Hepatectomy combined with apatinib and camrelizumab for CNLC stage IIIb hepatocellular carcinoma: a phase II trial protocol

Jun Tao Huang, Jian-Hong Zhong, Jie Zhang, Wen Feng Gong, Liang Ma, Le Qun Li, Bang-De Xiang

ABSTRACT

Introduction  Current clinical guidelines recommend systematic antitumour therapy as the primary treatment option for patients with stage IIIb hepatocellular carcinoma (HCC) based on the China liver cancer (CNLC) staging criteria. Several different targeted therapeutics have been applied in combination with immunotherapeutic regimens to date in patients with advanced HCC. The present study was developed to evaluate the relative safety and efficacy of hepatectomy of HCC in combination with targeted apatinib treatment and immunotherapeutic camrelizumab treatment CNLC-IIIb stage HCC patients with the goal of providing evidence regarding the potential value of this therapeutic regimen in individuals diagnosed with advanced HCC.

Methods and analysis  This is a multicentre phase II trial with single-arm in which patients undergo hepatectomy in combination with targeted treatment (apatinib) and immunotherapy (camrelizumab). Patients will undergo follow-up every 2–3 months following treatment initiation to record any evidence of disease progression and adverse event incidence for a minimum of 24 months following the discontinuation of treatment until reaching study endpoint events or trial termination. The primary endpoint for this study is patient mortality.

Ethics and dissemination  This study protocol was approved by the Ethics Committee of the Guangxi Medical University Cancer Hospital (KS2022[124]). The results of this study will be submitted for publication in a peer-reviewed journal.

Trial registration number  NCT05062837

INTRODUCTION

Hepatocellular carcinoma (HCC) is the seventh most common form of cancer and causes roughly 830,000 deaths annually.\(^1\) As early-stage HCC generally fails to exhibit any specific symptoms, patients are primarily diagnosed with this disease when it is already in a more advanced stage in China.\(^2\) Between 2003 and 2013, our group identified 6241 patients with HCC in the Guangxi Medical University Cancer Hospital, with 54% of these patients exhibiting disease consistent with stage C Barcelona Clinic Liver Cancer (BCLC) Staging.\(^2\) Similarly, studies conducted in Hong Kong (n=3856) and Italy (n=5183) have, respectively, reported stage C HCC patient proportions of 40% and 45%.\(^3\) The median survival of advanced BCLC stage C patients is just 4–6 months, even with optimal supportive treatment.\(^4\) Advanced HCC cases can be further stratified into those exhibiting macrovascular invasion (China liver cancer (CNLC) staging IIIa) and those regardless of tumour size and vascular invasion but exhibiting extrahepatic metastases (CNLC IIIb).\(^7\) Molecular targeted drug-based treatment is currently recommended in many countries for patients with CNLC-IIIb HCC.\(^7\) However, the single-agent efficacy of these targeted therapeutics is generally reported to be relatively limited when used to treat advanced HCC, and patients generally exhibit unsatisfactory improvements in long-term prognostic outcomes.\(^14\) Immune checkpoint inhibitor (ICI) use in patients with advanced-stage HCC has been a focus of growing interest in recent years owing to evidence of their efficacy in several solid tumour types.\(^20\) Patients who undergo ICI treatment in combination with targeted therapy have been reported to exhibit significantly improved overall survival (OS) and
Local progression of intrahepatic tumours is the leading cause of death for patients with advanced HCC, which is far more lethal than extrahepatic metastases. While hepatectomy is not recommended for CNLC stage IIIb HCC patients under international guidelines,7–13 some retrospective evidence suggesting that patients with extrahepatic metastasis who undergo hepatic resection exhibit significantly improved outcomes relative to those who do not undergo surgical treatment,29–32 with this duration being significantly longer than that achieved by patients who do not undergo surgical treatment and are instead treated with combinations of targeted drugs and ICI.22 28

Given the above evidence, we hypothesise that surgical resection of intrahepatic tumours can benefit patients by reducing the tumour load and proinflammatory cytokine release. After that, the combination of vascular endothelial growth factor (VEGF) inhibitors and ICI immunotherapy can promote the shrinkage or regression of extrahepatic metastases and ultimately prolong the survival time of CNLC stage IIIb HCC patients.33–36 As such, the present study protocol was formulated based on a combined regimen of apatinib plus camrelizumab as data from several studies have indicated that this combination is associated with the longest median survival time for treated patients.22 24 25 This study will prospectively enrol CNLC stage IIIb HCC patients with extrahepatic metastases and which intrahepatic lesions are considered suitable for radical resection. Recruitment and analyses will be performed across multiple clinical centres in China with the goal of assessing the OS for these patients’ following treatment via hepatectomy in combination with apatinib plus camrelizumab and the PFS, objective response rate (ORR), disease control rate (DCR), duration of response (DoR) and time to progression of extrahepatic lesions.

