Proposed title: Safety and pharmacokinetics of lenvatinib in patients with advanced hepatocellular carcinoma

Running title: A phase 1 study of lenvatinib in advanced HCC

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Keywords: hepatocellular carcinoma, lenvatinib, pharmacokinetics, phase 1, safety

Financial support: The study was funded by Eisai Co., Ltd., Japan

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Conflicts of interest:

Masafumi Ikeda received funding, travel support, and payment for manuscript preparation from Eisai Co., Ltd., Japan. The author reports paid expert testimony from Eisai Co., Ltd., Japan and Nanocarrier Co. Ltd.

Shuichi Mitsunaga received funding, travel support and payment for manuscript preparation from Eisai Co., Ltd., Japan.

Takuji Okusaka and Hideki Uno received funding and payment for manuscript preparation from Eisai Co., Ltd., Japan.

Takuya Suzuki, Toshiyuki Tamai, Tadashi Kadowaki and Seiichi Hayato are employees of Eisai Co., Ltd., Japan who funded the study.

Toshiyuki Tamai, Tadashi Kadowaki and Seiichi Hayato own stocks in Eisai Co., Ltd., Japan.

Kiwamu Okita received travel support and consulting fees from Eisai Co., Ltd., Japan and was a consultant for Otsuka Pharmaceutical Company Ltd. Japan and Kowa Company Ltd. Japan.

Hiromitsu Kumada received funding, payment for manuscript preparation and consulting fees from Eisai Co., Ltd., Japan.

Word count (excluding references): 3829 words

Number of tables/figures: 6

Supplementary figures: 1

Statement of translational relevance:
This Phase I study is the first trial to investigate the efficacy, safety, PK, and PD of lenvatinib in patients with advanced HCC. This study demonstrated favorable safety and tolerability, and preliminary antitumor activity of lenvatinib in patients with advanced HCC. Pharmacodynamic studies suggested that multistep angiogenesis was inhibited by administration of lenvatinib at the doses used in this study. Antitumor activity was demonstrated and tumor shrinkage was observed in 14 patients. The findings also provide preliminary recommendations for the use of 12 mg QD and 8 mg QD regimens in CP-A and CP-B, respectively, in future studies in patients with advanced HCC.
Abstract

**Purpose:** To determine the maximum tolerable dose (MTD), safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy of lenvatinib in patients with advanced hepatocellular carcinoma (HCC).

**Experimental Design:** This multicenter, open-label, phase 1, dose-escalation study included patients aged 20-80 years, refractory to standard therapy, and stratified by hepatic function measured using Child-Pugh (CP) scores: CP-A (score: 5-6) and CP-B (score: 7-8). Lenvatinib was administered continually once daily (QD) for 4-week cycles. MTD was defined as the maximum dose associated with ≤ 1 dose-limiting toxicity (DLT) occurring in Cycle 1 among 6 patients.

**Results:** In total, twenty patients (9 in CP-A and 11 in CP-B) were enrolled. The MTD was 12 and 8 mg QD in CP-A and CP-B, respectively; DLTs included proteinuria, hepatic encephalopathy, and hyperbilirubinemia. The most common Grade 3 toxicities included hypertension in CP-A and hyperbilirubinemia in CP-B. Lenvatinib plasma concentration at 24 hours after administration (C_{24h}) for 12 mg QD was higher in patients with HCC versus patients with other solid tumors shown in previous phase 1 study, but C_{24h} for 25 mg QD lenvatinib was comparable. After lenvatinib treatment, the number of circulating endothelial and c-Kit(+) cells decreased and the levels of interleukin (IL)-6, IL-10, granulocyte-colony stimulating factor, and vascular endothelial growth factor increased (P < 0.05). Partial responses were observed in 3 patients and tumor shrinkage occurred in 14 patients.

**Conclusion:** Lenvatinib (12 mg QD) demonstrated preliminary efficacy with manageable toxicity and is the recommended dose for phase 2 studies in patients with HCC and CP-A.
INTRODUCTION

According to World Health Organization estimates in 2012, primary liver cancer is the fifth most common cancer, affecting over 780,000 patients worldwide, and is the second most common cause of cancer-related mortality worldwide, with a higher incidence in Asia (1). Hepatocellular carcinoma (HCC) accounts for 85% to 90% of primary liver cancer. Compromised hepatic function due to the underlying liver disease often complicates treatment (2). The primary underlying risk factors for HCC are chronic viral hepatitis (types B and C), excessive alcohol intake, and exposure to aflatoxin, the contributions of which may vary depending upon geographical location (3).

HCC progression has been associated with growth factors such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF). VEGF levels have been shown to correlate with angiogenic activity, tumor progression, and poor prognosis; its effects are mediated by interactions with the tyrosine kinase receptors VEGFR-1, VEGFR-2, and VEGFR-3 (4).

