1 TITLE page

Clinical Study Protocol

Study Protocol Number: 2018-111

Study Protocol Title: A Research of PD-1 Inhibitors Combined with Lenvatinib for Advanced Unresectable Liver Cancer as the Conversion Therapy: A Prospective Open-label Exploratory Clinical Study

Sponsor: None

Investigational Product Name:

Lenvatinib (LENVIMA™/ KISPLYX®)

Sindilizumab (Sindilizumab Injection)

Triplimumab (Triplimumab Injection)

Tislelizumab（Tislelizumab Injection）

Pembrolizumab (KEYTRUDA®)

Indication: Hepatocellular carcinoma

Phase: Phase II

Approval Date:

V1.0 25 Oct 2018 (Original Protocol)

V2.0 20 May 2019 (Amendment 01)

V3.0 30 Nov 2021 (Amendment 03)

IND Number: 115650

ChiCT Number: ChiCTR 1900023914

GCP Statement: This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human

Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.

Confidentiality Statement:

This document is confidential. Any viewing or disclosure of such information that is not

authorized in writing by the investigator(s) is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

Summary of Changes

Revisions to Amendment 01

Date: 20 May 2019

Change	Rationale Affected	Affected Protocol Sections
Add introduction of two drugs Toripalimab and Camrelizumab	Increased drug choices in actual clinical practice	• Clinical Protocol synopsis • 2.4 Drug introduction
Definition of SUCCESSFUL CONVERSATION Modification (④ intact vascular structure (both inflow and outflow) of the reserved liver; ⑤ Functional residual liver volume (FRLV) ≥ 40%.)	The added statement is very important for definition of Primary study endpoint	• Clinical Protocol synopsis • 3.2 Primary study endpoint
Add observation indices: Research identifies candidate biomarkers which can predict the outcome of patients. Observation indicators: The relationship between tumor gene mutation, the number of tumor-infiltrating immune cells in the tumor and the following indicators: conversion success rate, ORR, pathological remission, RFS, OS.	Beneficial for further exploration of research	• Clinical Protocol synopsis • 3.5 Exploratory study endpoints
New research procedures were Added： Screening period test as □ Urine routine □ Pregnancy test (female)	Revised based on AE categories	• Clinical Protocol synopsis • 7.1 Screening period
Add the information on	Based on update of the drug labels.	• 6.1.2 Monitoring, Dose

monitoring, dose modification, and discontinuation of lenvatinib		Adjustment and Discontinuation
Add the information on monitoring and discontinuation of anti-PD-1 inhibitors	Based on update of the drug labels.	• 6.2 How to use PD-1 antibody

Summary of Changes

Revisions to Amendment 01

Date: 30 Nov 2021

Change	Rationale Affected	Affected Protocol Sections
Definition of SUCCESSFUL CONVERSATION Modification (③ No extrahepatic lesions assessed by PET-CT (or lung CT, bone scan, etc.) or extrahepatic lesions can be R0 resected，or extrahepatic lesions are tend to be judged inactive by MDT)	The added statement is very important for definition of Primary study endpoint	• Clinical Protocol synopsis • 3.2 Primary study endpoint

2 CLINICAL PROTOCOL SYNOPSIS

Name of Active Ingredient: Lenvatinib, Pembrolizumab/ Nivolumab/ Sintilimab/ Toripalimab/ Tislelizumab
Study Protocol Title： A Research of PD-1 Inhibitors Combined with Lenvatinib for Advanced Unresectable Hepatocellular Carcinoma as the Conversion Therapy: a prospective, open-label single-arm exploratory study
Study Regions (Country)： China
Study Period and Phase of Development： Approximately 20 months， Phase II
Objectives： **Primary Objectives：** To observe the efficacy of conversion therapy with PD-1 inhibitors plus lenvatinib for patients with BCLC stage C or unresectable BCLC stage B hepatocellular carcinoma (HCC). **Secondary Objectives:** To observe the ORR of the intention-to-treat (ITT) patients assessed by IIR per mRECIST and RECIST1.1, the progression-free survival and 12-month recurrence survival rate (12mo RFS %) assessed by IIR per mRECIST, R0 resection rate, and overall survival time (OS). To assess the safety and tolerability of conversion therapy, sequential surgery, and postoperative adjuvant therapy. **Exploratory study endpoints:** To identify candidate biomarkers that can predict the response to conversion therapy.

Study Design:

Overall Design:

This is an open-label Phase II study. This study will observe the conversion success rate of the combination therapy of PD-1 inhibitors and lenvatinib as conversion therapy for patients with HCC.

All eligible patients received lenvatinib (12 mg/day for bodyweight ≥ 60 kg or 8 mg/day for bodyweight < 60 kg) orally once daily and a PD-1 inhibitor intravenously on day 1 of a 21-day treatment cycle. The anti-PD-1 antibodies and their single-dose infusion used in this study were sintilimab 200 mg, pembrolizumab 200 mg, tislelizumab 200 mg, or toripalimab 240 mg. The choice of anti-PD-1 antibodies was at the discretion of the patient.

There will be a visit every 6-7 weeks to evaluate by the criteria of Definition of SUCCESSFUL CONVERSATION: ① Eastern Cooperative Oncology Group performance status (ECOG PS) score ≤1 (see Appendix 6); ② Child-Pugh liver function classification A or B (see Appendix 4); ③ No extrahepatic lesions assessed by PET-CT (or lung CT, bone scan, etc.) or extrahepatic lesions can be R0 resected，

or extrahepatic lesions are tend to be judged inactive by MDT ④ intact vascular structure (both inflow and outflow) of the reserved liver; ⑤ Functional residual liver volume (FRLV) ≥ 45% for patients with chronic liver disease and ≥35% for patients without chronic liver disease.

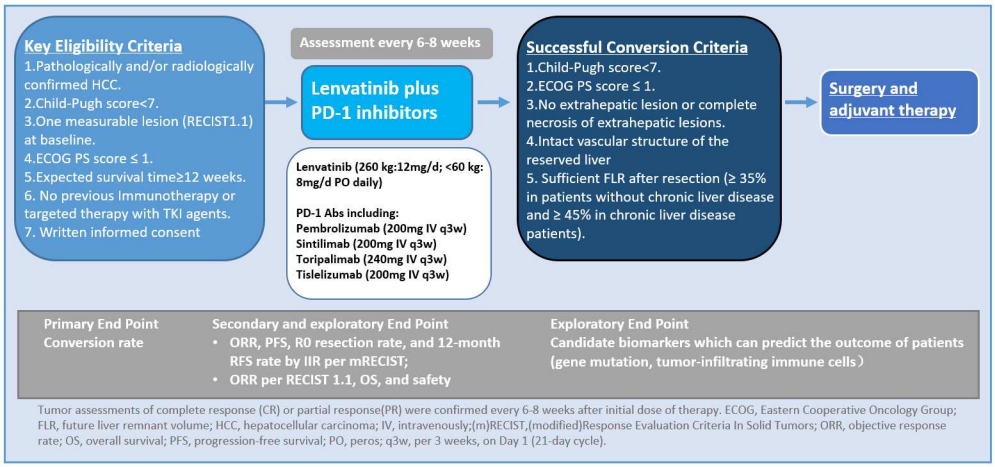
Patients with "SUCCESSFUL CONVERSATION " were recommended to be treated with sequential surgery after fully informed consent, and the post-operative therapy was continued after surgery until disease progression (PD).

If an adverse event occurred, interruption, discontinuation, or reduction of the dose was permitted for lenvatinib according to the trial protocol; anti-PD-1 treatment was not dose reduced but interrupted or discontinued depending on tolerability. Treatment was resumed when protocol-defined criteria for treatment resumption were reached. In addition to unacceptable toxicity, treatment discontinuation also included the withdrawal of consent, disease progression, non-compliance, or other reasons that the

investigators deemed would substantially affect the patient's safety.

Study Phases:

The study consisted of three major phases: (i) conversion therapy, (ii) surgery resection, and (iii) post-operative management. The CONSORT diagram and study design were illustrated as follows:



Sample Size:

The sample size of the combined drug group was calculated as 60 cases.

Inclusion Criteria:

1. Sign written informed consent and be able to comply with the visits and related procedures specified in the protocol.

2. Age ≥18 years old and ≤75 years old.

3. Confirmed by histology/cytology or meet the clinical diagnostic criteria of the American Society for Clinical Diagnosis of Liver Diseases (AASLD) for HCC.

4. Not suitable for radical surgery and/or local-regional therapy or disease progression after surgery and/or local-regional therapy.

5. According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1), at least 1 measurable lesion has not been treated locally or that has clearly progressed after local treatment.

6. Child-Pugh score ≤9 points (Child-Pugh A-B).

7. The Barcelona Clinic Liver Cancer (BCLC) stage is C stage or B stage, not suitable for transcatheter arterial chemoembolization (TACE).

8. ECOG performance status score of 0 or 1.

9. Expected survival time ≥ 12 weeks.

10. Female subjects of childbearing age or male subjects whose sexual partners are females of childbearing age should take effective contraceptive measures throughout the treatment period and 6 months after the treatment period.

11. Have sufficient organ and bone marrow function, and the laboratory test values within 7 days before enrollment meet the following requirements (no blood components, cell growth factors, albumin, and other drugs for corrective treatment are not allowed within the first 14 days of obtaining laboratory tests), details as follows:

- Blood routine: absolute neutrophil count (ANC) ≥1.5×10^9/L; platelet count (PLT) ≥50×10^9/L; hemoglobin (HGB) ≥8.5 g/dL.
- Liver function: serum total bilirubin (TBIL)≤3×upper limit of normal value (ULN); alanine aminotransferase (ALT) and aspartate aminotransferase (aspartate transferase, AST)≤5×ULN; serum albumin≥28 g/L; alkaline phosphatase (alkaline phosphatase, ALP)≤5×ULN.
- Renal function: serum creatinine (Cr) ≤ 1.5×ULN or creatinine clearance (clearance of creatinine, CCr) ≥ 50 mL/min (Cockcroft-Gault formula); urine routine results show urine protein <2+.
- Coagulation function: International normalized ratio (INR) ≤ 2, and activated partial thromboplastin time (APTT) ≤ 1.5 times ULN.

Exclusion Criteria:

1. Histology includes fibrous lamellar hepatocellular carcinoma, sarcomatoid hepatocellular carcinoma, cholangiocarcinoma, and other components.

2. A history of hepatic encephalopathy, or a history of liver transplantation.

3. Patients with pleural effusion, ascites, and pericardial effusion with clinical

symptoms or needing drainage, only a small amount of pleural effusion, ascites, and pericardial effusion shown by imaging and asymptomatic can be selected.

4. Acute or chronic active hepatitis B or hepatitis C infection, hepatitis B virus (HBV) DNA> 2000 IU/ml or 10^6 copies/ml; hepatitis C virus (HCV) RNA> 10^4 copies/ml; hepatitis B Surface antigen (HbsAg) and anti-HCV antibodies were positive at the same time.

5. Symptomatic central nervous system metastases.

Patients with asymptomatic brain metastases or patients with stable brain metastases after treatment were eligible to participate in this study as long as they met all of the following criteria: measurable lesions outside the central nervous system; no midbrain, pons, cerebellum, meninges, Medullary or spinal metastases; maintain clinical stability for at least 4 weeks; stop glucocorticoid therapy two weeks before the first dose of study drug.