METHODS AND ANALYSIS

Patient eligibility criteria

1. Age: 18–75 years.

2. CNLC stage IIIb HCC with extrahepatic metastases including lymph node, bone and lung metastases, but excluding brain metastases, as diagnosed via clinical imaging based on the Liver Imaging Reporting and Data System.

3. Patients are considered candidates for the curative hepatic resection of local liver tumours.

4. Liver function: grade A Child-Pugh score.

5. Indo-Cyanine Green retention value: 15 min <10%.

6. Eastern Cooperative Oncology Group-Performance status: 0 or 1.

7. Expected survival duration: ≥ 6 months.37

8. Haematological indexes that do not exceed the following thresholds: haemoglobin ≥90 g/L; absolute neutrophil count ≥1.5×10^9/L; platelets ≥80×10^9/L; total bilirubin ≤1.5×the upper limit of normal (ULN); alanine transaminase (ALT) ≤3×ULN; aspartate aminotransferase (AST) <3×ULN or less; alkaline phosphatase ≤2.5×ULN; serum albumin ≥28 g/L; serum creatinine ≤1.5×ULN.

9. Patients do not wish to go through radiotherapy or transcatheter arterial chemoembolisation (TACE). Based on the recommendations of CNLC guideline, radiotherapy and TACE are also recommended for patients with CNLC stage IIIb HCC.7

10. All women of childbearing age will be required to use contraception (eg, condoms, contraceptive pills or intrauterine devices) for the duration of the trial and for 3 months following trial completion and must exhibit negative serum or urine human chorionic gonadotropin test result within 72 hours prior to study enrolment. All male study participants with female partners of childbearing age will be required to use effective contraception throughout the study duration and for 3 months following study completion.

Patient exclusion criteria

Patients will not be eligible for inclusion if they meet any of the following criteria:

1. A history of prior or concurrent malignancies, with the exception of cured cases of cutaneous basal cell carcinoma or carcinoma in situ of the cervix.

2. A history of using other chemotherapeutic or immunosuppressive drugs to treat HCC, including but not limited to toripalimab, atezolizumab, sintilimab, pembrolizumab, tislelizumab, nivolumab, adriamycin and S-1.

3. Previous radiotherapy, TACE or systemic treatment within the past 6 months.

4. Evidence of congenital or acquired immunodeficiency disorders, including HIV positivity.

5. A known severe allergy to PD-1 monoclonal antibody treatment.

6. A temperature ≥38.5°C or a white cell count ≥15×10^9/L of undetermined aetiology within 7 days prior to study enrolment.

7. Patients diagnosed with combined bleeding disorders within 3 months of study enrolment including but not limited to moderate/severe gastro-oesophageal varices, gastrointestinal bleeding, bleeding gastric ulcers, haemoptysis (>2.5 mL/day). In cases where patients exhibit positive faecal occult blood test results, repeat
testing and gastroenteroscopy should be conducted as appropriate.

8. Individuals with a history of arterial or venous thrombotic events within 6 months prior to study enrolment, including deep vein thrombosis, pulmonary infarction or cerebrovascular accidents including cerebral ischaemia, cerebral infarction and transient ischaemic attack.

9. Patients with a history of active psychotropic drug or alcohol abuse or with diagnosed mental health disorders.

10. Women who are currently lactating.

11. Individuals with active or previously diagnosed autoimmune diseases including autoimmune hepatitis, interstitial pneumonia, uveitis, enteroclitis, hypophysitis, vasculitis, nephritis and hyperthyroidism.

12. Reported utilisation of immunosuppressive drugs or hormonal therapies within 2 weeks prior to study enrolment.

13. Most recent molecular-targeted therapy use (including but not limited to: sorafenib, erlotinib, lenvatinib, donafenib and regorafenib) for less than five drug half-lives or failure to recover from prior therapy-related adverse event (AE) to grade 1 of the common terminology criteria for AEs.

14. Individuals exhibiting combined hepatic encephalopathy or brain metastases.

15. Patients affected by hypertension not effectively controlled with medication (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mmHg).

16. Patients exhibiting uncontrolled heart disease or symptoms such as myocardial infarctions within the last 12 months, unstable angina, class II or higher cardiac function or supraventricular or ventricular arrhythmias necessitating treatment or intervention.

17. Patients with abnormal coagulatory function (INR >2.0, PT >16s), bleeding tendencies or a requirement for thrombolytic or anticoagulation therapy, but prophylactic use of low-dose aspirin or low-molecular weight heparin is permitted.

