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Radiotherapy combined with atezolizumab plus bevacizumab for hepatocellular carcinoma with portal vein tumor thrombus

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Manuscripts

1
2 **Radiotherapy combined with atezolizumab plus bevacizumab for hepatocellular carcinoma**
3
4 **with portal vein tumor thrombus**
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6

7 **Short running title: Radiotherapy plus T+A for HCC with PVTT**
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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 tumor 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 enroll patients diagnosed with unresectable hepatocellular carcinoma complicated by PVTT. Radiotherapy combined with atezolizumab plus bevacizumab will be administered for treatment. Patients will initially receive radiotherapy, with each radiotherapy cycle lasting for 28 days and the total dose of tumor (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 d 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 10% dropout 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.

Registration details: ChiCTR.org, registration number: ChiCTR2100049831.

Keywords: *Hepatocellular carcinoma, portal vein tumor thrombus, radiotherapy, atezolizumab, bevacizumab*

Strengths and limitations of this study

- While optimal treatment are yet to be determined, this study might help explore effective treatment strategies for patients with HCC complicated by PVTT.
- The combination of radiotherapy and immunotherapy plus targeted therapy in this study might improve the efficacy in patients with HCC complicated by PVTT.
- This study was a single-arm trial without a control group with small sample size.

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 prevalence of liver cancer is about 26.67/100000,² 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 tumors, 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 antitumor activity and favorable safety profile in the IMbrave150 trial with the mortality risk being decreased by 42% comparing 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 tumor

1
2 thrombosis (PVTT).⁷ In addition, the range and severity of PVTT have been significantly associated
3
4 with the prognosis of unresectable HCC patients, with the median overall survival was just 2.7 to 4
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6 months in naive HCC patients with PVTT.⁸ However, there are significant differences between
7
8 eastern and western countries in the treatment strategies used for HCC patients with PVTT.⁹
9
10 Guidelines from western countries argue that HCC complicated with PVTT represents the advanced
11
12 stage of HCC, advocating sorafenib as the only treatment option.¹⁰⁻¹² On the contrary, eastern
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14 countries adopt positive strategies, such as surgical resection, radiotherapy, transcatheter arterial
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16 chemoembolization (TACE), and surgery combined with multidisciplinary therapies, which are
17
18 expected to improve the long-term survival of these patients.¹³
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24 Radiotherapy is recommended for unresectable HCC patients with types I, II, and III PVTT, whose
25
26 liver function is graded as Child-Pugh A and B. In addition, previous studies have shown that
27
28 radiotherapy can synergistically enhance the anti-tumor effect of immunotherapy and targeted therapy
29
30 by changing the tumor microenvironment.^{14 15} At present, radiotherapy combined with
31
32 immunotherapy and targeted therapy is currently one of the dominant research topics within the tumor
33
34 area. A number of studies have also suggested that radiotherapy combined with sorafenib alone
35
36 improves OS in patients with HCC complicated by PVTT.¹⁶ In addition, the results of a previous
37
38 retrospective study showed that radiotherapy combined with atezolizumab plus bevacizumab was
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40 feasible in unresectable HCC.¹⁷ However, whether the combination of radiotherapy and
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42 immunotherapy plus targeted therapy can improve the efficacy in patients with HCC complicated by
43
44 PVTT needs to be further verified.
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51 Therefore, we proposed an open-label, multi-center, single-arm phase II clinical trial. Patients
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53 diagnosed with locally advanced or metastatic and/or unresectable HCC complicated with PVTT will
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55 be preliminarily enrolled to explore the efficacy and safety of radiotherapy combined with
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57 atezolizumab plus bevacizumab, which is expected to provide an efficacious therapeutic regimen for
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1
2 HCC patients with PVTT and further improve the treatment response and prognosis. Here, we present
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4 the protocol in accordance with the SPIRIT reporting checklist.
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6

7 **Methods and analysis**

8 **Study design and objective**

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14 This open-label, multi-center, single-arm clinical trial will enroll patients diagnosed with locally
15 advanced or metastatic and/or unresectable HCC complicated with PVTT from the departments of
16 hepatobiliary surgery of our Hospitals between August 2021 and December 2021 so as to initially
17 explore the efficacy and safety of radiotherapy combined with atezolizumab plus bevacizumab in
18 naive patients with unresectable HCC complicated by PVTT.
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27 **Eligibility criteria**

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30 The key inclusion criteria are as follows: 1) Males or non-pregnant females aged between 18 and 70
31 years old; 2) Signed informed consent form; 3) Able to comply with the study protocol according to
32 the investigator's judgment; 4) Histologically, cytologically or clinically diagnosed with
33 hepatocellular carcinoma (HCC); 5) Confirmed portal vein tumor thrombus by imaging findings; 6)
34 Not suitable for radical surgical treatment; 7) Have not received any anti-tumor treatment; 8) At least
35 one measurable untreated lesion (per RECIST 1.1); 9) Pre-treatment tumor tissue sample (if available);
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10) ECOG Performance Status of 0 or 1 within 7 days prior to initiation of study treatment; 11) Child-
Pugh class A within 7 days prior to initiation of study treatment; 12) Adequate hematologic and organ
functions, based on the following laboratory test results obtained within 7 days prior to initiation of
study treatment; 13) Resolution of any acute, clinically significant treatment-related toxicity from
prior therapy to grade < 1 prior to study entry, with the exception of alopecia; 14) Negative HIV test
at screening.

1
2 The key exclusion criteria are as follows: 1) History of the leptomenigeal disease; 2) Active or
3
4 history of autoimmune disease or immune deficiency; 3) History of idiopathic pulmonary fibrosis,
5
6 organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic
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8 pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan.
9
10 History of radiation pneumonitis in the radiation field (fibrosis) is permitted; 4) Active tuberculosis;
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13 5) Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac
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15 disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to initiation of
16
17 study treatment, unstable arrhythmia, or unstable angina; 6) History of congenital long QT syndrome
18
19 or corrected QT interval > 500 ms (calculated with the use of the Fridericia method) at screening; 7)
20
21 History of uncorrectable electrolyte disorder affecting serum levels of potassium, calcium, or
22
23 magnesium; 8) The major surgical procedure, other than for diagnosis, within 4 weeks prior to
24
25 initiation of study treatment, or anticipation of the need for a major surgical procedure during the
26
27 study; 9) History of malignancy other than HCC within 5 years prior to screening; 10) Severe
28
29 infection within 4 weeks prior to initiation of study treatment; 11) Treatment with therapeutic oral
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31 or intravenous antibiotics within 2 weeks prior to initiation of study treatment; 12) Prior allogeneic
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33 stem cell or solid organ transplantation; 13) Untreated or incompletely treated esophageal and/or
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35 gastric varices that are bleeding or have a high risk for bleeding; 15) Co-infection of HBV and HCV;
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41 16) Symptomatic, untreated, or actively progressing central nervous system (CNS) metastases.
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45 **Treatment plan**

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48 Patients will initially receive radiotherapy with each cycle for 28 days. A treatment plan will be
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50 established after CT location. The clinical target volume (CTV) includes tumors and tumor thrombi.
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52 The planning target volume (PTV) will be expanded by 0.5-1.0 cm, with conventional fractionation
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54 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
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56 end of every cycle, and the treatment plan will be reformulated after field constriction. The treatment
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58 will continue until the total DT is up to 54-56 Gy/27-28 f.
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2 The treatment with atezolizumab plus bevacizumab will be started at 3 ± 1 d after the initiation of
3
4 radiotherapy. Each treatment cycle will last for 21 days. On the first day of each cycle, atezolizumab
5
6 injection will be intravenously administered at a fixed dose of 1,200 mg (initial intravenous injection
7
8 for 60 min, and subsequent intravenous injections for 30 min if well-tolerated). Bevacizumab at a
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10 dose of 15 mg/kg will be intravenously administered at least 5 min apart (initial intravenous injection
11
12 for 90 min, and subsequent intravenous injections reduced to 60 min and 30 min if well-tolerated).

13
14
15 The treatment will continue until any unacceptable toxicity is found or disease progression occurs.

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19 In case of severe toxicity, the administration will be delayed and/or the dose will be reduced. If any
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21 serious adverse event (SAE) occurs during the radiotherapy, or the radiotherapy is delayed for more
22
23 than 4 weeks for any reason, radiotherapy sessions will be terminated. The doses of atezolizumab and
24
25 bevacizumab will be adjusted according to the drug's instructions.

26 27 28 29 **Endpoints**

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31
32
33 The primary endpoint is ORR, which is defined as the proportion of patients with Complete Response
34
35 (CR) and Partial Response (PR). CR or PR is assessed in accordance with Response
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37 Evaluation Criteria In Solid Tumors (RECIST) 1.1.

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41 Secondary endpoints include: (1) OS, defined as the time between first study treatment and death (for
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43 any reason). (2) Disease control rate (DCR), defined as the percentage of subjects with the best
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45 response as CR, PR, or stable disease (SD). (3) Progression free survival (PFS), defined as the time
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47 between first treatment and first tumor progression or appearance of a new lesion or death due to any
48
49 cause, whichever occurs first. (4) Time to progression (TTP), defined as the time between first
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51 treatment to first tumor progression. (5) Duration of response (DOR), defined as the time from first
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53 tumor remission to first tumor progression or death due to any cause. The DCRs, PFSs, TTPs and
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55 DORs will be calculated in accordance with the RECIST version 1.1, modified RECIST (mRECIST),
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57 and immune-modified RECIST (imRECIST), respectively. (6) The rate of surgical conversions is
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1
2 defined as the proportion of subjects who receive the study treatment and are assessed to be viable
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4 for surgical resection. The resectability criteria include successful down-staging of the tumor,
5
6 sufficient future liver remnant (FLR), and technically resectable assessed by the investigator.
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10 Adverse events (AEs) are assessed in accordance with the NCI Common Terminology Criteria for
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12 Adverse Event (CTCAE V5.0). Monitoring will be performed from the date on which the patient
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14 signs the informed consent to 90 days after the last treatment.
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16

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18 Biomarkers for exploratory endpoints include metagenomic sequencing of fecal organisms, 5 gene
19
20 indexes of hepatocellular carcinoma (HN1, RAN, RAMP3, KRT19, TAF9), immune correlation
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22 detection (programmed death-ligand 1 [PD-L1] expression, CD8 expression; microsatellite instability
23
24 [MSI], and tumor mutational burden [TMB], immune-related gene expression, RNA-seq) and other
25
26 checkpoint proteins and cell surface markers.
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29 30 **Participant timeline**

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32 **Table 1** lists the time points for assessing efficacy, adverse events, laboratory safety assessments
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34 (hematology, coagulation, and chemistry), physical examination, electrocardiogram (ECG), and
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36 tumor measurements.
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Table 1. Schema of Single-arm Clinical Trial

Item	Screening Period		Treatment Period			End of Trial	Survival Follow-up
	-28 - 0d	-7 - 0d	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							
Past medical history	×						
History of tumor treatment							
Physical examination		×	×	Every 3 weeks		×	
Vital signs		×	×	Every 3 weeks		×	
ECOG		×	×	Every 3 weeks		×	
Pregnancy test		×					
Infection screening	×						
Imaging	×		×	Every 6 weeks		×	×
Tumor markers		×	×	Every 6 weeks		×	
Echocardiography	×						
Tumor tissue	×						
12-lead electrocardiogram		×	When clinically indicated				×
Blood biochemistry		×	×	Every 3 weeks			×

1							
2				Every 3 weeks			
3	Routine blood test	×	×				×
4							
5				Every 3 weeks			
6	Routine urine test	×	×				×
7							
8	Routine stool test	×	×	Every 3 weeks			×
9							
10	Thyroid function, pituitary						
11	function, coagulation	×	×	Every 3 weeks			×
12							
13	Gut microbiome testing for the						
14	stool sample	×		×			×
15							
16	Biomarker testing for the blood						
17	sample	×		×			×
18							
19	Surgical resection					×	
20							
21	Surgical complications					×	
22							
23	Concomitant medication	×	×	×	Every 3 weeks		×
24	Adverse events	×	×	×	Every 3 weeks		×
25							
26	Compliance evaluation	×	×	×	Every 3 weeks		
27	Dispensing of drugs			×	Every 3 weeks		
28							
29	Recovery of drugs			×	Every 3 weeks		×
30							
31	Follow-up on survival status and						
32	anti-tumor treatment						×
33							

1
2 Furthermore, for the testing of biomarkers as exploratory endpoints, stool and blood samples will be
3
4 collected from patients prior to the first treatment, at 7 weeks after the first treatment, and after
5
6 treatment discontinuation, respectively.
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10 **Data collection and management**

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

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31 According to the results of IMbrave150,⁶ the ORR of atezolizumab plus bevacizumab in unresectable
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33 HCC patients was 27.3%. Assuming an ORR of 47%, with a two-sided alpha error of 0.1, 90% power,
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35 and 10% dropout rate, the required number of evaluable patients is 42.
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40 The efficacy assessment is based on the full analysis set (FAS). The intention-to-treat (ITT) efficacy
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42 analysis will be performed for subjects who received at least one session of the study treatment based
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44 on the FAS. No supplementation will be made for missing values. The safety analysis set (SAS)
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46 includes all enrolled subjects who have received at least one session of study treatment and have a
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48 post-treatment safety record. This dataset will be used for safety analysis.
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52 **Monitoring**

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55 An independent Data and Safety Monitoring Committee has been established to assess the safety data
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57 if serious adverse events occur. Any adverse events will be registered. A qualified and independent
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1
2 auditor is appointed to audit the trial systems, and the audit will be conducted before and during the
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4 study following a written procedure.
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7 **Patient and public involvement**

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10 The patients and general public were not involved in the trial design.
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13 **Discussion**

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18 Atezolizumab plus bevacizumab is the standard first-line therapy for unresectable HCC patients.
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20 Although the combination can significantly improve the prognosis in patients, the ORR is still not
21
22 satisfactory.⁶ Improving the therapeutic effect in patients is still a great clinical challenge. For patients
23
24 with HCC, vascular invasion and metastasis are important reasons these patients cannot undergo
25
26 surgical resection as well as poor prognostic factors. Radiotherapy has an important role in treating
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28 patients with PVTT; however, the therapeutic effects are still limited. Previous clinical studies have
29
30 shown that radiotherapy combined with targeted therapy, such as sorafenib, tends to prolong the
31
32 overall survival of patients with HCC complicated by PVTT. In the meanwhile, a retrospective study
33
34 reported the feasibility of radiotherapy combined with atezolizumab plus bevacizumab in
35
36 unresectable HCC.¹⁷ However, evidence on whether the combination of radiotherapy with
37
38 atezolizumab plus bevacizumab can improve the therapeutic effects in unresectable HCC patients
39
40 with PVTT are still warranted. Accordingly, this open-label, multi-center, single-arm clinical trial
41
42 was designed to preliminarily explore the efficacy and safety of radiotherapy combined with
43
44 atezolizumab plus bevacizumab in naive unresectable HCC patients with PVTT.
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52 There are several limitations in the present study that should be considered. First, this is a single-arm
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54 clinical trial without a control group that could be used to compare the efficacy and safety between
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56 treatment regimens. Second, since this study is an exploratory trial with small sample size, no
57
58 confirmatory efficacy conclusions can be drawn. The conclusions of this study may serve as
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60 preliminary evidence for subsequent large-scale, randomized, controlled clinical trials.