Sorafenib is the current standard of care for advanced HCC patients. In the SHARP study, the sorafenib group had an improved overall survival (OS) versus placebo (median OS 10.7 months and 7.9 months, respectively) (5). However, the response rate was low and several studies have reported substantial toxicities associated with sorafenib such as hand-foot skin reactions (6-10). Therefore, alternative agents with lower toxicities and higher efficacy are needed. To date, studies of other agents including the mTOR inhibitor (everolimus) and other tyrosine kinase inhibitors (TKIs) including sunitinib, linifanib, brivanib, and erlotinib have failed to demonstrate improvements in OS (11-15).
Lenvatinib is an orally active inhibitor of multiple receptor tyrosine kinases, VEGFR 1-3, FGFR 1-4, PDGFRα, RET (Rearranged during Transfection), and KIT (16-18). Lenvatinib has shown promising antitumor efficacy in advanced solid tumors (16, 17, 19, 20). Preliminary studies suggested the use of up to 25 mg QD lenvatinib for solid tumors in phase 1 studies (19, 20) and 24 mg QD was used as the starting dose in patients with solid tumors in subsequent studies. Recently, Schlumberger and colleagues in a phase 3, double-blind, placebo-controlled trial in patients with radioiodine-refractory differentiated thyroid cancer (SELECT) demonstrated improved progression-free survival and manageable safety profiles with lenvatinib 24 mg QD (21). However, since lenvatinib is metabolized in the liver (26) through a cytochrome P450 3A (CYP3A)-based mechanism (22), the impaired hepatic function in patients with HCC may affect lenvatinib exposure and drug doses used in other tumor types may not be appropriate in this patient group (23, 24). Therefore, dose-finding studies have been recommended in patients with HCC stratified by Child–Pugh (CP) classes A and B (25).

We evaluated the maximum tolerable dose (MTD) of lenvatinib administered continually once daily (QD) for 4-week cycles in patients with advanced HCC stratified by hepatic function, CP scores 5–6 (CP-A) and 7–8 (CP-B). In addition, we analyzed biomarkers to evaluate the effect of lenvatinib on anti-angiogenesis.

MATERIALS AND METHODS

Study Design

This phase 1, open-label, dose-escalation study of lenvatinib was conducted at 2 investigational sites in Japan. All patients provided written informed consent, and the study was approved by the institutional review boards of the respective medical institutions. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.
After screening for eligibility, patients were divided into 2 groups based on their CP scores. In the CP-A group, the starting dose was 12 mg QD, which was approximately 50% of the MTD recommended for solid tumors (19, 20, 26); when this dose was considered tolerable (≤ 1 dose-limiting toxicity [DLT] in 6 patients in Cycle 1), dose escalation to 16 mg QD and subsequently to 20 mg QD was allowed for each 6-patient cohort. Three CP-B group patients were assigned per dose level, starting with the lowest tolerable dose confirmed in CP-A. In both CP-A and CP-B groups, a lower dose level of 8 mg QD was planned if 12 mg QD was not tolerable. DLTs observed in Cycle 1 were defined as ≥ Grade 4 hematologic toxicities, Grade 3 thrombocytopenia requiring blood transfusion, any ≥ Grade 3 nonhematologic toxicity (except for laboratory abnormalities without treatment, controlled hypertension, aspartate aminotransferase [AST] or alanine aminotransferase [ALT] ≤ 10 × upper limit of normal, or diarrhea/vomiting/nausea controlled by treatment), or any toxicity that necessitates the interruption of lenvatinib for > 7 days. MTD was defined as the maximum dose associated with ≤ 1 DLT occurring in Cycle 1 among 6 patients.

Starting on Day 1/Cycle 1, each cycle comprised 4 weeks (28 days) of continuous lenvatinib administration until disease progression, development of unacceptable toxicity, withdrawal of consent, subject request, or end of study. Once-daily oral doses of lenvatinib (Eisai Co., Ltd., Japan) were administered on an empty stomach each morning. The concomitant use of strong CYP3A4 inhibitors was prohibited. If a DLT or other toxicity occurred, lenvatinib was interrupted until recovery and restarted at a reduced dose. All subjects who demonstrated a DLT or completed Cycle 1 could continue treatment after additional written informed consent for continuation in the study was obtained.
**Patient Eligibility**

Patients aged 20 to 80 years with a histologically or clinically confirmed diagnosis of advanced HCC (hypervascularity in arterial phase and washout in venous or delayed phase by dynamic computed tomography [CT]) that was resistant to standard therapy eg, transarterial chemoembolization, sorafenib (i.e., progressive disease [PD] or intolerance to standard therapy) or for which no standard therapy existed, with Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 1, < Grade 2 toxicity from prior therapy, absolute neutrophil count (ANC) $\geq 1.5 \times 10^3/\mu L$, hemoglobin $\geq 9.0$ g/dL, platelet count $\geq 50 \times 10^9/L$, serum albumin $\geq 2.8$ g/dL, total bilirubin $\leq 3.0$ mg/dL, alanine aminotransferase (ALT), aspartate aminotransferase (AST) $\leq 5$ times the upper limit of normal (ULN), international normalized ratio (INR) $\leq 2.3$, serum creatinine $\leq 2.0$ mg/dL or calculated creatinine clearance $\geq 40$ mL/min. Perimenopausal women with amenorrhea for $\geq 12$ months or women of childbearing potential, who were not pregnant, were eligible for inclusion. All women and fertile men had to use adequate contraceptive methods during the study.