18. Patients with hereditary or acquired blood disorders (eg, haemophilia, thrombocytopenia or coagulation disorders).

19. Individuals with urinary protein levels ≥ ++ during routine urine and 24-hour urine protein levels≥1.0 g.

Study protocol
This is a multicentre single-arm phase II trial. Investigators will introduce the study to patients deemed eligible to participate based on the above criteria, after which informed consent forms (see online supplemental file 1) will be proffered. Those patients who provide written informed consent will be enrolled in the treatment group and will be assigned an independent study number for data collection and follow-up. Hepatectomy will be scheduled within 1 week of study enrollment, with apatinib and camrelizumab therapy being initiated 2–4 weeks later (figure 1).

Recruitment
In total, this study will enrol 62 patients from Guangxi Medical University Cancer Hospital and other hospitals. Recruitment began in November 2021 and is expected to end in November 2023.

Trial intervention
Patients who, following clinical evaluation, are considered to be able to tolerate hepatectomy will undergo curative liver tumour resection which is performed following the techniques described by Zhong et al,38 while intubated under general anaesthesia. The surgery will be started with an L-shaped laparotomy performed from the midabdominal line to the right subcostal area. Retractors were used to fully expose the liver lobe where the tumour was located. The location of liver tumours and the direction of blood vessels were accurately located through imaging localisation and intraoperative B-mode ultrasound. The incisal margin was more than 1 cm above the tumour envelope to ensure complete tumour resection. Both electrotome and mechanical blades will be used to reduce intraoperative bleeding when the liver parenchyma is removed by intermittently through the Pringle’s manoeuvre method. The fluid of intake and output volume, nutrient supply and corresponding anti-infection were closely observed after surgery. For patients with lymph node and abdominal metastases, lymph nodes should be removed intraoperatively if patients exhibit other target lesions that can be used to observe the efficacy of targeted and immunotherapeutic treatment. Otherwise, no further surgical interventions will be performed. At 2–4 weeks following surgery, patients will be administered camrelizumab (200 mg/dose, intravenous drip, once every 3 weeks) combined with apatinib (250 mg, per os, quaquedie/everyday) if their liver function has returned to Child-Pugh grade A. If not, medication will be postponed for a maximum of 2 months to await the return of normal liver function. If liver function fails to reach normal levels within this interval, patients will be discharged from the trial. Patients who withdraw from the trial will be obtained other follow-up treatment plan and appropriate humanistic care according to their actual conditions being assessed by clinicians. The treatment plan and clinical data of patients after withdrawal from the trial will not be included in the analysis of the results of this study.

Patients will undergo treatment of camrelizumab and apatinib for 2 years, or until disease progression or unacceptable toxicity manifest. When unacceptable toxicities are deemed to be apatinib-related by study investigators, the dosage can be reduced or discontinued as appropriate. However, no change in the camrelizumab dose will be permitted. If patients exhibit a grade ≥3 AE that is deemed by the investigator to be camrelizumab-related, this drug can be temporarily discontinued until the AE grade is ≤1. Camrelizumab may be suspended for a maximum of 3 weeks, and treatment can resume if symptoms recover during this interval. Otherwise, camrelizumab use will be
permanently discontinued. This drug will also be permanently discontinued if patients exhibit AEs exceeding the following levels, including but not limited to: grade 2 pneumonia, grade 2 or 3 diarrhoea or enterocolitis, grade 3 dermatitis, grade 2 AST or ALT or TBIL with a duration <7 days, grade 2 pituitary inflammation, grade 2 adrenocortical insufficiency, grade 2 hyperthyroidism, grade 3 hyperglycaemia; grade 2 or grade 3 creatinine elevation, grade 2 neurotoxicity, or other grade 3 AE first presentation.

**Evaluation and follow-up**

Patients will be screened to ensure that they meet eligibility criteria, after which informed consent will be taken. Demographic characteristics, previous medical history, history of medication use and physical examination will then be completed, including measurements of height, weight, temperature, respiration, blood pressure and heart rate. ECOG PS scores, liver function, renal function, blood counts, and thyroid function will also be evaluated.

Participants will undergo follow-up for a minimum of 24 months following the end of treatment, with follow-up being performed every 2–3 months until endpoint events are reached or the trial is completed. Follow-up will include: routine blood tests, liver function testing, adenocarcinoma marker panels: α-fetoprotein (AFP), it is a glycoprotein closely related to the malignant growth of tumours. Multiple studies have shown that the serum level of AFP is elevated in the vast majority of HCC patients, so it is also used as a specific tumour marker for HCC diagnosis and prognosis.

Figure 1. Study flow. DCR, disease control rate; DoR, duration of response; ORR, objective response rate; PFS, progression-free survival; TTR, time to response.
emission CT will additionally be performed in patients harbouring bone metastases.

**Study endpoints**

Patient OS is the primary endpoint for this study, and it is defined by the interval between hepatectomy and all-cause mortality. Secondary endpoints include PFS, ORR, DCR, DoR and time to response (TTR) of extrahepatic target lesions.

