BMJ Open

Efficacy and safety of radiotherapy combined with atezolizumab plus bevacizumab in treating hepatocellular carcinoma with portal vein tumour thrombus: a study protocol

Kang Wang,[1] Hong-Ming Yu,[1] Yan-Jun Xiang,[1] Yu-Qiang Cheng,[1] Qian-Zhi Ni,[1,2] Wei-Xing Guo,[1] Jie Shi,[1] Shuang Feng,[3] Jian Zhai,[3] Shu-Qun Cheng [1]

To cite: Wang K, Yu H-M, Xiang Y-J, *et al*. Efficacy and safety of radiotherapy combined with atezolizumab plus bevacizumab in treating hepatocellular carcinoma with portal vein tumour thrombus: a study protocol. *BMJ Open* 2022;**12**:e064688. doi:10.1136/bmjopen-2022-064688

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-064688).

Received 18 May 2022
Accepted 27 September 2022

[1]Department of Hepatic Surgery VI, Eastern Hepatobiliary Surgery Hospital, Shanghai, China
[2]Shanghai Institute of Nutrition and Health, University of Chinese Academy of Sciences, Shanghai, China
[3]Department of Radiotherapy, Eastern Hepatobiliary Surgery Hospital, Shanghai, China

Correspondence to
Dr Shu-Qun Cheng;
chengshuqun@smmu.edu.cn

ABSTRACT

Introduction Vascular invasion and metastasis are poor prognostic factors in patients with hepatocellular carcinoma (HCC). The efficacy of available therapeutic regimens for unresectable HCC is not satisfactory in HCC with portal vein tumour thrombosis (PVTT). Therefore, this open-label, single-arm phase II clinical trial aims to investigate the efficacy and safety of radiotherapy combined with atezolizumab plus bevacizumab in treating HCC patients with PVTT.

Methods and analysis We plan to enrol patients diagnosed with unresectable HCC complicated by PVTT. Intensity-modulated radiotherapy (IMRT) combined with atezolizumab plus bevacizumab will be administered for treatment. Patients will initially receive radiotherapy, with each IMRT cycle lasting for 28 days and the total dose of tumour (DT) of 40 Gy/20 f/26 d. CT scan will be performed again, and the treatment plan will be reformulated after field constriction. The treatment will continue until the total DT is up to 54–56 Gy/27–28 f. The treatment with atezolizumab plus bevacizumab will be started at 3±1 days after the initiation of radiotherapy and will continue until unacceptable toxicity or disease progression. The primary endpoint is objective response rate (ORR), while the secondary endpoints include overall survival, disease control rate, progression-free survival, time to progression, duration of response and the rate of surgical conversions. Assuming an ORR of 47%, with a two-sided alpha error of 0.1, 90% power, and a 10% drop-out rate, the required number of evaluable patients is 42.

Ethics and dissemination This study will be conducted according to the standards of Good Clinical Practice and in compliance with the principles of the Declaration of Helsinki. The Ethics Committee of our Hospital has approved the protocol (EHBHKY2021-K-017). All participants are required to provide written informed consent. The results of the trial will be published in peer-reviewed journals and presented at international conferences.

Trial registration number ChiCTR2100049831.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study was a single-arm trial without a control group.
⇒ This study is an exploratory trial with a small sample size.
⇒ The conclusions of this study may serve as preliminary evidence for subsequent large-scale, randomised, controlled clinical trials.