Patients were excluded if they had a history of medical conditions that could affect investigational drug absorption, brain metastasis or meningeal carcinomatosis, pericardial or pleural effusion, ascites, a hemorrhagic or thrombotic event within 4 weeks of study entry, significant cardiovascular disease, proteinuria, $\geq$ Grade 2 nausea, psychotic disorder, drug or alcohol abuse, progressive central nervous system disease, human immunodeficiency virus (HIV) or other serious infections, an inadequate washout period from prior therapy, treatments that affect the CYP3A4 enzyme, or were judged by the investigator to be medically unfit. Patients were withdrawn from the study if they required dose reduction $< 4$ mg, upon disease progression, or if they experienced an adverse event (AE) that prohibited continuation of study treatment or needed $> 14$ days for recovery, or if treatment compliance was $< 75%$. 
Assessments

Blood samples were obtained for pharmacokinetic (PK) analysis on Day 1 (predose and 0.5, 1, 2, 4, 6, 8, and 24 hours postdose), Day 8 (predose), Day 15 (predose and 0.5, 1, 2, 4, 6, 8, and 24 hours postdose), and Day 22 (predose) of Cycle 1. Lenvatinib was quantified using a validated liquid chromatography/mass spectrometry method. Predose blood samples for pharmacodynamic (PD) markers were collected on Days 1, 8, 15, and 22 (Cycle 1). Circulating endothelial cells (CECs) and circulating endothelial progenitor cells (CEPs), which indicate active vascular turnover and angiogenesis (16, 27), were measured as described previously (20). Briefly, peripheral blood mononuclear cells were incubated with fluorescein isothiocyanate-conjugated antihuman CD34 (Beckman Coulter, Inc.), PerPC-conjugated anti-human CD45 (Becton Dickinson), phycoerythrin-conjugated antihuman CD117 (c-kit; Beckman Coulter, Inc.), and APC-conjugated antihuman CD133 (Miltenyi Biotec K.K). The cells were then washed with phosphate-buffered saline and fixed in 4% paraformaldehyde prior to fluorescence-activated cell sorting (FACS) analysis and measured by LSI Medience Corporation using a BD FACS Calibur HG cytometer and CellQuest software (Becton Dickinson). Plasma samples were analyzed in triplicate for baseline and posttreatment levels of 10 angiogenic proteins and cytokines using BioPlex PRO™ human group I cytokine 6-Plex (VEGF, PDGF-BB, interleukin [IL]-6, IL-8, IL-10, and granulocyte-colony stimulating factor [G-CSF]) and group II 3-plex (stem cell factor [SCF], stromal cell-derived factor-1α, and HGF) panel assays (Bio-Rad Laboratories Inc) and the Invitrogen™ FGF-basic singleplex bead kit (Life technologies) by LSI Medience Corporation.

Safety assessments measured during the study included AEs, laboratory variables (hematology, chemistry, urinalysis, viral tests [HIV, hepatitis B and C], prothrombin time, thyroid-stimulating hormone [TSH], free thyroxine [FT]3, FT4, KL-6, human chorionic gonadotropin), vital signs (systolic and diastolic
blood pressure, pulse rate, and body temperature), height, weight, and physical examination. The severity of AEs was graded according to Common Terminology Criteria for Adverse Events (CTCAE, version 3.0). All AEs were coded by standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA version 17.0). Efficacy was assessed using Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) by the investigator, and assessments were conducted every 8 weeks.

**Statistical analysis**

All patients who received at least one dose of lenvatinib were eligible for safety, efficacy, and PK analyses. Demographic and baseline characteristics were summarized using descriptive statistics. The main efficacy parameter was time to progression (TTP), defined as duration from the time of study entry to the first documentation of disease progression. Median TTP with 95% confidence interval (CI) was calculated and plotted using Kaplan–Meier product limit estimates stratified by hepatic function group.

The objective response rate (ORR) and disease control rate (DCR) were evaluated according to RECIST 1.1 and presented using (Clopper–Pearson) 95% CIs. ORR was defined as the number of patients with complete response (CR) + partial response (PR) divided by the number of patients in the analysis set. DCR was defined as the number of patients with CR + PR + stable disease (SD) divided by the number of patients in the analysis set. PK parameters were estimated by noncompartmental methods on WinNonlin (version 6.2.1 or later) software. The PK profile of lenvatinib in patients with HCC from this study was also compared with the PK profile of lenvatinib in patients with advanced refractory solid tumors from a previously published study (19).

For the PD analysis, pretreatment versus posttreatment changes in the levels of each parameter were analyzed using Wilcoxon signed rank test. Statistical analyses were performed using SAS for Windows (ver.8.2 or later), WinNonlin (version 6.2.1 or later), and R (version 3.1.1 or later).
RESULTS

Patients

A total of twenty patients, 9 in the CP-A and 11 in the CP-B group, were enrolled in this study between August 3, 2009 and Nov 22, 2011; all patients received the study treatment and completed the study. The median age (range) was 63.5 (47–74) years, 85% were men, and all patients were Asian. The ECOG PS was 0 in 65% patients and 1 in the remaining 35%. All 20 patients had target lesions according to RECIST 1.1, and a majority (80%) of them exhibited ≥ 4 liver tumors at baseline. In addition, 8 (40%) patients had portal vein invasion and 14 (70%) had extrahepatic metastasis. The most frequently reported carcinogenic factors for HCC were hepatitis C (45% patients), hepatitis B (35% patients), and alcohol abuse (15% patients). No patient had hepatic encephalopathy. Baseline and disease characteristics were comparable between CP-A and CP-B groups (Table 1).

Most patients (65%) had undergone targeted therapy/systemic chemotherapy, predominantly with sorafenib. Other prior anticancer treatments included local therapy, such as transarterial chemoembolization (80%) and radiofrequency ablation (40%), hepatic intra-arterial chemotherapy (40%), surgery (40%), and radiotherapy (25%).

