Efficacy and Safety of Lenvatinib in Patients with Recurrent Hepatocellular Carcinoma after Liver Transplantation

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Research Article

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Abstract

Background: Lenvatinib is approved for patients with metastatic or recurrent hepatocellular carcinoma (HCC); however, its clinical outcomes in patients experiencing HCC recurrence after liver transplantation (LT) remain unclear. Thus, we investigated the efficacy and safety of lenvatinib in patients with recurrent HCC after LT.

Methods: This multinational, multicenter, retrospective study included 45 patients with recurrent HCC after LT who received lenvatinib at six institutions in three countries (Korea, Italy, and Hong Kong) from June 2017 to October 2021.

Results: At the time of lenvatinib initiation, 95.6% (n = 43) of patients were Child–Pugh A, with 35 (77.8%) and 10 (22.2%) patients classified as albumin-bilirubin (ALBI) grades 1 and 2, respectively. The objective response rate was 20.0%. With a median follow-up duration of 12.9 months (95% confidence interval [CI]: 11.2–14.7), median progression-free survival and overall survival (OS) were 7.6 (95% CI: 5.3–9.8) months, and 14.5 (95% CI: 0.8–28.2) months, respectively. Patients with ALBI grade 1 showed significantly better OS (52.3 months, [95% CI: not assessable]) than patients with ALBI grade 2 (11.1 months [95% CI: 0.0–30.4 months], $p = 0.003$). The most common adverse events were hypertension (n = 25, 55.6%), fatigue (n = 17, 37.8%), and anorexia (n = 14, 31.1%).

Conclusion: Lenvatinib showed consistent efficacy and toxicity profiles in patients with recurrent HCC after LT compared to the results of previous studies of non-LT HCC patients. The baseline ALBI grade was correlated with better OS in lenvatinib-treated patients with LT.

Background

Hepatocellular carcinoma (HCC) is the sixth most commonly diagnosed cancer and the third leading cause of cancer-related deaths globally [1]. HCC is an extremely heterogenous disease, and the selection of treatment strategy may vary based on tumor burden, the degree of underlying liver cirrhosis, and the patient's performance status. Surgical resection, liver transplantation (LT), and locoregional therapies, such as radiofrequency ablation (RFA), are all potentially curative treatment modalities for patients with early stage HCC [2].

LT offers the possibility of curing both the tumor and any underlying liver disease, such as cirrhosis. However, the recurrence of HCC after LT has been reported in 10–18% of patients, with a median time from LT to HCC recurrence of 12–13 months [3–5]. For patients with HCC recurrence following LT, local therapies such as RFA, transarterial chemoembolization (TACE), and surgical resection may be considered based on the recurrence pattern. Systemic therapy should be considered in patients with extrahepatic metastasis or those who may be refractory to local therapy [5].

For more than a decade, sorafenib, an oral multikinase inhibitor (MKI), has been the only systemic drug for patients with HCC recurrence after LT. Most of the small retrospective studies evaluating sorafenib

have shown variable clinical outcomes with 1-year overall survival (OS) rates of 18–90% [6–7].

Lenvatinib is an MKI for vascular endothelial growth factor (VEGF) receptors 1–3, fibroblast growth factor receptors 1–4, PDGFRα, RET, and KIT. In a phase 3, multicenter, randomized trial (REFLECT), lenvatinib demonstrated non-inferior OS and statistically significant improvements in progression-free survival (PFS), time to progression, and objective response rate (ORR) compared with sorafenib [8]. Given these data, lenvatinib was approved as a first-line standard therapy for unresectable or metastatic HCC. However, patients with prior LT were excluded from the prior prospective studies of lenvatinib [8–10]. As only a limited number of studies—mostly including < 15 patients—have been reported [11], further investigation is required to assess the efficacy and safety of lenvatinib in patients with recurrent HCC after LT. Therefore, we conducted a multinational, multicenter, retrospective study of lenvatinib in patients with recurrent HCC and with prior LT.

