Study Protocol

SPONSOR: Huashan Hospital, Fudan University

TITLE: Lenvatinib and transarterial chemoembolization （TACE） versus TACE alone as adjuvant therapy for hepatocellular carcinoma patients with high-risk of recurrence: a multicenter prospective cohort study (LANCE)

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1 Study Synopsis

Title	Lenvatinib and transarterial chemoembolization （TACE） versus TACE alone as adjuvant therapy for hepatocellular carcinoma patients with high-risk of recurrence: a multicenter prospective cohort study (LANCE)
Study objective	To evaluate the efficacy and safety of lenvatinib plus TACE as adjuvant treatment in HCC patients with high risks of recurrence
Study population and sample size	HCC patients with high risks of recurrence following curative resection at least N= 116
Enrollment criteria	1) Pathologically diagnosed with primary hepatocellular carcinoma (HCC). 2) Aged ≥ 18 and ≤ 75 years old. 3) American Society of Anesthesiologists (ASA) score I-III. 4) No history of severe arrhythmia or heart failure. 5) No history of ventilation dysfunction or severe pulmonary infectious diseases. 6) No acute or chronic renal failure; with the creatinine clearance rate > 40 ml/min. 7) Total bilirubin ≤ 3.0 mg/dL, albumin ≥ 28 g/L, AST, ALT and ALP ≤ five times the upper limit of normal range. 8) Hematology: absolute neutrophil count ≥ 1.5×109/L, Hb ≥ 8.5g/L, PLT ≥ 75×109/L. 9) Coagulation function: INR ≤ 2.3. 10) Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0. 11) Child-Pugh score of 5-7 (Child score 7 allowed only in the absence of ascites and hepatic encephalopathy). **12) With at least one high risk factor of recurrence defined, and confirmed radiologically and pathologically after surgery:** i. Pathological examination of tumor reveals grade II microvascular invasion, along with any of these three situations below: a) Lesion number ≥ 3. b) The maximum tumor diameter ≥ 8cm. c) The tumor shows infiltrative growth, with unclear boundaries and incomplete capsules.

	ii. Accompanied with gross vascular or bile duct invasion (tumor thrombi in portal vein, hepatic vein or bile duct). iii. Tumor rupture or invasion of adjacent organs. 13) No extrahepatic metastasis. 14) Signed informed consent form.
Exclusion criteria	1) Diagnosed with fibrolamellar sarcomatoid or intrahepatic cholangiocarcinoma or mixed cholangiocarcinoma-hepatocellular carcinoma. 2) Pregnant or lactating women. 3) A history of other malignancies. 4) Participating in other clinical trials in the past three months. 5) Received preoperative systemic drug therapy. 6) Intrahepatic residual tumors during postoperative TACE 4-6 weeks after surgery: Digital subtraction angiography (DSA) indicated residual lesions. 7) Receiving other targeted drugs, anti-PD-1 immunotherapy, systemic chemotherapy with FOLFOX, and Huaier Granules simultaneously during study intervention period.
Primary endpoint	• Disease free survival (DFS)
Secondary endpoint	• Overall survival (OS) • Safety
Estimated enrollment period	2 years
Estimated duration of trial	4 years

2 Background

2.1 Study Background

Liver cancer is the second leading cause of absolute years of life lost according to the Global Burden of Disease study [1]. In China, liver cancer ranks second among cancer-related mortalities [2]. Hepatocellular carcinoma (HCC) accounts for 85%-90% of patients with liver cancer.

Surgical treatment is the first choice for the treatment for HCC, because it presents the best chance for long-term survival. However, postoperative metastasis and recurrence are the main obstacles to the long-term survival of HCC patients. The five-year recurrence rate is as high as 60-70% after curative resection [3]. Despite the overall development of some potentially effective treatments for the prevention and treatment of postoperative recurrence of HCC, there is no standardized adjuvant treatment universally yet. A variety of approaches including locoregional therapy [4,5], anti-viral therapy [6], autologous cytokine-induced killer cells [7] and interferon alpha [8] have been explored by investigators as adjuvant therapy over the decades, aiming to reduce the tumor recurrence rate. Adjuvant transarterial chemoembolization (TACE) is a widely used postoperative treatment due to definite benefit indicated by multiple trials [9-13] and is recommended as alternative adjuvant therapy in Chinese guideline [14].

Meanwhile, systemic therapy in adjuvant setting was also explored. Before lenvatinib was approved as the first-line treatment for hepatocellular carcinoma, sorafenib was the only targeted drug for liver cancer for over 10 years. The STORM study was the first randomized controlled trial (RCT) to evaluate sorafenib as adjuvant treatment. However, sorafenib failed to prolong the recurrence free survival (RFS) , which may be related to the selection of inclusion criteria in the study [15].