6. Hemorrhage from esophageal or gastric fundus varices caused by portal hypertension in the past 6 months. Patients with evidence of portal hypertension (including splenomegaly detected by imaging examination) must undergo endoscopy within 3 months, and those with severe varicose veins were not eligible.

7. Any life-threatening bleeding events in the past 3 months, including the need for blood transfusion therapy, surgery or local therapy, and continuous drug therapy.

8. Arterial and venous thromboembolic events within the past 6 months, including myocardial infarction, unstable angina, cerebrovascular accident or transient ischemic attack, pulmonary embolism, deep vein thrombosis or any other history of severe thromboembolism. Implantable venous port or catheter-derived thrombosis, or superficial vein thrombosis, except those with stable thrombus after conventional anticoagulation. Prophylactic use of low-dose aspirin and low-molecular-weight heparin is allowed.

9. Uncontrolled hypertension, systolic blood pressure ≥150mmHg or diastolic blood pressure ≥100mmHg after optimal medical treatment, history of hypertensive crisis or hypertensive encephalopathy.

10. Symptomatic congestive heart failure (New York Heart Association class II-

IV). Symptomatic or poorly controlled cardiac arrhythmias. QT interval prolongation, QTc>450ms (male), QTc>470ms (female).

11. Severe bleeding tendency or coagulation dysfunction or receiving thrombolytic therapy.

12. History of gastrointestinal perforation and/or fistula within the past 6 months, history of intestinal obstruction (including incomplete intestinal obstruction requiring parenteral nutrition), inflammatory bowel disease or extensive bowel resection (partial colectomy or extensive small bowel resection) , complicated by chronic diarrhea), Crohn's disease, ulcerative colitis, or chronic diarrhea.

13. History of interstitial pneumonia, drug-induced pneumonia, idiopathic pneumonia or active pneumonia. Radiation pneumonitis within the radiotherapy area is allowed.

14. Active pulmonary tuberculosis (TB), who are receiving anti-tuberculosis treatment or who have received anti-tuberculosis treatment within 1 year before the first study drug.

15. Human immunodeficiency virus (HIV) infection (HIV 1/2 antibody positive).

16. Active or clinically poorly controlled serious infections. Severe infection within 4 weeks prior to the first study drug, including but not limited to hospitalization due to complications of infection, bacteremia, or severe pneumonia.

17. Active autoimmune disease requiring systemic treatment or history of the disease within the past 2 years (Vitiligo, psoriasis, alopecia or Grave's disease not requiring systemic treatment within the past 2 years, only thyroid hormones are required Hypothyroidism with replacement therapy and type 1 diabetes mellitus requiring only insulin replacement therapy can be included). Known history of primary immunodeficiency. Only patients with positive autoimmune antibodies need to confirm whether there is an autoimmune disease according to the judgment of the investigator.

18. Use of immunosuppressive drugs within the past 4 weeks, excluding nasal, inhaled, or other local glucocorticoids or systemic glucocorticoids at physiological doses (that is, not more than 10 mg/day prednisone or etc.) other glucocorticoids in

effective doses), temporary use of glucocorticoids is permitted for the treatment of dyspnea symptoms of asthma, chronic obstructive pulmonary disease and other diseases.

19. Received live attenuated vaccine within the past 4 weeks or planned to receive during the study.

20. Received systemic immunostimulant therapy within the past 4 weeks.

21. Major surgery (craniotomy, thoracotomy or laparotomy) or unhealed wound, ulcer or fracture within the past 4 weeks.

22. Uncontrolled metabolic disorders or other non-malignant organ or systemic diseases or secondary reactions to cancer, which can lead to higher medical risk and/or uncertainty in the assessment of survival.

23. Other acute or chronic diseases, psychiatric disorders, or abnormal laboratory values that may result in increased risks associated with study participation or study drug administration, or interfere with the interpretation of study listed as ineligible to participate in this study.

24. Diagnosed with other malignancies within 5 years prior to the first administration, excluding basal cell carcinoma of the skin, squamous cell carcinoma of the skin and/or carcinoma in situ after radical resection. If other malignant tumors or liver cancer are diagnosed more than 5 years before administration, pathological or cytological diagnosis of recurrent and metastatic lesions is required.

25. Previously received any anti-PD-1, anti-PD-L1/L2 antibody, anti-CTLA4 antibody, or other immunotherapy. Previously received anti-VEGF and/or targeted therapy of VEGFR, RAF, MEK, PDGFR, FGFR and other signaling pathways.

26. Known allergies to any antibody drug, small molecule targeted drug components; or previous severe allergic reactions to other monoclonal antibodies.

27. Received investigational drug therapy within 28 weeks prior to initiation of study treatment.28. Pregnant or breastfeeding female patients

Study Treatments

All eligible patients received lenvatinib (12 mg/day for bodyweight ≥ 60 kg or

8 mg/day for bodyweight < 60 kg) orally once daily and a PD-1 inhibitor intravenously on day 1 of a 21-day treatment cycle. The anti-PD-1 antibodies and their single-dose infusion used in this study were sintilimab 200 mg, pembrolizumab 200 mg, tislelizumab 200 mg, or toripalimab 240 mg. The choice of anti-PD-1 antibodies was at the discretion of the patient.

All PD-1 inhibitors will be administered as a 30-minute IV infusion, Q3W. (25 minutes to 40 minutes are acceptable).

Study Treatment Dose Modification:

Lenvatinib Dose Reduction and Interruption Instructions

Adverse Reaction	**Severity** [a]	Dosage Modifications for LENVIMA
Hepatotoxicity	Grade 3 or 4	• Withhold until improves to Grade 0 to 1 or baseline. • Either resume at a reduced dose or discontinue depending on the severity and persistence of hepatotoxicity. • Permanently discontinue for hepatic failure.
Renal Failure or Impairment	Grade 3 or 4	• Withhold until improves to Grade 0 to 1 or baseline. • Resume at a reduced dose or discontinue depending on the severity and persistence of renal impairment.
Proteinuria	2 g or greater proteinuria in 24 hours	• Withhold until less than or equal to 2 grams of proteinuria per 24 hours. • Resume at a reduced dose. • Permanently discontinue for nephrotic syndrome.
Gastrointestinal Perforation	Any Grade	• Permanently discontinue.
Fistula Formation	Grade 3 or 4	• Permanently discontinue.
QT Prolongation	Greater than 500 ms or greater than 60 ms increase from baseline	• Withhold until it improves to less than or equal to 480 ms or baseline. Resume at a reduced dose.
Reversible Posterior Leukoencephalopathy Syndrome	Any Grade	• Withhold until fully resolved. • Resume at a reduced dose or discontinue depending on the severity and persistence of neurologic symptoms

Indication	**First Dosage Reduction To**	**Second Dosage Reduction To**	**Third Dosage Reduction To**
Actual weight 60 kg or greater	8 mg once daily	4 mg once daily	4 mg every other day

Actual weight less than 60 kg	4 mg once daily	4 mg every other day	Discontinue
Life-threatening adverse reactions (Grade 4): Permanently discontinue.			

PD-1 inhibitors Dose Reduction and Interruption Instructions

Adverse events associated with PD-1 inhibitors	**Grading**	**Management**
Rash/inflammatory dermatitis	G3	Hold ICPi therapy and consult with dermatology to determine appropriateness of resuming
	G4	Permanently discontinue.
pneumonia	G2	Withhold until fully resolved.
	Recurrent grade 2 pneumonia, G3 or G4 pneumonia	Permanently discontinue.
Diarrhea/enterocolitis	G3 or G2	Withhold until fully resolved.
	G4	Permanently discontinue.
Hepatitis	For subjects with normal ALT, AST, or TBIL at baseline, grade 2 AST, ALT, or TBIL increased; For subjects with baseline AST, ALT, or TBIL>ULN, AST, ALT, or TBIL increases ≥50% (meeting level 2 requirements) and duration <7 days	Withhold until fully resolved.
	For subjects with normal ALT, AST, or TBIL at baseline, grade 3 or 4 AST, ALT, or TBIL were elevated; For subjects with baseline AST, ALT, or TBIL>ULN, AST, ALT, or TBIL increases ≥50% (meeting grade 3 or 4 requirements) and duration ≥7 days	Permanently discontinue.
Hypophysitis	G2	Withhold until fully resolved.
	G3 or G4	Permanently discontinue.
Adrenocortical insufficiency	G2	Withhold until fully resolved.
	G3 or G4	Permanently discontinue.
Hyperthyroidism	G3 or G4	Permanently discontinue.
Type 1 diabetes	Grade 3 hyperglycemia	Withhold until fully resolved.
	Grade 4 hyperglycemia	Permanently discontinue.
Renal insufficiency	Grade 2 or 3 elevated Cr	Withhold until fully resolved.
	Grade 4 elevated Cr	Permanently discontinue.
Neurotoxicity	G2	Withhold until fully resolved.

	G3 or G4	Permanently discontinue.
Other AE	Other G3 AE appears for the first time	Withhold until fully resolved.
	Same G3 AE appears for the first time	Permanently discontinue.
	Fail to improve to G0-2 / baseline within 7 days or recover to G 0-1 / baseline level within 14 days of G3 AE	Permanently discontinue.
	G4 AE	Permanently discontinue.

NOTE:

A: Resuming dosing after symptom improvement to level 0-1 or baseline.

B: Pituitaritis, adrenocortical insufficiency, hypothyroidism/hypothyroidism, and type 1 diabetes can be re-administered when fully controlled and only physiologic hormone replacement therapy is required.

C: In the case of abnormal Grade 4 laboratory results, the decision to discontinue medication should be based on concomitant clinical symptoms/signs and the investigator's clinical judgment.

Resumption of the use of antibody drugs requires a return to level 0-1 or baseline AE and an ECOG PS score of 0-1.

Duration of Study

The study duration for each subject is estimated to be: 20 months.

Concomitant Drug/Therapy Prohibited Concomitant Medications:

Allowed Concomitant therapy：

1) □ Medications that are determined by the investigator to be in compliance with protocol requirements (e.g., for the treatment of disease-related symptoms and concomitant treatment of treatment-related AE).

2) □ Subjects who need long-term medication due to underlying diseases such as hypertension and diabetes can continue medication.

3) □ Allows topical glucocorticoid administration, such as topical skin use, eye drops, nasal spray, inhalation, etc.

Contraindicated Concomitant therapy：

1) □ Biotherapeutics with antitumor effects (except cytogenic drugs used to treat adverse events caused by chemotherapeutic drugs), and proprietary Chinese medicines with antitumor effects

2) □ Drugs with immunomodulatory effects, including but not limited to non-specific immunomodulators (such as thymosin, interferon, interleukin, immunoglobulin, gamma globulin) and proprietary Chinese medicines with immunomodulatory effects, etc

3) Chemotherapy not specified in this protocol

4) Live vaccines are administered within 30 days prior to the initial administration of antibody drugs and during study participation. Live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, typhoid (oral) vaccines. To be allowed to receive injectable inactivated virus vaccines against seasonal influenza; however, intranasal live attenuated influenza vaccines are not allowed.

5) □ Inhaled steroids are permitted as part of fixation therapy for asthma or chronic obstructive pulmonary disease (COPD). Corticosteroids are permitted for the management of adverse events with underlying immune etiology. Physiological doses of corticosteroids may be approved after consultation with the principal investigator.

（Note: Prophylactic corticosteroids are permitted to avoid anaphylaxis）

It is important for investigators to review each drug (prescription and over-the-counter) that subjects received prior to study initiation and during each study visit.

