
1	1	2.8
HBs Ag, positive	8	22.2
HCV Ab, positive	8	22.2
Child-Pugh score		
A5	25	69.4
A6	11	30.6
Ascites, present	3	8.3
Prior treatment	22	61.1
Resection	12	33.3
Local ablation	10	27.8
TACE	17	47.2
Radiation	1	2.8
Others	2	5.6
BCLC stage		
B	20	55.6
C	16	44.4
Portal vein tumor thrombosis, present	16	44.4
Vp1	5	13.9
Vp2	2	5.6
Vp3	6	16.7
Vp4	3	8.3
Extrahepatic spread, present	8	22.2
Lung	2	5.6
Bone	0	0
Lymph node	2	5.6
Adrenal	0	0
Other	4	11.1
Number of tumors		
1–4	13	36.1
≥5	23	63.9
Maximum tumor size, cm		
Median	5.6	
Range	1.2–15.2	
α-Fetoprotein, ng/mL		
Median	131.6	
Range	1.4–108,160	
PIVKA-II, mAU/mL		
Median	1,317.5	
Range	5.2–124,000	

Vp1, Vp2, Vp3, and Vp4 refer to tumor thrombosis in the third branch or peripheral portal vein, second branch of the portal vein, first branch of the portal vein, and the main or contralateral branch of the portal vein, respectively. ECOG, Eastern Cooperative Oncology Group; HBs Ag, hepatitis B surface antigen; HCV Ab, hepatitis C viral antibody; TACE, transarterial chemoembolization; BCLC, Barcelona Clinic Liver Cancer; PIVKA-II, protein induced by vitamin K absence or antagonist-II.

Tumor Assessment

Computed tomography was performed every 6 weeks during the combination therapy and every 12 weeks during the monotherapy. The antitumor effect of treatment in each patient was judged by each investigator using modified RECIST (mRECIST) [22] and assessed by the Independent Review Committee (IRC) on the basis of mRECIST and RECIST 1.1 [23].

Statistical Analysis

This was a multicenter open-labeled phase II trial. The primary endpoint was ORR using mRECIST by the IRC, and the secondary endpoints were ORR using RECIST 1.1 by the IRC, ORR using mRECIST by investigators, progression-free survival on the basis of mRECIST by IRC assessment, time to progression, overall survival, and the frequencies of adverse events and serious adverse events. Assuming a threshold response rate of 20%, an expected response rate of 40%, detection power of 80%, and α of 5% on one side (10% on both sides), 35 patients were required.

The following predefined subgroup analyses were performed on the ORR by IRC, disease control rate (DCR) by IRC, progression-free survival, and overall survival: (1) presence or absence of portal vein tumor thrombosis, (2) presence or absence of previous TACE history, (3) Child-Pugh 5 or 6 points, (4) α-fetoprotein (AFP) <400 or ≥400 ng/mL, (5) Barcelona Clinic Liver Cancer (BCLC) stage B or C, and (6) presence or absence of extrahepatic metastasis. All the data were fixed on April 28, 2021, and all the efficacy analyses were performed on the basis of the full analysis set by the trial statistician (T.S.) using SAS 9.4 and JMP Pro 11.

Results

Feasibility Confirmation

This trial was initiated on September 26, 2018, and the first 6 patients enrolled in the trial were entered into the feasibility confirmation part of the study. Grade 3 hepatic encephalopathy that met the DLT criteria was found in one out of the 6 patients. Lenvatinib treatment was suspended in this patient, and branched-chain amino acid and lactulose were administered; ammonia level decreased rapidly, and encephalopathy recovered 5 days later. A reduced dose of lenvatinib was resumed, and no recurrence of hepatic encephalopathy was observed. The efficacy and safety evaluation committee judged that this combination treatment was tolerable because only one DLT event occurred. The phase II trial was then started.