Materials And Methods

Patients

Patients who were treated with lenvatinib for the management of recurrent HCC after LT from June 2017 to October 2021 were identified from six centers in three countries (Korea, Italy, and Hong Kong). Clinical and laboratory data were retrospectively obtained by reviewing the medical records. This study was approved by the institutional review board of each participating center and was performed in accordance with the ethical standards of institutional research and the Declaration of Helsinki.

Treatment and evaluation

Lenvatinib was administered per its standard dose for advanced HCC patients, as described in the REFLECT trial (12 mg/day for body weight ≥ 60 kg and 8 mg/day for body weight < 60 kg) [8]. Dose modification at the start or over the course of lenvatinib treatment (to 8 or 4 mg/day) was allowed at the discretion of the attending physicians.

Patients were examined every 6–8 weeks using computed tomography or magnetic resonance imaging. Tumor response was graded according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). All treatment-related adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

Statistical analysis

ORR and disease control rate (DCR) were evaluated according to the RECIST v1.1. PFS was defined as the time from the initiation of lenvatinib to the date of disease progression or death, whichever occurred first. OS was defined as the time from the initiation of lenvatinib to death from any cause. The time to response (TTR) was defined as the time between the initiation of lenvatinib and the best response. Survival outcomes were estimated using the Kaplan–Meier method. A two-sided p-value < 0.05 was

considered statistically significant. All statistical analyses were performed using Statistical Package for the Social Sciences version 23.0 (IBM, Armonk, NY, USA).

Results

Patient characteristics

A total of 45 patients who received lenvatinib for the management of recurrent HCC following LT were included in this analysis. The baseline patient characteristics are summarized in Table 1. The median age was 59 years (range, 20–87 years), and most patients (n = 43, 95.6%) were male. All patients had an Eastern Cooperative Oncology Group performance status of 0 or 1. The most common HCC etiology was hepatitis B (n = 25, 55.6%), followed by hepatitis C (n = 11, 24.4%) and alcohol consumption (n = 4, 8.9%).

Table 1
Baseline characteristics.

Variables	Total N = 45
Sex	
Male	43 (95.6%)
Female	2 (4.4%)
Age, years, median (range)	59 (20–87)
Ethnicity	
East Asian	24 (53.3%)
Caucasian	21 (46.7%)
ECOG performance status	
0	19 (42.2%)
1	26 (57.8%)
Etiology	
Hepatitis B	25 (55.6%)
Hepatitis C	11 (24.4%)
Alcohol	4 (8.9%)
Others	5 (11.1%)
Child–Pugh Score	
A	43 (95.6%)
B	2 (4.4%)
ALBI grade	
1	35 (77.8%)
2	10 (22.2%)
Site of recurrence or metastasis	
Liver	29 (64.4%)
Lung	24 (53.3%)
Peritoneum	11 (24.4%)
Bone	9 (20.0%)
Lymph node	8 (17.8%)

Variables	Total N = 45
AFP, U/mL, median (range)	37 (1-373072)
< 400 U/mL	31 (68.9%)
≥ 400 U/mL	14 (31.1%)
Reason for liver transplantation	
Hepatocellular carcinoma	45 (100.0%)
LDLT	21 (46.7%)
DDLT	24 (53.3%)
Immunosuppressants	
Tacrolimus	41 (91.1%)
Everolimus	34 (75.6%)
Mycophenolate mofetil	5 (11.1%)
Interval between the liver transplantation and the start of lenvatinib, months, median (range)	28.1 (4.2-231.9)
BCLC stage	
B	4 (8.9%)
C	41 (91.1%)
Treatment line of lenvatinib	
First	42 (93.3%)
Second	3 (6.7%)

ECOG, Eastern Cooperative Oncology Group; ALBI, albumin-bilirubin; AFP, alpha fetoprotein; LDLT, living donor liver transplantation; DDLT, deceased donor liver transplantation; BCLC, Barcelona Clinic Liver Cancer.