1) □ At each visit, subjects must be asked about any new medications they receive.

2) □ To reduce the risk of adverse drug interactions, all measures must be taken to limit the number of concomitant drugs that are truly necessary.

3) □ During administration, avoid receiving drugs with hepatotoxicity (i.e., drugs warned of hepatotoxicity in the product label). Investigators are encouraged to review each potential hepatotoxic agent by searching the website www.livertox.nih.gov.

Treatment Assessments:

General condition/ AE of the patient:

Vital signs and body weight were recorded. If the subject's body weight fluctuated less than 10% relative to the baseline (first dose study treatment day), the baseline body weight was used to calculate the dose; if not, the actual dosage was calculated according to the body weight on the day of planned administration. Others including vital signs, height and weight, system physical examination, and ECOG PS score.

Laboratory tests such as Blood routine, Blood biochemistry (including liver function, kidney function, electrolytes, pancreatic function, troponin T), Urine routine, Blood coagulation, Thyroid function, HIV antibody, HCV antibody, hepatitis B (HBsAg, HBsAb, HBcAb, HBeAg, HBeAb) and □12-lead ECG.

Evaluation of treatment effect of tumor:

Liver-enhanced MRI/enhanced CT, Chest CT, PET-CT, AFP.

Tumor evaluation: Tumor evaluation according to mRECIST 1.1 will be performed every 6-8 weeks (before cycle 4 dosing) for 48 weeks from the randomization date until confirmed " successful conversion " or PD.

Surgery decision-making and post-operative therapy

Patients who met the criteria for SUCCESSFUL CONVERSATION were informed of the benefits and risks associated with surgery. Surgical treatment can be performed after obtaining signed informed consent. Under the premise of radical resection, the type of surgery was determined based on the intraoperative exploration situation.

The samples from resected tumors were collected and analyzed by pathologists. Morbidity, mortality, and surgical complications were monitored during the first 30 days after surgery. Post-hepatectomy liver failure was evaluated according to the International Study Group of Liver Surgery criteria. Post-operative complications were graded using the Clavien-Dindo classification.

The pathological response of all resected specimens was evaluated and classified as a pathological complete response. The patients with pNR were treated with the regimes recommended by the multidisciplinary team (MDT) according to the results of the

pathological examination and/or next-generation sequencing (NGS). Tumors were assessed in the post-operative first month and then every 12 weeks using the serum alpha-fetoprotein (AFP) level as well as imaging examination.

Statistical Methods

Study Endpoints:

The primary endpoint was the conversion success rate by investigator assessment according to the criteria for successful conversion. Secondary endpoints included ORR, margin-negative (R0) resection rate, PFS, OS, and 12-month RFS rate per mRECIST, and safety. Biomarker analyses for predicting the response to conversion therapy were considered exploratory endpoints. Primary and secondary outcome analyses were performed on an intention-to-treat (ITT) population, i.e., all patients who have received at least one dose of therapy, except that the 12-month RFS rate was based on the patients who underwent curative-intended resection following successful conversion.

Statistical analyses:

Data on baseline characteristics of study participants were expressed as median values (range minimum-maximum) or as numbers (%). Continuous variables were compared using Student's t-test or the non-parametric Wilcoxon signed-rank test, whereas differences between pretreatment and post-treatment samples were analyzed using paired t-test or Wilcoxon matched-paired signed-rank test. Categorical variables were assessed by the chi-square test or Fisher's exact test. Uni- and multivariate Cox regression analyses were used to evaluate the association between conversion therapy and survival outcomes. Survival outcomes were analyzed using the Kaplan-Meier method with the log-rank test. All data were analyzed using SPSS version 23 (SPSS Statistics Version 23, IBM Corp., Armonk, NY, USA). A two-tailed $P < 0.05$ was considered statistically different.

Safety Analyses:

Safety analyses will be performed on the Safety Analysis Set. The number (percentage) of subjects with treatment-emergent AEs (TEAEs) and treatment emergent SAEs will be summarized by system organ class (SOC) and preferred term

(PT). Summary statistics will be presented for laboratory test values, vital signs, and 12-lead ECG parameters. If needed, the changes from baseline will also be summarized.

1. Ethics and Informed Consent

1.1 Ethics Committee

Relevant documents need to be submitted to the ethics committee (EC), including the trial protocol, informed consent, investigator brochure, subject recruitment materials or advertisements, and other documents required by regulations. Written approval from the EC must be obtained prior to commencing this study.

Research centers must follow the requirements of the center's EC. It may include revision of the protocol, revision of informed consent, revision of subject recruitment materials, which need to be submitted to EC for approval, local safety reporting requirements, regular reports and updates in accordance with EC regulations, and submission of the final report.

1.2 Ethics of this study

The research process and the acquisition of informed consent shall comply with the Declaration of Helsinki, relevant GCP requirements and Chinese laws and

regulations related to drug and data protection.

GCP provides ethical, scientific, and global quality standards for the design, conduct, documentation, and reporting of clinical studies involving human subjects. This research will be conducted in accordance with GCP and relevant national regulations and in compliance with the relevant ethical principles in the Declaration of Helsinki to protect the rights, safety and health of subjects.

The investigators should follow the procedures specified in this protocol and any breach will be reported to the EC or regulatory authority.

1.3 Subject Information and Informed Consent

Before any research process begins, use an Informed Consent Form (ICF) to explain the possible risks and benefits of this research to potential subjects using an Informed Consent Form (ICF) in simple and understandable language. The ICF statement should make it clear that informed consent is voluntary, the risks and benefits that may be brought about by participating in this study should be clearly defined, and subjects may withdraw from the study at any time. Only after the researcher has fully explained the details of the study, the subjects' questions have been answered satisfactorily, given sufficient time to consider, and obtained the written consent of the subjects or their legal representatives the subjects can be enrolled. All signed informed consent forms must be in the investigator file or in the subject folder.

The investigator is responsible for explaining the content of informed consent to the subjects and obtaining the informed consent form signed and dated by the subjects or their legal representatives before the start of the study. After signing, the investigator should send the subject a copy of the signed informed consent form. Researchers need to record the process of informed consent in the original trial documents.

1.4 Protection of subject data

The ICF will contain (or, in some cases, separate files) information related to data protection and privacy protection. The investigator shall take precautions to ensure the confidentiality of the documents and to prevent the identification of the subject. In exceptional cases, however, some personnel may have access to a subject's genetic data and pin. For example, in the event of a medical emergency, a doctor or researcher could know a subject's identification number and have access to that subject's genetic data. In addition, relevant regulatory authorities have requested access to relevant documents.

2. Research background

2.1 Hepatobiliary Surgery and Precision Medicine

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related death worldwide and the second leading cause of cancer death in men. The incidence and prognosis of HCC have large regional differences, mainly due to different causative factors, such as hepatitis B and C virus infection and alcohol intake.

Patients with early-stage and focal HCC with well-maintained liver function can be treated with potentially curative approaches, such as surgical resection, liver transplantation, and/or radiofrequency ablation (RFA). Only about 30% of HCC patients are eligible for curative treatment, while other patients with intermediate/advanced HCC are usually treated with palliative care. Patients with advanced unresectable HCC who are not suitable for curative therapy are usually treated with systemic therapy for palliative purposes. However, HCC expresses high levels of multidrug resistance proteins and is inherently resistant to chemotherapy.

With the development of modern hepatobiliary surgery, great progress has been made in the treatment of liver cancer in the past 50 years. The five-year survival rate of patients with resectable liver cancer has increased to over 50%, and even some early-stage liver cancer can reach about 70%. The extensive application of curative surgical techniques has made small hepatocellular carcinoma close to radical cure,

with a five-year survival rate of nearly 80%. However, we still need to recognize a basic fact: there are 780,000 new cases of liver cancer every year in the world, of which more than 350,000 are in China. According to the statistics of the "China Cancer Registration Annual Report," the five-year overall survival rate of liver cancer from 2003 to 2015 was only 12.5%, which is extremely severe. Currently available treatments can bring survival benefits to HCC patients; however, the overall prognostic profile and QoL remain poor. Therefore, HCC remains a medical challenge with a significant unmet medical need. Therefore, new therapeutic approaches are needed for HCC patients who are not suitable for loco-regional therapy. Although precise, minimally invasive, and multidisciplinary comprehensive treatment has become the mainstream paradigm of liver cancer treatment in the new era, in order to improve the overall survival rate of liver cancer patients, the new concept of liver cancer precision medicine needs to be further popularized and promoted.

In the clinical treatment of advanced liver cancer, the use of immune checkpoint inhibitors (ICIs) and multi-targeted kinase inhibitors (TKIs) alone has achieved clinical benefits superior to conventional treatments, and ICIs combined with vascular-targeted drugs have become a hotspot for HCC clinical research.

In 2011, the first ICI was approved for clinical use in tumors, which greatly changed the traditional treatment pattern of various malignant tumors with satisfactory efficacy, and HCC is no exception. In September 2017, the PD-1 inhibitor Opdivo was approved by the US FDA for the second-line treatment of advanced HCC, which started in the era of immunotherapy for HCC. In the Checkmate-040 study, which has been carried out for advanced HCC immunotherapy research, the disease control rate (DCR) of a PD-1 inhibitor in the treatment of HCC reached 55%, reflecting a good therapeutic advantage. Although PD-1 inhibitors have shown initial advantages in the treatment of advanced HCC, there are still shortcomings, including the low effective rate of monotherapy and no tumor response for some patients. In 2018, ASCO reported that a phase Ib study about Keytruda combined with lenvatinib

as first-line treatment for HCC, and Among 26 evaluable patients, the overall response rate(ORR) reached 42.3% (including unconfirmed responses). How to improve the response rate of PD-1 and immune response rate through combination therapy is the current hotspot of HCC research.

In the treatment of hepatobiliary tumors, the rise of the concept of precision medicine in the field of hepatobiliary surgery has brought us more hope and choices. Surgery is the only possible curative strategy for HCC at now, and up to 75% of HCC patients have lost the opportunity for radical surgical treatment on the first visit. Today, for unresectable "advanced" HCC patients, we can achieve the goal of "downstaging" the tumor through precise conversion therapy, which means that some unresectable HCC can be converted into resectable HCC.

This concept has been proposed for a long time, and based on the historical data of HCC treatment; it is feasible for a proportion of unresectable liver cancer cases to achieve the goal of downstaging before surgery under the guidance of the concept of precision medicine. In recent years, immune and targeted therapy have achieved encouraging clinical research results in solid tumors. Studies have shown that immune or targeted therapy can significantly shrink HCC and reduce extrahepatic lesions or intrahepatic satellite lesions, which means the possibility of radical surgery for some patients. At the same time, the combination of immunotherapy and traditional surgery, precision radiotherapy, chemotherapy, and targeted therapy is also the future direction. These treatments can release new tumor antigens in the process of necrosis of tumor cells, which can enhance immunity. Therefore, the conversion of unresectable intermediate/advanced HCC into resectable HCC through immune plus targeted therapy, followed by radical surgery, will undoubtedly bring more survival benefits for patients who have achieved complete remission (CR) or partial remission (PR) after systemic treatment. However, there is a lack of high-level evidence in similar studies

Therefore, researchers initiated this study in order to observe and analyze whether

① PD-1 inhibitors combined with lenvatinib, which is a TKIs agent as conversion therapy, can covert unresectable HCC into resectable HCC; ② after combination treatment, Whether radical surgery/local-regional therapy can bring more survival benefits in eligible patients.