Lenvatinib is a multi-target tyrosine kinase inhibitor (TKI) that targets VEGF receptors 1-3, fibroblast growth factor receptors (FGFR) 1–4, PDGFα receptor, RET, and KIT, thereby inhibiting tumor cell proliferation, inducing apoptosis, and suppressing angiogenic activities [16]. Based on REFLECT study, non-inferiority of lenvatinib was proved to sorafenib that the median OS of patients receiving lenvatinib was 13.6 months (95% CI, 12.1-14.9) vs. 12.3 months for patients receiving sorafenib (95% CI, 10.4-13.9). Besides, all secondary endpoints in the lenvatinib group were significantly better compared with the sorafenib group. The median progression-free survival (PFS) was 7.3 and 3.6 months, respectively (HR=0.64, P<0.0001). The median time to progression (TTP) was 7.4 and 3.7 months (HR=0.60, P<0.0001) and the objective response rate (ORR) was 24.1% and 9.2% (P<0.0001) [16]. Levatinib was approved as first line treatment for unresectable HCC worldwide. A subgroup analysis among Chinese patients demonstrated lenvatinib favored better in Chinese population. OS, PFS, and ORR of patients receiving lenvatinib was significantly

outperformed than sorafenib [17]. Thus, lenvatinib is expected to become a new treatment option as adjuvant treatment for HCC patients.

Here, we recommended adjuvant TACE with lenvatinib to prevent recurrence following resection of HCC with high risks for recurrence. Depending on the treatment regimen chosen for the patients, the patients will be divided into lenvatinib plus TACE group and TACE alone group. The efficacy and safety of the two treatments are evaluated, aiming to explore a more effective and promising treatment to prevent postoperative recurrence.

2.2 Lenvatinib

Angiogenesis, the formation of new blood vessels from a pre-existing vascular network, is essential for tumor growth and metastasis. VEGF and its family of receptors (VEGRs 1-3) play a major role in tumor angiogenesis [18,19]. Accumulated evidence suggests that FGF and its receptor tyrosine kinase, FGFR also play important roles for tumor angiogenesis [20,21].

Lenvatinib is a potent multiple RTK inhibitor that selectively inhibits VEGF receptors, VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), FGFR1-4, PDGFRα, KIT, and RET. Among known kinase inhibitors in clinical use, lenvatinib is one of the only inhibitors currently labeled with a mechanism of action as an inhibitor of not only VEGFRs but also FGFRs, both of which are currently believed to be very important for tumor angiogenesis.

Lenvatinib inhibited cell free kinase activities for VEGFR1-3 and FGFR1-3 with Ki values around 1 nmol/L, and 8-22 nmol/L, respectively. In cell-based assays, lenvatinib inhibited VEGF-derived and FGF-derived tube formation of HUVEC with IC50 values of 2.1 and 7.3 nmol/L, respectively. Analysis of the signal transduction molecules revealed that lenvatinib inhibited both the MAPK pathway and the mTOR-S6K-S6 pathway in HUVECs triggered by activated VEGFR and FGFR. Furthermore, lenvatinib (10, 30 mg/kg) significantly inhibited both VEGF- and FGF-driven angiogenesis in a murine in vivo model [22]. In vivo, lenvatinib exhibited antitumor activity against various human tumor xenografts in athymic mice including 5 types of thyroid carcinomas (differentiated [papillary and follicular], anaplastic, squamous, and medullary thyroid carcinomas), RCC, HCC, melanoma, gastric cancer, NSCLC, ovarian cancer, Ewing's sarcoma, and osteosarcoma. In addition, the antitumor activity of lenvatinib in combination with other anticancer agents in several xenograft models was greater than that of lenvatinib or the other agents alone.

In summary, lenvatinib inhibited VEGF-driven VEGFR2 phosphorylation and suppressed proliferation and tube formation in human umbilical vein endothelial cell (HUVEC) models. Antitumor activity of lenvatinib in vivo has been shown in numerous xenograft animals. These results suggest that lenvatinib may be a novel anticancer therapy through inhibition of angiogenesis and may be useful as either monotherapy or in combination with other anticancer

drugs.

2.3 Transcatheter arterial chemoembolization

Since the 1970s, cTACE has been the main treatment modality for incurable, non-metastatic HCC. A recent systematic review of the literature (n=10,108) showed a median OS of 19.4 months [23]. A recent phase III TACE trial comparing orantinib + TACE to TACE (ORIENTAL) showed a median OS of 32.3 months in the placebo group [24]. The PFS of the TACE trials varied slightly, but in a large phase III trial comparing sorafenib + TACE to TACE (TACE-2), the median PFS for TACE was 7.8 months [25].cTACE uses an embolic agent (usually lipiodol) in combination with a chemotherapy drug (most commonly doxorubicin).