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2 As the prognosis in unresectable HCC patients with PVTT remains poor, there is an urgent need to
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4 find an efficacious and safe therapeutic regimen. In this study, the efficacy and safety of radiotherapy
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6 combined with atezolizumab plus bevacizumab in native unresectable HCC patients with PVTT will
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8 be investigated so as to explore a new therapeutic regimen and further improve the efficacy and
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10 prognosis in these patients.
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13 14 **Ethics and dissemination**

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18 This study will be conducted according to the standards of Good Clinical Practice and in compliance
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20 with the principles of the Declaration of Helsinki. The Ethics Committee of our Hospital has approved
21
22 the protocol (EHBHKY2021-K-017). All participants are required to provide written informed
23
24 consent. The results of the trial will be published in peer-reviewed journals and presented at
25
26 international conferences.
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29 30 **Trial status**

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34 The trial has been registered in ChiCTR.org (Registration number: ChiCTR2100049831; registration
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36 date: 2021-08-10; <http://www.chictr.org.cn/showproj.aspx?proj=126593>). Recruitment is ongoing.
37
38 The protocol version number is 1.0. The study protocol has been reported in accordance with the
39
40 Standard Protocol Items: Recommendations for Clinical Interventional Trials (SPIRIT) guidelines.
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42
43

44 45 **Acknowledgements**

46
47
48 The authors would like to thank the patients, their families, and all the investigators who will
49
50 participate in the present study.
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53 54 **Data Sharing Statement**

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56
57 We will widely disseminate the results of this clinical trial through conference presentations and
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59 publications in relevant journals. All evaluation forms, reports, and other records will be identified in
60

1
2 a manner designed to maintain participants' confidentiality. All records will be kept in a secure
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4 storage area with limited access. Data during the study are available from the study leader upon
5
6 reasonable request.
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10 **Authors' contributions**

11
12
13 Kang Wang and Yan-Jun Xiang drafted the manuscript. Kang Wang, Yan-Jun Xiang, and Hong-Ming
14
15 Yu contributed equally to this work. Shu-Qun Cheng, Kang Wang, Yan-Jun Xiang, and Hong-Ming
16
17 Yu designed the trial. Yu-Qiang Cheng, Qian-Zhi Ni, Wei-Xing Guo, Jie Shi, Shuang Feng, and Jian
18
19 Zhai are responsible for planning the data analysis and analyzing the data resulting from the trial. All
20
21 named authors adhere to the authorship guidelines of Trials. All authors have agreed to publication.
22
23 All authors read and approved the final manuscript.
24
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26
27

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38
39 of the study and collection, analysis, and interpretation of data and in writing the manuscript.
40
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44 **Conflict of interest**

45
46
47 The authors have no conflicts of interest to declare.
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8 First: 2022/04/24]
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For peer review only



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P2/10
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	P10
Funding	4	Sources and types of financial, material, and other support	P14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P14
	5b	Name and contact information for the trial sponsor	P14
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	P14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	P14
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	P3-4

1				
2		6b	Explanation for choice of comparators	NA
3				
4	Objectives	7	Specific objectives or hypotheses	P4
5				
6	Trial design	8	Description of trial design including type of trial (eg,	P4
7			parallel group, crossover, factorial, single group),	
8			allocation ratio, and framework (eg, superiority,	
9			equivalence, noninferiority, exploratory)	
10				
11				
12	Methods: Participants, interventions, and outcomes			
13				
14	Study setting	9	Description of study settings (eg, community clinic,	P5
15			academic hospital) and list of countries where data	
16			will be collected. Reference to where list of study	
17			sites can be obtained	
18				
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If	P5/16-21
20			applicable, eligibility criteria for study centres and	
21			individuals who will perform the interventions (eg,	
22			surgeons, psychotherapists)	
23				
24				
25	Interventions	11a	Interventions for each group with sufficient detail to	P5-6
26			allow replication, including how and when they will	
27			be administered	
28				
29				
30		11b	Criteria for discontinuing or modifying allocated	P6
31			interventions for a given trial participant (eg, drug	
32			dose change in response to harms, participant	
33			request, or improving/worsening disease)	
34				
35		11c	Strategies to improve adherence to intervention	P6
36			protocols, and any procedures for monitoring	
37			adherence (eg, drug tablet return, laboratory tests)	
38				
39				
40		11d	Relevant concomitant care and interventions that	P6
41			are permitted or prohibited during the trial	
42				
43	Outcomes	12	Primary, secondary, and other outcomes, including	P6-7
44			the specific measurement variable (eg, systolic	
45			blood pressure), analysis metric (eg, change from	
46			baseline, final value, time to event), method of	
47			aggregation (eg, median, proportion), and time point	
48			for each outcome. Explanation of the clinical	
49			relevance of chosen efficacy and harm outcomes is	
50			strongly recommended	
51				
52				
53	Participant	13	Time schedule of enrolment, interventions (including	P7
54	timeline		any run-ins and washouts), assessments, and visits	
55			for participants. A schematic diagram is highly	
56			recommended (see Figure)	
57				
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2	Sample size	14	Estimated number of participants needed to achieve	P8
3			study objectives and how it was determined,	
4			including clinical and statistical assumptions	
5			supporting any sample size calculations	
6				
7	Recruitment	15	Strategies for achieving adequate participant	P8
8			enrolment to reach target sample size	
9				

Methods: Assignment of interventions (for controlled trials)

Allocation:

14	Sequence	16a	Method of generating the allocation sequence (eg,	NA
15	generation		computer-generated random numbers), and list of	
16			any factors for stratification. To reduce predictability	
17			of a random sequence, details of any planned	
18			restriction (eg, blocking) should be provided in a	
19			separate document that is unavailable to those who	
20			enrol participants or assign interventions	
21				
22				
23				
24	Allocation	16b	Mechanism of implementing the allocation sequence	NA
25	concealment		(eg, central telephone; sequentially numbered,	
26	mechanism		opaque, sealed envelopes), describing any steps to	
27			conceal the sequence until interventions are	
28			assigned	
29				
30				
31	Implementation	16c	Who will generate the allocation sequence, who will	NA
32			enrol participants, and who will assign participants	
33			to interventions	
34				
35	Blinding	17a	Who will be blinded after assignment to	NA
36	(masking)		interventions (eg, trial participants, care providers,	
37			outcome assessors, data analysts), and how	
38				
39				
40		17b	If blinded, circumstances under which unblinding is	NA
41			permissible, and procedure for revealing a	
42			participant's allocated intervention during the trial	
43				

Methods: Data collection, management, and analysis

46	Data collection	18a	Plans for assessment and collection of outcome,	P7
47	methods		baseline, and other trial data, including any related	
48			processes to promote data quality (eg, duplicate	
49			measurements, training of assessors) and a	
50			description of study instruments (eg, questionnaires,	
51			laboratory tests) along with their reliability and	
52			validity, if known. Reference to where data collection	
53			forms can be found, if not in the protocol	
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2		18b	Plans to promote participant retention and complete	P7
3			follow-up, including list of any outcome data to be	
4			collected for participants who discontinue or deviate	
5			from intervention protocols	
6				
7	Data	19	Plans for data entry, coding, security, and storage,	P7
8	management		including any related processes to promote data	
9			quality (eg, double data entry; range checks for data	
10			values). Reference to where details of data	
11			management procedures can be found, if not in the	
12			protocol	
13				
14				
15	Statistical	20a	Statistical methods for analysing primary and	P8
16	methods		secondary outcomes. Reference to where other	
17			details of the statistical analysis plan can be found, if	
18			not in the protocol	
19				
20				
21		20b	Methods for any additional analyses (eg, subgroup	P8
22			and adjusted analyses)	
23				
24		20c	Definition of analysis population relating to protocol	P8
25			non-adherence (eg, as randomised analysis), and	
26			any statistical methods to handle missing data (eg,	
27			multiple imputation)	
28				
29				
30	Methods: Monitoring			
31				
32	Data monitoring	21a	Composition of data monitoring committee (DMC);	P8
33			summary of its role and reporting structure;	
34			statement of whether it is independent from the	
35			sponsor and competing interests; and reference to	
36			where further details about its charter can be found,	
37			if not in the protocol. Alternatively, an explanation of	
38			why a DMC is not needed	
39				
40				
41		21b	Description of any interim analyses and stopping	P8
42			guidelines, including who will have access to these	
43			interim results and make the final decision to	
44			terminate the trial	
45				
46				
47	Harms	22	Plans for collecting, assessing, reporting, and	P8
48			managing solicited and spontaneously reported	
49			adverse events and other unintended effects of trial	
50			interventions or trial conduct	
51				
52				
53	Auditing	23	Frequency and procedures for auditing trial conduct,	P8
54			if any, and whether the process will be independent	
55			from investigators and the sponsor	
56				
57				

Ethics and dissemination

1				
2	Research ethics	24	Plans for seeking research ethics	P9
3	approval		committee/institutional review board (REC/IRB)	
4			approval	
5				
6	Protocol	25	Plans for communicating important protocol	P10
7	amendments		modifications (eg, changes to eligibility criteria,	
8			outcomes, analyses) to relevant parties (eg,	
9			investigators, REC/IRBs, trial participants, trial	
10			registries, journals, regulators)	
11				
12				
13	Consent or	26a	Who will obtain informed consent or assent from	P9
14	assent		potential trial participants or authorised surrogates,	
15			and how (see Item 32)	
16				
17				
18		26b	Additional consent provisions for collection and use	NA
19			of participant data and biological specimens in	
20			ancillary studies, if applicable	
21				
22	Confidentiality	27	How personal information about potential and	P14
23			enrolled participants will be collected, shared, and	
24			maintained in order to protect confidentiality before,	
25			during, and after the trial	
26				
27				
28	Declaration of	28	Financial and other competing interests for principal	P14
29	interests		investigators for the overall trial and each study site	
30				
31	Access to data	29	Statement of who will have access to the final trial	P14
32			dataset, and disclosure of contractual agreements	
33			that limit such access for investigators	
34				
35	Ancillary and	30	Provisions, if any, for ancillary and post-trial care,	NA
36	post-trial care		and for compensation to those who suffer harm from	
37			trial participation	
38				
39				
40	Dissemination	31a	Plans for investigators and sponsor to communicate	P8
41	policy		trial results to participants, healthcare professionals,	
42			the public, and other relevant groups (eg, via	
43			publication, reporting in results databases, or other	
44			data sharing arrangements), including any	
45			publication restrictions	
46				
47				
48		31b	Authorship eligibility guidelines and any intended	NA
49			use of professional writers	
50				
51		31c	Plans, if any, for granting public access to the full	NA
52			protocol, participant-level dataset, and statistical	
53			code	
54				
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56	Appendices			
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1				
2	Informed consent	32	Model consent form and other related	NA
3	materials		documentation given to participants and authorised	
4			surrogates	
5				
6	Biological	33	Plans for collection, laboratory evaluation, and	NA
7	specimens		storage of biological specimens for genetic or	
8			molecular analysis in the current trial and for future	
9			use in ancillary studies, if applicable	
10				

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12 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013
13 Explanation & Elaboration for important clarification on the items. Amendments to the
14 protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT
15 Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)"
16 license.
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BMJ Open

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

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Primary Subject Heading:	Oncology
Secondary Subject Heading:	Oncology
Keywords:	RADIOTHERAPY, Hepatobiliary tumours < ONCOLOGY, Adult oncology < ONCOLOGY

SCHOLARONE™
Manuscripts

1
2 **Efficacy and safety of radiotherapy combined with atezolizumab plus bevacizumab in treating**
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4 **hepatocellular carcinoma with portal vein tumor thrombus: A study protocol**
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7 **Short running title:** Radiotherapy plus T+A for HCC with PVTT
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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 tumor 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 enroll patients diagnosed with unresectable hepatocellular carcinoma 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 tumor (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 d 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% dropout 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.

Registration details: ChiCTR.org, registration number: ChiCTR2100049831.