INTRODUCTION

Liver cancer is the seventh most common cancer and the second most deadly cancer, with more than 900 000 new cases being diagnosed worldwide every year.[1] In China, the age-standardised annual incidence of liver cancer is about 26.67/100 000,[2] while the 5-year survival rate is only around 12%.[3] Hepatocellular carcinoma (HCC) is the most common histological subtype of primary liver cancer,[4] and surgery is the preferred and most efficacious approach for the treatment of HCC. However, some patients lose the chance for surgery at the time of diagnosis due to their intermediate to advanced tumours, liver dysfunction, etc.[5] Local therapies (including radiotherapy) and systemic therapies are important options for prolonging the survival of HCC patients who cannot undergo surgical resection. Due to the promising antitumour activity and favourable safety profile in the IMbrave150 trial, with the mortality risk being decreased by 42% compared with sorafenib,[6] atezolizumab plus bevacizumab have become the standard first-line therapy for unresectable HCC. Yet, the objective response rate (ORR) with atezolizumab plus bevacizumab in unresectable HCC patients was reported to be only 27.3%.[6] Hence, improving the therapeutic effect in patients is still a great clinical challenge.

Vascular invasion and metastasis are commonly seen in patients with intermediate to advanced-stage HC, as 44%–62%

of patients with advanced HCC have been reported to develop portal vein tumour thrombosis (PVTT).[7] In addition, the range and severity of PVTT have been significantly associated with the prognosis of unresectable HCC patients, with the median overall survival being just 2.7–4 months in naive HCC patients with PVTT.[8] However, there are significant differences between eastern and western countries in the treatment strategies used for HCC patients with PVTT.[9] Guidelines from western countries argue that HCC complicated with PVTT represents the advanced stage of HCC, advocating sorafenib as the only treatment option.[10–12] On the contrary, eastern countries adopt positive strategies, such as surgical resection, radiotherapy, transcatheter arterial chemoembolisation and surgery combined with multidisciplinary therapies, which are expected to improve the long-term survival of these patients.[13–16]

Radiotherapy is recommended for unresectable HCC patients with types I, II and III PVTT, whose liver function is graded as Child-Pugh A and B. In addition, previous studies have shown that radiotherapy can synergistically enhance the antitumour effect of immunotherapy and targeted therapy by changing the tumour microenvironment.[17 18] At present, radiotherapy combined with immunotherapy and targeted therapy is currently one of the dominant research topics within the tumour area. A number of studies have also suggested that radiotherapy combined with sorafenib alone improves OS in patients with HCC complicated by PVTT,[19] and the feasibility of concurrent radiotherapy and sorafenib.[20 21] In addition, the results of a previous retrospective study showed that radiotherapy combined with atezolizumab plus bevacizumab was feasible in unresectable HCC.[22] However, whether the combination of radiotherapy and immunotherapy plus targeted therapy can improve the efficacy in patients with HCC complicated by PVTT needs to be further verified.

Therefore, we proposed an open-label, multicentre, single-arm phase II clinical trial. Patients diagnosed with locally advanced or metastatic and/or unresectable HCC complicated with PVTT will be preliminarily enrolled to explore the efficacy and safety of radiotherapy combined with atezolizumab plus bevacizumab, which is expected to provide an efficacious therapeutic regimen for HCC patients with PVTT and further improve the treatment response and prognosis. Here, we present the protocol in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) reporting checklist.

METHODS AND ANALYSIS

Study design and objective

This open-label, multicentre, single-arm clinical trial will enrol patients diagnosed with locally advanced or metastatic and/or unresectable HCC complicated with PVTT from the departments of hepatobiliary surgery of our Hospitals between August 2021 and December 2021 so as to initially exploring the efficacy and safety of radiotherapy combined with atezolizumab plus bevacizumab in naive patients with unresectable HCC complicated by PVTT.

Eligibility criteria

The inclusion criteria are as follows:

1. Men or non-pregnant women aged 18–70 years. 2. Sign the informed consent. 3. The investigator believes that the patient has the ability to comply with the research protocol. 4 HCC is diagnosed by histology or cytology or clinically. Patients with liver cirrhosis are clinically diagnosed by the American Association for the Study of Liver Diseases (AASLD) criteria, and patients without liver cirrhosis need to be diagnosed by histology. ; (5) Imaging examination confirmed the existence of PVTT; (6) The disease is not suitable for radical surgery. 7. Have not received any antitumour therapy before. 8. At least one measurable (measurable according to Response Evaluation Criteria In Solid Tumours (RECIST V.1.1)), untreated lesions. 9. Pretreatment tumour tissue samples (if available). If tumour tissue is available, submit 1 formalin-fixed, paraffin-embedded (FFPE) tumour sample in a paraffin block (preferred) or approximately 10–15 slides containing unstained, freshly cut, serial sections radiographs, together with a relevant pathology report within 4 weeks of enrolment. If the FFPE samples described above are not available, any type of sample (including fine needle aspiration biopsy samples, cell mass samples (eg, from pleural effusions) and lavage samples) is acceptable. A relevant pathology report should be provided with the sample. If tumour tissue was not available (eg, exhausted due to previous diagnostic testing), the patient was still eligible to participate in the study. 10. ECOG performance status score of 0 or 1 within 7 days before enrolment. 11. Child-Pugh Grade A within 7 days before enrolment. 12. Adequate haematology and organ function, based on the following laboratory test results obtained within 7 days prior to enrolment (unless otherwise stated): (1) absolute neutrophil count $\geq 1.5\times10^9$/L (1500/μL), without granulocyte colony-stimulating factor support; (2) lymphocyte count $\geq 0.5\times10^9$/L (500/μL); (3) platelet count $\geq 75\times10^9$/L (75 000/μL), no blood transfusion; haemoglobin ≥90 g/L, in order to meet this criterion, blood transfusion is allowed to the patient; (4) alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase ≤5 times the upper limit of normal (ULN); (5) serum bilirubin ≤3 times the ULN; (6) serum creatinine ≤1.5 times the ULN or calculated creatinine clearance ≥50 mL/min (calculated using the Cockcroft-Gault formula); (7) serum albumin ≥28 g/L (2.8 g/dL); (8) patients not receiving anticoagulation therapy: international normalised ratio or activated partial thromboplastin time ≤2 times the ULN; (9) proteinuria <2+ in urine cellulose test strip (performed within 7 days before the initiation of study treatment); (10) [atients with a baseline cellulose dipstick urine test result of ≥2+ proteinuria should collect 24-hour urine, and then must confirm that the urine protein content within 24 hours is less than 1 g. 13. Any acute, clinically significant treatment-related toxicity (due to previous treatment) must have been alleviated to ≤grade 1 before enrolling in

the study, except for alopecia; 14. HIV antibody test results are negative at the time of screening; 15. Patients with active hepatitis B virus (HBV) infection: HBV-DNA <500 IU/mL obtained within 28 days before the start of study treatment and received anti-HBV treatment for at least 14 days before entering the study (treatment according to local standard treatment, such as entecavir) and are willing to continue receiving treatment during the study; 16. Women of childbearing age must have a negative pregnancy test before starting treatment, and women of childbearing age and men (having sex with women of childbearing age) must agree to use without interruption during treatment and for 6 months after the last therapeutic dose is administered to be effective contraception.

The exclusion criteria are as follows:

1. History of leptomeningitis. 2. Current or past autoimmune disease or immunodeficiency, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener's granulomatosis, Sjgre's syndrome, Guillain-Barré syndrome or multiple sclerosis, with the following exceptions: patients with prior autoimmune-related hypothyroidism receiving thyroid hormone replacement therapy are eligible for study participation; patients receiving insulin therapy patients with controlled type 1 diabetes were eligible for study participation; only patients with dermatologically manifested eczema, psoriasis, chronic lichen simplex or vitiligo (eg, excluding patients with psoriatic arthritis), provided All of the following conditions are eligible to participate in the study: (1) The rash area must be less than 10% of the body surface area; (2) Good disease control at baseline, requiring only low-efficiency topical glucocorticoid therapy; (3) In the past 12 months, the pre-existing conditions did not require psoralen plus A-band UV radiation, methotrexate, vitamin A acid, biological agents, oral calcineurin inhibitors or highly effective or acute exacerbations of oral glucocorticoid therapy. 3. Idiopathic pulmonary fibrosis, organising pneumonia (eg, bronchiolitis obliterans), drug-induced pneumonia or idiopathic pneumonia or evidence of active pneumonia on chest CT images during screening. Radiation pneumonitis in the permissible radiation zone (fibrosis). 4. Known active tuberculosis. 5. Major cardiovascular disease within 3 months prior to initiation of study treatment (such as New York Heart Association class II or more severe heart disease, myocardial infarction or cerebrovascular accident within 3 months prior to initiation of study treatment), unstable Arrhythmia or unstable angina. 6. History of congenital long QT syndrome or corrected QT interval at screening >500 ms (calculated using Fridericia method). 7. History of uncorrectable serum potassium, calcium or magnesium electrolyte disturbances. 8. Received major surgery (except for diagnosis) within 4 weeks before starting the study treatment or is expected to undergo major surgery during the study period. 9. Malignant tumours other than HCC within 5 years prior to screening, except for malignancies with negligible risk of metastasis or death (eg, 5 year OS rate >90%), such as adequately treated in situ cervical cancer, non-melanoma skin cancer, localised prostate cancer, ductal carcinoma in situ or stage I uterine cancer. 10. Severe infection within 4 weeks prior to initiation of study treatment, including but not limited to hospitalisation due to complications of infection, bacteraemia or severe pneumonia. 11. Oral or intravenous therapeutic antibiotics within 2 weeks prior to initiation of study treatment. Patients receiving prophylactic antibiotics (eg, to prevent urinary tract infections or exacerbations of chronic obstructive pulmonary disease) are eligible to participate in the study. 12. Previous allogeneic stem cell or solid-organ transplantation. 13. Received a live attenuated vaccine within 4 weeks before starting study treatment, or is expected to receive such a vaccine during atezolizumab treatment or within 5 months after the last dose of atezolizumab. 14. Patients with untreated or incompletely treated oesophageal and/or gastric varices with associated bleeding or at high risk of bleeding. Before enrolment, patients must undergo B-ultrasound, CT, MRI or liver elastography to assess the size of all varicose veins (small to large) and treat according to local standard of care. Patients who have received corresponding examinations within 6 months before starting study treatment do not need to be reexamined. 15. Coinfection with HBV and hepatitis C virus (HCV). Patients with a history of HCV infection but negative PCR results for HCV RNA can be considered HCV uninfected. 16. Symptomatic, untreated or progressively progressive central nervous system (CNS) metastases. Asymptomatic patients with treated CNS lesions were eligible for study participation as long as all of the following criteria were met: Must have disease outside the CNS measurable according to RECIST V.1.1; patients had no history of intracranial or intraspinal haemorrhage; metastases limited to the cerebellum or supratentorial (ie, no midbrain, pons, medulla or spinal cord metastases); no evidence of progression between completion of CNS-directed therapy and initiation of study treatment; patients not receiving stereotaxic within 28 days prior to initiation of study treatment Targeted, whole-brain radiotherapy and/or neurosurgical resection; patients did not require continuous glucocorticoid therapy for CNS disease. Dose-stabilised anticonvulsant therapy is permitted. Asymptomatic patients with newly detected CNS metastases at screening are eligible to participate in the study after radiotherapy or surgery without repeat screening brain scan results. 17. The patient cannot receive follow-up or is participating in other clinical trials. 18. Subjects deemed unsuitable for inclusion in this study by the investigator.

Treatment plan

Patients will initially receive intensity-modulated radiotherapy (IMRT) with each cycle for 28 days. A treatment plan will be established after CT location. The clinical target volume includes tumours and tumour

thrombi. The planning target volume will be expanded by 0.5–1.0 cm, with conventional fractionation at a single dose of 180–220 cGy. Total DT will be 40 Gy/20 f/26 d. CT scan will be performed at the end of every cycle, and the treatment plan will be reformulated after field constriction. The treatment will continue until the total DT is up to 54–56 Gy/27–28 f.