Patient Characteristics

A total of 36 eligible patients were enrolled from September 26, 2018 to March 5, 2020, and all patients received the protocol treatment. The patient characteristics are shown in Table 1. The median patient age was 68 years with a range of 23–78 years. ECOG performance status was zero in 35 patients (97.2%), and Child-Pugh score was 5 points in 25

patients (69.4%) and 6 in 11 patients (30.6%). BCLC stage was B in 20 patients (55.6%) and C in 16 patients (44.4%). In the overall group, 16 patients (44.4%) and 8 patients (22.2%) had portal vein tumor thrombosis and extrahepatic metastasis, respectively. The median AFP level was 131.6 ng/dL (range: 1.4–108,160).

Treatment

The median duration of lenvatinib administration was 186.3 days (range: 23–576 days), and the median dose intensity was 6.4 mg/day (1.9–12 mg/day). Among the overall patient group, 23 patients required a dose reduction of lenvatinib; the reasons for dose reduction were fatigue, nausea, and appetite loss (8 patients), palmar-plantar erythrodysesthesia (5 patients), diarrhea (3 patients), hepatic encephalopathy (3 patients), and other reasons (4 patients).

The median number of courses of HAIC with cisplatin was 4 (range: 1–7). The median dose of cisplatin was 110 mg/body/course, and the total dose was 464 mg/body (range: 94–817 mg/body). Most patients (31/36) did not require dose reduction; 4 patients had one dose reduction, and 1 patient had two dose reductions. The reasons for dose reduction were creatinine >2.0 mg/dL, grade 2 vomiting and increased bilirubin, grade 2 neutropenia, grade 3 neutropenia, and grade 2 leukocytopenia and neutropenia.

All patients discontinued the protocol treatment. The reasons for discontinuation were disease progression in 23 patients (intrahepatic lesions, 20 patients [87.0%]; extrahepatic lesions, 3 patients [13.0%]), adverse events in 10 patients, and other reasons in 3 patients. The adverse events that caused the discontinuation were biloma in 2 patients and cholangitis, cholecystitis, duodenal ulcer, Stevens-Johnson syndrome, fatigue, anorexia, and bleeding from pharynx ulceration because of late toxicity of radiotherapy for pharyngeal cancer in 1 patient each. Twenty-three patients (66.7%) underwent subsequent therapies after the discontinuation of protocol treatments. The subsequent therapies were molecular targeted agents in 29 patients (80.6%), immunotherapy (Atezo+Bev) in 5 patients (13.9%), HAIC in 5 patients (13.9%), TACE in 5 patients (13.9%), and others in 3 patients (8.3%).

Tumor Response

The investigators judged that all patients had measurable disease, but the IRC determined that 2 and 1 patient had no measurable lesions by mRECIST and RECIST 1.1, respectively. Therefore, these patients were excluded from the analysis of ORR and DCR by the IRC. Table 2 shows the confirmed ORR and DCR using mRECIST by IRC, RECIST by IRC, and mRECIST by the investigators' judgment. The confirmed ORR using mRECIST by IRC, RECIST by IRC, and mRECIST by investigators were 64.7% (95% confidence interval [CI]: 46.5–80.3%), 45.7% (95% CI: 28.8–63.4%), and 61.1% (95% CI: 43.5–76.9%), respectively. The median time to tumor response was 42 days (range: 28–175 days). The DCR using mRECIST by IRC, RECIST by IRC, and mRECIST by investigators was 76.5% (95% CI: 58.8–89.3%), 74.3% (95% CI: 56.7–87.5%), and 83.3% (95% CI: 67.2–93.6%), respectively.

Progression-Free Survival and Overall Survival

Figure 1 shows the Kaplan-Meier curve of progression-free survival on the basis of mRECIST by IRC assessment. The median progression-free survival (95% CI) was 6.3 months (5.1–7.9 months). The time to progression was mostly identical to the progression-free survival because all patients died after disease progression. Figure 2 shows the overall survival evaluated by the Kaplan-Meier method. The median overall survival (95% CI) was 17.2 months (95% CI: 10.9 – not estimated).