1
2 **Keywords:** *Hepatocellular carcinoma, portal vein tumor thrombus, radiotherapy, atezolizumab,*
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4 *bevacizumab*

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8 **Strengths and limitations of this study**
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- 10
11 ● This study was a single-arm trial without a control group.
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13 ● This study is an exploratory trial with a small sample size.
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15 ● The conclusions of this study may serve as preliminary evidence for subsequent large-scale,
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17 randomized, controlled clinical trials.
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25 **Introduction**
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27
28 Liver cancer is the seventh most common cancer and the second most deadly cancer, with more than
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30 900,000 new cases being diagnosed worldwide every year.¹ In China, the age-standardized annual
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32 incidence of liver cancer is about 26.67/100,000,² while the 5-year survival rate is only around 12%.³
33
34 Hepatocellular carcinoma (HCC) is the most common histological subtype of primary liver cancer,⁴
35
36 and surgery is the preferred and most efficacious approach for the treatment of HCC. However, some
37
38 patients lose the chance for surgery at the time of diagnosis due to their intermediate to advanced
39
40 tumors, liver dysfunction, etc. ⁵ Local therapies (including radiotherapy) and systemic therapies are
41
42 important options for prolonging the survival of HCC patients who cannot undergo surgical resection.
43
44 Due to the promising antitumor activity and favorable safety profile in the IMbrave150 trial, with the
45
46 mortality risk being decreased by 42% compared with sorafenib,⁶ atezolizumab plus bevacizumab
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48 have become the standard first-line therapy for unresectable HCC. Yet, the objective response rate
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50 (ORR) with atezolizumab plus bevacizumab in unresectable HCC patients was reported to be only
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52 27.3%.⁶ Hence, improving the therapeutic effect in patients is still a great clinical challenge.
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2 Vascular invasion and metastasis are commonly seen in patients with intermediate to advanced-stage
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4 HC, as 44%-62% of patients with advanced HCC have been reported to develop portal vein tumor
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6 thrombosis (PVTT).⁷ In addition, the range and severity of PVTT have been significantly associated
7
8 with the prognosis of unresectable HCC patients, with the median overall survival being just 2.7 to 4
9
10 months in naive HCC patients with PVTT.⁸ However, there are significant differences between
11
12 eastern and western countries in the treatment strategies used for HCC patients with PVTT.⁹
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14 Guidelines from western countries argue that HCC complicated with PVTT represents the advanced
15
16 stage of HCC, advocating sorafenib as the only treatment option.¹⁰⁻¹² On the contrary, eastern
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18 countries adopt positive strategies, such as surgical resection, radiotherapy, transcatheter arterial
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20 chemoembolization (TACE), and surgery combined with multidisciplinary therapies, which are
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22 expected to improve the long-term survival of these patients.¹³⁻¹⁶
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28 Radiotherapy is recommended for unresectable HCC patients with types I, II, and III PVTT, whose
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30 liver function is graded as Child-Pugh A and B. In addition, previous studies have shown that
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32 radiotherapy can synergistically enhance the antitumor effect of immunotherapy and targeted therapy
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34 by changing the tumor microenvironment.^{17 18} At present, radiotherapy combined with
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36 immunotherapy and targeted therapy is currently one of the dominant research topics within the tumor
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38 area. A number of studies have also suggested that radiotherapy combined with sorafenib alone
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40 improves OS in patients with HCC complicated by PVTT,¹⁹ and the feasibility of concurrent
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42 radiotherapy and sorafenib.^{20 21} In addition, the results of a previous retrospective study showed that
43
44 radiotherapy combined with atezolizumab plus bevacizumab was feasible in unresectable HCC.²²
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46 However, whether the combination of radiotherapy and immunotherapy plus targeted therapy can
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48 improve the efficacy in patients with HCC complicated by PVTT needs to be further verified.
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54 Therefore, we proposed an open-label, multicenter, single-arm phase II clinical trial. Patients
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56 diagnosed with locally advanced or metastatic and/or unresectable HCC complicated with PVTT will
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58 be preliminarily enrolled to explore the efficacy and safety of radiotherapy combined with
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1
2 atezolizumab plus bevacizumab, which is expected to provide an efficacious therapeutic regimen for
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4 HCC patients with PVTT and further improve the treatment response and prognosis. Here, we present
5
6 the protocol in accordance with the SPIRIT reporting checklist.
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9

10 **Methods and analysis**

11 12 13 **Study design and objective**

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17 This open-label, multicenter, single-arm clinical trial will enroll patients diagnosed with locally
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19 advanced or metastatic and/or unresectable HCC complicated with PVTT from the departments of
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21 hepatobiliary surgery of our Hospitals between August 2021 and December 2021 so as to initially
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23 exploring the efficacy and safety of radiotherapy combined with atezolizumab plus bevacizumab in
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25 naive patients with unresectable HCC complicated by PVTT.
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29 **Eligibility criteria**

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33 The key inclusion criteria are as follows: 1) Males or non-pregnant females aged between 18 and 70
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35 years old; 2) Signed informed consent form; 3) Able to comply with the study protocol according to
36
37 the investigator's judgment; 4) Histologically, cytologically or clinically diagnosed with
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39 hepatocellular carcinoma (HCC); 5) Confirmed portal vein tumor thrombus by imaging findings; 6)
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41 Not suitable for radical surgical treatment; 7) Have not received any antitumor treatment; 8) At least
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43 one measurable untreated lesion (per RECIST 1.1); 9) Pre-treatment tumor tissue sample (if available);
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45 10) ECOG Performance Status of 0 or 1 within 7 days prior to initiation of study treatment; 11) Child-
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47 Pugh class A within 7 days prior to initiation of study treatment; 12) Adequate hematologic and organ
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49 functions, based on the following laboratory test results obtained within 7 days prior to initiation of
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51 study treatment; 13) Resolution of any acute, clinically significant treatment-related toxicity from
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53 prior therapy to grade < 1 prior to study entry, with the exception of alopecia; 14) Negative HIV test
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55 at screening.
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2 The key exclusion criteria are as follows: 1) History of the leptomenigeal disease; 2) Active or
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4 history of autoimmune disease or immune deficiency; 3) History of idiopathic pulmonary fibrosis,
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6 organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic
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8 pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan.
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10 History of radiation pneumonitis in the radiation field (fibrosis) is permitted; 4) Active tuberculosis;
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13 5) Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac
14
15 disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to initiation of
16
17 study treatment, unstable arrhythmia, or unstable angina; 6) History of congenital long QT syndrome
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19 or corrected QT interval > 500 ms (calculated with the use of the Fridericia method) at screening; 7)
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21 History of uncorrectable electrolyte disorder affecting serum levels of potassium, calcium, or
22
23 magnesium; 8) The major surgical procedure, other than for diagnosis, within 4 weeks prior to
24
25 initiation of study treatment, or anticipation of the need for a major surgical procedure during the
26
27 study; 9) History of malignancy other than HCC within 5 years prior to screening; 10) Severe
28
29 infection within 4 weeks prior to initiation of study treatment; 11) Treatment with therapeutic oral or
30
31 intravenous antibiotics within 2 weeks prior to initiation of study treatment; 12) Prior allogeneic stem
32
33 cell or solid organ transplantation; 13) Untreated or incompletely treated esophageal and/or gastric
34
35 varices that are bleeding or have a high risk for bleeding; 15) Co-infection of HBV and HCV; 16)
36
37 Symptomatic, untreated, or actively progressing central nervous system (CNS) metastases.
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45 **Treatment plan**

46
47 Patients will initially receive intensity-modulated radiotherapy (IMRT) with each cycle for 28 days.
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49 A treatment plan will be established after CT location. The clinical target volume (CTV) includes
50
51 tumors and tumor thrombi. The planning target volume (PTV) will be expanded by 0.5-1.0 cm, with
52
53 conventional fractionation at a single dose of 180-220 cGy. Total DT will be 40 Gy/20 f/26 d. CT
54
55 scan will be performed at the end of every cycle, and the treatment plan will be reformulated after
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57 field constriction. The treatment will continue until the total DT is up to 54-56 Gy/27-28 f.
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1
2 The treatment with atezolizumab plus bevacizumab will be started at 3 ± 1 d after the initiation of
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4 IMRT. Each treatment cycle will last for 21 days. On the first day of each cycle, atezolizumab
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6 injection will be intravenously administered at a fixed dose of 1,200 mg (initial intravenous injection
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8 for 60 min, and subsequent intravenous injections for 30 min if well-tolerated). Bevacizumab at a
9
10 dose of 15 mg/kg will be intravenously administered at least 5 min apart (initial intravenous injection
11
12 for 90 min, and subsequent intravenous injections reduced to 60 min and 30 min if well-tolerated).
13
14 The treatment was discontinued when there was no additional clinical benefit, as judged by the
15
16 investigator (based on imaging, biochemical indicators, and clinical status of the patient). Then, the
17
18 patient received the guideline-recommended second-line therapy.
19
20
21
22

23
24 Delayed treatment or dose reduction will be determined by the clinical team, and the specific
25
26 adjustment plan will be determined by the investigator based on the patient's clinical condition. In
27
28 case of severe toxicity, the administration will be delayed, and/or the dose will be reduced. If any
29
30 serious adverse event (SAE) occurs during the radiotherapy, or the radiotherapy is delayed for more
31
32 than 4 weeks for any reason, radiotherapy sessions will be terminated. The doses of atezolizumab and
33
34 bevacizumab will be adjusted according to the drug's instructions.
35
36
37

38 39 **Endpoints**

40
41
42 The primary endpoint is ORR, which is defined as the proportion of patients with Complete Response
43
44 (CR) and Partial Response (PR). CR or PR is assessed in accordance with Response
45
46 Evaluation Criteria In Solid Tumors (RECIST) 1.1. The responses will be independently evaluated
47
48 by three to six experienced senior physicians who are not investigators in this study.
49
50
51

52
53 Secondary endpoints include (1) OS, defined as the time between the first study treatment and
54
55 death (for any reason). (2) Disease control rate (DCR), defined as the percentage of subjects with the
56
57 best response as CR, PR, or stable disease (SD). (3) Progression-free survival (PFS), defined as the
58
59 time between the first treatment and the first tumor progression or appearance of a new lesion or death
60

1
2 due to any cause, whichever occurs first. (4) Time to progression (TTP), defined as the time between
3
4 the first treatment to first tumor progression. (5) Duration of response (DOR), defined as the time
5
6 from first tumor remission to first tumor progression or death due to any cause. The DCRs, PFSs,
7
8 TTPs, and DORs will be calculated in accordance with the RECIST version 1.1, modified RECIST
9
10 (mRECIST), and immune-modified RECIST (imRECIST), respectively. (6) The rate of surgical
11
12 conversions is defined as the proportion of subjects who receive the study treatment and are assessed
13
14 to be viable for surgical resection. The resectability criteria include successful down-staging of the
15
16 tumor, sufficient future liver remnant (FLR), and technically resectable assessed by the investigator.
17
18 The definition of successful downstaging was based on the CSCO guideline, which was 1) stage Ia,
19
20 Ib, and IIa, 2) IIb, if the tumor is confined to the same segment or the same side of the liver or
21
22 intraoperative radiofrequency ablation can be performed at the same time to treat the lesions outside
23
24 the resection range, and 3) IIIa/b, if the tumor is confined to the hemi-liver, and it is expected that the
25
26 tumor thrombus can be completely removed during the operation, surgical resection of the tumor and
27
28 thrombectomy through the portal vein can be considered.
29
30
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34

35 Adverse events (AEs) are assessed in accordance with the NCI Common Terminology Criteria for
36
37 Adverse Events (CTCAE V5.0). Monitoring will be performed from the date on which the patient
38
39 signs the informed consent to 90 days after the last treatment.
40
41
42

43 Biomarkers for exploratory endpoints include metagenomic sequencing of fecal organisms, five gene
44
45 indexes of hepatocellular carcinoma (HN1, RAN, RAMP3, KRT19, TAF9), immune correlation
46
47 detection (programmed death-ligand 1 [PD-L1] expression, CD8 expression; microsatellite instability
48
49 [MSI], and tumor mutational burden [TMB], immune-related gene expression, RNA-seq) and other
50
51 checkpoint proteins and cell surface markers.
52
53
54

55 56 **Participant timeline**

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58
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1
2 **Table 1** lists the time points for assessing efficacy, adverse events, laboratory safety assessments
3
4 (hematology, coagulation, and chemistry), physical examination, electrocardiogram (ECG), and
5
6 tumor measurements.
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Table 1. Schema of Single-arm Clinical Trial

Item	Screening Period		Treatment Period			Perioperative Period	End of Trial	Survival Follow-up
	-28 - 0d	-7 - 0d	4 weeks after the first treatment session	7 weeks after the first treatment session	n cycles		30 days after checkout	
Window period (days)	—	—					±7	
Informed consent	×							
Demographics								
Past medical history	×							
History of tumor treatment								
Physical examination		×	×	Every 3 weeks		×	×	
Vital signs		×	×	Every 3 weeks		×	×	
ECOG		×	×	Every 3 weeks			×	
Pregnancy test		×					×	
Infection screening	×						×	
Imaging	×		×	Every 6 weeks			×	×
Tumor markers		×	×	Every 6 weeks			×	
Echocardiography	×						×	
Tumor tissue	×							
12-lead electrocardiogram		×	When clinically indicated				×	
Blood biochemistry		×	×	Every 3 weeks			×	
Routine blood test		×	×	Every 3 weeks			×	

1									
2									
3									
4	Routine urine test	×	×		Every 3 weeks				×
5									
6	Routine stool test	×	×		Every 3 weeks				×
7									
8	Thyroid function, pituitary								
9		×	×		Every 3 weeks				×
10	function, coagulation								
11	Gut microbiome testing for								
12		×			×				×
13	the stool sample								
14	Biomarker testing for the								
15		×			×				×
16	blood sample								
17	Surgical resection							×	
18									
19	Surgical complications							×	
20									
21	Concomitant medication	×	×	×	Every 3 weeks				×
22									
23	Adverse events	×	×	×	Every 3 weeks				×
24									
25	Compliance evaluation	×	×	×	Every 3 weeks				
26									
27	Dispensing of drugs			×	Every 3 weeks				
28									
29	Recovery of drugs			×	Every 3 weeks				×
30									
31	Follow-up on survival status								
32									
33	and antitumor treatment								×
34									
35									
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2 Furthermore, for the testing of biomarkers as exploratory endpoints, stool and blood samples will be
3
4 collected from patients prior to the first treatment, at 7 weeks after the first treatment, and after
5
6 treatment discontinuation, respectively.
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9

10 **Data collection and management**

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12
13 The completed CRFs will be submitted to the respective sites for archiving. All data will be recorded
14
15 in an electronic case report form (eCRF) by investigators or clinical research coordinators. All study
16
17 documents will be confidential. All study data, including confirmation of all patients (effective check
18
19 on recorded information, such as study cases), all original copies of signed ICFs, as well as detailed
20
21 original records of drug distribution, shall be kept uniformly by the study institution until 5 years after
22
23 the end of the trial.
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27

28 **Statistical methods**

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30
31 According to the results of IMbrave150,⁶ the ORR of atezolizumab plus bevacizumab in unresectable
32
33 HCC patients was 27.3%. Assuming an ORR of 47%, with a two-sided alpha error of 0.1, 90% power,
34
35 and 10% dropout rate, the required number of evaluable patients is 42.
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40 The efficacy assessment is based on the full analysis set (FAS). The intention-to-treat (ITT) efficacy
41
42 analysis will be performed for subjects who received at least one session of the study treatment based
43
44 on the FAS. No supplementation will be made for missing values. The safety analysis set (SAS)
45
46 includes all enrolled subjects who have received at least one session of study treatment and have a
47
48 post-treatment safety record. This dataset will be used for safety analysis.
49
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51

52 **Monitoring**

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54
55 An independent Data and Safety Monitoring Committee has been established to assess the safety data
56
57 if serious adverse events occur. Any adverse events will be registered. A qualified and independent
58
59 auditor is appointed to audit the trial systems, and the audit will be conducted before and during the
60

1 study following a written procedure. The stopping rules for the trial are 1) the investigators find
2 serious safety issues, or 2) the administrative department cancels the trial. The termination of the trial
3
4 can be temporary or permanent. When terminating the trial, all records will be kept for future
5
6
7
8
9 reference.