DLT and MTD

Overall, DLTs occurred in 5 (25%) patients, 3 in the CP-A and 2 in the CP-B group. The initial dose was 12 mg QD in the CP-A group; since only 1 patient experienced a DLT (≤ Grade 2 fever/vomiting) among 6 patients, the dose in the next cohort was increased to 16 mg. There were 2 reported DLTs in the 16-mg cohort (Grade 3 proteinuria and Grade 3 hepatic encephalopathy) among 3 patients. Thus, 16 mg was considered not tolerable and 12 mg was determined to be the MTD for the CP-A group.
After the MTD dose was evaluated for the CP-A group, this dose was evaluated in the CP-B group. One patient experienced Grade 3 hepatic encephalopathy and one patient experienced Grade 3 increased AST, Grade 3 hyperbilirubinemia, and Grade 2 increased creatinine as DLTs in 5 patients of the 12-mg cohort in the CP-B group. Therefore, the dose was reduced to 8 mg. No DLTs were experienced among the 6 patients who received 8 mg lenvatinib; therefore, 8 mg lenvatinib was determined to be the MTD for patients with CP-B hepatic function.

**Safety**

Incidences of AEs were generally comparable between the CP-A and CP-B groups with the exception of hyperbilirubinemia of any grade and Grade 3 (CP-A, 22.2% and 11.1%; CP-B, 72.7% and 27.3%, respectively), and any-grade increase in TSH levels (CP-A, 66.7%; CP-B, 27.3%) (Table 2). The most frequent treatment-emergent AEs included diarrhea (all grades, 90%; Grade 3–4, 10%), fatigue (90%; 5%), decreased appetite (80%; 10%), hypertension (75%; 50%), hyperbilirubinemia (60%; 20%), palmar-plantar erythrodysesthesia syndrome (PPES) (65%; 5%), nausea (60%; 0%), and vomiting (50%; 0%). Grade 3–4 AEs were reported in 7 (77.8%) patients in the CP-A and 8 (72.7%) patients in the CP-B group. Patients were exposed to a mean 5.5 cycles of lenvatinib, and dose reductions were required in 14 (70%) patients.

Serious AEs (SAEs) were reported in 4 patients in the CP-A and 6 in the CP-B group. There were 2 deaths in the CP-B group that occurred due to hematemesis (8 mg) or hepatic failure (12 mg) as a result of progression of HCC after discontinuation of the study drug. Both deaths were considered unrelated to the study drug by the investigator. Other SAEs were hyperbilirubinemia (1 patient in CP-A group and 1
patient in CP-B), tumor hemorrhage (2 patients in CP-B), and hepatic encephalopathy (1 patient in CP-A and 1 patient in CP-B).

Major AEs leading to dose reduction were hyperbilirubinemia (3 patients in CP-B) and decreased appetite, hepatic encephalopathy, and PPES (one patient in CP-A and one in CP-B). Three patients discontinued lenvatinib due to AEs; Grade 2 abnormal hepatic function and Grade 3 hepatic encephalopathy in 1 patient (CP-A, 16 mg), Grade 2 ascites in 1 patient (CP-B, 8 mg), and Grade 2 hyperbilirubinemia in 1 patient (CP-B, 12 mg).

**Pharmacokinetics**

Following oral administration, lenvatinib was absorbed rapidly, with maximum concentration reached within 2 hours. In both dose groups, exposure, as measured by $C_{\text{max}}$ and $\text{AUC}_{(0-24\,\text{h})}$, increased with increasing lenvatinib dose (Table 3). Similarly, after administration over 15 days in both CP-A and CP-B groups, exposure, as measured by $C_{ss,\text{max}}$, $C_{24\,\text{h}}$, and $\text{AUC}_{(0-\tau)}$, increased with increasing lenvatinib dose. Plasma lenvatinib concentrations increased after repeated dosing, with mean accumulation index ($R_{ac}$) of $\text{AUC}_{(0-24\,\text{h})}$ and $C_{\text{max}}$ ranging from 1.23 to 2.11. The PK of lenvatinib did not appear to be affected by CP score.

Most of the PK parameters were comparable between the 12 mg CP-A and the 12 mg groups of patients with solid tumors, except $C_{24\,\text{h}}$, which was higher in the 12 mg CP-A group but comparable with that of the 25 mg MTD in solid tumors (Figure 1). No conclusive comparisons could be made in the 12 mg CP-B group because of insufficient data ($n = 2$).

**Pharmacodynamics**
The total number of CEPs significantly decreased 15 days posttreatment with lenvatinib compared with the baseline levels (P < 0.05); this was attributable to a significant decrease in the number of c-Kit(+) CEPs (P < 0.01), but not c-Kit(−) CEPs (P > 0.05; Figure 2A). The total number of CECs remained unchanged (P > 0.05), but the number of c-Kit(+) CECs decreased significantly (P < 0.001) whereas c-Kit(−) CECs increased significantly (P < 0.01; Figure 2B).

Among the blood/plasma angiogenic factors and cytokines tested, the levels of IL-6, IL-10, G-CSF, and VEGF increased significantly (P ≤ 0.01), whereas those of SCF decreased (P < 0.001) on Day 15 posttreatment compared with baseline levels (Figure 2C and D).

