Clinical Trial Study Protocol

Clinical Outcomes of Initially Unresectable Hepatocellular Carcinoma Patients Receiving TACE/HAIC Plus Anti-Angiogenic Agents and Immune Checkpoint Inhibitors as Conversion Therapy, Achieving Complete Radiological Response or Resectability, Followed by Systemic Treatment or Surgical Resection: A Prospective Cohort Study

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1. PROJECT SUMMARY

Title：	Clinical Outcomes of Initially Unresectable Hepatocellular Carcinoma Patients Receiving TACE/HAIC Plus Anti-Angiogenic Agents and Immune Checkpoint Inhibitors as Conversion Therapy, Achieving Complete Radiological Response or Resectability, Followed by Systemic Treatment or Surgical Resection: A Prospective Cohort Study
Research Description：	Combined TACE/HAIC with anti-angiogenic drugs and immune checkpoint inhibitors (referred to as targeted immunotherapy) for initially unresectable hepatocellular carcinoma (uHCC) shows a high tumor response rate, potentially reducing tumor burden and successfully converting to resectable liver cancer, providing an opportunity for curative treatment, thus improving long-term survival. Current evidence shows that the conversion success rate of TACE/HAIC combined with targeted immunotherapy is between 22% and 50%, demonstrating encouraging preliminary efficacy. However, there are still some unresolved issues. Whether surgical resection after achieving radiographic complete response (rCR) or meeting resectable criteria can provide a survival advantage for these patients remains controversial. Monotherapy with targeted immunotherapy can bring nearly 2 years of overall survival, with a median progression-free survival (PFS) of 7-9 months, while long-term survival data for conversion therapy are still insufficient. In this prospective cohort study, we will evaluate and compare the clinical outcomes of uHCC patients who have achieved radiographic complete response or met resectable criteria after TACE or HAIC combined with anti-angiogenic drugs and immune checkpoint inhibitors, and then continue with systemic therapy or undergo surgical resection, aiming to further optimize the treatment strategy for liver cancer.
Purpose and endpoint：	**primary purpose：** • Median event-free survival (EFS)
	Secondary purpose： • 2-year event-free survival rate (2-y EFS rate) • Overall survival (OS) • Security • Cost-effectiveness analysis of two treatment modes
Study population and sample size：	This study will enroll at least 278 newly diagnosed uHCC patients who have achieved radiographic complete response or resectability criteria after TACE

	or HAIC combined with anti-angiogenic drugs and immune checkpoint inhibitors. These patients will be divided into a systemic treatment group (at least 139 cases) and a surgery group (at least 139 cases). Potential subjects will be eligible to participate in this study after completing the screening examinations and procedures for study enrollment.
Participating research institutions：	Zhongshan Hospital, Fudan University
Research treatment/intervention：	Systemic therapy (TACE or HAIC combined with anti-angiogenic drugs and immune checkpoint inhibitors) or hepatectomy
Research period：	24-36 months
Subject participation period：	up to 36 months

2. RESEARCH PURPOSE AND ENDPOINTSPrimary research endpoint

- Event-free survival (EFS)：Defined as the time from the date of achieving rCR or resectability criteria to the time of becoming inoperable, recurrence, progression, or death from any cause for uHCC patients.

Secondary research endpoints

- 2-year event-free survival rate (2-y EFS rate)：Defined as the rate of no events (recurrence, progression, or death from any cause) occurring in rCR patients over 2 years.
- Overall survival (OS)：Defined as the survival time from the day of achieving rCR to death from any cause。
- Security
- Cost-effectiveness analysis of two treatment modes

2. Research Design This study is a prospective cohort study aimed at observing the efficacy and safety of continuing systemic treatment or surgical resection in patients with initially unresectable hepatocellular carcinoma who achieve radiological complete remission or resectable standards after combined treatment with TACE/HAIC, anti-angiogenic drugs, and immune checkpoint inhibitors.

According to the inclusion criteria (refer to the subject conditions), screen TACE/HAIC combined anti-angiogenic drugs and immune checkpoint inhibitors for patients with initially unresectable hepatocellular carcinoma who have reached rCR or resectable standards after conversion therapy, and subjects who meet the inclusion criteria can enter this study after signing an informed consent form. After the subject screening is qualified, patients are divided into surgical groups and systemic treatment groups according to the treatment plan chosen by the patient (surgery or continued systemic treatment). Patients are required to undergo regular check-ups every 3 months, including blood routine, liver and kidney function, tumor markers, thyroid function, myocardial enzymes, and liver enhanced CT/MRI. If tumor recurrence or progression is found, the original treatment plan is terminated, and the corresponding optimal treatment plan is provided. During the follow-up process, detailed records of any other anti-tumor treatments and survival status of the enrolled patients during the study period are kept.