All patients had previously received LT for the management of HCC, and approximately half of them (n = 21, 46.7%) had received living-donor liver transplantations. Most of the patients received a combination of immunosuppressants, including tacrolimus (TAC; n = 41, 91.1%), everolimus (EVE; n = 34, 75.6%), or mycophenolate mofetil (MMF; n = 5, 11.1%). The distribution of immunosuppressant use was as follows: TAC only, n = 6; EVE only, n = 2; MMF only, n = 1; TAC + EVE, n = 31; TAC + MMF, n = 2; and TAC + EVE + MMF, n = 1. The median time to recurrence of HCC from LT was 22.4 months (95% confidence interval [CI]: 1.1–207.0 months). Prior to systemic therapy, TACE (n = 17, 37.8%) was the most commonly used therapy for recurrent HCC after LT, followed by surgical resection (n = 15, 33.3%) and radiotherapy (n = 8, 17.8%).

At the time of lenvatinib treatment, most patients had Barcelona Clinic Liver Cancer stage C disease (n = 41, 91.1%) and the most common locations of disease were the liver (n = 29, 64.4%) and lungs (n = 24, 53.3%), followed by the peritoneum (n = 11, 24.4%) and bone (n = 9, 20.0%). Most patients (n = 43, 95.6%) had Child–Pugh A liver function, and 35 (77.8%) and 10 (22.2%) patients belonged to albumin-bilirubin (ALBI) grades 1 and 2, respectively.

Most patients (n = 42, 93.3%) received lenvatinib as the first-line therapy. Three patients (6.7%) received lenvatinib as a second-line therapy after progression on first-line sorafenib. The median time between LT and the start of lenvatinib was 28.1 months (range, 4.2–231.9 months), and the starting dose of lenvatinib was 12 mg/day for 29 patients (64.4%) and 8 mg/day for the remaining 15 patients (33.3%). Seven patients with a body weight > 60 kg received a reduced starting dose of lenvatinib, and the most common reasons were decreased renal (n = 2) and hepatic (n = 1) function and tumor bleeding (n = 1). At data cut-off (December 9, 2021), 13 (28.9%) patients were receiving ongoing lenvatinib treatment (1.0 + to 20.0 + months), and the median duration of lenvatinib treatment was 6.6 months (range, 0.1–20.0 months). Tumor progression was the most common reason for the discontinuation of lenvatinib (28 of 35, 80.0%). Seventeen patients were dead, and the cause of death for all these patients was the progression of HCC.

Efficacy of lenvatinib

Efficacy outcomes in lenvatinib-treated patients with recurrent HCC after LT are summarized in Table 2. According to the RECIST v1.1, partial response (PR), stable disease, and progressive disease were graded in 9 (20.0%), 31 (68.9%), and 3 (6.7%) patients, respectively. None of the patients achieved a complete response (CR). The ORR was 20.0% and the DCR was 88.9%. In patients who achieved partial response, the median TTR was 2.4 months (95% CI: 1.5–7.4 months). With a median follow-up duration of 12.9 months (95% CI: 11.2–14.7 months), median PFS and OS were 7.6 months (95% CI: 5.3–9.8 months), and 14.5 months (95% CI: 0.8–28.2 months), respectively (Fig. 1). The 6-month PFS and OS rates were 60.1% and 86.0%, respectively.

Table 2
Efficacy of lenvatinib in patients with recurrent hepatocellular carcinoma after liver transplantation.

Variables	Lenvatinib (N = 45)
Best response	
CR	0 (0.0%)
PR	9 (20.0%)
SD	31 (68.9%)
PD	3 (6.7%)
Not evaluable	2 (4.4%)
Overall response rate	20.0%
Disease control rate	88.9%
Median TTR, months (range)	2.4 (1.5–7.4)
Median PFS, months (95% CI)	7.6 (5.3–9.8)
6-month PFS rate	60.1%
Median OS, months (95% CI)	14.5 (0.8–28.2)
6-month OS rate	86.0%

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; TTR, time to response; PFS, progression-free survival; CI, confidence interval; OS, overall survival.