This study aims to observe the therapeutic effect of PD-1 antibody combined with lenvatinib followed by surgery for patients whose unresectable HCC is converted into resectable HCC through a prospective cohort.

2.2 Immunotherapy

It is increasingly recognized that cancer can be recognized by the immune system, and in some cases, the immune system can control or even eliminate tumors.

Programmed death ligand 1 (PD-L1), a member of the B7 ligand family, binds to the programmed death factor (PD-1) receptor and cluster of differentiation (CD) 80, thereby inhibiting T cells active. PD-L1 expression is an adaptive response that helps tumors escape the immune system's surveillance and clearance mechanisms. In contrast, cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) is constitutively expressed on regulatory T cells and is upregulated on the surface of activated T cells. Expression of PD-L1 protein is induced by inflammatory signals typically associated with adaptive immune responses (e.g., interferon-gamma [IFNγ]) and can be found on tumor cells (TC) and tumor-infiltrating immune cells (IC). PD-L1 binds to PD-1 on activated T cells and transmits inhibitory signals to T cells, resulting in T cells' exhaustion to kill targeted TCs, allowing tumors to evade clearance by the immune system. PD-L1 also inhibits T cells by binding to CD80, but the exact mechanism is unclear.

PD-L1 is highly expressed in a variety of cancers, even as high as 88% in some cancers. Based on these results, anti-PD-L1 antibodies may be considered for the treatment of cancer patients to enhance anti-tumor immune responses. Nonclinical and clinical findings of monoclonal antibodies (mAbs) targeting the PD-L1/PD-1 pathway show evidence of clinical activity and a manageable safety profile,

supporting the use of anti-PD-L1 antibodies in the treatment of cancer patients. In order to strengthen the anti-tumor immune response, such efficacy is more obvious in patients with tumors expressing PD-L1. In addition, immunotherapy may be more effective in patients with a high mutational burden (e.g., bladder cancer).

2.3 Antiangiogenic targeting agents

Antiangiogenic targeting agents (AATDs) have been a hotspot in tumor treatment research in recent years and have attracted much attention due to their good specificity, high efficacy, and tolerance. Sorafenib is a multi-kinase inhibitor. The SHARP study has strongly demonstrated the efficacy and safety of sorafenib for advanced liver cancer. Thus, sorafenib has become the first targeted drug approved by the United States Food and Drug Administration (FDA) and the European Medicines Evaluation Agency (EMEA) for patients with advanced liver cancer. After the success of sorafenib, a growing number of studies have been done on targeted therapy. It is no longer the only option for first-line drugs, and alternative second-line drugs have been discovered, which have greatly improved the prognosis of liver cancer patients.

Lenvatinib acts as a multi-targeted kinase inhibitor against alleles of VERGR-1, VERGR-2, VERGR-3, RET, FGFR (1-4), c-KIT, PDGFR-α, and PDGFR-β, and it can inhibit tumor angiogenesis and tumor cell proliferation at the same time. Recently, a study published by Kudo *et al.* compared the efficacy and safety of lenvatinib and sorafenib. The results showed that the mOS (13.6 mo) of the lenvatinib group was not significantly different from that of the sorafenib group (12.3 mo); furthermore, lenvatinib was comprehensively superior to sorafenib in terms of PFS (7.4 mo: 3.4 mo), TTP (8.9 mo: 3.7 mo), ORR (24.1%: 9.2%), and the adverse reactions of the two drugs were not significantly different. As a result, lenvatinib has also been approved by many countries as the second first-line targeted drug for the treatment of advanced liver cancer and has a tendency to replace sorafenib, but the current first-line drug of choice is sorafenib or lenvatinib; further research is needed to find out which one is a better choice. Kimura et al. studied the combination of lenvatinib and programmed

cell death 1 (PD-1) antibody to understand the anti-tumor and immunomodulatory activities of lenvatinib. This study found that in mice, the anti-tumor activity of lenvatinib combined with PD-1 antibody is enhanced, with a better reduction rate of tumor size and response rate. The strategy of lenvatinib combined with PD-1 antibody deserves further study.

2.4 Drug introduction

Lenvatinib

Targets: VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α, FGFR1, FGFR2, FGFR3, FGFR4, KIT, RET.

A phase 1 trial of the lenvatinib (E7080) in 82 patients with advanced solid tumors determining the maximum tolerated dose of 25 mg and found PR in 7 patients (9%) and SD in 38 patients (46%). A phase 1 study of lenvatinib in 77 patients with advanced solid tumors reported PR in 15.6% (12/77) and SD lasting more than 23 weeks in 24.7% (19/77) with good tolerance. A phase 1 clinical study of lenvatinib in 20 patients with advanced HCC reported that 3 patients showed PR and 14 patients showed tumor shrinkage with manageable toxicity. A phase 2 study of lenvatinib in 46 patients with advanced HCC reported a median TTP of 7.4 months. Seventeen patients (37%) showed PR, and 19 patients (41%) showed SD (ORR: 37%; DCR: 78%), and the mOS was 18.7 months. The most common adverse events (AEs) of any grade were hypertension (76%), palmar-plantar erythematosus syndrome (65%), decreased appetite (61%), and proteinuria (61%). In phase III clinical trial comparing lenvatinib versus sorafenib as first-line therapy in 954 patients with unresectable HCC, the mOS, mPFS, mTTP, and ORR were 13.6 vs12.3 months, 7.4 months vs. 3.7 months, 8.9 months vs. 3.7 months, and 24% vs. 9%, respectively. Lenvatinib was non-inferior in OS compared to Sorafenib and significantly improved the PFS, TTP, and ORR as the first-line treatment for unresectable HCC. Similar numbers of patients in both groups experienced treatment-related adverse events (TEAEs). The most common TEAEs in lenvatinib were hypertension (42%), diarrhea (39%), decreased

appetite (34%), weight loss (31%), and fatigue (30%).

In August 2018, Lenvima (Lenvatinib) was approved as a first-line treatment for patients with unresectable HCC in China.

Pembrolizumab: PD-1 inhibitor

A study of pembrolizumab (pembrolizumab) in 41 patients with metastatic cancer with and without mismatch repair deficiency reported the immune-related progression-free survival(PFS) rates in MMR-deficient colorectal cancer, MMR-deficient non-colorectal cancer, and MMR-type colorectal cancer were 78%(7/9), 67% (4/6) and 11% (2/18). In patients with brain metastases, a phase 2 trial of pembrolizumab reported a response rate of 33% (6/18) in enrolled patients with brain metastases from non-small cell lung cancer. A phase 1 trial of pembrolizumab in 30 patients with advanced solid tumors reported 2 CR (melanoma and Merckel cell carcinoma), 3 PR (melanoma), and 15 SD patients, with good tolerance.

Nivolumab: PD-1 inhibitor

A phase 1 study of nivolumab (MDX-1106) in 296 patients with advanced solid tumors reported that among 236 patients with evaluable response, 18.4% (14/76) of non-small cell lung cancer, 27.7% (26/ 94) Melanoma and 27.3% of patients with renal cell carcinoma (9/33) experienced tumor response. Grade 3/4 AEs (mainly immune-related) were reported in 14% of patients and there are 3 patients died due to pulmonary toxicity. Phase 1 study of nivolumab (MDX-1106) in 39 patients with refractory solid tumors, including melanoma, colorectal cancer, non-small cell lung cancer and renal cell carcinoma reported 1 durable CR and 2 PRs and the drug was well tolerated with only one serious AE (colitis).

Sintilimab: PD-1 inhibitor

A Phase Ia dose escalation trial of sintilimab (Study Code CIBI308A101-1a) was initiated in September 2016. In Phase Ia subjects with advanced solid tumors who had failed standard therapy, the dose escalation decision followed a classic "3+3" design,

with 4 dose levels (1 mg/kg, 3 mg/kg, 200 mg, and 10 mg/kg) kg) for evaluation. After completion of the 1 mg/kg dose group, subjects were randomized 1:1 to independent assessments of the 3 mg/kg and 200 mg dose groups. In a phase Ia pharmacodynamic study in patients with advanced solid tumors, a single dose of 1 mg/kg sintilimab (N=3) resulted in rapid (24-hour) saturation of mass-occupying (mean ≥95%) in the PD-1 receptor on the surface of CD3+ T cells in the peripheral blood, and it can be maintained at the occupied level during the study period (28 days) when the concentration is continuously decreased and in continuous multi-dose treatment. The results of PD-1 mass in the 3 mg/kg (N=3), 200 mg (N=3), and 10 mg/kg (N=3) dose groups were similar to those of 1 mg/kg, suggesting that there was no dose or concentration dependence at the 1-10 mg/kg dose range for PD-1 receptors occupy. Sintilimab has also demonstrated favorable antitumor activity in subjects with various advanced solid tumors who have failed standard therapy. According to RECIST1.1 assessment and irRECIST assessment, the best overall response was 2 PR plus 2 SD and 2 irPR plus 3 irSD, respectively.

Toripalimab: PD-1 inhibitor

Toripalimab is the first ICIs produced in China. HMO-JS 001-I-CRP-01 is an open-label, single-arm, multicenter, phase II clinical study in inoperable or metastatic melanoma after failure of prior systemic therapy to evaluate specific safety and efficacy of toripalimab. A total of 128 Chinese patients were enrolled in this study, 127 of whom were included in the full analysis set, with a median age of 52.5 years. The median follow-up time of 127 patients was 12.4 months, and the last enrolled subject was followed up for at least 12 months. The ORR of this study was 17.3%, and the 6-month OS rate was 87.8%.

Tislelizumab: PD-1 inhibitor

The aim of RATIONALE 208, a pivotal multicenter global phase 2 trial, was to evaluate the efficacy and safety of Tislelizumab Injection monotherapy in the treatment of patients with hepatocellular carcinoma (HCC) who had received at least

one previous systemic therapy. The study enrolled 249 HCC patients from 8 countries and regions in Asia and Europe, including 122 patients in China. Among all the enrolled patients, second-line patients accounted for 55.4%, third-line and posterior line patients accounted for 44.6%, patients with hepatitis B history accounted for 51.4%, and patients with hepatitis C history accounted for 14.5%. The median progression-free survival (PFS) was 2.7 months, the median overall survival (OS) was 13.2 months, and the objective response rate (ORR) was 13.3%. Nearly 80% of the patients had sustained response for more than one year.

3. Study endpoints and observation indicators

3.1 Research purpose

Observation：

① Whether the combination therapy of PD-1 inhibitors with lenvatinib as conversion therapy can convert unresectable HCC into resectable HCC; ② After the combination therapy of PD-1 inhibitors and lenvatinib, whether a radical surgery can prolong life expectancy for patients who are eligible for radical surgery.

3.2 Primary study endpoint

To observe the conversion efficiency of the combination therapy of PD-1 inhibitors and lenvatinib as conversion therapy for patients with unresectable HCC.

OUTCOME MEASURES: Conversion rate for all patients.

Definition of SUCCESSFUL CONVERSATION: ① Eastern Cooperative Oncology Group performance status (ECOG PS) score ≤1,(see Appendix 6); ② Child-Pugh liver function classification A or B (see Appendix 4); ③ No extrahepatic lesions assessed by PET-CT (or lung CT, bone scan, etc.) or extrahepatic lesions can be R0 resected，or extrahepatic lesions are tend to be judged inactive by MDT ④ intact vascular structure (both inflow and outflow) of the reserved liver; ⑤ Functional residual liver volume (FRLV) ≥ 45% for patients with chronic liver disease and

≥35% for patients without chronic liver disease .