The treatment with atezolizumab plus bevacizumab will be started at 3±1 days after the initiation of IMRT. Each treatment cycle will last for 21 days. On the first day of each cycle, atezolizumab injection will be intravenously administered at a fixed dose of 1200 mg (initial intravenous injection for 60 min, and subsequent intravenous injections for 30 min if well tolerated). Bevacizumab at a dose of 15 mg/kg will be intravenously administered at least 5 min apart (initial intravenous injection for 90 min, and subsequent intravenous injections reduced to 60 min and 30 min if well tolerated). The treatment was discontinued when there was no additional clinical benefit, as judged by the investigator (based on imaging, biochemical indicators and clinical status of the patient). Then, the patient received the guideline-recommended second-line therapy.

Delayed treatment or dose reduction will be determined by the clinical team, and the specific adjustment plan will be determined by the investigator based on the patient's clinical condition. In case of severe toxicity, the administration will be delayed, and/or the dose will be reduced. If any serious adverse event (SAE) occurs during the radiotherapy, or the radiotherapy is delayed for more than 4 weeks for any reason, radiotherapy sessions will be terminated. The doses of atezolizumab and bevacizumab will be adjusted according to the drug's instructions.

Endpoints

The primary endpoint is ORR, which is defined as the proportion of patients with complete response (CR) and partial response (PR). CR or PR is assessed in accordance with RECIST V.1.1. The responses will be independently evaluated by 3–6 experienced senior physicians who are not investigators in this study.

Secondary endpoints include (1) OS defined as the time between the first study treatment and death (for any reason). (2) Disease control rate (DCR), defined as the percentage of subjects with the best response as CR, PR or stable disease (SD). (3) Progression-free survival (PFS), defined as the time between the first treatment and the first tumour progression or appearance of a new lesion or death due to any cause, whichever occurs first. (4) Time to progression (TTP), defined as the time between the first treatment to first tumour progression. (5) Duration of response (DOR), defined as the time from first tumour remission to first tumour progression or death due to any cause. The DCRs, PFSs, TTPs and DORs will be calculated in accordance with the RECIST V.1.1, modified RECIST (mRECIST), and immune-modified RECIST (imRECIST), respectively. (6) The rate of surgical conversions is defined as the proportion of subjects who receive the study treatment and are assessed to be viable for surgical resection. The resectability criteria include successful downstaging of the tumour, sufficient future liver remnant, and technically resectable assessed by the investigator. The definition of successful downstaging was based on the CSCO guideline, which was (1) stage Ia, Ib and IIa, (2) IIb, if the tumour is confined to the same segment or the same side of the liver or intraoperative radiofrequency ablation can be performed at the same time to treat the lesions outside the resection range and (3) IIIa/b, if the tumour is confined to the hemiliver, and it is expected that the tumour thrombus can be completely removed during the operation, surgical resection of the tumour and thrombectomy through the portal vein can be considered.

AEs are assessed in accordance with the NCI Common Terminology Criteria for Adverse Events (CTCAE V.5.0). Monitoring will be performed from the date on which the patient signs the informed consent to 90 days after the last treatment.

Biomarkers for exploratory endpoints include metagenomic sequencing of faecal organisms, five gene indexes of HCC (HN1, RAN, RAMP3, KRT19, TAF9), immune correlation detection (programmed death-ligand 1 (PD-L1) expression, CD8 expression; microsatellite instability (MSI), and tumour mutational burden (TMB), immune-related gene expression, RNA-seq) and other checkpoint proteins and cell surface markers.

Participant timeline

Table 1 lists the time points for assessing efficacy, AEs, laboratory safety assessments (haematology, coagulation and chemistry), physical examination, ECG and tumour measurements.

Furthermore, for the testing of biomarkers as exploratory endpoints, stool and blood samples will be collected from patients prior to the first treatment, at 7 weeks after the first treatment, and after treatment discontinuation, respectively.