Subgroup Analysis

Table 3 shows the results of subgroup analysis on ORR (online suppl. Fig. 1; for all online suppl. material, see https://doi.org/10.1159/000531820) and DCR using mRECIST by the IRC and the results of progression-free survival and overall survival. The ORR and DCR tended to be lower in patients with extrahepatic metastasis than in patients without extrahepatic metastasis by 30% or more, and progression-free survival and overall survival were also much shorter in patients with extrahepatic metastases than in patients without extrahepatic metastases. However, there were no notable differences in ORR and DCR between the presence versus absence of portal vein tumor thrombosis, presence versus absence of TACE history, Child-Pugh A5 versus A6, AFP <400 versus ≥400 ng/mL, and BCLC stage B versus C subgroups.

Adverse Events

The main treatment-emergent adverse events are listed in Table 4. The main grade 3–4 adverse events were increased AST (33%), leukocytopenia (22%), neutropenia (19%), increased ALT (19%), increased bilirubin (11%), and hypertension (11%). Serious adverse events (17 events, 38.9%) occurred in 14 patients. Of these, serious adverse events relevant to the treatment were grade 2 and 3 hepatic encephalopathy, grade 3 cholecystitis, grade 3 perforation of duodenum, grade 4 acute renal failure, grade 3 Stevens-Johnson syndrome, grade 3 diarrhea, grade 3 increased bilirubin, and grade 4 pharyngeal

Table 2. Tumor response

	Independent Review Committee				Investigators	
	modified RECIST, *n* = 34		RECIST 1.1, *n* = 35		modified RECIST, *n* = 36	
	n	%	*n*	%	*n*	%
Tumor response						
CR	10	29.4	3	8.6	6	16.7
PR	12	35.3	13	37.1	16	44.4
SD	4	11.8	10	28.6	8	22.2
PD	8	23.5	9	25.7	6	16.7
Not evaluable	2	–	1	–	–	–
ORR (CR + PR)	64.7% (22/34)		45.7% (16/35)		61.1% (22/36)	
Exact 95% CI	46.5%, 80.3%		28.8%, 63.4%		43.5%, 76.9%	
DCR (CR + PR + SD)	76.5% (26/34)		74.3% (26/35)		83.3% (30/36)	
Exact 95% CI	58.8%, 89.3%		56.7%, 87.5%		67.2%, 93.6%	

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; CI, confidence interval.

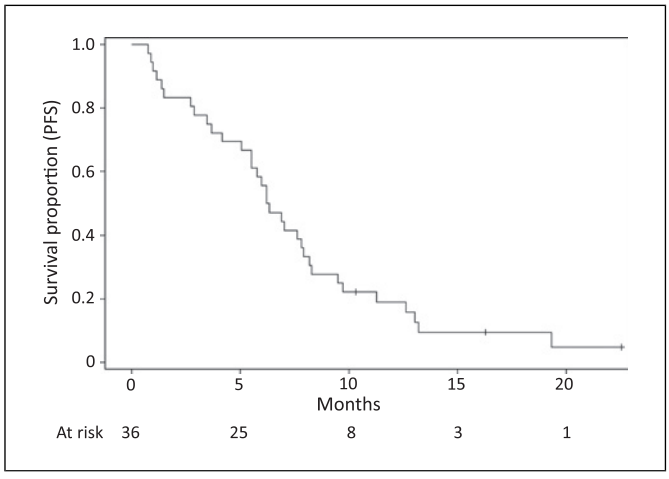

Fig. 1. Kaplan-Meier curves of progression-free survival. The tick marks indicate censored cases. PFS, progression-free survival.

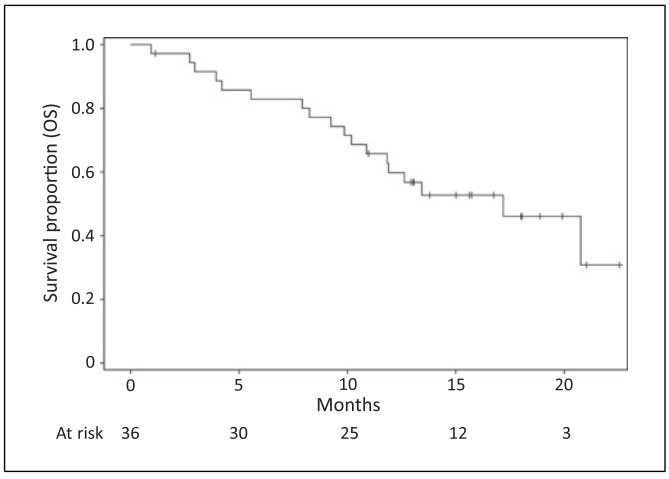

Fig. 2. Kaplan-Meier curves of overall survival. The tick marks indicate censored cases. OS, overall survival.

bleeding (each 1 patient). There was 1 patient (2.8%) with an early death within 30 days because of disease progression after the discontinuation of treatment, but no treatment-related deaths.