3.3 Secondary Study Endpoint 1

The ORR of the enrolled patients was-assessed by IIR per mRECIST and RECIST1.1, and the progression-free survival, 12-month recurrence survival rate (12m RFS %) assessed by IIR per mRECIST, R0 resection rate, and overall survival time (OS) were observed.

3.4 Secondary Study Endpoint 2

To assess the safety and tolerability of the conversion therapy, sequential surgery, and postoperative adjuvant therapy.

OUTCOME MEASURES: AEs and laboratory findings related to safety and tolerability.

3.5 Exploratory study endpoints

Research identifies candidate biomarkers which can predict the outcome of patients.

Observation indicators: The relationship between tumor gene mutation, the number of tumor-infiltrating immune cells in the tumor and the following indicators: conversion success rate, ORR, pathological remission, RFS, OS.

4. Research Design

4.1 Overall Study Design and Plan

This study will enroll near 60 patients with unresectable HCC who have not been systematically treated and are not suitable for local-regional therapy in a single center (details at the sample calculation). Through a prospective cohort design, to observe the conversion efficiency of the combination therapy of PD-1 inhibitors and lenvatinib in the conversion treatment of patients with unresectable liver cancer. And observe the survival benefit of sequential surgical for patients with "successful

conversion".

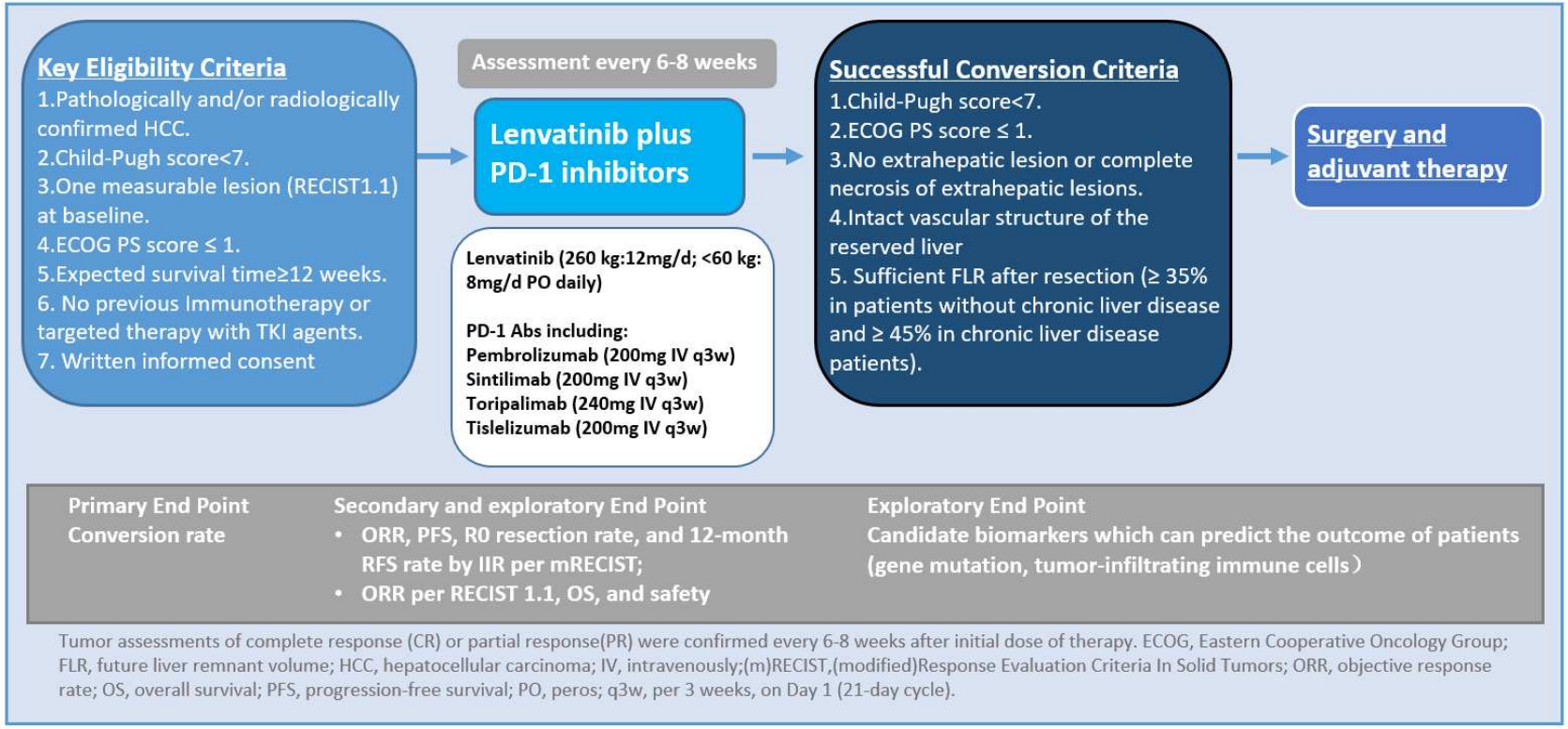
Patients with "successful conversion" were treated with sequential surgery, and the combination therapy was continued after surgery until disease progression (PD).

Previous studies have reported that the benefits of PD-1 inhibitors combined with the lenvatinib in the treatment of patients with unresectable HCC outweighed the risks. Given that the ORR and the disease control rate (DCR) have reached 60% and 93.3% (assessed by mRECIST (see Appendix 2), including confirmed and unconfirmed) among these studies, this study was not randomized based on ethical considerations.

Study Duration	2019-7~2021-3
Estimated date of enrollment of the first patient in the combination therapy group	2019-7
Estimated date of last patient completion of study	2021-3

After the patients signed informed consent, they were investigated and enrolled according to the inclusion and exclusion criteria. (For details at **5. Patient Selection, Enrollment, Restriction, Discontinuation and Withdrawal**)

Figure 1. Research flow chart



4.2 Sample Size

This study is a prospective single-arm clinical trial. According to previous studies reports, the (ORR) of patients with unresectable HCC treated with PD-1 inhibitors combined with lenvatinib reached 60% (evaluated by mRECIST criteria, Including confirmed and unconfirmed), the (DCR) was 93.3%. This study assumed that 50% of patients with disease control in the combination therapy group would be able to convert successfully, that is, a conversion success rate of 45% for all enrolled patients. Previous studies reported that the conversion success rate of advanced HCC treated with CCRT combined with HAIC was 16.9%; for HCC with large vascular invasion of the liver, the conversion success rate of CCRT combined with HAIC was 26.5%; the conversion success rates in other reports were in this range.

Therefore, the conversion success rate (p0) of the historical control is taken as 22%, α (test level) = 5%, 1-β (test power) = 80%; δ = 0.05 in the superiority hypothesis test; the sample size is calculated N = 48. Considering that the patients lost to follow-up and the dropout rate was about 20%, the sample size of the combined drug group was calculated as 60 cases.

$$n = p_0(1-p_0)\left(\frac{z_{1-\alpha} + z_{1-\beta}\sqrt{\frac{p(1-p)}{p_0(1-p_0)}}}{p-p_0}\right)^2$$

$$1-\beta = \Phi\left(\sqrt{\frac{p_0(1-p_0)}{p(1-p)}}\left(\frac{|p-p_0|\sqrt{n}}{\sqrt{p_0(1-p_0)}} - z_{1-\alpha}\right)\right)$$

The relevant formula is as follows:

Chow S, Shao J, Wang H. 2008. *Sample Size Calculations in Clinical Research*. 2nd Ed. Chapman & Hall/CRC Biostatistics Series. **page 85**.

5. Patient Selection, Enrollment, Restriction, Discontinuation and Withdrawal

5.1 Target patient population

The study population included patients aged ≥18 years with unresectable HCC, Barcelona Clinic Liver Cancer Grade C or B not suitable for local-regional therapy, and Child-Pugh A liver disease. The patient had not received any prior systemic therapy for unresectable HCC.

Each patient should meet all the inclusion criteria for this study and none of the exclusion criteria. This principle should not be violated under any situation.

5.2 Inclusion criteria

1. Sign written informed consent and be able to comply with the visits and related procedures specified in the protocol.

2. Age ≥18 years old and ≤75 years old.

3. Confirmed by histology/cytology or meet the clinical diagnostic criteria of the American Society for Clinical Diagnosis of Liver Diseases (AASLD) for HCC.

4. Not suitable for radical surgery and/or local-regional therapy, or disease progression after surgery and/or local-regional therapy.

5. According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1), at least 1 measurable lesion that has not been treated locally, or that has clearly progressed after local treatment.

6. Child-Pugh score ≤9 points (Child-Pugh A-B).

7. The Barcelona Clinic Liver Cancer (BCLC) stage is C stage or B stage not

suitable for transcatheter arterial chemoembolization (TACE).

8. ECOG performance status score of 0 or 1.

9. Expected survival time ≥ 12 weeks.

10. Female subjects of childbearing age or male subjects whose sexual partners are females of childbearing age should take effective contraceptive measures throughout the treatment period and 6 months after the treatment period.

11. Have sufficient organ and bone marrow function, and the laboratory test values within 7 days before enrollment meet the following requirements (no blood components, cell growth factors, albumin and other drugs for corrective treatment are not allowed within the first 14 days of obtaining laboratory tests),details as follows:

- Blood routine: absolute neutrophil count (ANC) ≥1.5×109/L; platelet count (PLT) ≥50×109/L; hemoglobin (HGB) ≥8.5 g/dL.
- Liver function: serum total bilirubin (TBIL)≤3×upper limit of normal value (ULN); alanine aminotransferase (ALT) and aspartate aminotransferase (aspartate transferase, AST)≤5×ULN; serum albumin≥28 g/L; alkaline phosphatase (alkaline phosphatase, ALP)≤5×ULN.
- □ Renal function: serum creatinine (Cr) ≤ 1.5×ULN or creatinine clearance (clearance of creatinine, CCr) ≥ 50 mL/min (Cockcroft-Gault formula); urine routine results show urine protein <2+.
- □ Coagulation function: International normalized ratio (INR) ≤ 2, and activated partial thromboplastin time (APTT) ≤ 1.5 times ULN.

5.3 Exclusion criteria

1. Histology includes fibrous lamellar hepatocellular carcinoma, sarcomatoid hepatocellular carcinoma, cholangiocarcinoma and other components.

2. A history of hepatic encephalopathy, or a history of liver transplantation.

3. Patients with pleural effusion, ascites, and pericardial effusion with clinical symptoms or needing drainage, only a small amount of pleural effusion, ascites, and pericardial effusion shown by imaging and asymptomatic can be selected.

4. Acute or chronic active hepatitis B or hepatitis C infection, hepatitis B virus (HBV) DNA> 2000IU/ml or 106 copies/ml; hepatitis C virus (HCV) RNA> 104 copies/ml; hepatitis B Surface antigen (HbsAg) and anti-HCV antibodies were positive at the same time.

5. Symptomatic central nervous system metastases.

Patients with asymptomatic brain metastases or patients with stable brain metastases after treatment were eligible to participate in this study as long as they met all of the following criteria: measurable lesions outside the central nervous system; no midbrain, pons, cerebellum, meninges, Medullary or spinal metastases; maintain clinical stability for at least 4 weeks; stop glucocorticoid therapy two weeks before the first dose of study drug.