Data collection and management

The completed CRFs will be submitted to the respective sites for archiving. All data will be recorded in an electronic case report form (eCRF) by investigators or clinical research coordinators. All study documents will be confidential. All study data, including confirmation of all patients (effective check on recorded information, such as study cases), all original copies of signed ICFs, as well as detailed original records of drug distribution, shall be kept uniformly by the study institution until 5 years after the end of the trial.

Statistical methods

According to the results of IMbrave150,[6] the ORR of atezolizumab plus bevacizumab in unresectable HCC patients was 27.3%. The lack of evidence of atezolizumab, bevacizumab and radiotherapy in patients with HCC and PVTT led to the difficulty of an evidence-based

Table 1 Schema of single-arm clinical trial

	Screening period		Treatment period				End of trial	Survival follow-up
Item	−28 to 0 days	−7 to 0 days	4 weeks after the first treatment session	7 weeks after the first treatment session	n cycles	Perioperative period	30 days after checkout	
Window period (days)	— —	— —					±7	
Informed consent	×							
Demographics Medical history History of tumour treatment	×							
Physical examination		×	×	Every 3 weeks		×	×	
Vital signs		×	×	Every 3 weeks		×	×	
ECOG		×	×	Every 3 weeks ×			×	
Pregnancy test		×					×	
Infection screening	×						×	
Imaging	×		×	Every 6 weeks			×	×
Tumour markers		×	×	Every 6 weeks			×	
Echocardiography	×						×	
Tumour tissue	×							
12-lead ECG		×	When clinically indicated				×	
Blood biochemistry		×	×	Every 3 weeks			×	
Routine blood test		×	×	Every 3 weeks			×	
Routine urine test		×	×	Every 3 weeks			×	
Routine stool test		×	×	Every 3 weeks			×	
Thyroid function, pituitary function, coagulation		×	×	Every 3 weeks			×	
Gut microbiome testing for the stool sample		×		×			×	
Biomarker testing for the blood sample		×		×			×	
Surgical resection						×		
Surgical complications						×		
Concomitant medication	×	×	×	Every 3 weeks			×	
Adverse events	×	×	×	Every 3 weeks			×	
Compliance evaluation	×	×	×	Every 3 weeks				
Dispensing of drugs			×	Every 3 weeks				
Recovery of drugs			×	Every 3 weeks			×	
Follow-up on survival status and antitumour treatment								×

estimated ORR. Instead, we searched for literatures of other systemic regimens combined with radiotherapy and found out the ORR was 61.1% in HCC patients with PVTT treated with sorafenib and MIRT in a retrospective study.[23] Hence, assuming an ORR of 47% after discussion among investigators based on the experience, with a two-sided alpha error of 0.1, 90% power, and 10% drop-out rate, the required number of evaluable patients is 42.

The efficacy assessment is based on the full analysis set (FAS). The intention-to-treat (ITT) efficacy analysis will be performed for subjects who received at least one session of the study treatment based on the FAS. No supplementation will be made for missing values. The safety analysis set includes all enrolled subjects who have received at least one session of study treatment and have a post-treatment safety record. This dataset will be used for safety analysis.

Monitoring

An independent Data and Safety Monitoring Committee has been established to assess the safety data if SAEs occur. Any AEs will be registered. A qualified and independent auditor is appointed to audit the trial systems, and the audit will be conducted before and during the study following a written procedure. The stopping rules for the trial are 1) the investigators find serious safety issues, or 2) the administrative department cancels the trial. The termination of the trial can be temporary or permanent. When terminating the trial, all records will be kept for future reference.

Patient and public involvement

The patients and general public were not involved in the trial design.

