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

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ABSTRACT

Introduction The exact role of hepatic arterial infusion chemotherapy (HAIC) in advanced hepatocellular carcinoma (aHCC) is still unknown. The combination of HAIC and sorafenib has been proven to be more effective than sorafenib alone in the first-line treatment of aHCC. The aim of the study is to evaluate the efficacy and safety of HAIC plus regorafenib in the second-line treatment of aHCC.

Methods and analysis This is a multicenter, open-label, randomised controlled phase III trial. A total of 294 patients with aHCC, who are unable to tolerate the first-line systemic therapy or progress after the first-line systemic therapy, will be enrolled in the study. The patients will be randomly (2:1) assigned into the combination treatment group (HAIC plus regorafenib, n=196) and the control group (regorafenib alone, n=98). HAIC and regorafenib (160 mg/day) will be given in a 4-week cycle. The primary endpoint is overall survival in the intention-to-treat population. The second endpoints include progression-free survival, overall response rate, time to progression, etc. The radiological assessments will be based on the criteria of Response Evaluation Criteria in Solid Tumors 1.1.

Ethics and dissemination This study is approved by the ethics committee of Cancer Hospital, Chinese Academy of Medical Sciences. All participants are required to provide written informed consent. The results of this study will be disseminated through peer-reviewed publications and esteemed academic conferences.

Trial registration number Chinese Clinical Trial Registry (ChiCTR2300073075).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first investigator-initiated, multicenter, randomised controlled phase III trial to investigate the role of hepatic arterial infusion chemotherapy in the second-line treatment of advanced hepatocellular carcinoma (HCC).
⇒ The primary endpoint is overall survival, which will be complemented by progression-free survival, objective response rate, time to progression, disease control rate, surgical conversion rate and adverse events.
⇒ This study would allow us to clarify the exact role of hepatic arterial infusion chemotherapy (HAIC) in patients with advanced HCC and find the subgroup of patients who can benefit most from the combination of HAIC and regorafenib.
⇒ It could be a limitation that regorafenib, not the other drugs developed in recent years for HCC, is chosen to be the standard treatment in the control group.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver cancer.[1 2] Advanced HCC (aHCC) represents those with macrovascular invasion, extrahepatic spread or cancer-related symptoms. The median survival time of aHCC is merely 6–8 months without any treatment.[3] Multiple first-line (ie, sorafenib, lenvatinib, atezolizumab plus bevacizumab and tremelimumab plus durvalumab) and second-line (ie, regorafenib, cabozantinib and ramucirumab) treatments have been successfully used to improve the prognosis of aHCC.[4 5] However, the median overall survival of aHCC is still less than 2 years.[3] Therefore, novel treatments are warranted to further improve the prognosis of aHCC.

Hepatic arterial infusion chemotherapy (HAIC) using oxaliplatin, leucovorin and fluorouracil showed better efficacy than transarterial chemoembolization (TACE) in patients with large HCC,[6] and HAIC combined with sorafenib has shown better survival outcomes than sorafenib for the first-line treatment of aHCC.[7] However, with the rapid development of novel systemic treatments for aHCC, the exact role of HAIC in advanced HCC is still unknown.[8–10] To the best of our knowledge, no published phase I or phase II trials have yet evaluated

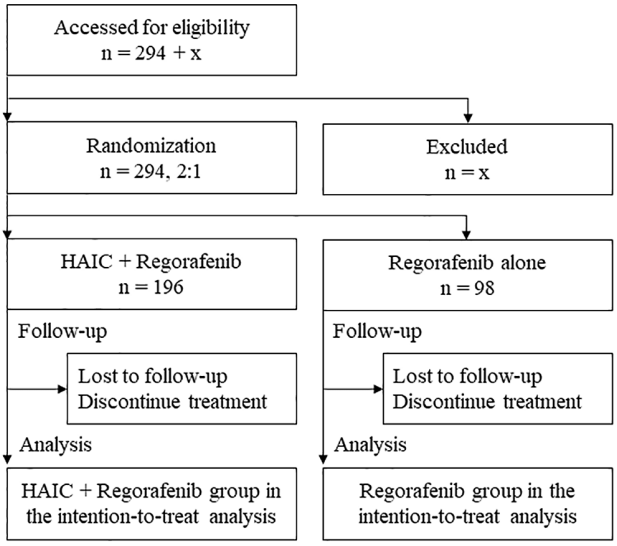

Figure 1 Consolidated Standards of Reporting Trials diagram. HAIC, hepatic arterial infusion chemotherapy.

the efficacy of HAIC in combination with regorafenib for the treatment of advanced HCC. Nevertheless, this combination therapy has garnered increasing attention and application in patients with unresectable colorectal liver metastases, where several retrospective studies have demonstrated its effectiveness and tolerability.[11] Therefore, we hypothesise that HAIC might be able to improve the efficacy of regorafenib in the second-line treatment of aHCC. Thus, this study aims to compare the efficacy and safety of HAIC plus regorafenib with regorafenib alone for the second-line treatment of aHCC.