10 11 12 **Patient and public involvement**

13
14
15
16 The patients and general public were not involved in the trial design.

17 18 19 **Discussion**

20
21
22 Atezolizumab plus bevacizumab is the standard first-line therapy for unresectable HCC patients.
23
24 Although the combination can significantly improve the prognosis in patients, the ORR is still not
25
26 satisfactory.⁶ Improving the therapeutic effect in patients is still a great clinical challenge. For patients
27
28 with HCC, vascular invasion and metastasis are important reasons these patients cannot undergo
29
30 surgical resection, as well as poor prognostic factors. Radiotherapy has an important role in treating
31
32 patients with PVTT; however, the therapeutic effects are still limited. Previous clinical studies have
33
34 shown that radiotherapy combined with targeted therapy, such as sorafenib, tends to prolong the
35
36 overall survival of patients with HCC complicated by PVTT. In the meanwhile, a retrospective study
37
38 reported the feasibility of radiotherapy combined with atezolizumab plus bevacizumab in
39
40 unresectable HCC.²² However, evidence on whether the combination of radiotherapy with
41
42 atezolizumab plus bevacizumab can improve the therapeutic effects in unresectable HCC patients
43
44 with PVTT is still warranted. Accordingly, this open-label, multicenter, single-arm clinical trial was
45
46 designed to preliminarily explore the efficacy and safety of radiotherapy combined with atezolizumab
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48 plus bevacizumab in naive unresectable HCC patients with PVTT.
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56 There are several limitations in the present study that should be considered. First, this is a single-arm
57
58 clinical trial without a control group that could be used to compare the efficacy and safety between
59
60 treatment regimens. Second, since this study is an exploratory trial with a small sample size, no

1
2 confirmatory efficacy conclusions can be drawn. The conclusions of this study may serve as
3
4 preliminary evidence for subsequent large-scale, randomized, controlled clinical trials.
5
6

7
8 As the prognosis in unresectable HCC patients with PVTT remains poor, there is an urgent need to
9
10 find an efficacious and safe therapeutic regimen. In this study, the efficacy and safety of IMRT
11
12 combined with atezolizumab plus bevacizumab in native unresectable HCC patients with PVTT will
13
14 be investigated so as to explore a new therapeutic regimen and further improve the efficacy and
15
16 prognosis in these patients.
17

18 19 20 **Ethics and dissemination**

21
22
23 This study will be conducted according to the standards of Good Clinical Practice and in compliance
24
25 with the principles of the Declaration of Helsinki. The Ethics Committee of our Hospital has approved
26
27 the protocol (EHBHKY2021-K-017). All participants are required to provide written informed
28
29 consent. The results of the trial will be published in peer-reviewed journals and presented at
30
31 international conferences.
32
33

34 35 36 **Trial status**

37
38
39 The trial has been registered in ChiCTR.org (Registration number: ChiCTR2100049831; registration
40
41 date: 2021-08-10; <http://www.chictr.org.cn/showproj.aspx?proj=126593>). Recruitment is ongoing.
42
43 The protocol version number is 1.0. The study protocol has been reported in accordance with the
44
45 Standard Protocol Items: Recommendations for Clinical Interventional Trials (SPIRIT) guidelines.
46
47
48

49 50 **Acknowledgments**

51
52
53 The authors would like to thank the patients, their families, and all the investigators who will
54
55 participate in the present study.
56
57

58 59 **Data Sharing Statement**

60

1 We will widely disseminate the results of this clinical trial through conference presentations and
2 publications in relevant journals. All evaluation forms, reports, and other records will be identified in
3 a manner designed to maintain participants' confidentiality. All records will be kept in a secure
4 storage area with limited access. Data during the study are available from the study leader upon
5 reasonable request.
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13 **Authors' contributions**

14
15 Kang Wang and Yan-Jun Xiang drafted the manuscript. Kang Wang, Yan-Jun Xiang, and Hong-Ming
16 Yu contributed equally to this work. Shu-Qun Cheng, Kang Wang, Yan-Jun Xiang, and Hong-Ming
17 Yu designed the trial. Yu-Qiang Cheng, Qian-Zhi Ni, Wei-Xing Guo, Jie Shi, Shuang Feng, and Jian
18 Zhai are responsible for planning the data analysis and analyzing the data resulting from the trial. All
19 named authors adhere to the authorship guidelines of Trials. All authors have agreed to publication.
20 All authors read and approved the final manuscript.
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34
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40 manuscript.
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51 **Conflict of interest**

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55 The authors have no conflicts of interest to declare.
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STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P2/10
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	P10
Funding	4	Sources and types of financial, material, and other support	P14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P14
	5b	Name and contact information for the trial sponsor	P14
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	P14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	P14
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	P3-4

	6b	Explanation for choice of comparators	NA
Objectives	7	Specific objectives or hypotheses	P4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	P4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	P5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	P5/16-21
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P5-6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	P6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	P6
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P6
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	P6-7
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	P7

1 2 3 4 5 6	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	P8
7 8 9	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P8

Methods: Assignment of interventions (for controlled trials)

Allocation:

14 15 16 17 18 19 20 21 22 23	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA
24 25 26 27 28 29 30	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA
31 32 33 34	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
35 36 37 38 39	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
40 41 42 43		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA

Methods: Data collection, management, and analysis

46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	P7
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1				
2		18b	Plans to promote participant retention and complete	P7
3			follow-up, including list of any outcome data to be	
4			collected for participants who discontinue or deviate	
5			from intervention protocols	
6				
7	Data	19	Plans for data entry, coding, security, and storage,	P7
8	management		including any related processes to promote data	
9			quality (eg, double data entry; range checks for data	
10			values). Reference to where details of data	
11			management procedures can be found, if not in the	
12			protocol	
13				
14				
15	Statistical	20a	Statistical methods for analysing primary and	P8
16	methods		secondary outcomes. Reference to where other	
17			details of the statistical analysis plan can be found, if	
18			not in the protocol	
19				
20				
21		20b	Methods for any additional analyses (eg, subgroup	P8
22			and adjusted analyses)	
23				
24		20c	Definition of analysis population relating to protocol	P8
25			non-adherence (eg, as randomised analysis), and	
26			any statistical methods to handle missing data (eg,	
27			multiple imputation)	
28				
29				
30	Methods: Monitoring			
31				
32	Data monitoring	21a	Composition of data monitoring committee (DMC);	P8
33			summary of its role and reporting structure;	
34			statement of whether it is independent from the	
35			sponsor and competing interests; and reference to	
36			where further details about its charter can be found,	
37			if not in the protocol. Alternatively, an explanation of	
38			why a DMC is not needed	
39				
40				
41		21b	Description of any interim analyses and stopping	P8
42			guidelines, including who will have access to these	
43			interim results and make the final decision to	
44			terminate the trial	
45				
46				
47	Harms	22	Plans for collecting, assessing, reporting, and	P8
48			managing solicited and spontaneously reported	
49			adverse events and other unintended effects of trial	
50			interventions or trial conduct	
51				
52				
53	Auditing	23	Frequency and procedures for auditing trial conduct,	P8
54			if any, and whether the process will be independent	
55			from investigators and the sponsor	
56				
57				
58	Ethics and dissemination			
59				
60				

1				
2	Research ethics	24	Plans for seeking research ethics	P9
3	approval		committee/institutional review board (REC/IRB)	
4			approval	
5				
6	Protocol	25	Plans for communicating important protocol	P10
7	amendments		modifications (eg, changes to eligibility criteria,	
8			outcomes, analyses) to relevant parties (eg,	
9			investigators, REC/IRBs, trial participants, trial	
10			registries, journals, regulators)	
11				
12				
13	Consent or	26a	Who will obtain informed consent or assent from	P9
14	assent		potential trial participants or authorised surrogates,	
15			and how (see Item 32)	
16				
17				
18		26b	Additional consent provisions for collection and use	NA
19			of participant data and biological specimens in	
20			ancillary studies, if applicable	
21				
22	Confidentiality	27	How personal information about potential and	P14
23			enrolled participants will be collected, shared, and	
24			maintained in order to protect confidentiality before,	
25			during, and after the trial	
26				
27				
28	Declaration of	28	Financial and other competing interests for principal	P14
29	interests		investigators for the overall trial and each study site	
30				
31	Access to data	29	Statement of who will have access to the final trial	P14
32			dataset, and disclosure of contractual agreements	
33			that limit such access for investigators	
34				
35	Ancillary and	30	Provisions, if any, for ancillary and post-trial care,	NA
36	post-trial care		and for compensation to those who suffer harm from	
37			trial participation	
38				
39				
40	Dissemination	31a	Plans for investigators and sponsor to communicate	P8
41	policy		trial results to participants, healthcare professionals,	
42			the public, and other relevant groups (eg, via	
43			publication, reporting in results databases, or other	
44			data sharing arrangements), including any	
45			publication restrictions	
46				
47				
48		31b	Authorship eligibility guidelines and any intended	NA
49			use of professional writers	
50				
51		31c	Plans, if any, for granting public access to the full	NA
52			protocol, participant-level dataset, and statistical	
53			code	
54				
55				

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.

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BMJ Open

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

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Keywords:	RADIOTHERAPY, Hepatobiliary tumours < ONCOLOGY, Adult oncology < ONCOLOGY

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Manuscripts

1
2 **Efficacy and safety of radiotherapy combined with atezolizumab plus bevacizumab in treating**
3
4 **hepatocellular carcinoma with portal vein tumor thrombus: A study protocol**
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6
7

8 **Short running title:** Radiotherapy plus T+A for HCC with PVTT
9

10
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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 tumor 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 enroll patients diagnosed with unresectable hepatocellular carcinoma 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 tumor (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 d 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% dropout 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.

Registration details: ChiCTR.org, registration number: ChiCTR2100049831.

1
2 **Keywords:** *Hepatocellular carcinoma, portal vein tumor thrombus, radiotherapy, atezolizumab,*
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4 *bevacizumab*

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8 **Strengths and limitations of this study**
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- 10
11 ● This study was a single-arm trial without a control group.
12
13 ● This study is an exploratory trial with a small sample size.
14
15 ● The conclusions of this study may serve as preliminary evidence for subsequent large-scale,
16
17 randomized, controlled clinical trials.
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24
25 **Introduction**
26

27
28 Liver cancer is the seventh most common cancer and the second most deadly cancer, with more than
29 900,000 new cases being diagnosed worldwide every year.¹ In China, the age-standardized annual
30 incidence of liver cancer is about 26.67/100,000,² while the 5-year survival rate is only around 12%.³
31
32 Hepatocellular carcinoma (HCC) is the most common histological subtype of primary liver cancer,⁴
33 and surgery is the preferred and most efficacious approach for the treatment of HCC. However, some
34 patients lose the chance for surgery at the time of diagnosis due to their intermediate to advanced
35 tumors, liver dysfunction, etc. ⁵ Local therapies (including radiotherapy) and systemic therapies are
36 important options for prolonging the survival of HCC patients who cannot undergo surgical resection.
37
38 Due to the promising antitumor activity and favorable safety profile in the IMbrave150 trial, with the
39 mortality risk being decreased by 42% compared with sorafenib,⁶ atezolizumab plus bevacizumab
40 have become the standard first-line therapy for unresectable HCC. Yet, the objective response rate
41 (ORR) with atezolizumab plus bevacizumab in unresectable HCC patients was reported to be only
42 27.3%.⁶ Hence, improving the therapeutic effect in patients is still a great clinical challenge.
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2 Vascular invasion and metastasis are commonly seen in patients with intermediate to advanced-stage
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4 HC, as 44%-62% of patients with advanced HCC have been reported to develop portal vein tumor
5
6 thrombosis (PVTT).⁷ In addition, the range and severity of PVTT have been significantly associated
7
8 with the prognosis of unresectable HCC patients, with the median overall survival being just 2.7 to 4
9
10 months in naive HCC patients with PVTT.⁸ However, there are significant differences between
11
12 eastern and western countries in the treatment strategies used for HCC patients with PVTT.⁹
13
14 Guidelines from western countries argue that HCC complicated with PVTT represents the advanced
15
16 stage of HCC, advocating sorafenib as the only treatment option.¹⁰⁻¹² On the contrary, eastern
17
18 countries adopt positive strategies, such as surgical resection, radiotherapy, transcatheter arterial
19
20 chemoembolization (TACE), and surgery combined with multidisciplinary therapies, which are
21
22 expected to improve the long-term survival of these patients.¹³⁻¹⁶
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27