Discussion

In this multicenter phase II trial, lenvatinib combined with HAIC with cisplatin yielded an extremely favorable ORR (64.7% [95% CI: 46.5–80.3%]) using mRECIST by the IRC in patients with advanced HCC. In the assessment by mRECIST, target lesions in the liver are defined as tumor-enhanced lesions in the arterial phase, and disappearances of tumor enhancement by anticancer treatment are considered to be necrosis. It is often used to determine the efficacy of VEGF-targeted therapy such as lenvatinib, and the assessment by mRECIST criteria generally results in higher response rates than RECIST criteria. While assessments tend to yield higher response rates by mRECIST, the ORR in this trial was better than anticipated, and the primary endpoint was met. The proportions of patients with performance status of 1–2 and extrahepatic metastases in this trial

Table 3. Subgroup analysis of ORR, DCR, progression-free survival, and overall survival

	ORR		DCR		Progression-free survival		Overall survival	
	%	exact 95% CI	%	exact 95% CI	median, months	95% CI	median, months	95% CI
Portal vein tumor thrombosis								
Present	62.5	35.4%, 84.8%	75.0	47.6%, 92.7%	5.7	2.7, 6.3	12.6	9.2, NA
Absent	66.7	41.0%, 86.7%	77.8	47.6%, 92.7%	8.0	4.2, 13.0	20.8	8.2, NA
Prior TACE								
Present	66.7	38.4%, 88.2%	73.3	44.9%, 92.2%	7.0	3.7, 12.6	17.2	8.2, NA
Absent	63.2	38.4%, 83.7%	78.9	54.4%, 93.9%	6.2	2.9, 8.2	16.3	9.2, NA
Child-Pugh score								
A5	70.8	48.9%, 87.4%	79.2	57.8%, 92.9%	6.3	5.5, 9.5	NA	10.9, NA
A6	50.0	18.7%, 81.3%	70.0	34.8%, 93.3%	6.2	1.0, 8.3	11.8	2.7, 20.8
AFP (ng/mL)								
<400	63.2	38.4%, 83.7%	73.7	48.8%, 90.9%	6.6	2.7, 9.5	NA	10.2, NA
≥400	66.7	38.4%, 88.2%	80.0	51.9%, 95.7%	6.2	2.9, 7.6	11.9	5.6, 20.8
BCLC stage								
B	66.7	41.0%, 86.7%	77.8	52.4%, 93.6%	8.0	4.2, 11.3	20.8	11.9, NA
C	62.5	35.4%, 84.8%	75.0	47.6%, 92.7%	5.7	2.7, 6.3	10.9	8.2, 13.4
Extrahepatic spread								
Present	37.5	52.2%, 88.4%	50.0	8.5%, 75.5%	3.9	0.8, 7.9	10.0	1.0, 12.6
Absent	73.1	65.1%, 95.6%	84.6	15.7%, 84.3%	7.0	5.8, 9.5	20.8	11.9, NA

Objective response rate and disease control rate was judged using modified RECIST by the Independent Review Committee. TACE, transcatheter arterial chemotherapy; AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; NA, not available.