METHODS AND ANALYSIS

This investigator-initiated, multicenter, open-label, randomised controlled phase III trial has been approved by the local ethics committee and registered in the Chinese Clinical Trial Registry (identifier: ChiCTR2300073075). A total of 294 patients recruited from three institutions, including Cancer Hospital of Chinese Academy of Medical Sciences, Shenzhen Cancer Hospital and Hebei Cancer Hospital, will be randomly (2:1) assigned into the combination treatment group (HAIC plus regorafenib, n=196) and the control group (regorafenib alone, n=98) (figure 1). The study will commence patient enrollment from August 2023 and conclude this phase by January 2025, with the subsequent follow-up period extending until July 2026. The study protocol is in accordance with clinical practice guidelines, the Consolidated Standards of Reporting Trials statement, the Standard Protocol Items: Recommendations for Interventional Trials 2013 checklist and the Declaration of Helsinki. All patients will provide written informed consent (online supplemental file 1).

Inclusion and exclusion criteria

Patients who tolerate first-line systemic therapy or whose tumour is found to progress after first-line systemic therapy will be enrolled in the study.[4 5] HCC diagnosis will be determined by biopsy or imaging examinations, according to the criteria of the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases.[3 12] Advanced HCC is referred to as being at the Barcelona Clinic Liver Cancer (BCLC) stage C, according to the BCLC staging system.[4] Inclusion and exclusion criteria are listed in table 1.

Interventions

Patients in the combination treatment group will receive HAIC and regorafenib (160 mg/day) in a 4-week cycle (figure 2). And patients in the control group will receive regorafenib (160 mg/day) for the first 3 weeks in a 4-week cycle.[13] Interruptions and dose reductions of regorafenib are allowed to manage the related toxicity according to the judgement of the physician. Generally, when grade 3 or higher regorafenib-related adverse events (AEs) occur, regorafenib will be discontinued. If no recovery occurs (ie, if the AEs are not reduced to grade 2 or lower) after a 30-day delay, regorafenib will be discontinued permanently. If the AEs are reduced to grade 2 or lower within 30 days, regorafenib treatment will continue at a reduced dose level (ie, initially 120 mg/day, then 80 mg/day if necessary), and the subject will be closely monitored weekly for at least 4 weeks. For patients in the combination group, HAIC will be administered at the beginning of the first week during the 4-week cycle. After determining and catheterising the intrahepatic tumour blood supply, the microcatheter and sheath will be fixed, and oxaliplatin (85 mg/m^2), leucovorin (400 mg/m^2), fluorouracil (400 mg/m^2) (bolus) and fluorouracil (2400 mg/m^2) (mFOLFOX6) will be sequentially infused through the microcatheter in the next 48 hours.[14] HAIC treatment will be repeated every 4 weeks until (1) intolerable serious adverse reactions occur (continued HAIC according to the drug reduction plan if the adverse reactions decrease to level one or two within 28 days and permanent discontinuation of HAIC if it cannot be reduced to level one or two after 28 days of discontinuation), (2) tumour progression, (3) death, (4) patient withdrawal of the informed consent or (5) other situations that the physician deems it necessary to stop HAIC. Concomitant best supportive care is allowed during the trial. After eight treatment cycles, patients are allowed to use any treatment that the clinical practice guidelines allow. It is acceptable for patients in the regorafenib alone group to use HAIC as a treatment after tumour progression.

Outcomes

The primary endpoint is overall survival, which is defined as the time between the date of randomisation and the date of death (or the date of the last follow-up when the patient is alive). The secondary endpoints include overall progression-free survival, hepatic progression-free

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
► Age≥18 years old	► Previously treated with HAIC or regorafenib
► Pathologically or radiologically confirmed advanced HCC according to EASL and AASLD guidelines	► Participated, participating or is going to participate in other therapeutic trials within 28 days before the treatment
► Previously received first-line systemic therapy for advanced HCC	► Absence of hepatic lesions
► ECOG-PS score: 0–1	► Have received or plan to undergo liver transplantation
► At least one measurable lesion by RECIST version 1.1	► Permanently stopped using sorafenib because of toxicity
► Child-Pugh A or Child-Pugh B without cirrhosis	► Clinically significant cardiovascular diseases
► Adequate organ and haematologic function*	► Active bleeding or there is a risk of bleeding
► Sign the written informed consent and be able to comply with the treatment and follow-up procedures stipulated in the research programme	► Recent, persistent or active infection
	► Serious unhealed injury, abdominal wall fistula, gastrointestinal fistula, gastrointestinal perforation, abdominal abscess, unhealed gastrointestinal ulcer or gastrointestinal obstruction within 6 months before the start of treatment
	► Allergic to any research drugs or related excipients
	► Other malignant tumours
	► Women during pregnancy or breastfeeding
	► Other diseases or states that could affect the results of the study or increase the occurrence of treatment-related adverse reactions based on the investigator's consideration