28 Radiotherapy is recommended for unresectable HCC patients with types I, II, and III PVTT, whose
29
30 liver function is graded as Child-Pugh A and B. In addition, previous studies have shown that
31
32 radiotherapy can synergistically enhance the antitumor effect of immunotherapy and targeted therapy
33
34 by changing the tumor microenvironment.^{17 18} At present, radiotherapy combined with
35
36 immunotherapy and targeted therapy is currently one of the dominant research topics within the tumor
37
38 area. A number of studies have also suggested that radiotherapy combined with sorafenib alone
39
40 improves OS in patients with HCC complicated by PVTT,¹⁹ and the feasibility of concurrent
41
42 radiotherapy and sorafenib.^{20 21} In addition, the results of a previous retrospective study showed that
43
44 radiotherapy combined with atezolizumab plus bevacizumab was feasible in unresectable HCC.²²
45
46 However, whether the combination of radiotherapy and immunotherapy plus targeted therapy can
47
48 improve the efficacy in patients with HCC complicated by PVTT needs to be further verified.
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54 Therefore, we proposed an open-label, multicenter, single-arm phase II clinical trial. Patients
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56 diagnosed with locally advanced or metastatic and/or unresectable HCC complicated with PVTT will
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58 be preliminarily enrolled to explore the efficacy and safety of radiotherapy combined with
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1
2 atezolizumab plus bevacizumab, which is expected to provide an efficacious therapeutic regimen for
3
4 HCC patients with PVTT and further improve the treatment response and prognosis. Here, we present
5
6 the protocol in accordance with the SPIRIT reporting checklist.
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9

10 **Methods and analysis**

13 **Study design and objective**

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17 This open-label, multicenter, single-arm clinical trial will enroll patients diagnosed with locally
18
19 advanced or metastatic and/or unresectable HCC complicated with PVTT from the departments of
20
21 hepatobiliary surgery of our Hospitals between August 2021 and December 2021 so as to initially
22
23 exploring the efficacy and safety of radiotherapy combined with atezolizumab plus bevacizumab in
24
25 naive patients with unresectable HCC complicated by PVTT.
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28

29 **Eligibility criteria**

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31
32
33 The key inclusion criteria are as follows: 1) Males or non-pregnant females aged between 18 and 70
34
35 years old; 2) Signed informed consent form; 3) Able to comply with the study protocol according to
36
37 the investigator's judgment; 4) Histologically, cytologically or clinically diagnosed with
38
39 hepatocellular carcinoma (HCC); 5) Confirmed portal vein tumor thrombus by imaging findings; 6)
40
41 Not suitable for radical surgical treatment; 7) Have not received any antitumor treatment; 8) At least
42
43 one measurable untreated lesion (per RECIST 1.1); 9) Pre-treatment tumor tissue sample (if available);
44
45 10) ECOG Performance Status of 0 or 1 within 7 days prior to initiation of study treatment; 11) Child-
46
47 Pugh class A within 7 days prior to initiation of study treatment; 12) Adequate hematologic and organ
48
49 functions, based on the following laboratory test results obtained within 7 days prior to initiation of
50
51 study treatment; 13) Resolution of any acute, clinically significant treatment-related toxicity from
52
53 prior therapy to grade < 1 prior to study entry, with the exception of alopecia; 14) Negative HIV test
54
55 at screening.
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2 The key exclusion criteria are as follows: 1) History of the leptomenigeal disease; 2) Active or
3
4 history of autoimmune disease or immune deficiency; 3) History of idiopathic pulmonary fibrosis,
5
6 organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic
7
8 pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan.
9
10 History of radiation pneumonitis in the radiation field (fibrosis) is permitted; 4) Active tuberculosis;
11
12
13 5) Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac
14
15 disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to initiation of
16
17 study treatment, unstable arrhythmia, or unstable angina; 6) History of congenital long QT syndrome
18
19 or corrected QT interval > 500 ms (calculated with the use of the Fridericia method) at screening; 7)
20
21 History of uncorrectable electrolyte disorder affecting serum levels of potassium, calcium, or
22
23 magnesium; 8) The major surgical procedure, other than for diagnosis, within 4 weeks prior to
24
25 initiation of study treatment, or anticipation of the need for a major surgical procedure during the
26
27 study; 9) History of malignancy other than HCC within 5 years prior to screening; 10) Severe
28
29 infection within 4 weeks prior to initiation of study treatment; 11) Treatment with therapeutic oral or
30
31 intravenous antibiotics within 2 weeks prior to initiation of study treatment; 12) Prior allogeneic stem
32
33 cell or solid organ transplantation; 13) Untreated or incompletely treated esophageal and/or gastric
34
35 varices that are bleeding or have a high risk for bleeding; 15) Co-infection of HBV and HCV; 16)
36
37 Symptomatic, untreated, or actively progressing central nervous system (CNS) metastases.
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45 **Treatment plan**

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47 Patients will initially receive intensity-modulated radiotherapy (IMRT) with each cycle for 28 days.
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49 A treatment plan will be established after CT location. The clinical target volume (CTV) includes
50
51 tumors and tumor thrombi. The planning target volume (PTV) will be expanded by 0.5-1.0 cm, with
52
53 conventional fractionation at a single dose of 180-220 cGy. Total DT will be 40 Gy/20 f/26 d. CT
54
55 scan will be performed at the end of every cycle, and the treatment plan will be reformulated after
56
57 field constriction. The treatment will continue until the total DT is up to 54-56 Gy/27-28 f.
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2 The treatment with atezolizumab plus bevacizumab will be started at 3 ± 1 d after the initiation of
3
4 IMRT. Each treatment cycle will last for 21 days. On the first day of each cycle, atezolizumab
5
6 injection will be intravenously administered at a fixed dose of 1,200 mg (initial intravenous injection
7
8 for 60 min, and subsequent intravenous injections for 30 min if well-tolerated). Bevacizumab at a
9
10 dose of 15 mg/kg will be intravenously administered at least 5 min apart (initial intravenous injection
11
12 for 90 min, and subsequent intravenous injections reduced to 60 min and 30 min if well-tolerated).
13
14 The treatment was discontinued when there was no additional clinical benefit, as judged by the
15
16 investigator (based on imaging, biochemical indicators, and clinical status of the patient). Then, the
17
18 patient received the guideline-recommended second-line therapy.
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24 Delayed treatment or dose reduction will be determined by the clinical team, and the specific
25
26 adjustment plan will be determined by the investigator based on the patient's clinical condition. In
27
28 case of severe toxicity, the administration will be delayed, and/or the dose will be reduced. If any
29
30 serious adverse event (SAE) occurs during the radiotherapy, or the radiotherapy is delayed for more
31
32 than 4 weeks for any reason, radiotherapy sessions will be terminated. The doses of atezolizumab and
33
34 bevacizumab will be adjusted according to the drug's instructions.
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36
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38 39 **Endpoints**

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41
42 The primary endpoint is ORR, which is defined as the proportion of patients with Complete Response
43
44 (CR) and Partial Response (PR). CR or PR is assessed in accordance with Response
45
46 Evaluation Criteria In Solid Tumors (RECIST) 1.1. The responses will be independently evaluated
47
48 by three to six experienced senior physicians who are not investigators in this study.
49
50
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52
53 Secondary endpoints include (1) OS, defined as the time between the first study treatment and
54
55 death (for any reason). (2) Disease control rate (DCR), defined as the percentage of subjects with the
56
57 best response as CR, PR, or stable disease (SD). (3) Progression-free survival (PFS), defined as the
58
59 time between the first treatment and the first tumor progression or appearance of a new lesion or death
60

1
2 due to any cause, whichever occurs first. (4) Time to progression (TTP), defined as the time between
3
4 the first treatment to first tumor progression. (5) Duration of response (DOR), defined as the time
5
6 from first tumor remission to first tumor progression or death due to any cause. The DCRs, PFSs,
7
8 TTPs, and DORs will be calculated in accordance with the RECIST version 1.1, modified RECIST
9
10 (mRECIST), and immune-modified RECIST (imRECIST), respectively. (6) The rate of surgical
11
12 conversions is defined as the proportion of subjects who receive the study treatment and are assessed
13
14 to be viable for surgical resection. The resectability criteria include successful down-staging of the
15
16 tumor, sufficient future liver remnant (FLR), and technically resectable assessed by the investigator.
17
18 The definition of successful downstaging was based on the CSCO guideline, which was 1) stage Ia,
19
20 Ib, and IIa, 2) IIb, if the tumor is confined to the same segment or the same side of the liver or
21
22 intraoperative radiofrequency ablation can be performed at the same time to treat the lesions outside
23
24 the resection range, and 3) IIIa/b, if the tumor is confined to the hemi-liver, and it is expected that the
25
26 tumor thrombus can be completely removed during the operation, surgical resection of the tumor and
27
28 thrombectomy through the portal vein can be considered.
29
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35 Adverse events (AEs) are assessed in accordance with the NCI Common Terminology Criteria for
36
37 Adverse Events (CTCAE V5.0). Monitoring will be performed from the date on which the patient
38
39 signs the informed consent to 90 days after the last treatment.
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43 Biomarkers for exploratory endpoints include metagenomic sequencing of fecal organisms, five gene
44
45 indexes of hepatocellular carcinoma (HN1, RAN, RAMP3, KRT19, TAF9), immune correlation
46
47 detection (programmed death-ligand 1 [PD-L1] expression, CD8 expression; microsatellite instability
48
49 [MSI], and tumor mutational burden [TMB], immune-related gene expression, RNA-seq) and other
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51 checkpoint proteins and cell surface markers.
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55 56 **Participant timeline**

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Table 1 lists the time points for assessing efficacy, adverse events, laboratory safety assessments (hematology, coagulation, and chemistry), physical examination, electrocardiogram (ECG), and tumor measurements.

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Table 1. Schema of Single-arm Clinical Trial

Item	Screening Period		Treatment Period			Perioperative Period	End of Trial	Survival Follow-up
	-28 - 0d	-7 - 0d	4 weeks after the first treatment session	7 weeks after the first treatment session	n cycles		30 days after checkout	
Window period (days)	—	—					±7	
Informed consent	×							
Demographics								
Past medical history	×							
History of tumor treatment								
Physical examination		×	×	Every 3 weeks		×	×	
Vital signs		×	×	Every 3 weeks		×	×	
ECOG		×	×	Every 3 weeks			×	
Pregnancy test		×					×	
Infection screening	×						×	
Imaging	×		×	Every 6 weeks			×	×
Tumor markers		×	×	Every 6 weeks			×	
Echocardiography	×						×	
Tumor tissue	×							
12-lead electrocardiogram		×	When clinically indicated				×	
Blood biochemistry		×	×	Every 3 weeks			×	
Routine blood test		×	×	Every 3 weeks			×	

1									
2									
3									
4	Routine urine test	×	×		Every 3 weeks				×
5									
6	Routine stool test	×	×		Every 3 weeks				×
7									
8	Thyroid function, pituitary								
9		×	×		Every 3 weeks				×
10	function, coagulation								
11	Gut microbiome testing for								
12		×			×				×
13	the stool sample								
14	Biomarker testing for the								
15		×			×				×
16	blood sample								
17	Surgical resection							×	
18									
19	Surgical complications							×	
20									
21	Concomitant medication	×	×	×	Every 3 weeks				×
22									
23	Adverse events	×	×	×	Every 3 weeks				×
24									
25	Compliance evaluation	×	×	×	Every 3 weeks				
26									
27	Dispensing of drugs			×	Every 3 weeks				
28									
29	Recovery of drugs			×	Every 3 weeks				×
30									
31	Follow-up on survival status								
32									
33	and antitumor treatment								×
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2 Furthermore, for the testing of biomarkers as exploratory endpoints, stool and blood samples will be
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4 collected from patients prior to the first treatment, at 7 weeks after the first treatment, and after
5
6 treatment discontinuation, respectively.
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10 **Data collection and management**

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13 The completed CRFs will be submitted to the respective sites for archiving. All data will be recorded
14
15 in an electronic case report form (eCRF) by investigators or clinical research coordinators. All study
16
17 documents will be confidential. All study data, including confirmation of all patients (effective check
18
19 on recorded information, such as study cases), all original copies of signed ICFs, as well as detailed
20
21 original records of drug distribution, shall be kept uniformly by the study institution until 5 years after
22
23 the end of the trial.
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27

28 **Statistical methods**

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31 According to the results of IMbrave150,⁶ the ORR of atezolizumab plus bevacizumab in unresectable
32
33 HCC patients was 27.3%. The lack of evidence of atezolizumab, bevacizumab and radiotherapy in
34
35 patients with HCC and PVTT led to the difficulty of an evidence-based estimated ORR. Instead, we
36
37 searched for literatures of other systemic regimens combined with radiotherapy and found out the
38
39 ORR was 61.1% in HCC patients with PVTT treated with sorafenib and MIRT in a retrospective
40
41 study.²³ Hence, assuming an ORR of 47% after discussion among investigators based on the
42
43 experience, with a two-sided alpha error of 0.1, 90% power, and 10% dropout rate, the required
44
45 number of evaluable patients is 42.
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51
52 The efficacy assessment is based on the full analysis set (FAS). The intention-to-treat (ITT) efficacy
53
54 analysis will be performed for subjects who received at least one session of the study treatment based
55
56 on the FAS. No supplementation will be made for missing values. The safety analysis set (SAS)
57
58 includes all enrolled subjects who have received at least one session of study treatment and have a
59
60 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 serious adverse events occur. Any adverse events 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, multicenter, single-arm clinical trial was

1
2 designed to preliminarily explore the efficacy and safety of radiotherapy combined with atezolizumab
3
4 plus bevacizumab in naive unresectable HCC patients with PVTT.
5
6

7
8 There are several limitations in the present study that should be considered. First, this is a single-arm
9
10 clinical trial without a control group that could be used to compare the efficacy and safety between
11
12 treatment regimens. Second, since this study is an exploratory trial with a small sample size, no
13
14 confirmatory efficacy conclusions can be drawn. The conclusions of this study may serve as
15
16 preliminary evidence for subsequent large-scale, randomized, controlled clinical trials.
17
18

19
20 As the prognosis in unresectable HCC patients with PVTT remains poor, there is an urgent need to
21
22 find an efficacious and safe therapeutic regimen. In this study, the efficacy and safety of IMRT
23
24 combined with atezolizumab plus bevacizumab in native unresectable HCC patients with PVTT will
25
26 be investigated so as to explore a new therapeutic regimen and further improve the efficacy and
27
28 prognosis in these patients.
29
30

31 32 33 **Ethics and dissemination**

34
35
36 This study will be conducted according to the standards of Good Clinical Practice and in compliance
37
38 with the principles of the Declaration of Helsinki. The Ethics Committee of our Hospital has approved
39
40 the protocol (EHBHKY2021-K-017). All participants are required to provide written informed
41
42 consent. The results of the trial will be published in peer-reviewed journals and presented at
43
44 international conferences.
45
46

47 48 49 **Trial status**

50
51
52 The trial has been registered in ChiCTR.org (Registration number: ChiCTR2100049831; registration
53
54 date: 2021-08-10; <http://www.chictr.org.cn/showproj.aspx?proj=126593>). Recruitment is ongoing.
55
56 The protocol version number is 1.0. The study protocol has been reported in accordance with the
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58 Standard Protocol Items: Recommendations for Clinical Interventional Trials (SPIRIT) guidelines.
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The authors would like to thank the patients, their families, and all the investigators who will participate in the present study.