2. Eligibility Criteria

Inclusion Criteria:

1. Signed written informed consent.
2. Age 18–75 years.
3. Hepatocellular carcinoma (HCC) confirmed by histology/cytology or diagnosed according to the AASLD criteria.
4. Initially unresectable HCC (uHCC), defined according to the Chinese Guidelines for Diagnosis and Treatment of Primary Liver Cancer (2024 edition) and the Chinese Expert Consensus on Conversion and Perioperative Therapy for Primary Liver Cancer (2024 edition): HCC considered unsafe for curative resection due to inability to ensure both oncological completeness (R0 resection) and functional hepatic reserve (adequate future liver remnant with good vascular supply and biliary drainage to maintain postoperative liver function and minimize morbidity and mortality). Mainly includes CNLC stage Ib–IIIa or potentially resectable cases. Some stage Ia patients may also be considered uHCC if the tumor is adjacent to major intrahepatic vessels or involves the first/second hepatic hilum making R0 resection infeasible, or if severe cirrhosis increases risk of postoperative liver failure and complications; these can be considered after successful conversion and supportive treatment.
5. No prior systemic therapy before conversion treatment.
6.Conversion therapy regimen must include TACE or HAIC plus anti-angiogenic agents and immune checkpoint inhibitors (ICIs).
7. Anti-angiogenic agents may include lenvatinib, sorafenib, apatinib, donafenib, anlotinib, bevacizumab.
8. ICIs may include pembrolizumab, atezolizumab, nivolumab, sintilimab, tislelizumab, toripalimab, penpulimab, cadonilimab, KN-046.
9. After conversion therapy, hepatic lesions achieve radiological complete response (rCR) by mRECIST criteria on contrast-enhanced CT or MRI, or are assessed to have reached resectability criteria (eligible for curative hepatectomy or downstaging enabling safe surgery).
10. After achieving rCR or resectability, patients must have received either liver resection or continued systemic therapy with scheduled follow-up.
11. Child–Pugh class A or B liver function.
12. Eastern Cooperative Oncology Group performance status (ECOG PS) 0–1.

Exclusion Criteria:

1. Presence of another primary malignancy in other organs.

2. History of other malignancies.

3. Recurrent HCC occurring <2 years after previous curative surgery or adjuvant therapy.

4. Received treatments other than TACE or HAIC plus anti-angiogenic agents and ICIs during the conversion phase.

5. Received treatments during postoperative or maintenance systemic therapy that differ from the initial conversion regimen.

6. Severe organ dysfunction.

7. Incomplete radiological assessment data after treatment.

8. Child–Pugh class C liver function.

9. Pregnant or breastfeeding women.

10. Patients undergoing only functional future liver remnant (FLR) hypertrophy procedures (e.g., ALPPS or PVE) for insufficient FLR without other criteria for uHCC conversion.

3. RESEARCH EVALUATION AND PROCEDURES

Baseline/Pre-treatment

Before enrollment, participants will undergo a screening evaluation to determine eligibility, including baseline medical history, physical examination, CBC, serum chemistry, urine analysis, EKG, serum tumor markers, history of neoadjuvant treatment, and baseline and neoadjuvant treatment-enhanced CT and/or MRI, etc.

Systemic treatment for initially unresectable HCC: This study only included patients who received the following combined treatment regimens: TACE/HAIC + anti-angiogenic drugs + ICI. The main anti-angiogenic drugs were lenvatinib, sorafenib, apatinib, donafenib, anlotinib, bevacizumab. The main ICI drugs were pembrolizumab, atezolizumab, nivolumab, sintilimab, tiragolumab, tremelimumab, paminaplimab, cadonilimab, KN-046.

The rCR was determined according to the mRECIST criteria. Two independent researchers assessed the tumor response and discussed discrepancies when they occurred. rCR was defined as the complete disappearance of the arterial enhancement area of all target lesions.

Resectability standard assessment: Two independent researchers assessed the feasibility of surgical resection (R0 resection, sufficient remaining liver volume, and the surgery could obtain neoadjuvant tumor therapeutic effect compared to the initial treatment), and discussed discrepancies when they occurred.