6. Hemorrhage from esophageal or gastric fundus varices caused by portal hypertension in the past 6 months. Patients with evidence of portal hypertension (including splenomegaly detected by imaging examination) must undergo endoscopy within 3 months, and those with severe varicose veins were not eligible.

7. Any life-threatening bleeding events in the past 3 months, including the need for blood transfusion therapy, surgery or local therapy, and continuous drug therapy.

8. Arterial and venous thromboembolic events within the past 6 months, including myocardial infarction, unstable angina, cerebrovascular accident or transient ischemic attack, pulmonary embolism, deep vein thrombosis or any other history of severe thromboembolism. Implantable venous port or catheter-derived thrombosis, or superficial vein thrombosis, except those with stable thrombus after conventional anticoagulation. Prophylactic use of low-dose aspirin and low-molecular-weight heparin is allowed.

9. Uncontrolled hypertension, systolic blood pressure ≥150mmHg or diastolic blood pressure ≥100mmHg after optimal medical treatment, history of hypertensive crisis or hypertensive encephalopathy.

10. Symptomatic congestive heart failure (New York Heart Association class II-IV). Symptomatic or poorly controlled cardiac arrhythmias. QT interval prolongation, QTc>450ms (male), QTc>470ms (female).

11. Severe bleeding tendency or coagulation dysfunction, or receiving thrombolytic therapy.

12. History of gastrointestinal perforation and/or fistula within the past 6 months, history of intestinal obstruction (including incomplete intestinal obstruction requiring parenteral nutrition), inflammatory bowel disease or extensive bowel resection (partial colectomy or extensive small bowel resection) , complicated by chronic diarrhea), Crohn's disease, ulcerative colitis, or chronic diarrhea.

13. History of interstitial pneumonia, drug-induced pneumonia, idiopathic pneumonia or active pneumonia. Radiation pneumonitis within the radiotherapy area is allowed.

14. Active pulmonary tuberculosis (TB), who are receiving anti-tuberculosis treatment or who have received anti-tuberculosis treatment within 1 year before the first study drug.

15. Human immunodeficiency virus (HIV) infection (HIV 1/2 antibody positive).

16. Active or clinically poorly controlled serious infections. Severe infection within 4 weeks prior to the first study drug, including but not limited to hospitalization due to complications of infection, bacteremia, or severe pneumonia.

17. Active autoimmune disease requiring systemic treatment or history of the disease within the past 2 years (Vitiligo, psoriasis, alopecia or Grave's disease not requiring systemic treatment within the past 2 years, only thyroid hormones are required Hypothyroidism with replacement therapy and type 1 diabetes mellitus

requiring only insulin replacement therapy can be included). Known history of primary immunodeficiency. Only patients with positive autoimmune antibodies need to confirm whether there is an autoimmune disease according to the judgment of the investigator.

18. Use of immunosuppressive drugs within the past 4 weeks, excluding nasal, inhaled or other local glucocorticoids or systemic glucocorticoids at physiological doses (that is, not more than 10 mg/day prednisone or etc.) other glucocorticoids in effective doses), temporary use of glucocorticoids is permitted for the treatment of dyspnea symptoms of asthma, chronic obstructive pulmonary disease and other diseases.

19. Received live attenuated vaccine within the past 4 weeks or planned to receive during the study.

20. Received systemic immunostimulant therapy within the past 4 weeks.

21. Major surgery (craniotomy, thoracotomy or laparotomy) or unhealed wound, ulcer or fracture within the past 4 weeks.

22. Uncontrolled metabolic disorders or other non-malignant organ or systemic diseases or secondary reactions to cancer, which can lead to higher medical risk and/or uncertainty in the assessment of survival.

23. Other acute or chronic diseases, psychiatric disorders, or abnormal laboratory values that may result in increased risks associated with study participation or study drug administration, or interfere with the interpretation of study listed as ineligible to participate in this study.

24. Diagnosed with other malignancies within 5 years prior to the first administration, excluding basal cell carcinoma of the skin, squamous cell carcinoma of the skin and/or carcinoma in situ after radical resection. If other malignant tumors or liver cancer are diagnosed more than 5 years before administration, pathological or cytological diagnosis of recurrent and metastatic lesions is required.

25. Previously received any anti-PD-1, anti-PD-L1/L2 antibody, anti-CTLA4 antibody, or other immunotherapy. Previously received anti-VEGF and/or targeted therapy of VEGFR, RAF, MEK, PDGFR, FGFR and other signaling pathways.

26. Known allergies to any antibody drug, small molecule targeted drug components; or previous severe allergic reactions to other monoclonal antibodies.

27. Received investigational drug therapy within 28 weeks prior to initiation of study treatment.

28. Pregnant or breastfeeding female patients

5.4 Removal of Subjects from Therapy or Assessment

For safety or administrative reasons, the investigator may stop treating a subject with study treatment or withdraw the subject from the research at any time. For any reason, the subject has the right to stop receiving study treatment or withdraw from the study at any time. The following reasons for the termination will be recorded. The investigator should make every effort to enable each subject to continue treatment unless it is in the subject's best interest to discontinue study participation. If the subject's study treatment is discontinued, the investigator should use his best efforts to evaluate the subject's study results. After discontinuing treatment or dropping out of the study, subjects will also be followed up periodically (every 6 weeks) to determine their survival status until death or the end of the study.

The subject withdraws informed consent and asks to withdraw.

1) □ Subjects cannot tolerate small molecule targeted therapy or immunotherapy.
2) □Other circumstances in which the investigator considers withdrawal from the study necessary.
3) □The patient showed significant disease progression during treatment and continued treatment was judged to have no clinical benefit for the subject.

4) □ Subjects present with severe disobedience.

5) □ Pregnancy, death or loss to follow-up.

6) □ Researchers terminated the study.

6. Treatment strategy

6.1 How to use lenvatinib

6.1.1 Administration and dosage:

For patients weighing less than 60 kg, the recommended daily dose is 8 mg (2 4 mg capsules), once daily; For patients weighing ≥60 kg, the recommended daily dose is 12 mg (3 4 mg capsules), once daily. Treatment should be continued until disease progression or toxicity becomes intolerable.

6.1.2 Monitoring, Dose Adjustment and Discontinuation

Suspension of administration, dose adjustment, or discontinuation of treatment may be necessary to manage some adverse events. Mild to moderate adverse events (e.g., grade 1 or 2) generally do not require suspension of administration unless intolerance persists after active treatment. Severe (e.g., grade 3) or unacceptable adverse events require suspension until the adverse events improve to grade 0-1 or baseline. For details of dose adjustment based on adverse reactions, see **Table 1**. For details of monitoring, dose adjustment, and discontinuation in HCC patients, see **Table 2.**

Table 1. Lenvatinib dose adjustment based on adverse reactions

Adverse Reaction	**Severity** [a]	Dosage Modifications for LENVIMA
Hepatotoxicity	Grade 3 or 4	• Withhold until improves to Grade 0 to 1 or baseline. • Either resume at a reduced dose or discontinue depending on severity and persistence of hepatotoxicity. • Permanently discontinue for hepatic failure.
Renal Failure or Impairment	Grade 3 or 4	• Withhold until improves to Grade 0 to 1 or baseline. • Resume at a reduced dose or discontinue depending on severity and persistence of renal impairment.
Proteinuria	2 g or greater proteinuria in 24 hours	• Withhold until less than or equal to 2 grams of proteinuria per 24 hours. • Resume at a reduced dose. • Permanently discontinue for nephrotic syndrome.
Gastrointestinal Perforation	Any Grade	• Permanently discontinue.
Fistula Formation	Grade 3 or 4	• Permanently discontinue.
QT Prolongation	Greater than 500 ms or greater than 60 ms increase from baseline	• Withhold until improves to less than or equal to 480 ms or baseline. Resume at a reduced dose.
Reversible Posterior Leukoencephalopathy Syndrome	Any Grade	• Withhold until fully resolved. • Resume at a reduced dose or discontinue depending on severity and persistence of neurologic symptoms

Table 2. Details of Monitoring, Dose Adjustment, and Discontinuation-

Indication	**First Dosage Reduction To**	**Second Dosage Reduction To**	**Third Dosage Reduction To**
Actual weight 60 kg or greater	8 mg once daily	4 mg once daily	4 mg every other day
Actual weight less than 60 kg	4 mg once daily	4 mg every other day	Discontinue
Life-threatening adverse reactions (Grade 4): Permanently discontinue.			

6.2 How to use PD-1 antibody

Each PD-1 inhibitors should be given according to the dosage and usage of the instructions.

The dose of PD-1 inhibitors is not allowed to be adjusted during the whole study. The principles of suspension and permanent withdrawal of antibody drugs are shown in **Table 3.**

Table 3. dose adjustment program for PD-1 inhibitors

Adverse events associated with PD-1 inhibitors	**Grading**	**Management**
Rash/inflammatory dermatitis	G3	Hold ICPi therapy and consult with dermatology to determine appropriateness of resuming
	G4	Permanently discontinue.
pneumonia	G2	Withhold until fully resolved.
	Recurrent grade 2 pneumonia, G3 or G4 pneumonia	Permanently discontinue.
Diarrhea/enterocolitis	G3 or G2	Withhold until fully resolved.
	G4	Permanently discontinue.
Hepatitis	For subjects with normal ALT, AST, or TBIL at baseline, grade 2 AST, ALT, or TBIL increased; For subjects with baseline AST, ALT, or TBIL>ULN, AST, ALT, or TBIL increases ≥50% (meeting level 2 requirements) and duration <7 days	Withhold until fully resolved.
	For subjects with normal ALT, AST, or TBIL at baseline, grade 3 or 4 AST, ALT, or TBIL were elevated; For subjects with baseline AST, ALT, or TBIL>ULN, AST, ALT, or TBIL increases ≥50% (meeting grade 3 or 4 requirements) and duration ≥7 days	Permanently discontinue.
Hypophysitis	G2	Withhold until fully resolved.
	G3 or G4	Permanently discontinue.
Adrenocortical insufficiency	G2	Withhold until fully resolved.
	G3 or G4	Permanently discontinue.
Hyperthyroidism	G3 or G4	Permanently discontinue.
Type 1 diabetes	Grade 3 hyperglycemia	Withhold until fully resolved.
	Grade 4 hyperglycemia	Permanently discontinue.
Renal insufficiency	Grade 2 or 3 elevated Cr	Withhold until fully resolved.
	Grade 4 elevated Cr	Permanently discontinue.
Neurotoxicity	G2	Withhold until fully resolved.
	G3 or G4	Permanently discontinue.
Other AE	Other G3 AE appears for the first time	Withhold until fully resolved.
	Same G3 AE appears for the first time	Permanently discontinue.
	Fail to improve to G0-2 / baseline within 7 days or recover to G 0-1 /	Permanently discontinue.

	baseline level within 14 days of G3 AE	
	G4 AE	Permanently discontinue.

NOTE:

A: Resuming dosing after symptom improvement to level 0-1 or baseline.

B: Pituitaritis, adrenocortical insufficiency, hypothyroidism/hypothyroidism, and type 1 diabetes can be re-administered when fully controlled and only physiologic hormone replacement therapy is required.

C: In the case of abnormal Grade 4 laboratory results, the decision to discontinue medication should be based on concomitant clinical symptoms/signs and the investigator's clinical judgment.

Resumption of the use of antibody drugs requires a return to level 0-1 or baseline AE and an ECOG PS score of 0-1.