**Data collection**

The following data will be collected from patient medical records by a study assistant:

1. Gender and age.
2. Vital signs of parameters measured during routine physical examination, including height, weight, temperature, respiration, heart rate and blood pressure.
3. Medical and family history.
4. Personal history of smoking, alcohol intake, and medication usage.
5. Laboratory test results including haematological indices, kidney function indices, liver function indices, thyroid function indices and cancer-related indicators.

6. Results of imaging tests including liver MRI/CT scans, chest CT scans, isotope bone scans, liver ultrasound and ECG results.

7. Schedule of assessments is detailed in table 1.

**Statistical methods**

**Sample size estimation**

The 2-year OS rate for advanced HCC patients with Child-Pugh grade A liver function in the RESCUE trial that underwent first-line treatment with camrelizumab and apatinib was 43.3%. Among patients with HCC involving macrovascular invasion, hepatectomy improved about 20% OS than TACE (1 year, 81% vs 68%; 3 years, 46% vs 22%; 5 years, 20% vs 5%). TACE or camrelizumab plus apatinib are palliative treatments for HCC. Given that the progression of intrahepatic lesions is the primary cause of mortality in individuals with advanced HCC, hepatectomy-mediated removal of intrahepatic lesions is expected to improve OS by a minimum of 20% to 63.3% at 2 years. Given the established 24-month enrolment and 24-month follow-up periods, the false-positive and false-negative error values for this trial were respectively set to 0.05 and 0.1, with 15% lost-to-follow-up, resulting in a calculated sample size of 62 patients.
Outcome measure analyses
A statistical analysis plan will be prepared based on the planned treatment scheme to analyse the resultant data, with the primary analytical methods being described below.

Endpoint measurement analysis
The main study goal is to determine whether a combination of targeted and ICI-based treatment can extend the survival of advanced HCC patients following the removal of the bulk of the immune-resistant intrahepatic tumour tissue. OS and PFS will be analysed with Kaplan-Meier curves, HRs and 95% CIs. Multivariate regression analyses will be used to identify factors that may influence patient prognosis based on those factors significant (p<0.05) in univariate analyses. All analyses will initially be performed on an intention-to-treat basis, followed by sensitivity analyses performed on a per-protocol basis. DCR, DoR, ORR and TTR will be compared with Fisher’s exact test. Safety outcomes will also be assessed. Parametric or non-parametric tests will be used for quantitative data, while Fisher’s exact probability test will be used for categorical data. A two-sided p<0.05 will be considered significant.

Interim analysis
An interim study analysis will be performed every 3 months following the beginning of recruitment, with study-related data being reported to an independent data monitoring committee. Reported data will include information pertaining to recruitment, case report form recovery rates, data quality, protocol deviations, patient dropout rates, patient characteristics, treatment, toxicity events and primary/secondary endpoint measures.

Terminal analysis
The trial will be completed within 24 months of patient recruitment, with final analyses being conducted after all patients have initiated treatment and undergone follow-up for a minimum of 24 months.

Patient and public involvement
Our study’s design, conduct, reporting or distribution strategies were not influenced by patients or the general public.

AEs and scheme adjustment

Adverse events
For this trial, AEs will include any of the following:
1. Any suspected adverse drug reactions.
2. All reactions due to drug overdose, abuse, allergy or toxicity.
3. Any apparently unrelated illnesses, including the exacerbation of pre-existing conditions.
4. Injuries or accidents, with a note being made regarding the resultant outcomes.
5. Any abnormalities detected on physical/physiological examination that require further investigation or clinical treatment.

6. Any hepatectomy, apatinib or camrelizumab-related complications.

All adverse medical events that occur between the time at which subjects sign the informed consent form and the last study visit will be classified as AEs, irrespective of whether these events are related to study treatment. When AEs occur, reasons for treatment cessation must be noted in detail in that patient’s case report form. All patients, including those exhibiting poor compliance, should continue to follow the study protocol unless they exit the trial. Following interruptions in trial therapies, investigators will determine an appropriate follow-up plan based on that patient’s current circumstances. Participants can exit the trial at any time without penalty, or can withdraw following investigator re-evaluation.

ETHICS AND DISSEMINATION

Research ethics approval
The study protocol, informed consent form and other submitted documents were reviewed and approved by the Ethics Committee of the Guangxi Medical University’s Affiliated Cancer Hospital (KS2022[124]).

Trial exit
All participants will be allowed to withdraw from the trial at any time without restrictions or may be asked to withdraw as investigators deem appropriate/necessary. The following reasons are causes for study withdrawal from the investigator’s perspective:
1. Unacceptable treatment-associated toxicity.
2. Any unforeseen events for which investigators do not recommend further treatment.
3. Serious violations of the study protocol, including non-compliance or repeated absences.
4. Elimination by the investigator for clinical reasons unrelated to study treatment.