Table 4. Adverse events

Adverse events	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1–4 (%)	Grade 3–4 (%)
Hematological adverse events						
Thrombocytopenia	7	18	2	0	75	6
Anemia	12	9	3	0	67	8
Leukocytopenia	2	13	8	0	64	22
Neutropenia	3	13	7	0	64	19
Non-hematological adverse events						
Increased AST	2	15	12	0	81	33
Increased ALT	14	8	7	0	81	19
Hypoalbuminemia	7	20	1	–	78	3
Appetite loss	11	14	2	0	75	6
Proteinuria	15	8	3	–	72	8
Malaise	11	10	–	–	58	–
Hypertension	3	10	4	0	47	11
Palmar-plantar erythrodysesthesia	9	7	0	–	44	0
Increased bilirubin	5	7	3	1	44	11
Hoarseness	15	0	0	–	42	0
Increased creatinine	11	3	0	1	42	3
Nausea	6	6	1	–	36	3
Fatigue	6	5	2	–	36	6
Diarrhea	4	4	4	0	28	11

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

were lower as compared with those in pivotal phase III trials of systemic therapy, including sorafenib [24, 25], lenvatinib [4], Atezo+Bev [5], and Durva+Treme [6] (online suppl. Table 1). However, other characteristics including AFP and portal vein tumor thrombosis were similar or at higher proportions. The confirmed ORR by IRC was favorable in mRECIST and RECIST evaluation methods in this trial. The overall survival from the combination therapy in this study was comparable to that of Atezo+Bev and Durva+Treme, although a large number of patients with tumor thrombosis (44.4%) were enrolled and only 5 patients (13.9%) received Atezo+Bev in this series. We also compared our results with other reports on HAIC including 5-FU plus cisplatin [17, 26], FOLFOX [27, 28], or cisplatin alone [15] ± multikinase inhibitors (online suppl. Table 2). The treatment outcomes of this regimen showed the highest ORR and longest OS compared with results in these previous studies. However, the combination of lenvatinib plus HAIC with cisplatin does not contain immune checkpoint inhibitors and is applicable for patients with contraindications for immune checkpoint inhibitors, such as autoimmune diseases. This regimen might thus be valuable as an alternative treatment for immune checkpoint inhibitors. Furthermore, the cost of the angiographic procedure and cisplatin is approximately USD 2,000 per session in Japan, which is lower than the cost of immune checkpoint inhibitors. This regimen will thus also be of great economic value.

In the subgroup analysis, we found that patients with extrahepatic metastases had poorer response and worse progression-free survival and overall survival compared with patients without extrahepatic metastases. When cisplatin is administered directly from the hepatic artery, it is metabolized in the liver and less likely to be distributed throughout the whole body, thus reducing adverse events [1, 15]. However, HAIC does not exhibit antitumor activity for extrahepatic metastasis, although it is effective against intrahepatic lesions. Therefore, the effectiveness of this combination therapy may also be difficult to demonstrate, and this was the expected result. This analysis clearly identified intrahepatic lesions as suitable targets for this combination therapy.

HAIC is not a standard treatment worldwide [1]. Several recent reports from Asia have suggested the effectiveness of HAIC. In a phase III trial of sorafenib plus HAIC with 5-FU/folinic acid and oxaliplatin (FOLFOX) versus sorafenib alone, He et al. [26] reported that sorafenib plus HAIC with FOLFOX had a clear survival benefit over sorafenib in patients with advanced-stage HCC with vascular invasion. In a phase III trial of HAIC with FOLFOX versus sorafenib alone, Lyu et al. [27] also reported that HAIC with FOLFOX was superior to sorafenib alone in advanced HCC patients with heavy intrahepatic tumor burden. Therefore, in some countries, especially China, HAIC with FOLFOX is often used in advanced HCC patients [1, 9]. Among HAIC regimens, cisplatin alone is a one-shot administration and can be easily administered using the Seldinger technique without the need for an indwelling reservoir system [1, 13–15]. While the administration of cisplatin requires hospitalization, lenvatinib plus HAIC with cisplatin is expected to be more effective than lenvatinib monotherapy or Atezo+Bev.

In this phase I/II trial, the main treatment-emergent grade 3–4 adverse events were leukocytopenia (22%), neutropenia (19%), increased total bilirubin (11%), increased AST (33%), increased ALT (19%), increased γGTP (19%), hyponatremia (25%), hyperpotassemia (11%), diarrhea (11%), and hypertension (11%). These adverse events were transient and not severe. No adverse events associated with the HAIC procedure were observed. However, the median dose intensity may be relatively lower than that in the REFLECT trial [4], which was a phase III trial of lenvatinib versus sorafenib for unresectable HCC. The proportion of dose reduction and treatment discontinuation because of adverse events might be slightly higher in response to the combination therapy. These adverse events require attention. However, our study indicates the combination treatment was well tolerated.