*Adequate organ and haematologic function: white blood cell≥3.0×10^9/L, neutrophils≥1.5×10^9/L, platelets>75×10^9/L, haemoglobin>85 g/L; total serum bilirubin≤30 mmol/L, serum albumin≥2.8 g/dL, aspartate transferase≤1.5×ULN (upper limit of normal), alanine transferase≤1.5×ULN, international normalised ratio≤1.5 or activated partial thromboplastin time≤1.5×ULN, serum creatinine≤1.5×ULN and left ventricular ejection fraction≥45%.
AASLD, American Association for the Study of Liver Diseases; EASL, European Association for the Study of the Liver; ECOG-PS, Eastern Cooperative Oncology Group-performance status; HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors.

survival, objective response rate, time to progression, disease control rate, surgical conversion rate and AEs.[6] The radiological assessment will be independently centralised and reviewed by investigators using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria, and the outcomes derived from mRECIST criteria will also be recorded. AEs after entry into the study will be recorded in line with the Common Terminology Criteria for Adverse Events V.5.0. Quality of life will be recorded using the quality-of-life questionnaires for hepatocellular carcinoma (QLQ-HCC18) and cancer (QLQ-C30) released by the European Organisation for Research and Treatment of Cancer.

Data collection and follow-up

Age, gender, underlying liver disease aetiology, contrast-enhanced CT/MRI scans, tumour marker testing, blood routine analysis, coagulation function assessment, liver function tests, Eastern Cooperative Oncology Group (ECOG) performance status and an assessment of quality

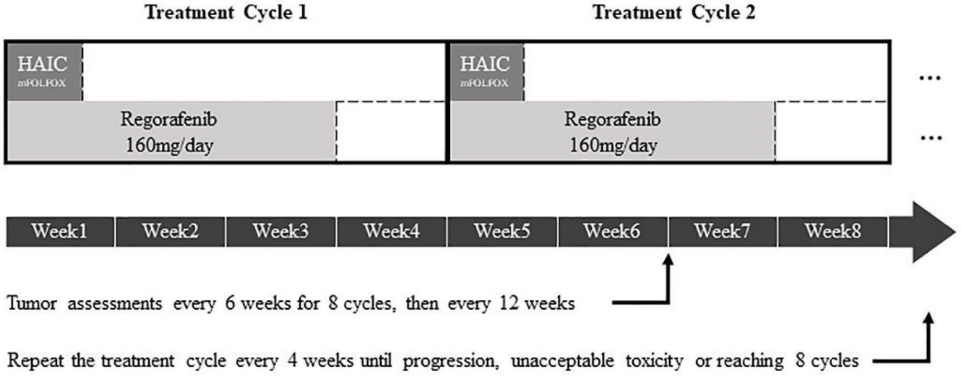

Figure 2 Timeline of the treatments. Patients in the combination treatment group will receive both HAIC and regorafenib treatment. And the patients in the control group will receive regorafenib alone. HAIC, hepatic arterial infusion chemotherapy.

of life will be collected at patient enrollment. Follow-up visits for tumour assessment, including contrast-enhanced CT/MRI, tumour marker testing, blood routine, coagulation function, liver function tests and AE monitoring, are scheduled every 6 weeks for the first eight treatment cycles and every 12 weeks thereafter, until death or the end of the study. Double data entry will be used to enhance the data quality. To promote participant retention and complete follow-up, e-mails or mobile messaging will be sent to the participants, reminding them of the upcoming data collection. Files of the participants will be stored in numerical order and stored in a secure place. The files will be stored for 3 years after the end of the study. All electronic databases will be secured with password-protected systems.

Randomisation

The patients will be randomly assigned (2:1) to receive regorafenib with or without HAIC by the method of stratified blocked randomisation.[15] The stratification factors include the ECOG performance status (0 vs 1), macrovascular invasion or extrahepatic disease (yes vs no) and prior systemic treatment (lenvatinib vs atezolizumab plus bevacizumab vs others).[3] The length of the blocks is also randomly determined by a computer and concealed to all investigators. The statistician will not be involved in the enrollment.