Confidentiality
All patient documentation will be recorded and preserved in strict confidence in accordance with the Protection of Personal Data Act’s strong data security requirements (draft). Investigators are required to maintain secrecy for all materials not presented to the trial office, including screening lists. Complete trial records may be made available to regulatory inquiries or in extraordinary circumstances, provided the privacy of patients is protected. The Trial Office will ensure that all patient information remains strictly confidential, with no identifiable information being released to any third parties. The representatives of the Trial Office may access patient information as necessary for quality control objectives, provided patient privacy is protected.

Dissemination policy
After the trial or analysis, the results will be submitted to a peer-reviewed publication, and the paper will be compiled by the Trial Management Group, with copyright...
distribution chosen jointly by the Trial Management Group.

Contributors D-X and J-HZ conceived the study; JTH, J-HZ, JZ, WFF, LM, LQL and D-X collected and analysed the data; JTH and J-HZ drafted the manuscript; D-X and J-HZ revised the manuscript; all authors read and approved the final version to be published.

Funding This work was supported by the Specific Research Project of Guangxi for Research Bases and Talents (Guil022305057), the High-level innovation team and outstanding scholar program in Guangxi Colleges and Universities; ‘139’ projects for training of high-level medical science talents from Guangxi (G201903001).

Competing interests Jiangsu Hengrui Pharmaceutical Company Limited provided both the camrelizumab and apatinib used in the trial free of charge, with the patients covering all other expenditures.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any errors and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Jun Tao Huang http://orcid.org/0000-0002-6541-7371
Jian-Hong Zhong https://orcid.org/0000-0002-1494-6936

REFERENCES


Hepatectomy combined with apatinib and camrelizumab for CNLC stage IIIb hepatocellular carcinoma: a phase II trial protocol

INFORMED CONSENT FORM

Subject Name: __________________________
Contact address: _______________________
Contact number: _______________________
Name of Research Center: __________________
Researcher: ____________________________

Version number : 1.0
Release date: November 2021
INFORMED CONSENT FORM

Dear Mr/ Ms ________:

You are hereby invited to participate in a study entitled "Single-arm, multicenter clinical study of hepatectomy Sequential Carrilizumab and Apatinib in the treatment of Stage III hepatocellular carcinoma of CNLC. The aid program is Carrilizumab (200mg/ dose), full donation of 2 years or progression disease(PD), whichever appears. Apatinib mesylate Tablets (250mg/ tablet), free for two years or PD, whichever appears.

Before you participate in this study, please read this informed consent carefully and carefully make the decision whether to participate in this study. You can ask your research doctor/researcher about anything you are not clear about and ask him/her to explain it to you until you fully understand. You can discuss this with your family and friends before making the decision to participate in the study. Participation in this study is entirely up to you and your treatment will not be affected by your non-participation. If you are participating in another study, please inform your study physician or researcher.

I. Study background

Hepatocellular carcinoma (HCC) is the seventh most common form of cancer, and causes roughly 830,000 deaths annually. As early-stage HCC generally fails to exhibit any specific symptoms, patients are primarily diagnosed with this disease when it is already in a more advanced stage in China. Between 2003 and 2013, our group identified 6,241 patients with HCC in the Guangxi Medical University Cancer Hospital, with 54% of these patients exhibiting disease consistent with stage C Barcelona Clinic Liver Cancer Staging (BCLC). Similarly, studies conducted in Hong Kong (n = 3,856) and Italy (n = 5,183) have respectively reported stage C HCC patient proportions of 40% and 45%. The median survival of advanced BCLC stage C patients is just 4-6 months, even with optimal supportive treatment. Advanced HCC cases can be further stratified into those exhibiting macrovascular invasion (China liver cancer (CNLC) staging IIIa) and those regardless of tumor size and vascular invasion but exhibiting extrahepatic metastases (CNLC IIIb).
Molecular targeted drug-based treatment is currently recommended in many countries for patients with CNLC-IIIb HCC. However, the single-agent efficacy of these targeted therapeutics is generally reported to be relatively limited when used to treat advanced HCC, and patients generally exhibit unsatisfactory improvements in long-term prognostic outcomes.

Immune checkpoint inhibitor (ICI) use in patients with advanced-stage HCC has been a focus of growing interest in recent years owing to evidence of their efficacy in several solid tumor types. Patients that undergo ICI treatment in combination with targeted therapy have been reported to exhibit significantly improved overall survival (OS) and progression-free survival (PFS) relative to patients that underwent monotherapy treatment. The combined treatment of advanced HCC patients with levatinib and ICIs has also been shown to be associated with markedly improved OS relative to monotherapy. As such, combinations of targeted therapeutics and ICIs represent the most promising treatment options for advanced-stage HCC. Accordingly, the CFDA has approved the use of targeted drug apatinib and the PD-1 inhibitor camrelizumab as second-line treatment for HCC, and the effectiveness and safety of this combination therapeutic regimen when used as a first-line treatment for advanced HCC have also been confirmed.