This study has several limitations. This was a single-arm, open-label trial, and only a small number of patients were enrolled in this phase II trial. However, the study had a multicenter design, and tumor response was centrally assessed by the IRC. Independent data management by the data center and proper and thorough data analysis by independent statisticians were carried out, supporting the reliability of these results. Another limitation was that the trial was conducted only in Japan. It is necessary to evaluate whether similar results will be obtained in other countries.

In conclusion, our results demonstrated encouraging response rates and overall survival with well-tolerated adverse events in the combination therapy of lenvatinib and HAIC with cisplatin for advanced HCC. Future studies will need to evaluate the usefulness of this regimen in phase III trials.

Acknowledgments

We thank the members of the LEOPARD data center of EP-CRSU for their support with the data management (Ms. Yoko Yoshimoto, Ms. Kumiko Maie, and Ms. Hisako Matsuba), the

members of audit (Ms. Kanae Kuriyama and Ms. Sayuri Hamada), the members of the study committee for safety and efficacy monitoring (Dr. Hiroshi Ishii, Dr. Yasuhiro Matsumura, and Dr. Keigo Osuga), the members of the study committee for response evaluation (Dr. Tatsushi Kobayashi, Dr. Shunsuke Sugawara), and all the investigators of this trial. This paper was critically reviewed by a native English speaker from the Translation Division of ASCA Corporation, Tokyo, Japan. A part of the content of this paper was reported in the European Society of Medical Oncology Cancer Congress 2021, September 17, 2021–September 21, 2021, Paris, France.

Statement of Ethics

This clinical trial was conducted in accordance with the Declaration of Helsinki and Clinical Trials Act (Act No. 16 of April 14, 2017). This trial is registered with Japan Registry of Clinical Trials; the identification number is jRCTs031180019. This clinical trial was conducted with the approval of the National Cancer Center Hospital East Certified Review Board (CRB3180009) and the permission of directors in each participating institution. All patients gave written informed consent before enrollment in this trial.