When stratified according to ALBI grade (grade 1 versus 2), patients with ALBI grade 1 had numerically higher median PFS (8.0 months [95% CI: 5.2–10.8 months]) than those with ALBI grade 2 (3.0 months [95% CI: 0.0–7.5 months]; $p = 0.078$; Fig. 2a). Patients with ALBI grade 1 also showed significantly better OS (52.3 months [95% CI: not assessable]) compared to patients with ALBI grade 2 (11.1 months [95% CI: 0.0–30.4 months]; $p = 0.003$; Fig. 2b).

There was no significant difference in PFS or OS according to immunosuppressant regimens at the time of lenvatinib initiation (EVE-containing regimens versus others, $p = 0.384$ [PFS] and $p = 0.480$ [OS]; Supplementary Fig. 1). The time to HCC recurrence after LT (< median [22.4 months] vs ≥ median) was not significantly associated with median PFS (7.6 months [95% CI: 4.5–10.7] vs 7.3 months [95% CI: 4.3–10.3]; $p = 0.826$) or OS (52.6 months [95% CI: not assessable] vs 13.3 months [95% CI: 10.1–16.5]; $p = 0.282$; Supplementary Fig. 2). In addition, the recurrence pattern at the time of lenvatinib initiation (only intrahepatic recurrence [n = 10] vs extrahepatic metastasis [n = 35]) did not show any relationship with median PFS (5.4 months [95% CI: 4.5–6.3] vs 7.6 months [95% CI: 5.8–9.5]; $p = 0.089$) or OS (11.4 months [95% CI: 10.9–not reached] vs 52.3 months [95% CI: not assessable]; $p = 0.204$; Supplementary Fig. 3).

Subsequent therapy

Among 31 patients who progressed on lenvatinib, 22 (71.0%) patients received subsequent systemic therapy. Sorafenib was the most commonly used agent (n = 19, 86.4%), followed by cabozantinib (n = 2, 9.1%) and regorafenib (n = 1, 4.5%). There was no patient who underwent re-transplantation for recurrent HCC after commencing lenvatinib treatment.

Safety profiles

Lenvatinib was interrupted or dose-reduced in 22 (48.9%) patients. The most common cause of dose modification was fatigue (7/22, 31.8%), followed by hypertension (4/22, 18.2%) and proteinuria (2/22, 9.1%). AEs that occurred in > 5% of patients are listed in Table 3. The majority (n = 44, 97.8%) of patients experienced an AE. Hypertension (n = 25, 55.6%) was the most frequent AE, followed by fatigue (n = 17, 37.8%) and anorexia (n = 14, 31.1%). The most common grade 3–4 AEs were hypertension (n = 9, 20.0%) and neutropenia (n = 4, 8.9%). Hematological AEs were more common in Asian patients (Asian vs Caucasian; anemia, 29.2% vs 0.0%, $p = 0.007$; thrombocytopenia, 33.3% versus 0.0%, $p = 0.004$), whereas anorexia was more common in Caucasian patients (Asian vs Caucasian; 16.7% vs 47.6%, $p = 0.025$; Supplementary Table 1). Four (8.9%) patients discontinued lenvatinib due to AEs (n = 2, grade 3 hypertension; n = 1, grade 3 proteinuria; n = 1, grade 3 fatigue).

Table 3
Adverse events in response to lenvatinib treatment.

	Adverse Events (Total N = 45)	
	Any grade	**Grade 3–4**
All, n (%)	44 (97.8%)	16 (35.6%)
Hematological AEs		
Neutropenia, n (%)	7 (15.6%)	4 (8.9%)
Anemia, n (%)	7 (15.6%)	0 (0.0%)
Thrombocytopenia, n (%)	8 (17.8%)	0 (0.0%)
Non-hematological AEs		
Hypertension, n (%)	25 (55.6%)	9 (20.0%)
Proteinuria, n (%)	10 (22.2%)	2 (4.4%)
Fatigue, n (%)	17 (37.8%)	4 (8.9%)
Anorexia, n (%)	14 (31.1%)	1 (2.2%)
Diarrhea, n (%)	12 (26.7%)	0 (0.0%)
Hand–foot syndrome, n (%)	7 (15.6%)	0 (0.0%)
Oral mucositis, n (%)	6 (13.3%)	0 (0.0%)
AE, adverse event.		

Discussion

This multinational, multicenter, retrospective analysis of patients with recurrent HCC after LT demonstrated that lenvatinib showed an ORR of 20.0% and median PFS and OS of 7.6 and 14.5 months, respectively. Our findings on the efficacy and safety of lenvatinib in patients with LT were comparable to those of the pivotal phase 3 REFLECT trial (ORR per RECIST v1.1 of 18.8%, median PFS of 7.4 months, and median OS of 13.6 months), which excluded patients with prior LT [8], and with previous real-world studies [12–15]. Our findings validate the clinical relevance of lenvatinib in patients with recurrent HCC following LT.

Although immune checkpoint inhibitors are now regarded as key components of the management of patients with advanced HCC [16–18], patients with prior LT may not benefit because of the risk of allograft rejection [19]. Therefore, targeted agents, mainly MKIs, should be the mainstay of managing patients with unresectable or metastatic HCC following LT. However, as patients with prior LT have been excluded from previous prospective randomized trials of currently approved agents for unresectable or

metastatic HCC, an optimal strategy for systemic therapy in patients with recurrent HCC following LT has not been well demonstrated.

As sorafenib is the only systemic therapy approved for unresectable or metastatic HCC, most studies of systemic therapy in patients with recurrent HCC after LT have included sorafenib [20–24], although most of them had small sample sizes (n = 5–50). In a previous meta-analysis of sorafenib for patients with recurrent HCC after LT, the median OS was 10.5 months (range, 5–21.3 months) and the median percentage of patients achieving CR and PR was 0% (range, 0–11.7%) and 4.8% (range, 0–26.7%), respectively [6]. Our findings suggest that lenvatinib may have better efficacy outcomes than sorafenib, as the ORR was 20% and the median OS was 14.5 months in the current study, although a direct comparison between our results for lenvatinib and those for sorafenib in previous studies was not possible. Further studies are necessary to define the optimal first-line therapy in patients with recurrent HCC following LT.

Previous studies have shown that baseline liver function classified by ALBI grade is associated with the efficacy of lenvatinib in non-LT patients with unresectable or metastatic HCC [25]. Consistent with these results, a lower ALBI grade was significantly associated with better OS and marginally related with better PFS with lenvatinib in our study population. As multiple targeted agents become available for the management of HCC, it may be important to provide timely initiation of these drugs prior to the deterioration of liver function, even in patients with prior LT, considering that repeated TACE may induce the deterioration of liver function [26–27]. Meanwhile, immunosuppressants were not associated with the efficacy of lenvatinib against recurrent HCC following LT, although a previous study for combination of sorafenib and mTOR inhibitors, including EVE, showed favorable survival outcomes [24]. Large multicenter studies are needed to define the relevant immunosuppressive regimens in combination with anti-cancer agents for recurrent HCC after LT.

The safety profiles of lenvatinib in patients with prior LT were consistent with the results of the REFLECT trial and other real-world studies of lenvatinib in non-LT HCC patients [8, 12, 28]. Although multiple immunosuppressants were used simultaneously with lenvatinib, there was no new safety signal observed for lenvatinib in the current study. There were discrepancies in the pattern of AEs between different ethnicities (more frequent hematological AEs in Asian patients and anorexia in Caucasian patients), but it is not clear whether these were due to ethnicity-related differences in the pharmacokinetics of lenvatinib.

Our study was limited by its retrospective design, which is subject to unintentional biases. Although the current analysis was based on the largest sample size for patients with prior LT, multivariate analysis to define the prognostic factors could not be performed because of insufficient statistical power. However, we did include a diverse range of ethnic groups from multiple countries under various patterns of clinical practice.

In conclusion, lenvatinib showed consistent efficacy and toxicity in patients with recurrent HCC following LT compared to those of the pivotal phase 3 REFLECT trial, which excluded patients with prior LT. Better liver function (ALBI grade 1) at the time of lenvatinib initiation correlated with better survival outcomes.

Abbreviations

AEs, adverse events

ALBI, albumin-bilirubin

CI, confidence interval

CR, complete response

DCR, disease control rate

EVE, everolimus

HCC, hepatocellular carcinoma

LT, liver transplantation

MKI, multikinase inhibitor

MMF, mycophenolate mofetil

ORR, objective response rate

OS, overall survival

PFS, progression-free survival

PR, partial response

RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1

RFA, radiofrequency ablation

TAC, tacrolimus

TACE, transarterial chemoembolization

TTR, time to response

VEGF, vascular endothelial growth factor

Declarations

Author Contributions

Study concept: CY; Study design: CY, ACG, MI, S-GL; Data acquisition: All authors; Data analysis and interpretation: All authors; Statistical analysis: KB, CY; Manuscript preparation: KB, ACG, CY, MI, S-GL; Manuscript editing: All authors; Manuscript review and approval: All authors.

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Data Availability

All data generated or analyzed during this study are included in this article and its supplementary material files. Further enquiries can be directed to the corresponding author.

Conflict of interest

CY received grants from Bayer, ONO Pharmaceuticals, and AstraZeneca and has consultancy and advisory roles with Bayer, Eisai, Ipsen, Merck Sharp & Dohme (MSD), AstraZeneca, and Bristol Myers Squibb (BMS). ACG received grants from AstraZeneca and has consultancy and advisory roles with Bayer, Eisai, Ipsen, MSD, GlaxoSmithKline, and AstraZeneca. MI has speaking/teaching and consultancy roles and is on the advisory board for Bayer, Gilead Sciences, BMS, Janssen, Ipsen, MSD, BTG-Boston Scientific, AbbVie, Guerbet, Eisai, and Roche. The other authors have no conflicts of interest to declare. CM received travel grant from Ipsen, and has advisory role with MSD and Ipsen.

Statement of Ethics

Study approval statement: This study protocol was approved by the Institutional Review Boards of Asan Medical Center (approval number 2020-1214), IRCCS San Raffaele Scientific Institute (DSAN854-A-OS/5), Sir YK Pao Centre for Cancer (2019.219), Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, ASST Ospedale Niguarda, and Papa Giovanni XXIII Hospital (480_2018bis). This study was performed in accordance with the ethical standards of the institutional research body and the Declaration of Helsinki.

Consent to participate statement: The need for informed consent in this study was waived considering the retrospective nature of this analysis.

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Figures

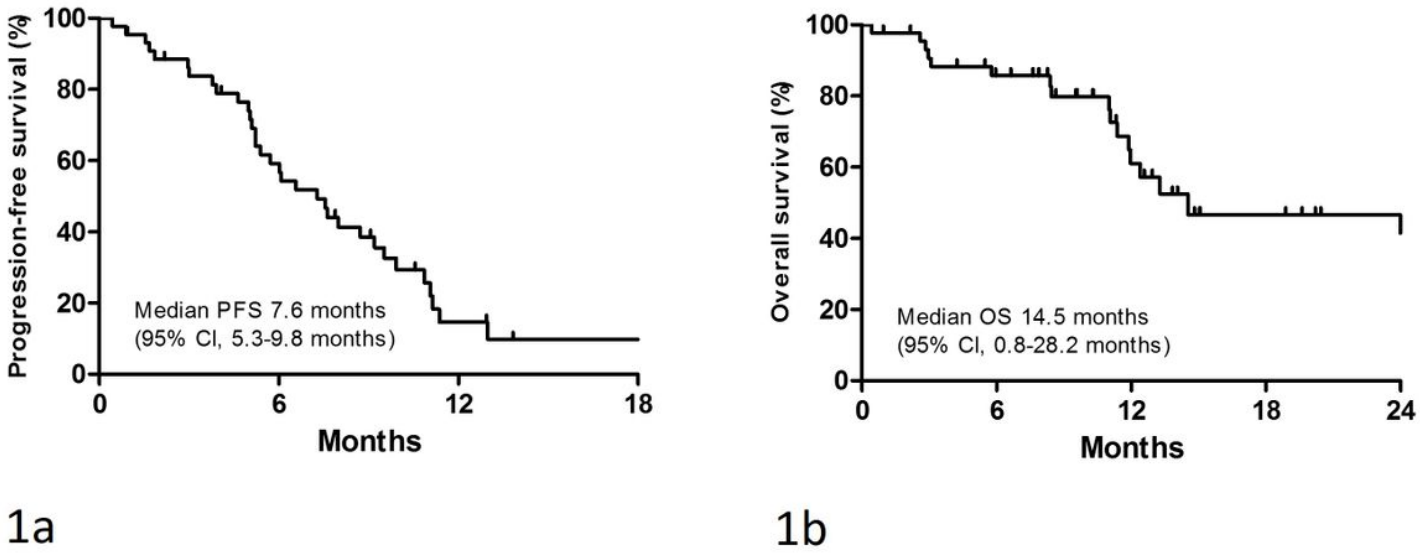

Figure 1

Kaplan–Meier curves of (a) PFS and (b) OS with lenvatinib in patients with recurrent hepatocellular carcinoma after liver transplantation. PFS, progression-free survival; CI, confidence interval; OS, overall survival.

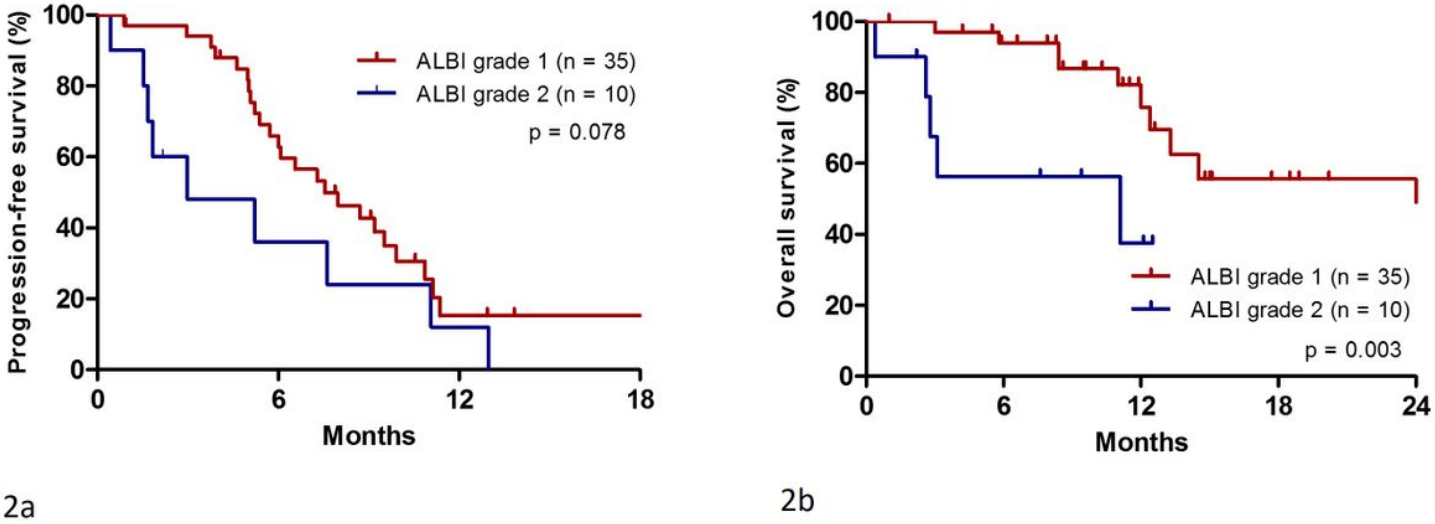

Figure 2

Kaplan–Meier curves of (a) PFS and (b) OS according to the albumin-bilirubin (ALBI) grade at the time of lenvatinib initiation.

Supplementary Files

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