2.4 Rationale of TACE in combination with lenvatinib

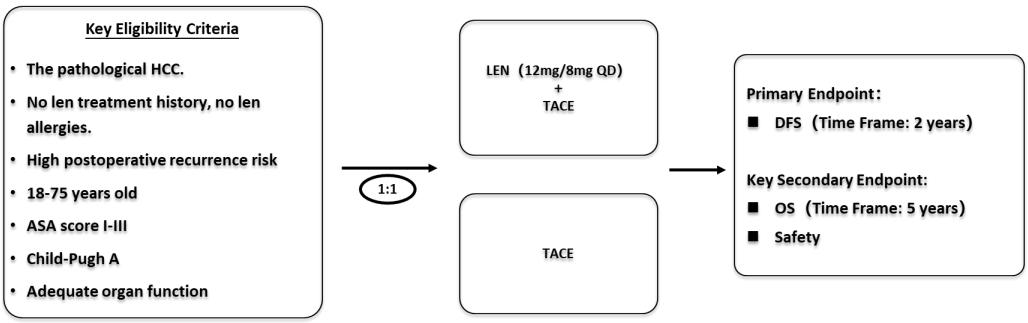
The main mechanism of action of TACE is to embolize the vasculature that nourishes HCC tumors, resulting in tumor necrosis. Lenvatinib, an anti-angiogenic drug, should be used in combination to prevent neovascularization in HCC tumors undergoing TACE, thereby further amplifying the effect.

3 Study Design

3.1 Study Schema

This was a prospective cohort study to evaluate the effect of Lenvatinib combined with TACE to prevent the recurrence in high-risk patients with hepatocellular carcinoma.

Figure 1. study design



HCC: hepatocellular carcinoma; Len: lenvatinib; ASA: American Society of Anesthesiologists; DFS: disease free survival; OS: overall survival.

The HCC patients receiving resection will be enrolled according to the inclusion and exclusion criteria (Section 5.1 and 5.2). Depending on the treatment regimen chosen, the patients are divided into lenvatinib plus TACE group and TACE group.

3.2 Schedule of Activities

Table 1. Schedule of Activities (SoA)

Procedure/Interventions	Screening	Intervention phase (Every 3 months)	End of Treatment	Survival follow up period (Every 3 months)	Notes
Informed consent	X				
Clinical examination					
Inclusion/ exclusion criteria	X				
History and physical exam	X				
Vital signs	X	X	X	X	
ECOG performance	X				

status					
Child-Pugh score	X				
Pathological diagnoses	X				
Electrocardiography (ECG)	X	X			
Adverse event		<----------			
Treatments					
Lenvatinib		X			Up to 24 months
TACE		X			Performed at 4-6 weeks after surgery
Survival status					
Survival status		<----------			
Subsequent Anti-tumor therapy				X	
Laboratory examination					
Urine beta HCG	X	X			For a woman of childbearing potential.
Hematology and Chemistry	X	X	X	X	Total bilirubin, direct bilirubin, albumin, alkaline phosphatase, ALT, AST, GGT, creatinine, BUN, sodium, potassium, chloride, glucose.
PT, INR	X	X	X		
HBV、HCV	X				
AFP	X	X	X	X	
CA199	X	X	X	X	
Urinalysis	X	X	X	X	
T3 (or Free T3), Free T4, and TSH	X	X	X		
Tumor assessments					
Abdomen contrast-enhanced MRI/CT	X	X	X	X	Abdomen contrast-enhanced MRI was preferred. One assessment method is selected for one patient during the

					treatment period.
Chest CT scan	X	X	X	X	Evaluate whether there is lung metastasis

4 Study Endpoints

4.1 Primary Endpoint

- Disease free survival (DFS)

  Defined as the time from surgery to first documented recurrence.

4.2 Secondary Endpoint

- Overall survival (OS)

  Defined as the time from surgery to death due to any cause in enrolled subjects.

- Safety

  The severity of adverse events will be graded according to Common Terminology Criteria for Adverse Events (CTCAE v5.0).

5 Study Population

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1) Pathologically diagnosed with primary hepatocellular carcinoma (HCC).
2) Aged ≥ 18 and ≤ 75 years old.
3) American Society of Anesthesiologists (ASA) score I-III.
4) No history of severe arrhythmia or heart failure.
5) No history of ventilation dysfunction or severe pulmonary infectious diseases.
6) No acute or chronic renal failure; with the creatinine clearance rate > 40 ml/min.
7) Total bilirubin ≤ 3.0 mg/dL, albumin ≥ 28 g/L, AST, ALT and ALP ≤ five times the upper limit of normal range.
8) Hematology: absolute neutrophil count ≥ 1.5×10^9/L, Hb ≥ 8.5g/L, PLT ≥ 75×10^9/L.
9) Coagulation function: INR ≤ 2.3.
10) Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0.
11) Child-Pugh score of 5-7 (Child score 7 allowed only in the absence of ascites and hepatic encephalopathy).
12) With at least one high risk factor of recurrence defined, and confirmed radiologically and pathologically after surgery:
    i. Pathological examination of tumor reveals grade II microvascular invasion, along with any of the situations below:
        a) Lesion number ≥ 3.
        b) The maximum tumor diameter ≥ 8cm.
        c) The tumor shows infiltrative growth, with unclear boundaries and incomplete capsules.
    ii. Accompanied with gross vascular or bile duct invasion (tumor thrombi in portal vein, hepatic vein or bile duct).
    iii. Tumor rupture or invasion of adjacent organs.
13) No extrahepatic metastasis.
14) Signed informed consent form.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