Data Sharing Statement

We will widely disseminate the results of this clinical trial through conference presentations and publications in relevant journals. All evaluation forms, reports, and other records will be identified in a manner designed to maintain participants' confidentiality. All records will be kept in a secure storage area with limited access. Data during the study are available from the study leader upon reasonable request.

Authors' contributions

Kang Wang and Yan-Jun Xiang drafted the manuscript. Kang Wang, Yan-Jun Xiang, and Hong-Ming Yu contributed equally to this work. Shu-Qun Cheng, Kang Wang, Yan-Jun Xiang, and Hong-Ming Yu designed the trial. Yu-Qiang Cheng, Qian-Zhi Ni, Wei-Xing Guo, Jie Shi, Shuang Feng, and Jian Zhai are responsible for planning the data analysis and analyzing 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.

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2 **Conflict of interest**
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5 The authors have no conflicts of interest to declare.
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For peer review only

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P2/10
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	P10
Funding	4	Sources and types of financial, material, and other support	P14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P14
	5b	Name and contact information for the trial sponsor	P14
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	P14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	P14
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	P3-4

1				
2		6b	Explanation for choice of comparators	NA
3				
4	Objectives	7	Specific objectives or hypotheses	P4
5				
6	Trial design	8	Description of trial design including type of trial (eg,	P4
7			parallel group, crossover, factorial, single group),	
8			allocation ratio, and framework (eg, superiority,	
9			equivalence, noninferiority, exploratory)	
10				
11				
12	Methods: Participants, interventions, and outcomes			
13				
14	Study setting	9	Description of study settings (eg, community clinic,	P5
15			academic hospital) and list of countries where data	
16			will be collected. Reference to where list of study	
17			sites can be obtained	
18				
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If	P5/16-21
20			applicable, eligibility criteria for study centres and	
21			individuals who will perform the interventions (eg,	
22			surgeons, psychotherapists)	
23				
24				
25	Interventions	11a	Interventions for each group with sufficient detail to	P5-6
26			allow replication, including how and when they will	
27			be administered	
28				
29				
30		11b	Criteria for discontinuing or modifying allocated	P6
31			interventions for a given trial participant (eg, drug	
32			dose change in response to harms, participant	
33			request, or improving/worsening disease)	
34				
35		11c	Strategies to improve adherence to intervention	P6
36			protocols, and any procedures for monitoring	
37			adherence (eg, drug tablet return, laboratory tests)	
38				
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40		11d	Relevant concomitant care and interventions that	P6
41			are permitted or prohibited during the trial	
42				
43	Outcomes	12	Primary, secondary, and other outcomes, including	P6-7
44			the specific measurement variable (eg, systolic	
45			blood pressure), analysis metric (eg, change from	
46			baseline, final value, time to event), method of	
47			aggregation (eg, median, proportion), and time point	
48			for each outcome. Explanation of the clinical	
49			relevance of chosen efficacy and harm outcomes is	
50			strongly recommended	
51				
52				
53	Participant	13	Time schedule of enrolment, interventions (including	P7
54	timeline		any run-ins and washouts), assessments, and visits	
55			for participants. A schematic diagram is highly	
56			recommended (see Figure)	
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2	Sample size	14	Estimated number of participants needed to achieve	P8
3			study objectives and how it was determined,	
4			including clinical and statistical assumptions	
5			supporting any sample size calculations	
6				
7	Recruitment	15	Strategies for achieving adequate participant	P8
8			enrolment to reach target sample size	
9				

Methods: Assignment of interventions (for controlled trials)

Allocation:

14	Sequence	16a	Method of generating the allocation sequence (eg,	NA
15	generation		computer-generated random numbers), and list of	
16			any factors for stratification. To reduce predictability	
17			of a random sequence, details of any planned	
18			restriction (eg, blocking) should be provided in a	
19			separate document that is unavailable to those who	
20			enrol participants or assign interventions	
21				
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24	Allocation	16b	Mechanism of implementing the allocation sequence	NA
25	concealment		(eg, central telephone; sequentially numbered,	
26	mechanism		opaque, sealed envelopes), describing any steps to	
27			conceal the sequence until interventions are	
28			assigned	
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30				
31	Implementation	16c	Who will generate the allocation sequence, who will	NA
32			enrol participants, and who will assign participants	
33			to interventions	
34				
35	Blinding	17a	Who will be blinded after assignment to	NA
36	(masking)		interventions (eg, trial participants, care providers,	
37			outcome assessors, data analysts), and how	
38				
39				
40		17b	If blinded, circumstances under which unblinding is	NA
41			permissible, and procedure for revealing a	
42			participant's allocated intervention during the trial	
43				

Methods: Data collection, management, and analysis

46	Data collection	18a	Plans for assessment and collection of outcome,	P7
47	methods		baseline, and other trial data, including any related	
48			processes to promote data quality (eg, duplicate	
49			measurements, training of assessors) and a	
50			description of study instruments (eg, questionnaires,	
51			laboratory tests) along with their reliability and	
52			validity, if known. Reference to where data collection	
53			forms can be found, if not in the protocol	
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2		18b	Plans to promote participant retention and complete	P7
3			follow-up, including list of any outcome data to be	
4			collected for participants who discontinue or deviate	
5			from intervention protocols	
6				
7	Data	19	Plans for data entry, coding, security, and storage,	P7
8	management		including any related processes to promote data	
9			quality (eg, double data entry; range checks for data	
10			values). Reference to where details of data	
11			management procedures can be found, if not in the	
12			protocol	
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15	Statistical	20a	Statistical methods for analysing primary and	P8
16	methods		secondary outcomes. Reference to where other	
17			details of the statistical analysis plan can be found, if	
18			not in the protocol	
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21		20b	Methods for any additional analyses (eg, subgroup	P8
22			and adjusted analyses)	
23				
24		20c	Definition of analysis population relating to protocol	P8
25			non-adherence (eg, as randomised analysis), and	
26			any statistical methods to handle missing data (eg,	
27			multiple imputation)	
28				
29				
30	Methods: Monitoring			
31				
32	Data monitoring	21a	Composition of data monitoring committee (DMC);	P8
33			summary of its role and reporting structure;	
34			statement of whether it is independent from the	
35			sponsor and competing interests; and reference to	
36			where further details about its charter can be found,	
37			if not in the protocol. Alternatively, an explanation of	
38			why a DMC is not needed	
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41		21b	Description of any interim analyses and stopping	P8
42			guidelines, including who will have access to these	
43			interim results and make the final decision to	
44			terminate the trial	
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47	Harms	22	Plans for collecting, assessing, reporting, and	P8
48			managing solicited and spontaneously reported	
49			adverse events and other unintended effects of trial	
50			interventions or trial conduct	
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53	Auditing	23	Frequency and procedures for auditing trial conduct,	P8
54			if any, and whether the process will be independent	
55			from investigators and the sponsor	
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Ethics and dissemination

1				
2	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P9
3				
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6	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	P10
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13	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P9
14				
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18		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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22	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	P14
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28	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P14
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31	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	P14
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35	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
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40	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P8
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48		31b	Authorship eligibility guidelines and any intended use of professional writers	NA
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51		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
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Appendices

1				
2	Informed consent	32	Model consent form and other related	NA
3	materials		documentation given to participants and authorised	
4			surrogates	
5				
6	Biological	33	Plans for collection, laboratory evaluation, and	NA
7	specimens		storage of biological specimens for genetic or	
8			molecular analysis in the current trial and for future	
9			use in ancillary studies, if applicable	
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12 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013
13 Explanation & Elaboration for important clarification on the items. Amendments to the
14 protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT
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BMJ Open

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

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Primary Subject Heading:	Oncology
Secondary Subject Heading:	Oncology
Keywords:	RADIOTHERAPY, Hepatobiliary tumours < ONCOLOGY, Adult oncology < ONCOLOGY

SCHOLARONE™
Manuscripts

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2 **Efficacy and safety of radiotherapy combined with atezolizumab plus bevacizumab in treating**
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4 **hepatocellular carcinoma with portal vein tumor thrombus: A study protocol**
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8 **Short running title:** Radiotherapy plus T+A for HCC with PVTT
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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 tumor 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 enroll patients diagnosed with unresectable hepatocellular carcinoma 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 tumor (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 d 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% dropout 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.

Registration details: ChiCTR.org, registration number: ChiCTR2100049831.

Keywords: *Hepatocellular carcinoma, portal vein tumor thrombus, radiotherapy, atezolizumab, bevacizumab*

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, randomized, 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-standardized 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 tumors, 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 antitumor activity and favorable 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 tumor

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2 thrombosis (PVTT).⁷ In addition, the range and severity of PVTT have been significantly associated
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4 with the prognosis of unresectable HCC patients, with the median overall survival being just 2.7 to 4
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6 months in naive HCC patients with PVTT.⁸ However, there are significant differences between
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8 eastern and western countries in the treatment strategies used for HCC patients with PVTT.⁹
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10 Guidelines from western countries argue that HCC complicated with PVTT represents the advanced
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12 stage of HCC, advocating sorafenib as the only treatment option.¹⁰⁻¹² On the contrary, eastern
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14 countries adopt positive strategies, such as surgical resection, radiotherapy, transcatheter arterial
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16 chemoembolization (TACE), and surgery combined with multidisciplinary therapies, which are
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18 expected to improve the long-term survival of these patients.¹³⁻¹⁶
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24 Radiotherapy is recommended for unresectable HCC patients with types I, II, and III PVTT, whose
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26 liver function is graded as Child-Pugh A and B. In addition, previous studies have shown that
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28 radiotherapy can synergistically enhance the antitumor effect of immunotherapy and targeted therapy
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30 by changing the tumor microenvironment.¹⁷⁻¹⁸ At present, radiotherapy combined with
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32 immunotherapy and targeted therapy is currently one of the dominant research topics within the tumor
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34 area. A number of studies have also suggested that radiotherapy combined with sorafenib alone
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36 improves OS in patients with HCC complicated by PVTT,¹⁹ and the feasibility of concurrent
37
38 radiotherapy and sorafenib.²⁰⁻²¹ In addition, the results of a previous retrospective study showed that
39
40 radiotherapy combined with atezolizumab plus bevacizumab was feasible in unresectable HCC.²²
41
42 However, whether the combination of radiotherapy and immunotherapy plus targeted therapy can
43
44 improve the efficacy in patients with HCC complicated by PVTT needs to be further verified.
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51 Therefore, we proposed an open-label, multicenter, single-arm phase II clinical trial. Patients
52
53 diagnosed with locally advanced or metastatic and/or unresectable HCC complicated with PVTT will
54
55 be preliminarily enrolled to explore the efficacy and safety of radiotherapy combined with
56
57 atezolizumab plus bevacizumab, which is expected to provide an efficacious therapeutic regimen for
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1 HCC patients with PVTT and further improve the treatment response and prognosis. Here, we present
2 the protocol in accordance with the SPIRIT reporting checklist.
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6

7 **Methods and analysis**

8 **Study design and objective**

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10
11 This open-label, multicenter, single-arm clinical trial will enroll patients diagnosed with locally
12 advanced or metastatic and/or unresectable HCC complicated with PVTT from the departments of
13 hepatobiliary surgery of our Hospitals between August 2021 and December 2021 so as to initially
14 exploring the efficacy and safety of radiotherapy combined with atezolizumab plus bevacizumab in
15 naive patients with unresectable HCC complicated by PVTT.
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26 **Eligibility criteria**