**Efficacy (Antitumor Response)**

There was no complete response. Partial response was observed in 1 patient in each of CP-A 12-mg, CP-A 16-mg, and CP-B 8-mg groups. The ORR was 22.2% (2/9) in the CP-A and 9.1% (1/11) in the CP-B group. Overall, 10 patients (50.0%) had a best overall tumor response of stable disease: 4 in the CP-A group (2 each in the 12-mg and 16-mg cohorts) and 6 in the CP-B group (4 in the 8-mg and 2 in the 12-mg cohorts). Progressive disease occurred in 2 (22.2%), 4 (36.4%), and 6 (30.0%) patients in the CP-A group, CP-B group, and in the overall study, respectively. The DCR was 66.7% in the CP-A and 63.6% in the CP-B group. The overall ORR and DCR were 15.0% (95% CI: 3.2, 37.9) and 65.0% (95% CI: 40.8, 84.6), respectively. Any tumor shrinkage from baseline was observed in 14 patients, 7 each in the CP-A and CP-B group (Figure 3A). The median TTP was 5.4 months (95% CI: 1.10, 7.50) in the CP-A and 3.6 months (95% CI: 1.00, 9.20) in the CP-B group (Figure 3B). Figure 3C and D depict computed tomographic image of a single patient treated with lenvatinib. The levels of alpha-fetoprotein (AFP) had reduced for a majority of patients and aligned with improvement in tumor response (Supplemental Figure 1).
DISCUSSION

This is the first study to investigate the efficacy, safety, PK, and PD of lenvatinib in patients with advanced HCC. Based on the occurrence of DLTs, the MTD for CP-A and CP-B groups was 12 mg QD and 8 mg QD, respectively. These MTDs are recommended for further clinical studies of lenvatinib in patients with HCC stratified by liver function. DLTs in this study included a class effect of VEGF-R inhibitors (ie, proteinuria) in the CP-A group and hepatic events such as hepatic encephalopathy and increased AST and bilirubin levels in both CP-A and CP-B groups. These findings deviate from previous studies of patients with solid tumors (and unspecified hepatic function); hepatic DLTs have not been reported in other phase 1 studies of QD regimen of lenvatinib and only rarely in those with twice-daily (BID) regimens (19, 20). Although previous phase 1 studies have evaluated the MTD as 25 mg QD or 10–13 mg BID with or without an off-treatment period, 25 mg QD has been recommended for future studies because this dose permits higher exposure (19, 20, 26).

Moreover, 24 mg QD is also the recommended dose in Japanese patients with solid tumors, and no differences were observed in PK profiles between Japanese and non-Japanese patients (18). Considering that lenvatinib is metabolized in the liver and patients with HCC have impaired liver function, the lower MTD in CP-A and CP-B observed in this study of patients from Japan with advanced HCC is likely explained by tumor type and hepatic function, and not by ethnic differences.

The patient profile in this study was similar to that of previous reports of Japanese HCC patients, with the exception of a relatively higher rate of hepatitis B infection as a cause of HCC in this study (30-32). There was no notable difference between patients with and without prior exposure to sorafenib with respect to AEs and biomarkers. The preliminary evidence for efficacy and safety of lenvatinib for patients with HCC aligned with that obtained from previous studies on solid tumors. As reported earlier,
the safety profile of lenvatinib included the common toxicities of VEGFR-TKIs, such as hypertension, diarrhea, anorexia, proteinuria, and PPES (18-20, 32). However, it is noteworthy that hepatic encephalopathy and hyperbilirubinemia have not been reported in previous clinical trials of lenvatinib for solid tumors; such events could be expected due to the impaired liver function of patients with advanced HCC.

The PK profile of 12-mg lenvatinib in patients with HCC and CP-A hepatic function might be different from that of patients with solid tumors who received 12- and 25-mg lenvatinib in a previous study. After administration of a single dose, the $C_{\text{max}}$ of 12-mg lenvatinib in the CP-A group was similar to that in patients with solid tumors who received a 12-mg dose, but lower than in those who received 25 mg. However, since lenvatinib oral clearance after administration of multiple doses in patients with HCC was decreased in this study, the $C_{24h}$ of 12 mg in the CP-A group was higher than that in patients with solid tumors who received 12 mg lenvatinib, and was comparable to that of those who received 25 mg. Shumaker and colleagues (28) showed that lenvatinib AUCs and oral clearance were similar for single-dose administration between healthy subjects and those with mild (CP-A) or moderate (CP-B) hepatic impairment. The reason for the discrepancy in PK outcomes related to hepatic impairment between subjects without HCC and patients with HCC is unknown, but may result from differences in underlying hepatic etiology (29). The higher $C_{24h}$ and different DLT profile observed in patients with HCC may contribute to the lower MTD determined in this study.

Prognostic and predictive biomarker analyses can be useful in identifying potential responders to treatment for various types of cancers. A preclinical study by Matsui and colleagues (2008) showed that 1-week lenvatinib treatment increased CEC number, whereas a 3-week treatment reduced it to basal levels (16). Similarly, while there was no change in overall CEC numbers in our study, the number of
CECs and CEPs negative for c-Kit expression had increased and those positive had reduced from baseline. C-Kit and its ligand SCF are expressed on activated endothelial cell (EC) layers and play a key role in the survival and differentiation of cultured EC and in CEP recruitment during tumor growth and vascularization (20). Lenvatinib suppressed production of c-Kit(+) CEPs, which might be caused by inhibition of recruitment of CEPs, thus normalizing tumor angiogenesis (16, 33).