8) Diagnosed with fibrolamellar sarcomatoid or intrahepatic cholangiocarcinoma or

mixed cholangiocarcinoma-hepatocellular carcinoma.

9) Pregnant or lactating women.
10) A history of other malignancies.
11) Participating in other clinical trials in the past three months.
12) Received preoperative systemic drug therapy.
13) Intrahepatic residual tumors during postoperative TACE 4-6 weeks after surgery: Digital subtraction angiography (DSA) indicated residual lesions.
14) Receiving other targeted drugs, anti-PD-1 immunotherapy, systemic chemotherapy with FOLFOX, and Huaier Granules simultaneously during study intervention period.

6 Trial Intervention(s)

6.1 Timing of Dose Administration

6.1.1 TACE

One TACE procedure was performed 4-6 weeks after surgery for all enrolled patients if patients did not have obvious complications of surgery like infection, bleeding or hepatic function impairment as well as contraindications for TACE therapy [14]. The TACE procedure was performed in the following manners. An angiographic catheter was inserted to proper hepatic artery through femoral artery using the Seldinger technique. Microcatheter was used to right and left hepatic artery and inject an emulsion of chemotherapy agent and lipiodol to the entire remnant liver.

6.1.2 Lenvatinib

Physicians recommended the TACE plus lenvatinib treatment as adjuvant therapy for patients and fully informed patients of the drug efficacy, potential safety, and costs. If the patient agreed to the physician's recommendation, lenvatinib was administered within 7 days after the TACE treatment if patients have recovered from the postembolization syndromes of TACE such as pain, nausea, and vomiting, as well as impaired liver function.

Lenvatinib (Eisai Inc., Woodcliff Lake, NJ, USA) is provided as 4-mg capsule. Lenvatinib will be administered with water orally once a day (with or without food) at approximately the same time each day. The initial dose is 12 mg qd for patients weighing≥ 60 kg and 8 mg qd, for patients weighing < 60 kg.

The maximum treatment duration of lenvatinib treatment lasted for 24 months at the longest after surgery. The interruptions or dosage modifications of lenvatinib were allowed according to Section 6.2.

All HBV positive patients should receive antiviral treatment during the treatment period.

6.2 Dose Modification and Toxicity Management

The starting dose of lenvatinib is 12 mg (BW ≥60 kg) or 8 mg (BW <60 kg) orally QD. Dose reductions of lenvatinib occur in succession based on the previous dose level. Dose reductions occur in succession based on the previous dose level (12, 8, and 4 mg QD, and 4 mg every other day [QOD]) per Table 2.

Table 2. Dose Modification for Lenvatinib Treatment-Related Toxicity

	Adjusted Dose To Be Administered		
Initial Lenvatinib Dose (mg, QD)	Reduction 1	Reduction 2	Reduction 3
12 mg QD	8 mg QD	4 mg QD	4 mg QOD
8 mg QD	4 mg QD	4 mg QOD	Discontinue

QD = once daily; QOD = every other day.

Refer to the subsections below for management of hypertension (Section 6.2.1), proteinuria (Section 6.2.2), diarrhea (Section 6.2.3), thromboembolic events (Section 6.2.4), posterior reversible encephalopathy syndrome/ reversible posterior leukoencephalopathy syndrome (PRES/RPLS; Section 6.2.5), hypocalcemia (Section 6.2.6), hemorrhage (Section 6.2.7) and gastrointestinal perforation or fistula formation (Section 6.2.8), as appropriate, before consulting the dose modification table (Table 3).

Table 3.Dose-Modification Guidelines for Lenvatinib-Related Adverse Events

Lenvatinib Dose Reduction and Interruption Instructions Dose adjustment for lenvatinib treatment-related toxicity is AFTER interruption and resolution of study intervention asdetailed in the table below. Dose reductions occur in succession based on the previous dose level (12, 8, and 4 mg/day, and 4 mg every other day [QOD]).		
Nonhematologic Toxicities		
Treatment-Related Toxicity	**Management**	**Dose Adjustment**
Grade 1 or Tolerable Grade 2		
	Continue treatment[a]	No change
Intolerable Grade 2[a] or Grade 3[b,c,f]		
First occurrence	Interrupt until resolved to Grade 0-1 or baseline	Reduce lenvatinib by 1 dose level
Second occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	Reduce lenvatinib by 1 more doselevel
Third occurrence[f] (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	Reduce lenvatinib by 1 more doselevel
Fourth occurrence	Interrupt until resolved to Grade 0-1 or	Discontinue lenvatinib