Local progression of intrahepatic tumors is the leading cause of death for patients with advanced HCC, which is far more lethal than extrahepatic metastases. While hepatectomy is not recommended for CNLC-IIIb HCC patients under international guidelines, some retrospective evidence suggesting that patients with extrahepatic metastasis who undergo hepatic resection exhibit significantly improved outcomes relative to those who do not undergo surgical treatment, with this duration being significantly longer than that achieved by patients who do not undergo surgical treatment and are instead treated with combinations of targeted drugs and ICIs.

Given the above evidence, we hypothesize that surgical resection of intrahepatic tumors can benefit patients by reducing the tumor load and proinflammatory cytokine release.
After that, the combination of VEGF inhibitors and ICI immunotherapy can promote the shrinkage or regression of extrahepatic metastases and ultimately prolong the survival time of CNLC-IIIb HCC patients. As such, the present study protocol was formulated based on a combined regimen of apatinib plus camrelizumab as data from several studies have indicated that this combination is associated with the longest median survival time for treated patients. This study will prospectively enroll stage CNLC-IIIb HCC patients with extrahepatic metastases and which intrahepatic lesions are considered suitable for radical resection. Recruitment and analyses will be performed across multiple clinical centers in China with the goal of assessing the OS for these patients’ following treatment via hepatectomy in combination with apatinib plus camrelizumab and the PFS, objective response rate (ORR), disease control rate (DCR), duration of response (DoR), and time to progression (TTP) of extrahepatic lesions.

II. Research design and process

This study was carried out by the Affiliated Cancer Hospital of Guangxi Medical University, and 62 subjects were expected to be included. The study will run from November 2021 to November 2023.

i. Patient eligibility/exclusion criteria

(i) Patient eligibility criteria

a. Age: 18-75 years.

b. CNLC stage IIIb HCC with extrahepatic metastases including lymph node, bone, and lung metastases, but excluding brain metastases, as diagnosed via clinical imaging based on the Liver Imaging Reporting and Data System.

c. Patients are considered candidates for the curative hepatic resection of local liver tumors.

d. Liver function: Grade A Child-Pugh score.

e. Indo-Cyanine Green retention value: 15 min (ICG R15) <10%.

f. Eastern Cooperative Oncology Group-Performance status (ECOG-PS): 0 or 1.

g. Expected survival duration: ≥ 6 months[39].

h. Hematological indexes that do not exceed the following thresholds: hemoglobin ≥ 90 g/L; absolute neutrophil count ≥ 1.5 x 10⁹/L; platelets ≥ 80 x 10⁹/L; total bilirubin ≤ 1.5x
the upper limit of normal (ULN); alanine transaminase (ALT) < 3x ULN; aspartate aminotransferase (AST) < 3x ULN or less; alkaline phosphatase (AKP) ≤ 2.5x ULN; serum albumin ≥ 28 g/L; serum creatinine ≤ 1.5 x ULN.

i. Patients do not wish to go through radiotherapy or transcatheter arterial chemoembolization (TACE). Based on the recommendation of CNLC guideline, radiotherapy and TACE are also recommended for patients with CNLC stage IIIb HCC[7].

j. All women of childbearing age will be required to utilize contraception (e.g., condoms, contraceptive pills, or intrauterine devices) for the duration of the trial and for 3 months following trial completion and must exhibit negative serum or urinary urine human chorionic gonadotropin (HCG) test result within 72 hours prior to study enrollment. All male study participants with female partners of childbearing age will be required to utilize effective contraception throughout the study duration and for 3 months following study completion.

(ii) Patient exclusion criteria

Patients will not be eligible for inclusion if they meet any of the following criteria:

a. A history of prior or concurrent malignancies, with the exception of cured cases of cutaneous basal cell carcinoma or carcinoma in situ of the cervix.

b. A history of using other chemotherapeutic or immunosuppressive drugs to treat HCC, including but not limited to toripalimab, atezolizumab, sintilimab, pembrolizumab, tislelizumab, nivolumab, adriamycin, and S-1.

c. Previous radiotherapy, TACE, or systemic treatment within the past 6 months.

d. Evidence of congenital or acquired immunodeficiency disorders, including HIV positivity.

e. A known severe allergy to PD-1 monoclonal antibody treatment.

f. A temperature ≥ 38.5°C or a white blood cell count >15 x 10⁹/L of undetermined etiology within 7 days prior to study enrollment.

g. Patients diagnosed with combined bleeding disorders within 3 months of study enrollment including but not limited to moderate/severe gastro-esophageal varices, gastrointestinal bleeding, bleeding gastric ulcers, hemoptysis (> 2.5 mL/day). In cases where patients exhibit positive fecal occult blood test results, repeat testing and
gastroentoscopy should be conducted as appropriate.