Furthermore, there was an increase in levels of IL-6, IL-10, G-CSF, and VEGF PD biomarkers that are important mediators of angiogenesis. For example, elevations in G-CSF and VEGF plasma levels immediately after anticancer treatment are associated with mobilization of CEPs, which contributes to the regrowth of tumors (34). IL-6 is a multifunctional cytokine that correlates with tumor size and IL-10 is an immunosuppressive factor that has been implicated in the disease prognosis of solid tumors. The inhibitory effect of lenvatinib on VEGF signaling has been evaluated in preclinical studies; VEGF-induced growth of human endothelial cells was suppressed by lenvatinib (35). The increase in VEGF levels observed in this study suggests that lenvatinib inhibited the VEGF-signaling pathway. Changes in levels of various PD markers in this study suggested that multistep angiogenesis was inhibited by administration of lenvatinib at the doses used in this study.

We also demonstrated antitumor activity of lenvatinib that was similar in both the CP-A and CP-B groups. Tumor shrinkage was observed in 14 patients (7 each in CP-A and CP-B groups). Confirmed PR and DCR in the CP-A group were 22.2% (2 patients) and 66.7 % (6 patients), respectively, with the median TTP of 5.40 months in the CP-A group. Of the 3 patients with PR, 2 had prior exposure to sorafenib. These efficacy findings are comparable to those in a phase 3 study (30) and a Japanese phase 1 study of sorafenib in HCC (10).
In conclusion, MTDs in patients with HCC were determined in the present phase 1 study; this study demonstrated favorable safety and tolerability, and preliminary antitumor activity of lenvatinib in patients with advanced HCC. Considering the DLT profile, our findings provide preliminary recommendations for the use of 12 mg QD and 8 mg QD regimens in future studies in patients with advanced HCC (CP-A or CP-B class, respectively). Further studies to evaluate the efficacy, including OS, of lenvatinib in patients with HCC, enrolling larger numbers of patients and with longer follow-up periods, are needed to confirm our findings.

Acknowledgments

We thank all the patients who participated and their families, as well as the investigators, physicians, nurses, and clinical research coordinators who helped with this study; the Efficacy and Safety Evaluation Committee: Drs. J.Furuse (Kyorin University School of Medicine), K. Koike (The University Tokyo) and S. Arii (Hamamatsu Rousai Hospital). Medical writing services were provided by Cactus Communications (funded by Eisai Co., Ltd.). All authors retained full control over the manuscript content

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REFERENCES


Figures and Tables

**Figure 1.** Mean ± standard deviation plasma concentration-time curves of lenvatinib after **A:** single dose and **B:** multiple doses for HCC and solid tumor.

**Figure 2:** To quantify CECs and CEPs, a number of CD34-positive and CD45-negative cells were isolated, and CD133-negative cells and CD133-positive cells were determined as CECs and CEPs, respectively. CECs and CEPs were divided into c-Kit positive [c-Kit(+) and negative [c-Kit(−)] subpopulations. C-Kit(+) ratio (%) was calculated as [c-Kit(+) CEC or CEP]/[total CEC or CEP]. The figure depicts change in **A:** number of circulating endothelial progenitor cells, **B:** number of circulating endothelial cells, and **C & D:** levels of biomarkers from predose baseline to Day 15. Data points for G-CSF, IL-6, IL-8, IL-10, PDGF-BB, and VEGF of one subject, IL-6 of a second subject on Day 15, and PDGF-BB of a third subject were beyond the scale and are not shown in the plots although they were included in the data analysis.

**Figure 3:** **A:** Assessment of tumor response according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 using the waterfall plot displaying percentage change from baseline in sums of lesion diameters and **B:** Kaplan–Meier plot of time to progression (TTP) presented for individual patients of both hepatic function groups- Child Pugh Score 5,6 and Child Pugh Score 7,8+ censored observations. Computed tomographic image of a single patient at **C:** baseline and **D:** posttreatment with lenvatinib.