(same toxicity or new toxicity)	baseline	
Grade 4[e,f]: Discontinue Lenvatinib		

Hematologic Toxicities and Proteinuria		
Treatment-Related Toxicity	**Management**	**Dose Adjustment**
Grade 1 or Grade 2[c]		
	Continue treatment[c]	No change
Grade 3[c, g]		
First occurrence	Interrupt until resolved to Grade 0-2 or baseline	No change
Second occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	Reduce lenvatinib by 1 dose level
Third occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	Reduce lenvatinib by 1 more doselevel
Fourth occurrence[d] (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	Reduce lenvatinib by 1 more doselevel
Fifth occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	Discontinue lenvatinib
Grade 4[h]		
First occurrence	Interrupt until resolved to Grade 0-2 or baseline	Reduce lenvatinib by 1 dose level
Second occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	Reduce lenvatinib by 1 more doselevel
Third occurrence[d] (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	Reduce lenvatinib by 1 more doselevel
Fourth occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	Discontinue lenvatinib

Note: Grading according to CTCAE v5.0.

AE = adverse event; CTCAE v5.0 = Common Terminology Criteria for Adverse Events Version5.0; QD = once daily.

a: Grade 2 toxicities will be determined to be tolerable or intolerable by both the participant and investigator. If Grade 2toxicity is determined to be intolerable, the dose of study drug will be reduced with or without dose interruption.

Interruption for Grade 3 toxicities is mandatory.

b: Obese participants (BMI >/= 30) with weight loss do not need to return to their baseline weight or within 10% of their baseline weight (ie, Grade 1 weight loss). These participants may restart study treatment at a lower dose once their weight loss remains stable for at least 1 week and they reach at least a BMI of 25. The new stable weight should be used for future dose reductions.

Lenvatinib Dose Reduction and Interruption Instructions

Dose adjustment for lenvatinib treatment-related toxicity is AFTER interruption and resolution of study intervention as detailed in the table below. Dose reductions occur in succession based on the previous dose level (12, 8, and 4 mg/day, and 4 mg every other day [QOD]).

c: Not applicable to abnormal clinical laboratory values that are not clinically relevant based on the judgment of the investigator.

d: Not applicable for participants who start at 8 mg QD.

e: Excluding laboratory abnormalities judged to be nonlife-threatening, which should be managed as Grade 3.

f: For asymptomatic Grade ≥3 elevations of amylase and lipase, Sponsor should be consulted to obtain permission to continue treatment.

g: For a Grade 3 thromboembolic event, with the exception of portal vein thrombosis developed during treatment, permanently discontinue lenvatinib. See Section 6.6.1.4

h: Applies to hematologic toxicities only.

6.2.1 Management of Hypertension

Hypertension is a recognized side effect of treatment with drugs inhibiting VEGF signaling. Investigators should therefore ensure that participants enrolled to receive treatment with lenvatinib have BP of ≤150/90 mm Hg at the time of study entry and, if known to be hypertensive, have been on a stable dose of antihypertensive therapy for at least 1 week before treatment. Early detection and effective management of hypertension are important to minimize the need for lenvatinib dose interruptions and reductions.

Regular assessment of BP should be as detailed in the SoA (Section 3.2, Table 1). Hypertension will be graded using NCI CTCAE v5.0, based on BP measurements only (and not on the number of antihypertensive medications). If the participant's initial BP measurement is elevated (ie, systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), the BP measurement should

be repeated at least 5 minutes later. One BP assessment is defined as the mean value of 2 measurements at least 5 minutes apart. If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) is elevated (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 5 minutes apart) to yield a mean value.

Antihypertensive agents should be started as soon as elevated BP (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg) is confirmed on 2 assessments at least 30 minutes apart. The choice of antihypertensive treatment should be individualized to the participant's clinical circumstances and follow standard medical practice. For previously normotensive participants, appropriate antihypertensive therapy should be started when systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg is first observed on 2 assessments at least 30 minutes apart. For those participants already on antihypertensive medication, treatment modification may be necessary if hypertension persists.

Lenvatinib should be withheld in any instance where a participant is at imminent risk to develop a hypertensive crisis or has significant risk factors for severe complications of uncontrolled hypertension (eg, BP ≥160/100 mm Hg, significant risk factors for cardiac disease, intracerebral hemorrhage, or other significant co-morbidities). Once the participanthas been on the same antihypertensive medications for at least 48 hours and the BP is controlled, lenvatinib should be resumed as described below.