6.3 Prior and Concomitant Therapy

Allowed Concomitant therapy：

1) □ Medications that are determined by the investigator to be in compliance with protocol requirements (e.g., for the treatment of disease-related symptoms and concomitant treatment of treatment-related AE).

2) □ Subjects who need long-term medication due to underlying diseases such as hypertension and diabetes can continue medication.

3) □ Allows topical glucocorticoid administration, such as topical skin use, eye drops, nasal spray, inhalation, etc.

contraindicated Concomitant therapy：

1) □ Biotherapeutics with antitumor effects (except cytogenic drugs used to treat adverse events caused by chemotherapeutic drugs), and proprietary Chinese medicines with antitumor effects

2) □ Drugs with immunomodulatory effects, including but not limited to non-specific immunomodulators (such as thymosin, interferon, interleukin, immunoglobulin, gamma globulin) and proprietary Chinese medicines with immunomodulatory effects, etc

3) Chemotherapy not specified in this protocol

4) □ Live vaccines are administered within 30 days prior to initial administration of antibody drugs and during study participation. Live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, typhoid (oral) vaccines. To be allowed to receive injectable inactivated virus vaccines against seasonal influenza; however, intranasal live attenuated influenza vaccines are not allowed.

5) □ Inhaled steroids are permitted as part of fixation therapy for asthma or chronic obstructive pulmonary disease (COPD). Corticosteroids are permitted for the

management of adverse events with underlying immune etiology. Physiological doses of corticosteroids may be approved after consultation with the principal investigator.（Note: Prophylactic corticosteroids are permitted to avoid anaphylaxis）

It is important for investigators to review each drug (prescription and over-the-counter) that subjects received prior to study initiation and during each study visit.

1) □ At each visit, subjects must be asked about any new medications they receive.
2) □ To reduce the risk of adverse drug interactions, all measures must be taken to limit the number of concomitant drugs that are truly necessary.
3) □ During administration, avoid receiving drugs with hepatotoxicity (i.e., drugs warned of hepatotoxicity in the product label). Investigators are encouraged to review each potential hepatotoxic agent by searching the website www.livertox.nih.gov.

7. Research Plan and Timing of Programs

7.1 Screening period

During the screening period (days -10~-1), the following research procedures must be completed to ensure that subjects are eligible for this study:

- Sign informed consent
- Check inclusion/exclusion criteria
- Blood routine
- Blood biochemistry (including liver function, kidney function, electrolytes, pancreatic function, troponin T)
- Urine routine
- Blood coagulation
- AFP
- Pregnancy test (female)
- Thyroid function
- HIV antibody, HCV antibody, two and a half of hepatitis B (HBsAg, HBsAb, HBcAb, HBeAg, HBeAb)
- HBV DNA, HCV-RNA
- Liver-enhanced MRI/enhanced CT
- Chest CT
- PET-CT
- 12-lead ECG□

□ (The following can be done by the research doctor)

- Recording of demographic data, past medical history and past medication

- Record vital signs, height and weight
- System physical examination
- ECOG PS score
- Pathological examination and genetic testing
- Concomitant medication
- Tumor imaging evaluation

7.2 Baseline (before dosing on Day 1 of Cycle 1)

- Record vital signs and weight
- ECOG PS score
- AEs assessment
- Record concomitant medication

7.3 Treatment Period Visits/Assessments (Every 6-8 Weeks, Before Cycle 4 Immunotherapy)

- Vital signs and body weight were recorded. If the subject's body weight fluctuated less than 10% relative to the baseline (first dose study treatment day), the baseline body weight was used to calculate the dose; if not, the actual dosage is calculated according to the body weight on the day of planned administration.
- Blood routine
- Blood biochemistry (including liver function, kidney function, electrolytes, pancreatic function, troponin T)
- Urine routine
- Blood coagulation
- AFP
- Pregnancy test (female)

- Thyroid function
- HIV antibody, HCV antibody, hepatitis B (HBsAg, HBsAb, HBcAb, HBeAg, HBeAb)
- HBV DNA, HCV-RNA
- Liver-enhanced MRI/enhanced CT
- Chest CT
- PET-CT
- 12-lead ECG
- Record vital signs, height and weight
- System physical examination
- ECOG PS score

Tumor evaluation: Tumor evaluation according to mRECIST 1.1 will be performed every 6-8 weeks (before cycle 4 dosing) for 48 weeks from randomization date until confirmed " successful conversion " or PD.

7.4 Surgical treatment

Patients with "successful conversion" should meet the following criteria:

- ECOG score remains at 0-1
- Child-Pugh liver function classification A/B
- Non-active extrahepatic lesions assessed by PET-CT (or lung CT, bone scan, etc.), or extrahepatic lesions can be surgically removed at the same time;
- The hepatic vascular structure of the liver to be preserved is normal
- Functional residual liver volume (FRLV) ≥ 35%（In patients without background liver disease）or 45%（In patients with background liver disease）。

Surgical treatment can be performed when the patient is assessed to meet the above conditions and has given full informed consent. The surgical procedure was determined by the investigator and included:

- Partial hepatectomy
- Radiofrequency ablation of liver tumors
- Portal vein/inferior vena cava tumor thrombus removal and revascularization

It can be open or laparoscopic, or percutaneous (radiofrequency ablation of liver tumors).

2-4 weeks after the operation, according to the pathological results, start the PD-1 antibody with/without Lenvatinib, or choose to change the treatment plan according to the condition. Patients entered the treatment period for evaluation until PD was reassessed.

7.5 Survival follow-up

All patients continued to have tumor assessments at the protocol-specified time points for imaging assessments during the follow-up period of the treatment period. Patients who could not participate in related treatments were directly entered into the survival follow-up (every 8 weeks).

After surgical treatment, both groups will enter a follow-up period every 12 weeks, and the evaluation contents include:

- Blood routine: including hemoglobin, hematocrit, platelet count, red blood cell count, white blood cell count, neutrophil count and lymphocyte count.
- Blood biochemistry (including liver function, kidney function, electrolytes, pancreatic function, troponin T)
- Coagulation function: prothrombin time (PT), activated partial

thromboplastin time (APTT), thrombin time (TT), international normalized ratio (INR).

- AFP
- HBV DNA, HCV RNA, in addition to planned visit measurements, may be performed as needed at the discretion of the investigator. HBV DNA testing is not required if the hepatitis B test results are all negative. HCV RNA testing is not required if the hepatitis C test results are all negative.
- Tumor imaging evaluation: The imaging data should be sent to the imaging center for evaluation. Including liver-enhanced MRI (preferred)/liver-enhanced CT examination (if MRI examination cannot be accepted), chest CT scan (those with bone pain symptoms should consider adding bone scan examination; headache, nausea, vomiting, limb movement disorders and other nerves Locating symptoms and signs should consider adding brain MRI).
- See Table 4.

Informed consent	●												
Inclusion/exclusion criteria 1	●												
Radical resection of liver cancer							●						
General information	●												
Medical history	●												
Physical examination	●		●	●	●	●		●	●	●	●	●	●
Past History	●												
Combination medication	●		●	●	●	●		●	●	●	●	●	
ECOG PS score	●		●	●	●	●		●	●	●	●	●	
Blood routine examination	●		●	●	●	●		●	●	●	●	●	
Serum biochemistry	●		●	●	●	●		●	●	●	●	●	
Cardiac enzyme	●		●	●	●	●		●	●	●	●	●	
Coagulation function	●		●	●	●	●		●	●	●	●	●	
Thyroid function	●												
Serum tumor marker	●		●	●	●	●		●	●	●	●	●	●
Hepatitis B or C (including DNA and RN	●		●	●	●	●		●	●	●	●	●	
Blood pregnancy test (women only)	○		○	○	○	○		○	○	○	○	○	
Routine urine and stool test	●		●	●	●	●			●	●	●	●	
ECG	●												
Chest X-ray	●												
Radiology of tumors	●		●	●	●	●		●	●	●	●	●	●
Pet-ct or ECT+ lung CT	●		●	●	●	●			●	●	●	●	●
child-pugh staging	●		●	●	●	●		●	●	●	●	●	
ECLC staging	●		●	●	●	●		●	●	●	●	●	
Medication			●	●	●	●			●	●	●	●	
Efficacy evaluation			●	●	●	●			●	●	●	●	●
Pathology	●						●						
AE			●	●	●	●			●	●	●	●	
mRECIST			●	●	●	●			●	●	●	●	●
Survival and subsequent anti-tumor therapy													●
Note: "●" refers to the items that all subjects are required to complete, ○ For the test group, the items are required to complete.													

Table 4. Research Plan and Timing of Programs

1. All subjects need to sign the informed consent.

2. Subjects who meet the inclusion criteria and do not meet the exclusion criteria will enter the study.

3. Assessment during each treatment, including whether meet the criteria of radical resection, if Subjects meet the criteria of "conversion success", they will enter into "surgical treatment".

4. General information: date of birth, gender, ethnicity.

5. Medical History: A complete medical and surgical history including all relevant diseases should be obtained. In particular, ask about the history of hepatitis B, hepatitis C, tumor history, surgery history, treatment history and medication history.

6. ECOG Physical Condition Scale (details in **Annex 1)**.

7. Vital signs: including body temperature, pulse, respiration, blood pressure.

8. Complete physical examination: including height, weight, and evaluation of head, eyes, ears, nose and throat, cardiovascular, dermatology, musculoskeletal, respiratory, gastrointestinal, and nervous system.

9. Blood routine: including hemoglobin, hematocrit, platelet count, red blood cell count, white blood cell count, neutrophil count and lymphocyte count.

10. Serum biochemical tests (including liver and kidney function): including sodium, potassium, chloride, bicarbonate, blood urea nitrogen,

creatinine, calcium, phosphorus, total bilirubin, total protein, albumin, ALT alanine aminotransferase , AST aspartate aminotransferase, LDH lactate dehydrogenase, alkaline phosphatase, uric acid. At the discretion of the investigator, the examination results within 7 days before signing the informed consent can be used as the results of the screening period.

11. Coagulation function: prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), international normalized ratio (INR). At the discretion of the investigator, the examination results within 7 days before signing the informed consent can be used as the results of the screening period.

12. Thyroid function test: including free thyroxine (FT3/FT4), thyroid stimulating hormone (TSH) test. At the discretion of the investigator, the examination results within 30 days before signing the informed consent can be used as the results of the screening period.

13. Hepatitis B complete list, HBV DNA, hepatitis C antibody, HCV RNA, in addition to the planned visit measurement, can also be carried out if necessary according to the judgment of the investigator. HBV DNA testing is not required if the hepatitis B test results are all negative. HCV RNA testing is not required if the hepatitis C test results are all negative. At the discretion of the investigator, the examination results within 30 days before signing the informed consent can be used as the results of the screening period.

14. Perform a serum pregnancy test on all women of reproductive age, including women with tubal ligation. During the study, re-examination can also be carried out if necessary according to the judgment of the investigator. Women over the age of 50 and 12 months after menopause may not be tested for this. At the discretion of the investigator, the examination results within 30 days before signing the informed consent can be used as the results of the screening period.

15. Urine routine: pH, urine sugar, white blood cells, red blood cells, protein, nitrite, ketone bodies, urobilinogen. Routine: occult blood, traits, white blood cells. At the discretion of the investigator, the urine/fecal routine can be used as the result of the screening period within 7 days before signing the informed consent.

16. See Appendix 4 for the Child-Pugh classification.

17. For pathological diagnosis and microvascular infiltration, please refer to the standard for pathological diagnosis of primary liver cancer.