**Table 1:** Demographic and Baseline Characteristics

**Table 2:** Most Frequently Reported Adverse Events in Each Dose Cohort, Presented as n (%) 

**Table 3:** Summary of Pharmacokinetic Parameters
### Table 1: Demographic and Baseline Characteristics

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<tr>
<th></th>
<th>Child–Pugh A (n = 9)</th>
<th>Child–Pugh B (n = 11)</th>
<th>Overall (N = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age, years (range)</strong></td>
<td>62 (52–74)</td>
<td>65 (47–72)</td>
<td>63.5 (47–74)</td>
</tr>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3 (33)</td>
<td>0 (0)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Male</td>
<td>6 (67)</td>
<td>11 (100)</td>
<td>17 (85)</td>
</tr>
<tr>
<td><strong>ECOG-PS, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>5 (56)</td>
<td>8 (73)</td>
<td>13 (65)</td>
</tr>
<tr>
<td>1</td>
<td>4 (44)</td>
<td>3 (27)</td>
<td>7 (35)</td>
</tr>
<tr>
<td><strong>Child–Pugh score, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>4 (44)</td>
<td>0 (0)</td>
<td>4 (20)</td>
</tr>
<tr>
<td>6</td>
<td>5 (56)</td>
<td>0 (0)</td>
<td>5 (25)</td>
</tr>
<tr>
<td>7</td>
<td>0 (0)</td>
<td>10 (91)</td>
<td>10 (50)</td>
</tr>
<tr>
<td>8</td>
<td>0 (0)</td>
<td>1 (9)</td>
<td>1 (5)</td>
</tr>
<tr>
<td><strong>Ascites, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3 (33)</td>
<td>11 (100)</td>
<td>14 (70)</td>
</tr>
<tr>
<td>No</td>
<td>6 (67)</td>
<td>0 (0)</td>
<td>6 (30)</td>
</tr>
<tr>
<td><strong>Portal vein invasion, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5 (56)</td>
<td>3 (27)</td>
<td>8 (40)</td>
</tr>
<tr>
<td>No</td>
<td>4 (44)</td>
<td>8 (73)</td>
<td>12 (60)</td>
</tr>
<tr>
<td><strong>Extrahepatic metastasis, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7 (78)</td>
<td>7 (64)</td>
<td>14 (70)</td>
</tr>
<tr>
<td>No</td>
<td>2 (22)</td>
<td>4 (36)</td>
<td>6 (30)</td>
</tr>
<tr>
<td><strong>Hepatic encephalopathy, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BCLC stage, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage B</td>
<td>1 (11)</td>
<td>2 (18)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Stage C</td>
<td>8 (89)</td>
<td>9 (82)</td>
<td>17 (85)</td>
</tr>
<tr>
<td><strong>Cause of HCC, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>4 (44)</td>
<td>3 (27)</td>
<td>7 (35)</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>4 (44)</td>
<td>5 (46)</td>
<td>9 (45)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>1 (11)</td>
<td>2 (18)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>1 (9)</td>
<td>1 (5)</td>
</tr>
<tr>
<td><strong>Median AFP, ng/mL (range)</strong></td>
<td>265</td>
<td>202</td>
<td>257.5</td>
</tr>
<tr>
<td>Prior therapy, n (%)</td>
<td>(4.3–52,000)</td>
<td>(2.3–43,800)</td>
<td>(2.3–52,000)</td>
</tr>
<tr>
<td>---------------------</td>
<td>---------------</td>
<td>---------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Surgery</td>
<td>3 (33)</td>
<td>5 (46)</td>
<td>8 (40)</td>
</tr>
<tr>
<td>Chemoembolization</td>
<td>6 (67)</td>
<td>10 (91)</td>
<td>16 (80)</td>
</tr>
<tr>
<td>Hepatic arterial chemotherapy</td>
<td>4 (44)</td>
<td>4 (36)</td>
<td>8 (40)</td>
</tr>
<tr>
<td>Radiation</td>
<td>2 (22)</td>
<td>3 (27)</td>
<td>5 (25)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior systemic chemotherapy, n (%)</th>
<th>(4.3–52,000)</th>
<th>(2.3–43,800)</th>
<th>(2.3–52,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>5 (56)</td>
<td>6 (55)</td>
<td>11 (55)</td>
</tr>
<tr>
<td>Others chemotherapy</td>
<td>1 (11.1)</td>
<td>1 (9.1)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>None</td>
<td>3 (33.3)</td>
<td>4 (36.4)</td>
<td>7 (35.0)</td>
</tr>
</tbody>
</table>

ECOG-PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma

BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein
Table 2: Most Frequently Reported Adverse Events in Each Dose Cohort, Presented as n (%)