h. Individuals with a history of arterial or venous thrombotic events within 6 months prior to study enrollment, including deep vein thrombosis, pulmonary infarction, or cerebrovascular accidents including cerebral ischemia, cerebral infarction, and transient ischemic attack.

i. Patients with a history of active psychotropic drug or alcohol abuse or with diagnosed mental health disorders.

j. Females who are currently lactating.

k. Individuals with active or previously diagnosed autoimmune diseases including autoimmune hepatitis, interstitial pneumonia, uveitis, enterocolitis, hypophysitis, vasculitis, nephritis, and hyperthyroidism.

l. Reported utilization of immunosuppressive drugs or hormonal therapies within 2 weeks prior to study enrollment.

m. Most recent molecular targeted therapy use (including but not limited to: sorafenib, erlotinib, lenvatinib, donafenib, and regorafenib) for less than 5 drug half-lives or failure to recover from prior therapy-related adverse event (AE) to grade 1 of the common terminology criteria for adverse events.

n. Individuals exhibiting combined hepatic encephalopathy or brain metastases.

o. Patients affected by hypertension not effectively controlled with medication (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg).

p. Patients exhibiting uncontrolled heart disease or symptoms such as myocardial infarctions within the last 12 months, unstable angina, class II or higher cardiac function, or supraventricular or ventricular arrhythmias necessitating treatment or intervention.

q. Patients with abnormal coagulatory function (INR > 2.0, PT > 16s), bleeding tendencies, or a requirement for thrombolytic or anticoagulation therapy, but prophylactic use of low-dose aspirin or low-molecular-weight heparin is permitted.

r. Patients with hereditary or acquired blood disorders (e.g., hemophilia, thrombocytopenia, or coagulation disorders).

s. Individuals with urinary protein levels ≥ ++ during routine urine and 24-hour urine protein levels ≥ 1.0 g.
ii. Screening treatment period

If you decide to participate in the study, in order to determine your eligibility for inclusion in the study, you will be required to provide basic information and prior history, and to undergo, but not limited to, the following tests and evaluations at the hospital, which are routine medical examinations and will not cost you additional treatment. The specific examination content required is determined by the clinician. Basic information collection and medical examination are as follows:

a. Basic information (including date of birth, age, gender, ethnicity, etc.)

b. Physical examination, vital signs (blood pressure, heart rate, respiration, etc.), ECOG score

c. Tumor history (clinical/pathological diagnosis, clinical/pathological staging, EGFR/ALK mutation, PD-L1, etc.)

d. Previous medical history, treatment history, food and drug allergies

e. Blood routine examination, blood biochemical examination, coagulation function examination

f. Urine routine examination, stool routine examination and occult blood examination

g. Tumor marker examination (routine package or quantitative protein chip detection)

h. Thyroid function examination and pituitary function examination (according to your actual needs)

i. Virological examination (HBV, HCV, HIV, TP, HPV, EBV, etc.)

j. Imaging examination (such as chest and abdomen CT, brain MRI, etc.)

k. Electrocardiogram or cardiac color ultrasound

The treatment plan after enrollment, including the specific dosage and cycle of the drug, should be formulated by the clinician according to the drug instructions. At the same time, the specific examination items and cycle, please follow the doctor's advice.

During the entire study period, you will be required to actively cooperate with the relevant researchers. The study doctor will truthfully inform you of your medication status, combination of medications, and symptoms of discomfort during this period. At the same time, it's important to keep in touch with the study physician so you can determine how well the drug is working for the patient. If a serious adverse event occurs during the study,
the study physician will refer you to the hospital for follow-up tests, even if the patient has completed a routine study visit.

iii. Ending treatment
When you plan to end study treatment, you will need to complete a follow-up visit to the hospital. Your study physician will discuss with you the next course of treatment or the best supportive treatment based on your physical state.

iv. Follow-up
The follow-up period consisted of two stages: safety follow-up and survival follow-up. Safety follow-up was 24 months after the last dose. If you start a new antitumor therapy during the safety follow-up period, the study physician will only collect adverse reactions and drug combinations associated with the study drug after starting a new antitumor therapy. Follow-up will be conducted by telephone contact, and the study physician will add additional visits as needed for actual adverse event follow-up, with the goal of tracking adverse event remission.

When you stop taking medication, you will enter the survival follow-up period, and we will follow up your follow-up situation. During the follow-up period, we will call you, your family members or local doctors at least once every 3 months to collect the information after the study treatment and record it in detail in the follow-up form. We hope you can continue to cooperate with us.

v. Confidentiality and privacy authorization
Your health information is protected by the relevant laws of China. By signing this informed consent, you consent to the collection and use of your health information data by the investigator, the research authority and the ethics Committee. In addition, the sponsor will strictly protect your privacy during the audit, inspection and audit process.