18. Tumor imaging evaluation: The imaging data should be sent to the imaging center for assessment. Including liver-enhanced MRI (preferred)/liver-enhanced CT examination (if MRI examination cannot be accepted), chest CT scan (those with bone pain symptoms should consider adding bone scan examination; headache, nausea, vomiting, limb movement disorders and other nerves) Additional brain MRI examinations should be considered for locating symptoms and signs; results within 30 days prior to signing the informed consent form are acceptable at the preoperative screening visit).

19. After obtaining accurate pathological information after surgery, the clinical staging of liver cancer is again based on BCLC (details in **Appendix 5)**.

8. Adverse event management system

8.1 Definition of Adverse Events

An adverse event is an unforeseen medical condition or deterioration of an existing medical condition, whether or not related to the study drug, within 28 days after the signing of the informed consent and the patient's completion or withdrawal from the study. Unforeseen medical conditions may be symptoms (e.g., nausea, chest pain), physical signs (e.g., tachycardia, liver enlargement), or abnormal test results (e.g., laboratory work, electrocardiogram). In clinical studies, beginning with the signing of informed consent, an adverse event can be an unforeseeable adverse medical condition that occurs at any time, including during the screening period, even if no treatment has been studied.

Adverse events occurring in humans (whether or not drug-related) include but are not limited to the following:

• Adverse events that occurred while the researcher was using the drug;

• Adverse events caused by drug overdoses (whether intentional or unintentional); Adverse events related to drug abuse;

• Adverse events caused by discontinuation of medication;

• Adverse events that may be caused solely by a subject's participation in a study must be reported as an adverse event, even if not related to the study medication.

The absence or failure to achieve desired clinical pharmacological effects which has documented in the corresponding section of the eCRF will not be considered as an adverse event. In this study, any event that was explicitly caused by disease progression was not reported as an adverse event.

8.2 Definition of Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the adverse

events it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

8.3 Assessment of Adverse Events

Researchers will assess all AEs in accordance with the NCI Common Terminology

for Adverse Events (CTCAE) Version 5.00 (details at **Appendix 7**). Any AE that changes the CTCAE grade will be recorded on the AE case report form/worksheet.

All AEs, regardless of CTCAE grade, must be assessed for SAEs.

8.4 Recording of Adverse Events

Researchers should use medical terms/concepts to document AEs or SAEs. Spoken words and abbreviations should be avoided. All AEs, including SAEs, should be recorded on the CRF's Adverse Events Form.

8.4.1 Adverse event collection and time period

Researchers were informed of AEs by asking subjects non-leading questions.

SAEs due to protocol-specified interventions (e.g., invasive procedures such as biopsy) were reported only after informed consent was signed but before initiation of study drug treatment.

All AEs whether related to study treatment or not, including SAEs, whether observed by the researchers or spontaneously reported by subjects will be collected from the Initiation of study to 30 days after the last dose or initiation of new treatment. After 30 days after the last dose, researchers should report SAEs that are considered to be related to the study drug or procedure.

8.4.2 Follow-up for adverse events

AEs should be followed up until they improve to baseline or grade 0-1, or the investigator considers that no further follow-up is necessary for reasonable reasons (eg, no recovery or improvement). If the adverse event is irreversible, a reasonable explanation should be recorded on the CRF. Whether or not related to study drug, the subject's recovery of AEs or SAEs and their dates should be documented in the CRF and medical records.

8.4.3 Contents of AE records

Researchers are required to fully record any AEs, including diagnosis (if no diagnosis, record symptoms, signs, including laboratory abnormalities), start and end dates (if applicable), CTCAE severity and changes (grade 3 or above events), whether is the SAEs, the action taken on the study drug, the treatment given due to the AEs and the outcome, the relationship of the AEs to the study drug.

For SAEs, researchers should also provide the date the AE met the SAE criteria, the date the researchers was informed of the SAE, the severity criteria, the date of hospitalization, the date of discharge, probable cause of death, date of death, whether an autopsy was performed, and Outcomes, assessment of relevance to study procedures, assessment of relevance to other drugs, and other possible causes of SAE. The researchers should also provide the basis for judging the relevance and a description of the SAEs. In the SAEs description, it is also necessary to include the subject's number, age, sex, height, and weight; the subject's trial drug treatment indications and disease stages, and related systemic conditions; SAEs occurrence, development, outcome, and results, etc. Clinical course; laboratory test results related to SAEs (examination time, unit and range of normal values must be provided); past history related to SAEs, co-morbidities and their occurrence and duration, etc.; drug history, concomitant drugs and their duration related to SAE Treatment start, duration, usage and dosage, etc.; detailed information on the initiation, duration, usage and dosage of study drug treatment.

Matters related to AE records are described below:

Diagnosis, symptoms, and signs: if a diagnosis has been made, the diagnosis rather than individual symptoms and signs should be recorded on the CRF (eg, liver failure rather than jaundice, elevated transaminases, and asterixis). If symptoms and signs cannot be determined to be attributable to the diagnosis at the time of reporting, they are recorded as a separate AE/SAE. If symptoms and signs are determined to be caused by the diagnosis, only the diagnosis is reported separately, and the symptoms and signs are included in the diagnosis. AEs need to delete records of symptoms and signs, and SAEs need to send follow-up update reports.

AEs secondary to other events: in general, AEs secondary to other events (eg, caused by other events or clinical sequelae) should be recorded as their primary event unless the

secondary event is severe. However, clinically significant secondary events should be recorded as independent AEs in the eCRF if they occur at different times from the primary event. If the relationship between events is unclear, they should be recorded separately in the CRF.

Persistent or recurring AEs: persistent AEs are those that persist without remission between the subject's two assessment time points. These AEs should only be recorded once on the CRF. The initial severity of the event should be recorded and updated as the event worsens to record the most severe event.

Recurrent AEs were defined as those that resolved between the two assessment time points but that occurred later. The occurrence of AEs should be recorded separately in the CRF.

Laboratory Abnormalities: clinically significant laboratory abnormalities should be reported as AEs. It is the researcher’s responsibility to review all abnormal laboratory results and to exercise medical judgment as to whether each laboratory abnormality should be reported as an AE.

Deaths: All deaths occurring throughout the trial period, whether related to study drug or not, should be recorded on the CRF's death reporting form. Deaths that occurred during the reporting period of AEs specified in the study protocol are only recorded on the CRF page of study completion/early termination if the researchers have determined that the death occurred during the reporting period of the AEs as specified in the study protocol alone as disease progression. All other study deaths, whether related to study drug or not, must be recorded as AEs and reported to the appropriate agency.

Pre-existing medical condition: subject's existing symptoms/signs during the trial screening period should be treated as AEs only when the severity, frequency, and nature of the aggravation (except for the worsening of the disease condition being studied) occur after entry into the trial. Records and reports. Changes from previous status, such as "increased headache frequency", should be reflected in the record.

Disease progression: disease progression is defined as the deterioration of the subject's condition caused by the primary tumor targeted by the investigational drug, the

appearance of new lesions relative to the primary tumor, or the progression of the original lesion is considered disease progression. Expected disease progression not reported as an AE, death due to signs and symptoms of expected disease progression, life-threatening, requiring or prolonged hospitalization, resulting in permanent or severe disability/incapacity, resulting in congenital anomalies/birth Defects, other important medical events are not expedited reporting as SAEs.

New anti-tumor therapy: Within 30 days of the last dose, if the subject starts new anti-tumor therapy, only SAEs related to the study drug will be recorded and reported.

8.5 SAE report

The reporting period of SAE is from the signing of informed consent to SAEs occurring within 30 days (including 30 days) after the last administration. Researchers should immediately report to the person in charge of the research within 24 hours of learning, and report to the national, provincial (or autonomous region, municipality) regulatory department and ethics committee in accordance with Chinese regulations.

SAEs that occur outside of the above period should also be reported if they are deemed to be related to the study drug.

9. Research risk and data management

9.1 Research Risks

1) The most common AEs caused by targeted and immunotherapy drugs include: abdominal pain, hand-foot skin reaction, fatigue, diarrhea/constipation, loss of appetite, hypertension, proteinuria, upper respiratory tract infection, hoarseness, abnormal liver function, fever, Mucositis, gastritis, weight loss, fever, dizziness, headache, nausea and vomiting, muscle and joint pain, gastrointestinal bleeding (including blood in the stool), hair loss, hair color change, cough, dyspnea, anemia, leukopenia/neutropenia, platelets Decreased, edema, paresthesia, itchy skin.

2) If the obtained specimen is fresh tumor puncture tissue, the puncture process may

cause bleeding, abdominal cavity organ damage and tumor seeding metastasis.

3) The mental impact and social problems caused by drug AEs or sudden tumor progression to patients.

4) Most of the drugs used in this study are self-paid and expensive and need to be taken for a long time.

Risk control:

1) During this study, patients may experience drug-related AEs. We will monitor all patients' adverse reactions. If any AEs occurs during following, patients can promptly call research doctors for consultation.

2) During following, if drug-related AEs are serious, the research doctor will adjust the drug dose or replace the optional drug for the patient, and treat the adverse reaction that has occurred accordingly.

3) If the research objects and drugs used in the ongoing aid project overlap with this study, it is recommended that the patient participate in the aid project at the same time, or try to arrange the drug clinical trial conducted by the same research center.

4) Patients can unconditionally withdraw from this study at any time, and it will not affect their routine treatment.

9.2 Data management and statistical analysis

1. Hospitals participating in this study should adopt GCP standard operating procedures to ensure the smooth implementation of this study.

2. In order to ensure the quality of the research, before the official start of the research, the principal person in charge of the research hospital and the principal investigator will discuss and formulate the research plan together, and conduct concurrent GCP training for the relevant medical staff.

3. All observed results and abnormal findings in the CRF table should be verified and recorded with the original medical records in a timely manner to ensure the reliability of the data.

4. Doctors in charge of the research should fill in the case report form (CRF) in a

timely, complete, detailed and accurate manner after the patient completes the treatment, and report or save it according to the aforementioned procedures.

5. Establish procedures for data storage, data transmission, and data query. The data to be kept include: medical records, imaging data, CRF form, drug use registration form, serious adverse event report form, etc. The transmitted data includes: CRF form, serious adverse event report form, and data and information to be used for summary data.

6. The original data of the trial is uploaded to the ResMan original data sharing platform of the China Clinical Trial Registration Center, so as to make the trial data transparent and improve the management level and quality of clinical research.

7. Use standard statistical analysis methods when summarizing and analyzing results. Mainly descriptive statistics. Continuous variables are described by the number of cases, mean, standard deviation, median, minimum and maximum values, and categorical variables are described by frequency and percentage. ORR, DCR, and 95% CI were calculated, and Kaplan-Meier was used to estimate median PFS, DOR, and OS.

8. Protect subject data confidentiality and data security through data anonymization and de-linking. Patient medical data is used only in the medical process and in this study.

10. Disclosure，Confidentiality and Report

1) The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the principal investigator.

2) The principal investigator reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the principal investigator will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IEC will also be informed

promptly and provided the reason(s) for the termination or suspension by the principal investigator.

3) No data collected as part of this study will be used in any written work, including publications, without the written consent of the principal investigator.All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the principal investigator in advance of submission pursuant. The review is aimed at protecting the investigator's proprietary information existing either at the date of the commencement of the study or generated during the study.

4) When publishing the paper, it should be clearly stated in the appropriate part of the paper: all participating clinical research units; the award-winning clinical research paper belongs to the clinical research hospital/department.

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