27 The inclusion criteria are as follows:
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34 1. Men or non-pregnant women aged 18 to 70 years. 2. Sign the informed consent. 3. The
35 investigator believes that the patient has the ability to comply with the research protocol. 4.
36 Hepatocellular carcinoma (HCC) is diagnosed by histology or cytology or clinically. Patients with
37 liver cirrhosis are clinically diagnosed by AASLD criteria, and patients without liver cirrhosis need
38 to be diagnosed by histology. 5. Imaging examination confirmed the existence of portal vein tumor
39 thrombus. 6. The disease is not suitable for radical surgery. 7. Have not received any anti-tumor
40 therapy before. 8. At least 1 measurable (measurable according to RECIST1.1), untreated lesions. 9.
41 Pre-treatment tumor tissue samples (if available). If tumor tissue is available, submit 1 formalin-fixed,
42 paraffin-embedded (FFPE) tumor sample in a paraffin block (preferred), or approximately 10-15
43 slides containing unstained, freshly cut, serial sections radiographs, together with a relevant pathology
44 report within 4 weeks of enrollment. If the FFPE samples described above are not available, any type
45 of sample (including fine needle aspiration biopsy samples, cell mass samples [eg, from pleural
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2 effusions], and lavage samples) is acceptable. A relevant pathology report should be provided with
3
4 the sample. If tumor tissue was not available (e.g., exhausted due to previous diagnostic testing), the
5
6 patient was still eligible to participate in the study. 10. ECOG performance status score of 0 or 1
7
8 within 7 days before enrollment. 11. Child-Pugh Grade A within 7 days before enrollment. 12.
9
10 Adequate hematology and organ function, based on the following laboratory test results obtained
11
12 within 7 days prior to enrollment (unless otherwise stated): (1) Absolute neutrophil count $\geq 1.5 \times 10^9/L$
13
14 (1500/ μL), without granulocyte colony-stimulating factor support; (2) Lymphocyte count $\geq 0.5 \times 10^9/L$
15
16 (500/ μL); (3) Platelet count $\geq 75 \times 10^9/L$ (75000/ μL), no blood transfusion; hemoglobin ≥ 90 g/L, in
17
18 order to meet this criterion, blood transfusion is allowed to the patient; (4) Alanine aminotransferase,
19
20 aspartate aminotransferase and alkaline phosphatase ≤ 5 times the upper limit of normal (ULN); (5)
21
22 Serum bilirubin ≤ 3 times the ULN; (6) Serum creatinine ≤ 1.5 times the ULN or calculated creatinine
23
24 clearance ≥ 50 mL/min (calculated using the Cockcroft-Gault formula); (7) Serum albumin ≥ 28 g/L
25
26 (2.8 g/dL); (8) Patients not receiving anticoagulation therapy: international normalized ratio or
27
28 activated partial thromboplastin time ≤ 2 times the ULN; (9) Proteinuria $< 2+$ in urine cellulose test
29
30 strip (performed within 7 days before the initiation of study treatment); (10) Patients with a baseline
31
32 cellulose dipstick urine test result of $\geq 2+$ proteinuria should collect 24-hour urine, and then must
33
34 confirm that the urine protein content within 24 hours is less than 1 g. 13. Any acute, clinically
35
36 significant treatment-related toxicity (due to previous treatment) must have been alleviated to \leq grade
37
38 1 before enrolling in the study, except for alopecia; 14. Human immunodeficiency virus antibody test
39
40 results are negative at the time of screening; 15. Patients with active hepatitis B virus (HBV) infection:
41
42 HBV-DNA < 500 IU/mL obtained within 28 days before the start of study treatment, and received
43
44 anti-HBV treatment for at least 14 days before entering the study (treatment according to local
45
46 standard treatment, such as entecavir) and are willing to continue receiving treatment during the study;
47
48 16. Women of childbearing age must have a negative pregnancy test before starting treatment, and
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50 women of childbearing age and men (having sex with women of childbearing age) must agree to use
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2 without interruption during treatment and for 6 months after the last therapeutic dose is administered
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4 to be effective Contraception.
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6
7 The exclusion criteria are as follows:
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10
11 1. History of leptomeningitis. 2. Current or past autoimmune disease or immunodeficiency, including
12
13 but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus,
14
15 rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener's
16
17 granulomatosis, Sjgre's syndrome, Guillain-Barré syndrome, or multiple sclerosis, with the following
18
19 exceptions: patients with prior autoimmune-related hypothyroidism receiving thyroid hormone
20
21 replacement therapy are eligible for study participation; patients receiving insulin therapy Patients
22
23 with controlled type 1 diabetes were eligible for study participation; only patients with
24
25 dermatologically manifested eczema, psoriasis, chronic lichen simplex, or vitiligo (eg, excluding
26
27 patients with psoriatic arthritis), provided All of the following conditions are eligible to participate in
28
29 the study: (1) The rash area must be less than 10% of the body surface area; (2) Good disease control
30
31 at baseline, requiring only low-efficiency topical glucocorticoid therapy; (3) In the past 12 months,
32
33 the pre-existing conditions did not require psoralen plus A-band UV radiation, methotrexate, vitamin
34
35 A acid, biological agents, oral calcineurin inhibitors, or highly effective or Acute exacerbations of
36
37 oral glucocorticoid therapy. 3. Idiopathic pulmonary fibrosis, organizing pneumonia (eg, bronchiolitis
38
39 obliterans), drug-induced pneumonia, or idiopathic pneumonia or evidence of active pneumonia on
40
41 chest computed tomography (CT) images during screening. Radiation pneumonitis in the permissible
42
43 radiation zone (fibrosis). 4. Known active tuberculosis. 5. Major cardiovascular disease within 3
44
45 months prior to initiation of study treatment (such as New York Heart Association class II or more
46
47 severe heart disease, myocardial infarction or cerebrovascular accident within 3 months prior to
48
49 initiation of study treatment), unstable Arrhythmia or unstable angina. 6. History of congenital long
50
51 QT syndrome or corrected QT interval at screening >500ms (calculated using Fridericia method). 7.
52
53 History of uncorrectable serum potassium, calcium or magnesium electrolyte disturbances. 8.
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1
2 Received major surgery (except for diagnosis) within 4 weeks before starting the study treatment or
3
4 is expected to undergo major surgery during the study period. 9. Malignant tumors other than HCC
5
6 within 5 years prior to screening, except for malignancies with negligible risk of metastasis or death
7
8 (eg, 5-year OS rate >90%), such as adequately treated in situ cervical cancer, Non-melanoma skin
9
10 cancer, localized prostate cancer, ductal carcinoma in situ, or stage I uterine cancer. 10. Severe
11
12 infection within 4 weeks prior to initiation of study treatment, including but not limited to
13
14 hospitalization due to complications of infection, bacteremia or severe pneumonia. 11. Oral or
15
16 intravenous therapeutic antibiotics within 2 weeks prior to initiation of study treatment. Patients
17
18 receiving prophylactic antibiotics (eg, to prevent urinary tract infections or exacerbations of chronic
19
20 obstructive pulmonary disease) are eligible to participate in the study. 12. Previous allogeneic stem
21
22 cell or solid organ transplantation. 13. Received a live attenuated vaccine within 4 weeks before
23
24 starting study treatment, or is expected to receive such a vaccine during atezolizumab treatment or
25
26 within 5 months after the last dose of atezolizumab. 14. Patients with untreated or incompletely
27
28 treated esophageal and/or gastric varices with associated bleeding or at high risk of bleeding. Before
29
30 enrollment, patients must undergo B-ultrasound, CT, MRI, or liver elastography to assess the size of
31
32 all varicose veins (small to large) and treat according to local standard of care. Patients who have
33
34 received corresponding examinations within 6 months before starting study treatment do not need to
35
36 be reexamined. 15. Co-infection with HBV and hepatitis C virus (HCV). Patients with a history of
37
38 HCV infection but negative PCR results for HCV RNA can be considered HCV-uninfected. 16.
39
40 Symptomatic, untreated or progressively progressive central nervous system (CNS) metastases.
41
42 Asymptomatic patients with treated CNS lesions were eligible for study participation as long as all
43
44 of the following criteria were met: Must have disease outside the CNS measurable according to
45
46 RECIST v1.1; patients had no history of intracranial or intraspinal hemorrhage; metastases limited to
47
48 the cerebellum or supratentorial (ie, no midbrain, pons, medulla, or spinal cord metastases); no
49
50 evidence of progression between completion of CNS-directed therapy and initiation of study
51
52 treatment; patients not receiving stereotaxic within 28 days prior to initiation of study
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1
2 Targeted, whole-brain radiotherapy, and/or neurosurgical resection; patients did not require
3
4 continuous glucocorticoid therapy for CNS disease. Dose-stabilized anticonvulsant therapy is
5
6 permitted. Asymptomatic patients with newly detected CNS metastases at screening are eligible to
7
8 participate in the study after radiotherapy or surgery without repeat screening brain scan results. 17.
9
10 The patient cannot receive follow-up or is participating in other clinical trials. 18. Subjects deemed
11
12 unsuitable for inclusion in this study by the investigator..
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14
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16

17 **Treatment plan**

18
19
20 Patients will initially receive intensity-modulated radiotherapy (IMRT) with each cycle for 28 days.
21
22 A treatment plan will be established after CT location. The clinical target volume (CTV) includes
23
24 tumors and tumor thrombi. The planning target volume (PTV) will be expanded by 0.5-1.0 cm, with
25
26 conventional fractionation at a single dose of 180-220 cGy. Total DT will be 40 Gy/20 f/26 d. CT
27
28 scan will be performed at the end of every cycle, and the treatment plan will be reformulated after
29
30 field constriction. The treatment will continue until the total DT is up to 54-56 Gy/27-28 f.
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32
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34

35 The treatment with atezolizumab plus bevacizumab will be started at 3 ± 1 d after the initiation of
36
37 IMRT. Each treatment cycle will last for 21 days. On the first day of each cycle, atezolizumab
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39 injection will be intravenously administered at a fixed dose of 1,200 mg (initial intravenous injection
40
41 for 60 min, and subsequent intravenous injections for 30 min if well-tolerated). Bevacizumab at a
42
43 dose of 15 mg/kg will be intravenously administered at least 5 min apart (initial intravenous injection
44
45 for 90 min, and subsequent intravenous injections reduced to 60 min and 30 min if well-tolerated).
46
47 The treatment was discontinued when there was no additional clinical benefit, as judged by the
48
49 investigator (based on imaging, biochemical indicators, and clinical status of the patient). Then, the
50
51 patient received the guideline-recommended second-line therapy.
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57 Delayed treatment or dose reduction will be determined by the clinical team, and the specific
58
59 adjustment plan will be determined by the investigator based on the patient's clinical condition. In
60

1
2 case of severe toxicity, the administration will be delayed, and/or the dose will be reduced. If any
3
4 serious adverse event (SAE) occurs during the radiotherapy, or the radiotherapy is delayed for more
5
6 than 4 weeks for any reason, radiotherapy sessions will be terminated. The doses of atezolizumab and
7
8 bevacizumab will be adjusted according to the drug's instructions.
9

10 11 12 **Endpoints** 13

14
15 The primary endpoint is ORR, which is defined as the proportion of patients with Complete Response
16
17 (CR) and Partial Response (PR). CR or PR is assessed in accordance with Response
18
19 Evaluation Criteria In Solid Tumors (RECIST) 1.1. The responses will be independently evaluated
20
21 by three to six experienced senior physicians who are not investigators in this study.
22
23
24
25

26
27 Secondary endpoints include (1) OS, defined as the time between the first study treatment and
28
29 death (for any reason). (2) Disease control rate (DCR), defined as the percentage of subjects with the
30
31 best response as CR, PR, or stable disease (SD). (3) Progression-free survival (PFS), defined as the
32
33 time between the first treatment and the first tumor progression or appearance of a new lesion or death
34
35 due to any cause, whichever occurs first. (4) Time to progression (TTP), defined as the time between
36
37 the first treatment to first tumor progression. (5) Duration of response (DOR), defined as the time
38
39 from first tumor remission to first tumor progression or death due to any cause. The DCRs, PFSs,
40
41 TTPs, and DORs will be calculated in accordance with the RECIST version 1.1, modified RECIST
42
43 (mRECIST), and immune-modified RECIST (imRECIST), respectively. (6) The rate of surgical
44
45 conversions is defined as the proportion of subjects who receive the study treatment and are assessed
46
47 to be viable for surgical resection. The resectability criteria include successful down-staging of the
48
49 tumor, sufficient future liver remnant (FLR), and technically resectable assessed by the investigator.
50
51 The definition of successful downstaging was based on the CSCO guideline, which was 1) stage Ia,
52
53 Ib, and IIa, 2) IIb, if the tumor is confined to the same segment or the same side of the liver or
54
55 intraoperative radiofrequency ablation can be performed at the same time to treat the lesions outside
56
57 the resection range, and 3) IIIa/b, if the tumor is confined to the hemi-liver, and it is expected that the
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1
2 tumor thrombus can be completely removed during the operation, surgical resection of the tumor and
3
4 thrombectomy through the portal vein can be considered.
5
6

7
8 Adverse events (AEs) are assessed in accordance with the NCI Common Terminology Criteria for
9
10 Adverse Events (CTCAE V5.0). Monitoring will be performed from the date on which the patient
11
12 signs the informed consent to 90 days after the last treatment.
13
14

15
16 Biomarkers for exploratory endpoints include metagenomic sequencing of fecal organisms, five gene
17
18 indexes of hepatocellular carcinoma (HN1, RAN, RAMP3, KRT19, TAF9), immune correlation
19
20 detection (programmed death-ligand 1 [PD-L1] expression, CD8 expression; microsatellite instability
21
22 [MSI], and tumor mutational burden [TMB], immune-related gene expression, RNA-seq) and other
23
24 checkpoint proteins and cell surface markers.
25
26

27 28 **Participant timeline** 29

30
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32 **Table 1** lists the time points for assessing efficacy, adverse events, laboratory safety assessments
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34 (hematology, coagulation, and chemistry), physical examination, electrocardiogram (ECG), and
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36 tumor measurements.
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Table 1. Schema of Single-arm Clinical Trial

Item	Screening Period		Treatment Period			Perioperative Period	End of Trial	Survival Follow-up
	-28 - 0d	-7 - 0d	4 weeks after the first treatment session	7 weeks after the first treatment session	n cycles		30 days after checkout	
Window period (days)	—	—					±7	
Informed consent	×							
Demographics								
Past medical history	×							
History of tumor treatment								
Physical examination		×	×	Every 3 weeks		×	×	
Vital signs		×	×	Every 3 weeks		×	×	
ECOG		×	×	Every 3 weeks			×	
Pregnancy test		×					×	
Infection screening	×						×	
Imaging	×		×	Every 6 weeks			×	×
Tumor markers		×	×	Every 6 weeks			×	
Echocardiography	×						×	
Tumor tissue	×							
12-lead electrocardiogram		×	When clinically indicated				×	
Blood biochemistry		×	×	Every 3 weeks			×	
Routine blood test		×	×	Every 3 weeks			×	