Blinding

Due to the nature of the intervention, both the participants and the investigators will be aware of the treatment assignments after the randomisation. The data collectors, statisticians and the independent radiologists who conduct the imaging review will be blinded to the allocation. An employee outside the team will input related data into the computer so that the investigators can analyse these data without having access to the information of allocation.

Statistical analyses

The primary and secondary endpoints between the two groups will be compared by intention to treat. Continuous variables will be compared by Student's t-test or Mann-Whitney U test as appropriate. χ^2 or Fisher's exact test will be used for categorical variables. The analyses of safety will be based on the patients receiving at least one full cycle of the assigned treatment. Subgroup analyses will be conducted according to age, sex, ECOG performance score, prior systemic treatment, macrovascular invasion, extrahepatic disease, alpha fetoprotein level, hepatitis B infection and hospitals. Kaplan-Meier survival analysis followed by multivariable Cox proportional hazards model will be used to compare the timed endpoints such as overall survival. Comparisons between the per-protocol groups will also be conducted to validate the results derived from the intention-to-treat groups. A two-sided p value<0.05 will be considered statistically significant. No interim analysis is planned.

Sample size

The median overall survival time of patients treated with regorafenib alone is estimated to be 10 months, according to previous studies.[13 16] A 50% increase in median overall survival time (ie, 15 months) in patients treated with HAIC plus regorafenib is expected, with a HR of 0.67. To detect the difference with 80% power and a two-sided α of 0.05, a total of 294 patients are needed, with an enrollment period of 18 months, a total study period of 36 months and a drop-out rate of 10%. Patients will be recruited at the study enters through two methods: (1) local advertising and (2) identification in the outpatient clinic.

Data monitoring and quality assurance

Monitoring visits will be scheduled every month to confirm the integrity and accuracy of the data in the electronic system by comparing it with the data in the original documents.

Reporting of the trial results

The results will be released to participants, investigators and the medical community. Abstract or article derived from the data of the current study must be reviewed and approved by the investigators about its appropriateness before submission.

Patient and public involvement statement

Before submitting the study protocol to the local ethic committee, investigators collaborated with three patient representatives with aHCC to comprehensively assess and improve the protocol. Their feedback was meticulously incorporated into the present trial design by making necessary clarifications and corrections.

DISCUSSION

According to the Barcelona Clinic Liver Cancer staging system and recent guidelines, second-line treatments of aHCC include regorafenib, cabozantinib, lenvatinib, sorafenib, pembrolizumab, ramucirumab, etc.[3–5] Lenvatinib and sorafenib are still widely used in patients seeking first-line treatment of aHCC due to their convenience and low price, especially in China.[17 18] And as of July 2023, cabozantinib, pembrolizumab and ramucirumab have not been listed in the national health insurance drug catalogue of China. Therefore, regorafenib is chosen as the standard treatment in this investigator-initiated study.

FOLFOX-HAIC has been proven to be more effective than TACE in patients with large HCC, and HAIC combined with sorafenib has shown better survival outcomes than sorafenib alone for the first-line treatment of aHCC.[6 7] In addition, HAIC is relatively more cost-effective than Yttrium-90 hepatic radioembolisation for patients with aHCC in China. In addition, HAIC plus regorafenib has been proven to be safe in advanced colorectal cancer in a real-world retrospective study, in which grade 3 or 4 AEs were observed in seven (18.4%)

patients and two patients discontinued the combination treatment because of AEs.[11] To further reduce the AEs of the combination therapy, the interval for conducting HAIC is extended from 3 weeks to 4 weeks. An extra advantage of this extension is that the treatment cycle of HAIC can be coordinated with the treatment cycle of regorafenib, which is more convenient for the physicians to monitor adverse reactions and for patients to follow the treatment plan. Thus, we regard that the combination of HAIC and regorafenib in a 4-week cycle might be the optimal second-line treatment for aHCC.

In conclusion, this randomised controlled trial would allow us to clarify the exact role of HAIC in patients with aHCC and find the subgroup of patients who can benefit most from the combination of HAIC and regorafenib.

Ethics and dissemination

This study is approved by the ethics committee of Cancer Hospital, Chinese Academy of Medical Sciences, and registered in the Chinese Clinical Trial Registry (identifier: ChiCTR2300073075). All participants are required to provide written informed consent. The results of this study will be disseminated through peer-reviewed publications and esteemed academic conferences.

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Contributors HZ contributed to the design, statistical analysis and writing of article. XZ, PT, YL, WS, YL, JL, TG and ZY contributed to the discussion of the protocol and data acquisition during study. PS contributed to the discussion of the protocol and critical revision and was the head of the data management team. XL contributed to the concept and design and study supervision and critical revision and was the head of the steering committee. XL is the guarantor of this study.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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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.