Conflict of Interest Statement

Ikeda M reports grants or contracts from AstraZeneca, Bayer, Bristol-Myers Squibb, Chiome Bioscience, Chugai, Eisai, Eli Lilly Japan, Delta-Fly Pharma, Invitae, J-Pharma, Merck Biopharma, Merus N.V., MSD, Novartis, Nihon Servier, Ono, Pfizer, Takeda, and Yakult, and personal fees and other funding from AstraZeneca, AbbVie, Abbott Japan, Bayer, Bristol-Myers Squibb, Chugai, Eisai, Eli Lilly Japan, E.A. Pharma, Fujifilm Toyama Chemical, Incyte Biosciences Japan, M.S.D., Nihon Servier, Nippon Kayaku, Novartis, Otsuka, Teijin, Taiho, Taisho Pharmaceutical, Takeda, and Yakult outside the submitted work. Yamashita T. reports personal fees and other funding from Eisai, Chugai, and Lilly outside the submitted work. Ogasawara S. reports grants or contracts from Bayer, Eisai, Eli Lilly, Chugai, and AstraZeneca; consulting fees from Eisai, Chugai, and AstraZeneca; and personal fees and other funding from Bayer, Eisai, Eli Lilly, Chugai, and AstraZeneca outside the submitted work. Kudo M. reports grants or contracts from Taiho, E.A. Pharma, Eisai, G.E. Healthcare, Otsuka, AbbVie, and Chugai; consulting fees from Chugai, AstraZeneca, Roche, and Eisai; and personal fees and other funding from Eli Lilly, Bayer, Eisai, Chugai, Takeda, and AstraZeneca; grants: Taiho, Otsuka, E.A. Pharma, AbbVie, Eisai, Chugai, G.E. Healthcare; advisory consulting: Chugai, Roche, AstraZeneca, and Eisai outside the submitted work. Inaba Y. and Morimoto M. report personal fees and other funding from Eisai, outside the submitted work. Tsuchiya K. reports personal fees and other funding from Chugai, Eisai, Takeda, and Eli Lilly, outside the submitted work. Shimizu S. reports grants or contracts from AstraZeneca, Incyte Corporation, and Delta-Fly Pharma, outside the submitted work. Kojima Y. reports grants or contracts from Takeda, Ono Pharmaceutical, Eisai, Chugai, and Daiichi Sankyo; personal fees and other funding from Chugai, Yakult, Daiichi Sankyo, and Eisai; and participation on a Data Safety Monitoring Board or Advisory Board of AstraZeneca, outside the submitted work. Hiraoka A. reports personal fees and other funding from Chugai, AstraZeneca, and Eli Lilly Japan, outside the submitted work. K. Nouso reports personal fees and other funding from Nihon Kayaku and Eisai, outside the submitted work. Aikata H. reports personal fees and other funding from Eisai and Chugai, outside the submitted work. Okusaka T. reports grants or contracts from AstraZeneca, Syneos Health, E.P. CRSU, Eisai, M.S.D., and Insight Japan; consulting fees from AstraZeneca, Eisai, Nihon Servier, Dainippon Sumitomo Pharma, Bristol-Myers, and FUJIFILM Toyama Chemical; and personal fees and other funding from AstraZeneca, Insight Japan, Eisai, Ono Pharmaceutical, Yakult Honsha, Johnson and Johnson, Daiichi Sankyo, Taiho Pharmaceutical, Chugai, Nihon Servier, Nippon Shinyaku, Eli Lilly Japan, Pfizer Japan, and Novartis, outside the submitted work. Furuse J reports grants from or contracts with Astellas, AstraZeneca, Incyte Biosciences Japan, Eisai, M.S.D., Ono Pharmaceutical, Sanofi, J-Pharma, Daiichi Sankyo, Sumitomo Dainippon, Taiho Pharmaceutical, Takeda, Delta-Fly Pharma, and Chugai; consulting fees from Fujifilm, Astellas, OncoTherapy Science, Delta-Fly Pharma, Merck Bio, Ono Pharmaceutical, M.S.D., Taiho, Chugai, AstraZeneca, Incyte Biosciences Japan, and J-Pharma; and personal fees and other funding from Ono Pharmaceutical, Chugai Pharma, Incyte Biosciences Japan, Eisai, Eli Lilly Japan, AstraZeneca, Yakult, Servier Japan, M.S.D., Novartis, Takeda, Bayer, Taiho, E.A. Pharma, Teijin Pharma, Daiichi Sankyo, Terumo; and participation on a Data Safety Monitoring Board or Advisory Board of OncoTherapy Science, Chugai, Astellas, AstraZeneca, Takara bio, Merck Bio, M.S.D., and Taiho, outside the submitted work. K. Numata and Sato T. report nothing to declare. Ikeda M., Yamashita T., Tsuchiya K., K. Nouso, and Furuse J. are Editorial Board Members of *Liver Cancer*, and Kudo M. is an Editor in Chief of *Liver Cancer*.

Funding Sources

This study received funding from Eisai Co., Ltd. The funding sources were not involved in collection or analysis of the data or preparation of the manuscript.

Author Contributions

M.I. designed the original concept of the study, discussed and modified the study protocol, helped in collection and/or assembly of data, interpreted data, created the first manuscript draft, and provided the final approval of the manuscript to be published. T.Y., S.O., M.K., Y.I., M.M., S.S., Y.K., T.O., and J.F. helped conceive the design of the study and the collection and/or assembly of data, interpreted data, critically reviewed the manuscript drafts, and provided the final approval of the manuscript to be published. K.T., A.H., K. Nouso, H.A., and K. Numata helped in collection and/or assembly of data,

interpreted data, critically reviewed the manuscript drafts, and provided the final approval of the manuscript to be published. T.S. helped conceive the design of the study, performed statistical analyses, interpreted data, critically reviewed the manuscript drafts, and provided the final approval of the manuscript to be published.

Data Availability Statement

The data obtained in this study may be used for secondary uses (e.g., meta-analyses) in Japan or the other countries with approval by the study committee for safety and efficacy monitoring. Inquiries can be directed to the corresponding author.

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