DISCUSSION

Atezolizumab plus bevacizumab is the standard first-line therapy for unresectable HCC patients. Although the combination can significantly improve the prognosis in patients, the ORR is still not satisfactory.[6] Improving the therapeutic effect in patients is still a great clinical challenge. For patients with HCC, vascular invasion and metastasis are important reasons these patients cannot undergo surgical resection, as well as poor prognostic factors. Radiotherapy has an important role in treating patients with PVTT; however, the therapeutic effects are still limited. Previous clinical studies have shown that radiotherapy combined with targeted therapy, such as sorafenib, tends to prolong the overall survival of patients with HCC complicated by PVTT. In the meanwhile, a retrospective study reported the feasibility of radiotherapy combined with atezolizumab plus bevacizumab in unresectable HCC.[22] However, evidence on whether the combination of radiotherapy with atezolizumab plus bevacizumab can improve the therapeutic effects in unresectable HCC patients with PVTT is still warranted. Accordingly, this open-label, multicentre, single-arm clinical trial was designed to preliminarily explore the efficacy and safety of radiotherapy combined with atezolizumab plus bevacizumab in naive unresectable HCC patients with PVTT.

There are several limitations in this study that should be considered. First, this is a single-arm clinical trial without a control group that could be used to compare the efficacy and safety between treatment regimens. Second, since this study is an exploratory trial with a small sample size, no confirmatory efficacy conclusions can be drawn. The conclusions of this study may serve as preliminary evidence for subsequent large-scale, randomised, controlled clinical trials.

As the prognosis in unresectable HCC patients with PVTT remains poor, there is an urgent need to find an efficacious and safe therapeutic regimen. In this study, the efficacy and safety of IMRT combined with atezolizumab plus bevacizumab in native unresectable HCC patients with PVTT will be investigated so as to explore a new therapeutic regimen and further improve the efficacy and prognosis in these patients.

ETHICS AND DISSEMINATION

This study will be conducted according to the standards of Good Clinical Practice and in compliance with the principles of the Declaration of Helsinki. The Ethics Committee of our Hospital has approved the protocol (EHBHKY2021-K-017). All participants are required to provide written informed consent. The results of the trial will be published in peer-reviewed journals and presented at international conferences.

Trial status

The trial has been registered in ChiCTR.org (Registration number: ChiCTR2100049831; registration date: 2021-08-10; http://www.chictr.org.cn/showproj.aspx?proj=126593). Recruitment is ongoing. The protocol version number is 1.0. The study protocol has been reported in accordance with the SPIRIT guidelines.

Acknowledgements The authors would like to thank the patients, their families, and all the investigators who will participate in the present study.

Contributors KW and Y-JX drafted the manuscript. KW, Y-JX and H-MY contributed equally to this work. S-QC, KW, Y-JX and H-MY designed the trial. Y-QC, Q-ZN, W-XG, JS, SF and JZ are responsible for planning the data analysis and analysing the data resulting from the trial. All named authors adhere to the authorship guidelines of Trials. All authors have agreed to publication. All authors read and approved the final manuscript.

Funding This work was supported by the Clinical Research Plan of SHDC (No. SHDC2020CR1004A), the State Key Programme of the National Natural Science Foundation of China (No: 81730097), the National Natural Science Foundation of China (No: 82072618) and the Science and Technology Commission Foundation of Shanghai Municipality (No: 19411967300).

Disclaimer The Fundings have no roles in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Competing interests None declared.

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

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD

Shu-Qun Cheng http://orcid.org/0000-0002-6098-8028

REFERENCES

1 Sung H, Ferlay J, Siegel RL, *et al*. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;71:209–49.
2 Zheng R, Qu C, Zhang S, *et al*. Liver cancer incidence and mortality in China: temporal trends and projections to 2030. *Chin J Cancer Res* 2018;30:571–9.
3 Zeng H, Chen W, Zheng R, *et al*. Changing cancer survival in China during 2003-15: a pooled analysis of 17 population-based cancer registries. *Lancet Glob Health* 2018;6:e555–67.