Participants who have had systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg must have their BP monitored more frequently as clinically indicated until systolic BP has been ≤150 mm Hg and diastolic BP has been ≤95 mm Hg for 2 consecutive cycles. If a repeat event of systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg occurs, the participant must resume evaluation until systolic BP has been ≤150 mm Hg and diastolic BP has been ≤95 mm Hg for 2 consecutive treatment cycles. A diary will be provided as a tool to aid the participant in collecting blood pressure evaluations between study visits.

The following guidelines should be followed for the management of systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg confirmed on 2 BP assessments at least 30 minutes apart:

Continue study drug and institute antihypertensive therapy for participants not already receiving this.

For those participants already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or 1 or more agents of a different class of antihypertensive should be added. Study treatment can be continued without dose modification.

If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg persists despite maximal antihypertensive therapy, then lenvatinib administration should be interrupted and restarted at 1

dose level reduction only when systolic BP ≤150 mm Hg and diastolic BP≤95 mm Hg and the participant has been on a stable dose of antihypertensive medication for at least 48 hours.

If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg recurs on the first dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and restarted at an additional dose reduction only when systolic BP ≤150 mm Hg and diastolic BP ≤95 mm Hg and the participant has been on a stable dose of antihypertensive medication for at least 48 hours.

If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg recurs on the second dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and restarted at a third dose reduction only when systolic BP ≤150 mm Hg and diastolic BP ≤95 mm Hg and the participant has been on a stable dose of antihypertensive medication for at least 48 hours.

The following guidelines should be followed for the management of Grade 4 hypertension (life-threatening consequences):

- Institute appropriate medical management
- Discontinue lenvatinib

6.2.2 Management of Proteinuria

Regular assessment of proteinuria should be conducted as detailed in the SoA (Section 3.2). Guidelines for assessment and management of proteinuria are as follows:

Detection and Confirmation

Perform urine dipstick testing per the SoA (Section 3.2).

A 24-hour urine collection or an immediate spot urine protein-to-creatinine ratio (UPCR) test is required in the following situations:

The first (initial) occurrence of ≥2+ proteinuria on urine dipstick while on lenvatinib.

A subsequent increase in severity of urine dipstick proteinuria occurring on the same lenvatinib dose level.

When there has been a lenvatinib dose reduction and at the new dose level the urine protein dipstick result is ≥2+.

A 24-hour urine collection (initiated as soon as possible and at least within 24 hours) to verify the grade of proteinuria is required when UPCR is ≥2.4.

Grading of Proteinuria

Grading according to NCI CTCAE v5.0 will be based on the 24-hour urinary protein result if one has been obtained.

Management of Proteinuria

Management of lenvatinib administration will be based on the grade of proteinuria according to Table 3.

In the event of nephrotic syndrome, lenvatinib must be discontinued.

Monitoring

Urine dipstick testing for participants with proteinuria ≥2+ should be performed frequently as clinically indicated until the results have been 1+ or negative for 2 consecutive treatment cycles.

6.2.3 Management of Diarrhea

An antidiarrheal agent should be recommended to the participant at the start of lenvatinib and participants should be instructed and educated to initiate antidiarrheal treatment at the first onset of soft bowel movements. The choice of antidiarrheal agent should be individualized to the participant's clinical circumstances and follow standard medical practice. If signs/symptoms of diarrhea persist despite optimal medical management, instructions contained in Table 3 should be followed.

6.2.4 Management of Thromboembolic Events

Participants should be advised to pay attention to symptoms suggestive of venous thromboembolic events, which include acute onset of shortness of breath, dyspnea, chest pain, cough, hemoptysis, tachypnea, tachycardia, cyanosis, deep vein thrombosis signs including lower-extremity swelling, and warmth to touch or tenderness. In case any of these symptoms appear, participants should be instructed to report such symptoms promptly to the treating physician. If a thromboembolic event is confirmed, instructions contained in Table 3 should be followed. Appropriate supportive care should be provided together with close monitoring. If a participant experiences a Grade 3 or a life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism, lenvatinib must be discontinued.

Arterial thromboembolic events (eg, new onset, worsening, or unstable angina, myocardial infarction, transient ischemic attack, and cerebrovascular accident) of any grade require lenvatinib discontinuation.

6.2.5 Management of Posterior Reversible Encephalopathy Syndrome/Reversible Encephalopathy Syndrome/ Reversible Posterior Leukoencephalopathy Syndrome

PRES/RPLS is a neurological disorder that can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances.

Mild to severe hypertension may be present. MRI is necessary to confirm the diagnosis of PRES/RPLS. Appropriate measures should be taken to control BP. In participants with signs or symptoms of PRES/RPLS, instructions in Table 3 should be followed.

6.2.6 Management of Hypocalcemia

Serum calcium should be monitored per the SoA (Section 3.2). Corrected serum calcium should be used to assess the grade of hypocalcemia per CTCAE v5.0, using the following formula:

Corrected calcium = ([4 – serum albumin in g/dL] × 0.8 + serum calcium)

The formula is not applicable when serum albumin concentration is normal (>4 g/dL); in such situations, the total (uncorrected) serum calcium should be used instead.