III. Risks, benefits, and adverse reactions
i. Possible risks
Participating in this study will not increase your risk beyond the usual treatment. The adverse drug reactions observed in early clinical studies of carrilizumab mainly included: skin and subcutaneous tissue diseases: reactive cutaneous capillary hyperplasia, pruritus, and rash; Abnormal liver function: increased aspartate aminotransferase, alanine
aminotransferase, bound bilirubin, blood bilirubin; Hematologic toxicity: anemia, low white blood cell count, low neutrophil count; Systemic symptoms: fatigue, fever; Gastrointestinal AE: nausea, diarrhea; Diseases of respiratory system, chest and mediastinum: cough, upper respiratory tract infection; Metabolic and nutritional diseases: hypoproteinemia, decreased blood sodium, decreased appetite; Renal and urinary diseases: albuminuria; Endocrine system diseases: hypothyroidism and other adverse reactions.

Common adverse reactions in clinical studies of Apatinib mesylate tablets included: the most common adverse reactions were hypertension (69.5%), albuminuria (47.8%), and hand-foot syndrome (45.6%). Other common adverse events include hematologic toxicity (leukopenia, granulocytopenia, thrombocytopenia, etc.) and non-hematologic toxicity (abnormal liver function, fatigue, gastrointestinal reactions, oral ulcers, rashes, skin hemorrhages, nervous system damage, etc.). You may experience changes similar to those described above, or you may experience some unknown adverse reactions that have not yet occurred.

Since the RESCUE study (Phase II) reported the efficacy of Apatinib combined with carralizumab in first-line (n= 70,68.6% CNLC IIIb) and second-line (n= 140,75.8% CNLC IIIb) treatment for advanced HCC, the objective response rates were 46% and 25%, respectively. The 2-year overall survival rates were 43% and 45%, respectively, and the median survival time was 20.1 and 21.8 months, respectively, so some patients may be at risk of disease progression.

If you develop any discomfort during the study period, or if your condition changes, or if anything unexpected happens, whether or not it is related to the study, you should inform your doctor promptly, and he/she will judge and take appropriate medical care. Since the drug is investigational, you must understand that there may be unknown side effects and that you may experience side effects that have not been previously reported. So, you must inform your doctor or one of the researchers of any new symptoms. During the study, any new and meaningful information will be provided to you as it becomes available, which may influence your decision to continue to participate in the study. During the study period, you need to visit the hospital on time and do some examinations, which will take up some of your time and may cause you trouble or inconvenience. We hope that you will
follow the doctor's advice during the study, actively cooperate with treatment, and accept observation and follow-up in accordance with the requirements of the experimental protocol.

ii. Possible benefits
This clinical study does not guarantee that you will achieve the desired clinical effect, but may contribute to the treatment of this tumor and may stop/slow the progression of the tumor. Participating in this study, you will benefit from:
(i). Through this clinical trial, it is possible to improve the quality of life and prolong the survival time;
(ii). Understand effective treatment methods and receive treatment;
(iii). Receive scientific and professional clinical guidance through medical attention;
(iv). Close follow-up by professional medical team.

iii. Possible adverse reactions (see instructions for details)
You may experience an adverse reaction similar to the one described in the drug label, or you may experience an adverse reaction that has not yet occurred. The treatment costs arising from the above adverse reactions will be borne by you. For the occurrence of adverse reactions, your attending doctor will follow up with you regularly, guide rational drug use and give corresponding plans to deal with adverse reactions. At the same time, he will also pay close attention to the therapeutic effect of the drugs you take. We hope that you will follow the doctor's advice during the study, actively cooperate with treatment, and accept observation and follow-up in accordance with the requirements of the experimental protocol.

IV. Voluntary participation
Please note that we cannot make promises about the results. Participation in this study is entirely out of your own will. You have the right to refuse to participate in this study or withdraw from the study at any time without discrimination, and your medical treatment and rights will not be affected.

V. Research expenses and financial compensation
The relevant medical examination you have done is a routine clinical item, therefore, the expenses of transportation and examination during the treatment, combined with the
expenses of treatment and examination required for other diseases, should be borne by you.

This informed consent is made in duplicate, with one copy for the subject and one copy for the researcher. It is valid after being signed by both parties.
Informed consent
Consent signature page

As a subject, I have read the above information and understand the purpose of the study and the potential risks and benefits associated with participating in the study. All my questions about the procedure and content of the study have been answered to my satisfaction. I voluntarily signed this informed consent form and volunteered to participate in the study.

Subject's signature: Date of Signature:
Contact information:
Signature of guardian:(if necessary) Date of signature: (if necessary)
Contact information:
Signature of witness:(if necessary) Date of signature:(if necessary)
Contact information:

As the researcher, I have read and explained the informed consent form to the subject and answered all his/her questions. He/she has personally understood and agreed to participate in the study.

Investigator signature: Date of Signature:
Contact information: