Hepatic arterial infusion chemotherapy plus regorafenib compared with regorafenib alone as second-line therapy for advanced hepatocellular carcinoma: a randomized controlled trial protocol

INFORMED CONSENT FORM

Protocol No.：01

Cancer Hospital,Chinese Academy of Medical Sciences

Primary investigatior：Xiao Li

Dear Participant：

We invite you to participate in a clinical study: "Hepatic arterial infusion chemotherapy plus regorafenib compared with regorafenib alone as second-line therapy for advanced hepatocellular carcinoma: a randomized controlled trial protocol" It is important for you to understand this study before you decide whether to participate. Please read the following information carefully and consider discussing it with your family and friends before making a decision. If you have fully understood the study, have no further questions, and decide to participate, you will need to sign this Informed Consent Form.

1. Background: This study, initiated by the Cancer Hospital, Chinese Academy of Medical Sciences, in collaboration with multiple domestic institutions, aims to evaluate the efficacy, safety, and effectiveness of hepatic arterial infusion chemotherapy (HAIC) combined with regorafenib versus regorafenib monotherapy in the second-line treatment of advanced liver cancer. Led by Principal Investigator Li Xiao, the study is important as primary liver cancer ranks seventh in global cancer incidence, with limited second-line treatment options. While HAIC has shown promising results in first-line treatment, its value in second-line treatment remains unclear. This open-label, randomized controlled clinical trial seeks to provide a more effective treatment option for patients with advanced liver cancer.

2. This study has been approved by the Ethics Committee of the Cancer Hospital, Chinese Academy of Medical Sciences. The Ethics Committee is an organization that protects the rights and interests of research subjects.

3. Research Objectives

Primary Research Objective: The primary endpoint is Median Overall Survival (OS).

Secondary Research Objectives: The secondary endpoints include Progression-Free Survival (PFS), Overall Response Rate (ORR), Disease Control Rate (DCR), Duration of Response (DOR), and Time to Progression (TTP), based on RECIST 1.1 and mRECIST criteria. Additionally, the incidence and severity of adverse events and serious adverse events will be assessed, based on NCI CTCAE v5.0.

Exploratory Research Objective: The exploratory endpoint includes quality of life scores, based on the EORTC QLQ C30 standard, as well as treatment costs and length of hospital stay.

4. Study Design

Study Participants: This study will enroll a total of 370 patients with advanced liver cancer who have progressed or are intolerant to first-line treatment, recruited from hospitals participating in this research project. The main inclusion and exclusion criteria are as follows:

Inclusion Criteria:

- Age ≥ 18 years old.
- Signed a written informed consent form and able to comply with the treatment and visit procedures specified in the study protocol.
- Diagnosis of HCC according to the AASLD clinical diagnostic criteria or histologically/cytologically confirmed HCC.
- Stage C HCC according to the BCLC staging system (i.e., portal vein invasion, extrahepatic metastasis, or ECOG score of 1 or 2).
- Received first-line standard systemic targeted and/or immunotherapy for HCC within the past 4 weeks.
- Presence of at least one measurable lesion according to RECIST 1.1 criteria on baseline imaging.
- Child-Pugh score: A or B.
- ECOG score of 0 to 2.
- Good organ and bone marrow function.

Exclusion Criteria:

- Participation in or currently participating in other therapeutic clinical research trials within 28 days before the start of treatment.
- Prior treatment with regorafenib or HAIC.
- Patients who have received or are planned to receive liver transplantation.
- Patients who have permanently discontinued sorafenib due to toxicity.
- Presence of clinically significant and active cardiovascular disease.
- Active bleeding or bleeding risk.
- Recent, persistent, or active infection.
- Presence of severe, unhealed wounds, fractures, or conditions such as abdominal wall or gastrointestinal fistulas, gastrointestinal perforations, abdominal abscesses, unhealed peptic ulcers, or gastrointestinal obstruction within 6 months before the start of treatment.
- Known hypersensitivity to any study drug or related excipients.
- Women who are pregnant, lactating, or planning to become pregnant within 6 months after the end of treatment during the study period.
- Presence of any other disease or condition that the investigator believes may affect the study results or increase the risk of treatment-related adverse reactions, including but not limited to metabolic disorders, abnormal physical examinations, or abnormal laboratory test results.

Study Design Type:

Domestic, multicenter, open-label, randomized controlled clinical trial. Randomization must be completed within 10 weeks after the end of the last line of treatment. Randomization will be conducted using the SAS statistical analysis system, with random allocation (2:1) to either combination therapy or regorafenib monotherapy under a given seed number, generating random numbers to form a random coding table. No specific stratification will be applied for randomization. Each study subject will be enrolled and assigned to treatment strictly according to the corresponding random coding table. Since the combination therapy group in this study requires additional invasive

interventional procedures, the study is designed as open-label. Additionally, imaging assessors and statisticians will not be informed of the patients' clinical group assignments and treatment information until the end of the study.

Study Procedures

1. Treatment Methods: Treatment and Grouping: The experimental group will receive HAIC combined with regorafenib, while the control group will receive regorafenib monotherapy. The rationale for the control group: Regorafenib has been recognized as the preferred second-line treatment option after sorafenib failure in both domestic and international guidelines due to its significant improvement in survival compared to placebo in Phase 3 clinical trials. Given that other first-line treatment options for advanced liver cancer do not have recognized effective second-line treatments, regorafenib is chosen as the control group in this study.

2. Follow-up Visits: You are required to visit the hospital according to the study protocol and continue until the end of the study. The purpose of follow-up visits is to assess the effectiveness of your treatment, monitor for adverse reactions, and provide appropriate management. Patients will undergo tumor assessments every 6-8 weeks. During each follow-up visit, your doctor will arrange for assessments including liver and kidney function, blood count, coagulation function, tumor markers, enhanced CT scans of the chest and abdomen or multi-phase enhanced MR scans of the upper abdomen, ECOG score, complications, and medication use. Your doctor may also recommend additional tests based on your condition.

5. Alternative Treatment

Participation in this study is completely voluntary. If you decide not to participate or withdraw from the study at any stage, you will receive alternative treatment. You can discuss specific alternative treatment options with your doctor before deciding whether to participate in this study.

6. Possible Risks

Anticancer treatments inherently carry risks. The drugs used in this study are already marketed in China, and previous studies have shown that this combination therapy does not significantly increase the incidence of treatment-related adverse events, thus not posing additional risks compared to conventional treatment. However, due to drug combinations, the disease itself, and other existing comorbidities, unforeseen or unpredictable adverse reactions may occur during the study.

7.Potential Benefits

By participating in this clinical study, there is a possibility that your disease may be alleviated. However, there is also a chance that the expected effects may not be achieved, or even that the disease may progress. While the relevant diagnosis and treatment may not directly benefit you, your participation contributes to the further research and understanding of this disease by the medical community, potentially leading to improved diagnostic and treatment levels in the future. We express our gratitude for your participation in scientific research and your contribution to medical development!

8.Study Costs

The drugs used in this study are already marketed in China, and the related examinations are routine examinations that have been clinically applied for many years. The costs of the study drugs and

related diagnostic and treatment services need to be borne by you.

9. Handling of Harm

If you experience serious adverse reactions during the study, your doctor will examine you and provide appropriate treatment. If you cannot tolerate the adverse drug reactions or fail to comply with the doctor's instructions, the doctor may recommend that you withdraw from the study.

10. Voluntary Participation

Participation in this study is completely voluntary, and you can withdraw at any time without giving a reason. Your decision to not participate or to withdraw from the study will not affect your relationship with medical staff or your diagnosis and treatment. If you decide to participate in this study, your doctor will inform you of any information that may affect your physical condition or your decision to continue participating in the study during the study process.

11. Privacy and Confidentiality Principles

Your information and medical records in this study will be kept confidential within the scope required by law. We will use personal identity information to protect your privacy through identification processing: after enrollment, you will be assigned a unified project number, and your personal information and medical records will be collected by your doctor or their research team. The data will be encoded, stored, and protected, with only individual numbers visible to users, and your name and other information will not be accessed. The refrigerator used to store your biological samples is a dedicated biological sample storage refrigerator, and the key is kept by a dedicated person responsible for sample management.

12. Study Termination

During your participation in the study, you may withdraw at any time without giving a reason, and your decision will not have any impact on your continued medical treatment. Your doctor may also stop your study medication for the following reasons:

- You fail to follow the instructions and requirements of the study doctor in taking medication.
- Disease progression or the occurrence of intolerable adverse reactions, where the study doctor believes that continuing participation in the study would pose a risk to you.
- You receive treatment that is not allowed in this study.
- The study doctor, ethics committee, or government regulatory authority requires the termination of this study.

When you withdraw from the study or the study is terminated, the study doctor will discuss subsequent diagnostic and treatment measures with you.

13. Study Consultation

If you have any questions about this study, you can directly contact Dr. Li Xiao at the Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College. The contact number is 010 87788395. If you have any questions related to participant rights, or if you wish to report difficulties, dissatisfaction, or concerns encountered during your participation in this study, or if you wish to provide opinions and suggestions related to this study, please contact the Ethics Committee of the Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union

Medical College. The contact number is 010 87788495, and the email address is cancergcp@163.com.

Informed Consent Form
Signature Page

Subject's Declaration

The research doctor has thoroughly explained to me the purpose, process, potential risks, and benefits of participating in this study (Hepatic arterial infusion chemotherapy plus regorafenib compared with regorafenib alone as second-line therapy for advanced hepatocellular carcinoma: a randomized controlled trial protocol). I have carefully read the Informed Consent Form, and all my questions have been satisfactorily answered. I fully understand its contents.

I consent to my research doctor collecting and using my medical information. I also consent to the Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College accessing my medical information and research results from this study for scientific research purposes. I agree that members of the Ethics Committee and representatives of government regulatory authorities, under the premise of confidentiality, may access my medical information within their respective authorities. I understand that the purpose of reviewing these records is to ensure that the data collected from this study are true, complete, and reliable.

I acknowledge that my participation in this study is voluntary, and I may withdraw from the study at any time without any impact on my subsequent medical treatment or legal rights.

I have received a copy of the signed Informed Consent Form. By signing this consent form, I have not relinquished any of my legal rights.

I consent to participate in the biomarker tests, including tumor tissue, blood, and other relevant samples, in this study.

Patient's Signature:
Date:

Legal Representative's Signature:
Relationship to the Patient:
Date:

Note: The signature of a legal representative is not required unless the subject is unable to read (e.g., due to illiteracy or blindness) or is unable to sign for other reasons.