Hypocalcemia should be treated per institutional guidelines (eg, using appropriate calcium, magnesium, and Vitamin D supplementation) until resolution.

6.2.7 Management of Hemorrhage

Instructions in Table 3 (Nonhematologic Toxicities) should be followed for the management of hemorrhage. Either resume at a reduced dose or discontinue lenvatinib depending on the severity and persistence of hemorrhage.

6.2.8 Management of Gastrointestinal Perforation or Fistula Formation

Lenvatinib should be discontinued in any participants who develop gastrointestinal perforation or life-threatening fistula.

6.3 Concomitant Medications/Vaccinations (allowed & prohibited)

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included.

Participants are prohibited from receiving the following therapies during the intervention phase:

- Other antineoplastic systemic chemotherapy or biological therapy
- Radiation therapy
- Immunotherapy

- Huaier Granules

6.4 Participant Discontinuation Criteria

1) Tumor recurrence or metastasis at any position is clinically confirmed (the recurrent patients will be given the optimal treatment depending on their conditions). Criteria for tumor progression:
   a) Intrahepatic recurrence diagnosed by contrast-enhanced MRI or CT scan of the liver: An intrahepatic space-occupying lesion above 1 cm is found, with apparent enhancement in the arterial phase; or, the growth speed of the tumor without typical enhancement in the arterial phase exceeds 1 cm after one or two months of follow-up.
   b) Lung metastases are diagnosed by chest CT scan or bone metastases diagnosed by isotopic bone scan.
   c) Progressive increase of tumor markers.
2) The patients are not tolerant to the adverse reactions associated with lenvatinib.
   a) Absolute neutrophil count $\geq 1.5\times10^9$/L，Hb $\geq$ 85g/L, or PLT $\geq 75\times10^9$/L;
   b) Total bilirubin $\leq$ 3.0 mg/dL, albumin $\geq$ 28 g/L, AST, ALT and ALP $\leq$ five times the upper limit of normal range.
   c) INR > 2.3;
   d) Serious bleeding events, including cerebral hemorrhage, upper gastrointestinal hemorrhage, intestinal hemorrhage, and tumor hemorrhage;
   e) Severe hypertension that cannot be controlled by antihypertensive drugs;
   f) Proteinuria of grade 3-4, palmar-plantar erythrodysesthesia of grade 3-4, diarrhea of grade 3-4.

   If any of the above AEs occurs, the dose of lenvatinib can be reduced for 2 weeks (for patients < 60 kg, down to 4 mg qd; for those $\geq$ 60 kg, down to 8 mg qd). The previous dosage will not be resumed until the relevant indicators return to normal. If the drug intolerance episodes occur twice consecutively, the medication will be discontinued, and the patients will withdraw from the study.

6.5 Participant Withdrawl Criteria

1) Misdiagnosis and wrong recruitment.
2) The patients withdraw the informed consent form and require a withdrawal from the study.
3) Severe protocol violation.
4) The investigators judge that the ongoing study is detrimental to the subjects.
5) Severe safety problems and intolerant drug-related adverse reactions.
6) The ethics committee or relevant department requests termination of the study after reviews.

7 Study Procedures

7.1 Enrollment and Conduct

- Study procedures and their timing are summarized in The Schedule of Activities, Section 3.2.
- Adherence to the study design requirements, including those specified in the Schedule of Activities is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. Additional evaluations/testing may be deemed necessary by the investigator for reasons related to participant safety.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- The Investigator must obtain documented consent from each potential participant or each participant's legally acceptable representative prior to participating in a clinical trial.

7.2 Follow-up and Assessment

Regular visits were performed every 12 weeks to monitor disease status until recurrence. Laboratory tests and radiological imaging were assessed during each visit. The tumor imaging assessment should be performed every 12 weeks until up to 2 year or until any initial recurrence (intra-hepatic or extra-hepatic).

Intra-hepatic disease recurrence will be defined as the appearance of one or more intrahepatic lesions with a longest diameter of at least 10 mm and a typical vascular pattern of HCC on triphasic CT scan or MRI of the abdomen (ie, hypervascularization in the arterial phase with washout in the portal venous or late venous phase). Intra-hepatic lesions larger than 10 mm that do not show a typical vascular pattern may be diagnosed as HCC by evidence of a growth interval of at least 10 mm in $\geqslant$4 weeks after the initial scan showing disease recurrence. Both de novo liver tumors and intra-hepatic metastases will be considered intra-hepatic disease recurrence.

Extra-hepatic disease recurrence will be defined as the appearance of one or more unequivocal new extra-nodal lesions or malignant enlargement of a previously normal lymph node as per Response Evaluation Criteria in Solid Tumors.

In survival follow-up visits, survival status was continuously assessed every 12 weeks after recurrence until up to 5 years or death, or withdrawal of consent, or the end of the study, whichever occurs first.

The mandatory safety follow-up visit should be conducted approximately 30 days after the last dose of study intervention or before the initiation of a new anti-cancer treatment, whichever comes first.

8 Adverse Events (AEs), Serious Adverse Events (SAEs), and Reporting

8.1 Definition of AE

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology “accidental or intentional overdose without adverse effect.”

8.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

- The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

- In offspring of participant taking the product regardless of time to diagnosis.

f. Other important medical events

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

8.3 Recording AE and SAE

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the adverse event record at each examination. It is necessary to ask patient about the occurrence of any adverse events at each visit after the treatment begins, and record the onset time, intensity/toxicity, causality and duration of the adverse events, and document the measures taken and outcomes.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

8.4 AE and SAE Reporting

The reporting period for all adverse events is from the time of enrollment to 28 days after ending of the last treatment. Regardless of the length of treatment, all SAE that are possibly

related to study treatment must be reported in a timely manner. An adverse event that occurs after the ending of this study needs to be reported only when it is a SAE and related to the study treatment.

8.5 Follow-up of AE and SAE

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

9 Statistical Analysis Plan

9.1 Sample Size Calculation

According to the follow-up data collected by Huashan Hospital, Fudan University, the median DFS of HCC patients receiving adjuvant TACE was assumed to be 8.6 months. The efficacy of lenvatinib plus TACE is expected to be 16 months. The enrollment timeframe was assumed to be 24 months and follow up timeframe 24 months. Based on 1:1 enrollment ratio and two-side alpha of 0.05, at least 49 patients in each cohort were required to achieve the power of 80%. Considering the dropout of 15% patients, the estimated participants will be at least 116 in total.

9.2 Statistical Methods

Median DFS and median OS, and 95% confidence interval will be estimated using the nonparametric Kaplan-Meier method.

10 Study Compliance

The present study will evaluate the efficacy of lenvatinib plus TACE in HCC patients with high risks of postoperative recurrence. Adverse reactions may occur during the study. The patients and their relatives will be fully explained about the potential adverse reactions, cost and potential efficacy before the study formally begins. Accurate instructions will be given if any adverse reactions occur during the study. Serious adverse reactions will be properly managed after surgery, including sufficient communication and fully inform with the patients and their relatives, giving response to their doubts, and enhanced trust and compliance of patients and their relatives. It must be ensured that the patient compliance lies within 80% - 120%.

11 Subject Coding and Data Management

The subjects were coded according to the time sequence of enrollment, and the case report form was k preserved by specially appointed personnel in the dedicated cabinet until 5 years after the study. These files can be used during study or at each follow-up only upon approval by the specially appointed personnel. The study data are entered by the specially appointed personnel to ensure the authenticity, integrity, traceability, and confidentiality of the data.

12 Quality Control

The principal investigator is responsible for organizing the training sessions to ensure stringent compliance with the study protocol. The case report form or the study record and other reports should be filled out according to the principles of GCP and the study protocol. TACE procedure and surgery procedure will be supervised and performed by one same experienced teamr in each center during the study. Lenvatinib is purchased by the patients themselves. The patients are required to fill in the medication card during the medication period. All data and treatments must be verifiable: All observations and findings should be verifiable to ensure the reliability of the study data. At each stage of the study, quality control will be implemented to ensure data reliability and accuracy of all investigational procedures. The principal investigator shall ensure that all investigators comply with the study protocol, confirm data accuracy and integrity of the record forms, and guarantee that all patients provide their informed consent before the study formally starts. Any protocol violation or deviation will be timely reported to the ethics committee. The research team will develop the Standard Operating Procedure if necessary. The quality control procedure will be implemented in each step of the study to ensure the stringent compliance with the Standard Operating Procedure and the reliability of the study implementation and data manipulation.

13 Study Ethics

The clinical trial will be conducted after approved by the ethics committee in each center and in strict accordance with China's relevant laws and regulations and Declaration of Helsinki. The study will accept the follow-up review by the ethics committee. All patients will be enrolled after their informed consent is signed.

14 Confidentiality Policy

The information of all participants in the study should be kept strictly confidential. The personal information of the subjects and the data engendered during the study period should be all kept confidential. The information and study data of the participants should be identified by the study No. rather by the participants' names. Any personal identifiable information shall not be disclosed to any party other than the research team members unless with the permission from the participants. All investigators will be required to keep the identity of the participants confidential. The dossiers of the participants shall be preserved in the locked file cabinet and available for review by the investigators only. To ensure the stringent compliance with the study protocol, the government authorities or members of the ethics review committee are allowed access to the personal information of the participants at the study site, if necessary, in accordance with relevant regulations. Upon publication of the study, no treatment offered to the participants will be disclosed.

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