4 Craig AJ, von Felden J, Garcia-Lezana T, *et al*. Tumour evolution in hepatocellular carcinoma. *Nat Rev Gastroenterol Hepatol* 2020;17:139–52.
5 Kudo M, Trevisani F, Abou-Alfa GK, *et al*. Hepatocellular carcinoma: therapeutic guidelines and medical treatment. *Liver Cancer* 2016;6:16–26.
6 Finn RS, Qin S, Ikeda M, *et al*. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med* 2020;382:1894–905.
7 Zhang Z-ming, Lai ECH, Zhang C, *et al*. The strategies for treating primary hepatocellular carcinoma with portal vein tumor thrombus. *Int J Surg* 2015;20:8–16.
8 Pawarode A, Voravud N, Sriuranpong V, *et al*. Natural history of untreated primary hepatocellular carcinoma: a retrospective study of 157 patients. *Am J Clin Oncol* 1998;21:386–91.
9 Lu J, Zhang X-P, Zhong B-Y, *et al*. Management of patients with hepatocellular carcinoma and portal vein tumour thrombosis: comparing East and West. *Lancet Gastroenterol Hepatol* 2019;4:721–30.
10 Heimbach JK, Kulik LM, Finn RS, *et al*. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology* 2018;67:358–80.
11 European Association For The Study Of The Liver, European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012;56:908–43.
12 Omata M, Lesmana LA, Tateishi R, *et al*. Asian Pacific association for the study of the liver consensus recommendations on hepatocellular carcinoma. *Hepatol Int* 2010;4:439–74.
13 Yoon SM, Ryoo B-Y, Lee SJ, *et al*. Efficacy and safety of transarterial chemoembolization plus external beam radiotherapy vs sorafenib in hepatocellular carcinoma with macroscopic vascular invasion: a randomized clinical trial. *JAMA Oncol* 2018;4:661–9.
14 Cheng S, Yang J, Shen F, *et al*. Multidisciplinary management of hepatocellular carcinoma with portal vein tumor thrombus - Eastern Hepatobiliary Surgical Hospital consensus statement. *Oncotarget* 2016;7:40816–29.
15 Kudo M, Kawamura Y, Hasegawa K, *et al*. Management of hepatocellular carcinoma in Japan: JSH consensus statements and recommendations 2021 update. *Liver Cancer* 2021;10:181–223.
16 Xie D-Y, Ren Z-G, Zhou J, *et al*. 2019 Chinese clinical guidelines for the management of hepatocellular carcinoma: updates and insights. *Hepatobiliary Surg Nutr* 2020;9:452–63.
17 Arina A, Gutiontov SI, Weichselbaum RR. Radiotherapy and Immunotherapy for Cancer: From "Systemic" to "Multisite". *Clin Cancer Res* 2020;26:2777–82.
18 Ozpiskin OM, Zhang L, Li JJ. Immune targets in the tumor microenvironment treated by radiotherapy. *Theranostics* 2019;9:1215–31.
19 Yu JI, Yoon SM, Park HC, *et al*. Multicenter validation study of a prognostic index for portal vein tumor thrombosis in hepatocellular carcinoma. *Cancer Res Treat* 2014;46:348–57.
20 Chen S-W, Lin L-C, Kuo Y-C, *et al*. Phase 2 study of combined sorafenib and radiation therapy in patients with advanced hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 2014;88:1041–7.
21 Rim CH, Park S, Shin I-S, *et al*. Is the concurrent use of sorafenib and external radiotherapy feasible for advanced hepatocellular carcinoma? A meta-analysis. *Cancers* 2021;13. doi:10.3390/cancers13122912. [Epub ahead of print: 10 06 2021].
22 Manzar GS, De BS, Abana CO, *et al*. Outcomes and toxicities of modern combined modality therapy with Atezolizumab plus bevacizumab and radiation therapy for hepatocellular carcinoma. *Cancers* 2022;14. doi:10.3390/cancers14081901. [Epub ahead of print: 09 04 2022].
23 Abulimiti M, Li Z, Wang H, *et al*. Combination intensity-modulated radiotherapy and sorafenib improves outcomes in hepatocellular carcinoma with portal vein tumor thrombosis. *J Oncol* 2021;2021:1–10.