1									
2									
3									
4	Routine urine test	×	×		Every 3 weeks				×
5									
6	Routine stool test	×	×		Every 3 weeks				×
7									
8	Thyroid function, pituitary								
9		×	×		Every 3 weeks				×
10	function, coagulation								
11	Gut microbiome testing for								
12		×			×				×
13	the stool sample								
14	Biomarker testing for the								
15		×			×				×
16	blood sample								
17	Surgical resection							×	
18									
19	Surgical complications							×	
20									
21	Concomitant medication	×	×	×	Every 3 weeks				×
22									
23	Adverse events	×	×	×	Every 3 weeks				×
24									
25	Compliance evaluation	×	×	×	Every 3 weeks				
26									
27	Dispensing of drugs			×	Every 3 weeks				
28									
29	Recovery of drugs			×	Every 3 weeks				×
30									
31	Follow-up on survival status								
32									
33	and antitumor treatment								×
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2 Furthermore, for the testing of biomarkers as exploratory endpoints, stool and blood samples will be
3
4 collected from patients prior to the first treatment, at 7 weeks after the first treatment, and after
5
6 treatment discontinuation, respectively.
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8
9

10 **Data collection and management**

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12

13 The completed CRFs will be submitted to the respective sites for archiving. All data will be recorded
14
15 in an electronic case report form (eCRF) by investigators or clinical research coordinators. All study
16
17 documents will be confidential. All study data, including confirmation of all patients (effective check
18
19 on recorded information, such as study cases), all original copies of signed ICFs, as well as detailed
20
21 original records of drug distribution, shall be kept uniformly by the study institution until 5 years after
22
23 the end of the trial.
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28 **Statistical methods**

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32 According to the results of IMbrave150,⁶ the ORR of atezolizumab plus bevacizumab in unresectable
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34 HCC patients was 27.3%. The lack of evidence of atezolizumab, bevacizumab and radiotherapy in
35
36 patients with HCC and PVTT led to the difficulty of an evidence-based estimated ORR. Instead, we
37
38 searched for literatures of other systemic regimens combined with radiotherapy and found out the
39
40 ORR was 61.1% in HCC patients with PVTT treated with sorafenib and MIRT in a retrospective
41
42 study.²³ Hence, assuming an ORR of 47% after discussion among investigators based on the
43
44 experience, with a two-sided alpha error of 0.1, 90% power, and 10% dropout rate, the required
45
46 number of evaluable patients is 42.
47
48
49
50

51 The efficacy assessment is based on the full analysis set (FAS). The intention-to-treat (ITT) efficacy
52
53 analysis will be performed for subjects who received at least one session of the study treatment based
54
55 on the FAS. No supplementation will be made for missing values. The safety analysis set (SAS)
56
57 includes all enrolled subjects who have received at least one session of study treatment and have a
58
59 post-treatment safety record. This dataset will be used for safety analysis.
60

Monitoring

An independent Data and Safety Monitoring Committee has been established to assess the safety data if serious adverse events occur. Any adverse events 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, multicenter, single-arm clinical trial was

1
2 designed to preliminarily explore the efficacy and safety of radiotherapy combined with atezolizumab
3
4 plus bevacizumab in naive unresectable HCC patients with PVTT.
5
6

7
8 There are several limitations in the present study that should be considered. First, this is a single-arm
9
10 clinical trial without a control group that could be used to compare the efficacy and safety between
11
12 treatment regimens. Second, since this study is an exploratory trial with a small sample size, no
13
14 confirmatory efficacy conclusions can be drawn. The conclusions of this study may serve as
15
16 preliminary evidence for subsequent large-scale, randomized, controlled clinical trials.
17
18

19
20 As the prognosis in unresectable HCC patients with PVTT remains poor, there is an urgent need to
21
22 find an efficacious and safe therapeutic regimen. In this study, the efficacy and safety of IMRT
23
24 combined with atezolizumab plus bevacizumab in native unresectable HCC patients with PVTT will
25
26 be investigated so as to explore a new therapeutic regimen and further improve the efficacy and
27
28 prognosis in these patients.
29
30

31 32 33 **Ethics and dissemination**

34
35
36 This study will be conducted according to the standards of Good Clinical Practice and in compliance
37
38 with the principles of the Declaration of Helsinki. The Ethics Committee of our Hospital has approved
39
40 the protocol (EHBHKY2021-K-017). All participants are required to provide written informed
41
42 consent. The results of the trial will be published in peer-reviewed journals and presented at
43
44 international conferences.
45
46

47 48 49 **Trial status**

50
51
52 The trial has been registered in ChiCTR.org (Registration number: ChiCTR2100049831; registration
53
54 date: 2021-08-10; <http://www.chictr.org.cn/showproj.aspx?proj=126593>). Recruitment is ongoing.
55
56 The protocol version number is 1.0. The study protocol has been reported in accordance with the
57
58 Standard Protocol Items: Recommendations for Clinical Interventional Trials (SPIRIT) guidelines.
59
60

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Data Sharing Statement

We will widely disseminate the results of this clinical trial through conference presentations and publications in relevant journals. All evaluation forms, reports, and other records will be identified in a manner designed to maintain participants' confidentiality. All records will be kept in a secure storage area with limited access. Data during the study are available from the study leader upon reasonable request.

Authors' contributions

Kang Wang and Yan-Jun Xiang drafted the manuscript. Kang Wang, Yan-Jun Xiang, and Hong-Ming Yu contributed equally to this work. Shu-Qun Cheng, Kang Wang, Yan-Jun Xiang, and Hong-Ming Yu designed the trial. Yu-Qiang Cheng, Qian-Zhi Ni, Wei-Xing Guo, Jie Shi, Shuang Feng, and Jian Zhai are responsible for planning the data analysis and analyzing 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.

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1
2 **Conflict of interest**
3
4

5 The authors have no conflicts of interest to declare.
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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P2/10
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	P10
Funding	4	Sources and types of financial, material, and other support	P14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P14
	5b	Name and contact information for the trial sponsor	P14
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	P14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	P14
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	P3-4

1				
2		6b	Explanation for choice of comparators	NA
3				
4	Objectives	7	Specific objectives or hypotheses	P4
5				
6	Trial design	8	Description of trial design including type of trial (eg,	P4
7			parallel group, crossover, factorial, single group),	
8			allocation ratio, and framework (eg, superiority,	
9			equivalence, noninferiority, exploratory)	
10				
11				
12	Methods: Participants, interventions, and outcomes			
13				
14	Study setting	9	Description of study settings (eg, community clinic,	P5
15			academic hospital) and list of countries where data	
16			will be collected. Reference to where list of study	
17			sites can be obtained	
18				
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If	P5/16-21
20			applicable, eligibility criteria for study centres and	
21			individuals who will perform the interventions (eg,	
22			surgeons, psychotherapists)	
23				
24				
25	Interventions	11a	Interventions for each group with sufficient detail to	P5-6
26			allow replication, including how and when they will	
27			be administered	
28				
29				
30		11b	Criteria for discontinuing or modifying allocated	P6
31			interventions for a given trial participant (eg, drug	
32			dose change in response to harms, participant	
33			request, or improving/worsening disease)	
34				
35		11c	Strategies to improve adherence to intervention	P6
36			protocols, and any procedures for monitoring	
37			adherence (eg, drug tablet return, laboratory tests)	
38				
39				
40		11d	Relevant concomitant care and interventions that	P6
41			are permitted or prohibited during the trial	
42				
43	Outcomes	12	Primary, secondary, and other outcomes, including	P6-7
44			the specific measurement variable (eg, systolic	
45			blood pressure), analysis metric (eg, change from	
46			baseline, final value, time to event), method of	
47			aggregation (eg, median, proportion), and time point	
48			for each outcome. Explanation of the clinical	
49			relevance of chosen efficacy and harm outcomes is	
50			strongly recommended	
51				
52				
53	Participant	13	Time schedule of enrolment, interventions (including	P7
54	timeline		any run-ins and washouts), assessments, and visits	
55			for participants. A schematic diagram is highly	
56			recommended (see Figure)	
57				
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2	Sample size	14	Estimated number of participants needed to achieve	P8
3			study objectives and how it was determined,	
4			including clinical and statistical assumptions	
5			supporting any sample size calculations	
6				
7	Recruitment	15	Strategies for achieving adequate participant	P8
8			enrolment to reach target sample size	
9				

Methods: Assignment of interventions (for controlled trials)

Allocation:

14	Sequence	16a	Method of generating the allocation sequence (eg,	NA
15	generation		computer-generated random numbers), and list of	
16			any factors for stratification. To reduce predictability	
17			of a random sequence, details of any planned	
18			restriction (eg, blocking) should be provided in a	
19			separate document that is unavailable to those who	
20			enrol participants or assign interventions	
21				
22				
23				
24	Allocation	16b	Mechanism of implementing the allocation sequence	NA
25	concealment		(eg, central telephone; sequentially numbered,	
26	mechanism		opaque, sealed envelopes), describing any steps to	
27			conceal the sequence until interventions are	
28			assigned	
29				
30				
31	Implementation	16c	Who will generate the allocation sequence, who will	NA
32			enrol participants, and who will assign participants	
33			to interventions	
34				
35	Blinding	17a	Who will be blinded after assignment to	NA
36	(masking)		interventions (eg, trial participants, care providers,	
37			outcome assessors, data analysts), and how	
38				
39				
40		17b	If blinded, circumstances under which unblinding is	NA
41			permissible, and procedure for revealing a	
42			participant's allocated intervention during the trial	
43				

Methods: Data collection, management, and analysis

46	Data collection	18a	Plans for assessment and collection of outcome,	P7
47	methods		baseline, and other trial data, including any related	
48			processes to promote data quality (eg, duplicate	
49			measurements, training of assessors) and a	
50			description of study instruments (eg, questionnaires,	
51			laboratory tests) along with their reliability and	
52			validity, if known. Reference to where data collection	
53			forms can be found, if not in the protocol	
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2		18b	Plans to promote participant retention and complete	P7
3			follow-up, including list of any outcome data to be	
4			collected for participants who discontinue or deviate	
5			from intervention protocols	
6				
7	Data	19	Plans for data entry, coding, security, and storage,	P7
8	management		including any related processes to promote data	
9			quality (eg, double data entry; range checks for data	
10			values). Reference to where details of data	
11			management procedures can be found, if not in the	
12			protocol	
13				
14				
15	Statistical	20a	Statistical methods for analysing primary and	P8
16	methods		secondary outcomes. Reference to where other	
17			details of the statistical analysis plan can be found, if	
18			not in the protocol	
19				
20				
21		20b	Methods for any additional analyses (eg, subgroup	P8
22			and adjusted analyses)	
23				
24		20c	Definition of analysis population relating to protocol	P8
25			non-adherence (eg, as randomised analysis), and	
26			any statistical methods to handle missing data (eg,	
27			multiple imputation)	
28				
29				
30	Methods: Monitoring			
31				
32	Data monitoring	21a	Composition of data monitoring committee (DMC);	P8
33			summary of its role and reporting structure;	
34			statement of whether it is independent from the	
35			sponsor and competing interests; and reference to	
36			where further details about its charter can be found,	
37			if not in the protocol. Alternatively, an explanation of	
38			why a DMC is not needed	
39				
40				
41		21b	Description of any interim analyses and stopping	P8
42			guidelines, including who will have access to these	
43			interim results and make the final decision to	
44			terminate the trial	
45				
46				
47	Harms	22	Plans for collecting, assessing, reporting, and	P8
48			managing solicited and spontaneously reported	
49			adverse events and other unintended effects of trial	
50			interventions or trial conduct	
51				
52				
53	Auditing	23	Frequency and procedures for auditing trial conduct,	P8
54			if any, and whether the process will be independent	
55			from investigators and the sponsor	
56				
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Ethics and dissemination

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1				
2	Research ethics	24	Plans for seeking research ethics	P9
3	approval		committee/institutional review board (REC/IRB)	
4			approval	
5				
6	Protocol	25	Plans for communicating important protocol	P10
7	amendments		modifications (eg, changes to eligibility criteria,	
8			outcomes, analyses) to relevant parties (eg,	
9			investigators, REC/IRBs, trial participants, trial	
10			registries, journals, regulators)	
11				
12				
13	Consent or	26a	Who will obtain informed consent or assent from	P9
14	assent		potential trial participants or authorised surrogates,	
15			and how (see Item 32)	
16				
17				
18		26b	Additional consent provisions for collection and use	NA
19			of participant data and biological specimens in	
20			ancillary studies, if applicable	
21				
22	Confidentiality	27	How personal information about potential and	P14
23			enrolled participants will be collected, shared, and	
24			maintained in order to protect confidentiality before,	
25			during, and after the trial	
26				
27				
28	Declaration of	28	Financial and other competing interests for principal	P14
29	interests		investigators for the overall trial and each study site	
30				
31	Access to data	29	Statement of who will have access to the final trial	P14
32			dataset, and disclosure of contractual agreements	
33			that limit such access for investigators	
34				
35	Ancillary and	30	Provisions, if any, for ancillary and post-trial care,	NA
36	post-trial care		and for compensation to those who suffer harm from	
37			trial participation	
38				
39				
40	Dissemination	31a	Plans for investigators and sponsor to communicate	P8
41	policy		trial results to participants, healthcare professionals,	
42			the public, and other relevant groups (eg, via	
43			publication, reporting in results databases, or other	
44			data sharing arrangements), including any	
45			publication restrictions	
46				
47				
48		31b	Authorship eligibility guidelines and any intended	NA
49			use of professional writers	
50				
51		31c	Plans, if any, for granting public access to the full	NA
52			protocol, participant-level dataset, and statistical	
53			code	
54				
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56	Appendices			
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2	Informed consent	32	Model consent form and other related	NA
3	materials		documentation given to participants and authorised	
4			surrogates	
5				
6	Biological	33	Plans for collection, laboratory evaluation, and	NA
7	specimens		storage of biological specimens for genetic or	
8			molecular analysis in the current trial and for future	
9			use in ancillary studies, if applicable	
10				

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12 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013
13 Explanation & Elaboration for important clarification on the items. Amendments to the
14 protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT
15 Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)"
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