Treatment phase

For patients who achieve rCR, the multidisciplinary team (MDT, including surgeons, internists, and interventional radiologists) discusses the subsequent treatment plan after discussion and fully discusses the potential benefits and risks of surgical intervention with the patient, selects based on the patient's wishes, and is divided into surgical groups and systemic treatment groups.

Continue systemic therapy: anti-angiogenic drugs and ICIs should be consistent with the preoperative conversion therapy selection, used according to their respective instructions, until disease progression (based on mRECIST criteria) or death or unacceptable toxicity. During treatment, TACE/HAIC can be performed as needed.

The specimens of patients who undergo surgical resection are routinely evaluated for pathological response. Whether to receive adjuvant therapy after surgery is chosen based on the analysis of potential benefits and risks by the MDT team, combined with the patient's wishes (preventive TACE/HAIC or targeted drugs, immune checkpoint inhibitors, or any combination thereof).

Patients in both groups were followed up every 3 months until tumor recurrence (based on mRECIST criteria) or death.

In both groups, TACE/HAIC can be performed as needed.

The routine follow-up program includes a comprehensive medical history, physical examination, blood routine, blood biochemistry, serological tumor marker assessment, coagulation function, thyroid function, myocardial enzyme profile, electrocardiogram, and chest plain CT and abdominal contrast-enhanced CT or MRI. Tumor progression is defined as the appearance of new lesions in any location, determined by contrast-enhanced CT or MRI based on the mRECIST criteria.

After treatment

For patients with tumor progression or recurrence, further treatment plans are decided after discussion by the MDT and consultation with the patient, and follow-up treatment and survival information continue until: 1) the subject's death; 2) the subject is lost to follow-up; or 3) the end of the study (follow-up period of 2 years).

Termination criteria for the study：

1) The participant withdraws the informed consent and requests to exit the clinical trial.
2) The researcher determines that the trial is disadvantageous to the subject, including the following situations:：
    a) Clinically confirmed tumor progression, recurrence, or metastasis at any site (patients with progression or recurrence will be given the best treatment plan based on their condition)
    b) Clinically confirmed tumor progression, recurrence, or metastasis at any site (patients with progression or recurrence will be given the best treatment plan based on their condition)
    c) Progressive increase in tumor markers
3) Unable to tolerate the adverse reactions of anti-angiogenic drugs or ICI

3. EVALUATION INDICATORS AND STATISTICAL METHODS

1、Primary endpoint: Event-free survival (EFS): defined as the time from the date of achieving rCR/resectability to intrahepatic recurrence, progression (based on mRECIST criteria), or death from any cause in patients who have achieved rCR/resectability. The Kaplan-Meier estimate of EFS and its corresponding 95% confidence interval will be calculated. The effect of the surgery group and the systemic treatment group on EFS will be evaluated using a Cox proportional hazards regression model, while controlling for other confounding factors. Point estimates of EFS based on exact binomial distribution and 95% confidence intervals, as well as the log-rank P-value for the comparison of EFS between the two groups, will be provided. A P-value < 0.05 is considered statistically significant.

2、secondary endpoint：

- 2-year EFS rate: Defined as the rate of event-free (recurrence, progression, or death from any cause, based on mRECIST criteria) rCR patients at 2 years. The Kaplan-Meier estimate of the 2-year EFS rate and its corresponding 95% confidence interval will be calculated.
- Overall survival (OS): Defined as the time from achieving rCR to death from any cause. The Kaplan-Meier estimate of overall survival and its corresponding 95% confidence interval will be calculated.
- Safety: The incidence of adverse events in the surgery group and the systemic therapy group. Adverse events recorded on the CRF will be mapped to preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). Severity, seriousness/grade, and the relationship with the study treatment will be assessed by the investigators. The seriousness/grade will be defined according to the National Cancer Institute (NCI) CTCAE v5.0.
- Cost-effectiveness analysis of the two treatment modalities: The cost-effectiveness ratio (C/E) is defined as the ratio of time to an event (EFS) or overall survival (death) from rCR to all direct costs (medical expenses, including outpatient and inpatient), and will be compared between the two groups.

3. SAMPLE SIZE CALCULATION

The expected EFS for the control group patients is 12 months, and for the experimental group patients is 18 months (corresponding HR=0.67). The trial plans to enroll participants over 12 months, with a 24-month follow-up. Considering a dropout rate of 20% for both the experimental and control groups, the trial would need at least 278 patients (at least 139 in each group) to achieve 80% power to detect this difference at a significance level of $\alpha=0.1$ (one-sided).