<table>
<thead>
<tr>
<th>AEs</th>
<th>Child–Pugh A</th>
<th></th>
<th>Child–Pugh B</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12 mg (MTD)</td>
<td>16 mg</td>
<td>8 mg (MTD)</td>
<td>12 mg</td>
</tr>
<tr>
<td></td>
<td>(n = 6)</td>
<td>(n = 3)</td>
<td>(n = 6)</td>
<td>(n = 5)</td>
</tr>
<tr>
<td><strong>Frequent AEs</strong></td>
<td>Any Grade</td>
<td>Grade 3–4</td>
<td>Any Grade</td>
<td>Grade 3–4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (100.0)</td>
<td>0 (0)</td>
<td>3 (100.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (83.3)</td>
<td>0 (0)</td>
<td>3 (100.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>6 (100.0)</td>
<td>1 (16.7)</td>
<td>2 (66.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5 (83.3)</td>
<td>4 (66.7)</td>
<td>3 (100.0)</td>
<td>2 (66.7)</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia syndrome</td>
<td>5 (83.3)</td>
<td>1 (16.7)</td>
<td>3 (100.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>2 (33.3)</td>
<td>1 (16.7)</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (33.3)</td>
<td>0 (0)</td>
<td>3 (100.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (50.0)</td>
<td>0 (0)</td>
<td>3 (100.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Increased TSH</td>
<td>5 (83.3)</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>3 (50.0)</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>2 (33.3)</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2 (33.3)</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (66.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Increased AST</td>
<td>4 (66.7)</td>
<td>1 (16.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>2 (33.3)</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>2 (33.3)</td>
<td>0 (0)</td>
<td>2 (66.7)</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>Ascites</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>3 (50.0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2 (33.3)</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>3 (50.0)</td>
<td>1 (16.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>3 (50.0)</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; MTD, maximum tolerable dose; TSH, thyroid-stimulating hormone
Table 3: Summary of Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>HCC, Child–Pugh A</th>
<th>HCC, Child–Pugh B</th>
<th>Solid tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12 mg (MTD) (n = 6)</td>
<td>16 mg (MTD) (n = 3)</td>
<td>8 mg (MTD) (n = 6)</td>
<td>12 mg (MTD) (n = 11)</td>
</tr>
<tr>
<td>AUC₀-2₄ h</td>
<td>ng*h/mL</td>
<td>2020 (170)</td>
<td>3280 (961)</td>
<td>1250 (399)</td>
</tr>
<tr>
<td>Cₚₘₐₓ</td>
<td>ng/mL</td>
<td>212 (70.8)</td>
<td>344 (166)</td>
<td>146 (56.9)</td>
</tr>
<tr>
<td>tₘₐₓ</td>
<td>h</td>
<td>2.00 (0.97, 5.95)</td>
<td>1.97 (0.97, 4.00)</td>
<td>2.02 (1.50, 3.93)</td>
</tr>
<tr>
<td>t₁/₂</td>
<td>h</td>
<td>7.19 (0.77)</td>
<td>8.18 (2.36)</td>
<td>9.10 (2.28)</td>
</tr>
<tr>
<td>CL/F</td>
<td>L/h</td>
<td>5.30 (0.34)</td>
<td>4.33 (0.83)</td>
<td>5.99 (2.25)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>HCC, Child–Pugh A</th>
<th>HCC, Child–Pugh B</th>
<th>Solid tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12 mg (MTD) (n = 6)</td>
<td>16 mg (MTD) (n = 3)</td>
<td>8 mg (MTD) (n = 6)</td>
<td>12 mg (MTD) (n = 11)</td>
</tr>
<tr>
<td>AUC₀-τ</td>
<td>ng*h/mL</td>
<td>3120 (566)</td>
<td>5110 (976)</td>
<td>1770 (340)</td>
</tr>
<tr>
<td>Cₛₛ,ₘₐₓ</td>
<td>ng/mL</td>
<td>346 (75.4)</td>
<td>402 (62.9)</td>
<td>167 (40.4)</td>
</tr>
<tr>
<td>C₂₄h</td>
<td>ng/mL</td>
<td>43.1 (21.7)</td>
<td>84.6 (33.1)</td>
<td>29.9 (13.4)</td>
</tr>
<tr>
<td>tₛₛ,ₘₐₓ</td>
<td>h</td>
<td>1.95 (1.00)</td>
<td>3.92 (3.83)</td>
<td>2.03 (1.98)</td>
</tr>
<tr>
<td>t₁/₂, ss</td>
<td>h</td>
<td>8.76 (2.62)</td>
<td>8.98 (2.15)</td>
<td>10.2 (3.1)</td>
</tr>
<tr>
<td>CLₛₛ/F</td>
<td>L/h</td>
<td>3.95 (0.78)</td>
<td>3.19 (0.608)</td>
<td>4.69 (1.07)</td>
</tr>
</tbody>
</table>

AUC₀-2₄ h, area under the concentration-time curve from zero time to 24 hours; AUC₀-τ, area under the concentration-time curve over the dosing interval on multiple dosing; Cₛₛ,ₘₐₓ, maximum observed concentration at steady-state; CL/F, oral clearance; CLₛₛ/F, oral clearance at steady state; HCC, hepatocellular carcinoma; MTD, maximum tolerable dose; tₘₐₓ, time at which drug concentration is the highest; tₛₛ,ₘₐₓ, time at which the highest drug concentration occurs at steady-state; t₁/₂, terminal elimination phase half-life; C₂₄h, plasma concentration at 24 hours after administration. The number of patients receiving multiple doses in each of the following groups: CP-A 12 mg, CP-A 16 mg, CP-B 8 mg, CP-B 12 mg, solid tumor 12 mg, and solid tumor 25 mg equals 5, 2, 6, 2, 8, and 4, respectively.

a) n = 5; b) n = 11; c) n = 23; d) n = 2; e) n = 8; f) n = 10; g) n = 4

Data are represented as mean (SD), except for tₘₐₓ and tₛₛ,ₘₐₓ, which are represented as median (minimum – maximum).
Figure 1

A

Plasma concentration (ng/mL)

Time (h)

HCC CP 5.6 - 12mg
HCC CP 7.8 - 8 mg
Solid tumor - 12 mg
Solid tumor - 25 mg

B

Plasma concentration (ng/mL)

Time (h)

HCC CP 5.6 - 12mg
HCC CP 7.8 - 8 mg
Solid tumor - 12 mg
Solid tumor - 25 mg
Figure 2

A

CEP number (cells/mL)

Total
P=0.014

c-Kit(+)
P<0.01

c-Kit(-)
P=0.169

B

CEC number (cells/mL)

Total
P=0.156

c-Kit(+)
P<0.001

c-Kit(-)
P<0.01

C

pg/mL

G-CSF
P<0.01

IL6
P<0.01

IL8
P=0.478

IL10
P<0.01

D

pg/mL

PDGF-BB
P=0.841

SCF
P<0.001

SDF-1α
P=0.014

VEGF
P<0.001

Pre dose

Day 15
Figure 3

A

% Change from Baseline

PD  PD  PD  SD  PD
SD  SD  PD  SD  NE  SD  SD  SD  PD  SD  SD  PR  PR  SD  PR

B

Estimated Probability (%)

*1 Child Pugh Score 5,6
*2 Child Pugh Score 7,8 + Censored Observations

TTP (Months)

Subjects At Risk:

(*1) 9 9 5 5 4 4 2 2 0 0 0 0 0 0 0

(*1) 11 10 6 5 3 3 3 3 1 1 1 1 0

C

D
Safety and pharmacokinetics of lenvatinib in patients with advanced hepatocellular carcinoma

Masafumi Ikeda, Takuji Okusaka, Shuichi Mitsunaga, et al.

Clin Cancer Res  Published OnlineFirst October 23, 2015.

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