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# BMJ Open

## Protocol of Notable-HCC: a phase Ib study of neoadjuvant Tislelizumab with stereotactic body radiotherapy in patients with resectable hepatocellular carcinoma

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4 **Protocol of Notable-HCC: a phase Ib study of neoadjuvant Tislelizumab**  
5 **with stereotactic body radiotherapy in patients with resectable**  
6 **hepatocellular carcinoma**  
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## Abstract

**Introduction** Liver resection is the mainstay of curative-intended treatment of hepatocellular carcinoma (HCC), but post-operative 5-year recurrence rate reach 70%, so far there is no adjuvant or neoadjuvant therapies recommended by major HCC guidelines that can reduce the risk of recurrence. In the recent decade, significant progression is achieved in the systemic treatment of HCC, mainly from immune checkpoint inhibitors (ICIs) and targeted therapy. In other malignancies, neoadjuvant ICIs shows better outcome than adjuvant setting. On the other hand, the addition of radiation to ICIs incrementally improves the systemic response from ICIs. Neoadjuvant therapy of ICIs plus SBRT (stereotactic body radiotherapy) has shown promising results in several types of solid tumors but not HCC. **Methods and analysis** Here we describe a phase Ib clinical trial of neoadjuvant SBRT plus PD-1 (Tislelizumab) prior to hepatic resection in HCC patients. Prior to resection, eligible HCC patients will receive 8 Gy × 3 fractions SBRT together with 2 cycles of tislelizumab with an interval of 3 weeks. HCC resection is scheduled 4 weeks after the second dose of tislelizumab, followed by adjuvant tislelizumab of 1 year. Primary study endpoints include: delay of surgery, tumor response, safety and tolerability of the sequential SBRT/tislelizumab, other endpoints are disease-free survival (DFS) and overall survival (OS) rate every 3 or 6 months after the surgery. **Ethics and dissemination** This trial has been approved by the Ethics Committee of Shandong Cancer Hospital and Institute (SDZLEC2022-021-01). The final results of this trial will be published in a peer-reviewed journal after completion. **Patient and public involvement** No patient involved. **Trial registration** ClinicalTrials.gov: NCT05185531.

## Strengths and limitations of this study

- We expect that this clinical trial can expand our knowledge about neoadjuvant therapy of HCC, thus improve the outcome of HCC resection.
- The results of this trial will be the first step to explore the combination of ICI and radiotherapy as the neoadjuvant therapy for resectable HCC
- The main limitations of this trial include limited sample number, design of single arm and lack of controlled group (upfront resection without neoadjuvant ICI plus SBRT, or the adjuvant setting of the combination)

**Key words**

clinical trial, hepatocellular carcinoma (HCC), neoadjuvant therapy, immune checkpoint inhibitor (ICI), stereotactic body radiotherapy (SBRT)

## **Background and rationale**

Hepatocellular carcinoma (HCC) remains prevalent worldwide, it accounts for 75% to 85% of all primary liver cancer (PLC). In 2020, PLC is the 6<sup>th</sup> most commonly diagnosed cancer but the 3<sup>rd</sup> leading cancer killer worldwide, only after lung cancer and colorectal cancer<sup>1</sup>.

Surgical therapies (hepatic resection, liver transplantation and ablation in well-selected patients) remains the backbone of curative therapies for HCC. In patients who meet guidelines and undergo resection, 5-year survival rate with these modalities is over 60%<sup>2</sup>. However, the global HCC BRIDGE study that cover 8656 newly diagnosed HCC patients from 20 leading worldwide liver centers show, less than 10% of HCC patients are “ideal” candidates for liver resection, and 27% received resection in the real-world scenario<sup>3</sup>. Since 70% of them will experience recurrence within 5 years after resection<sup>2</sup>, so theoretically, only less than 10% patients can be cured by surgery. So far neither adjuvant nor neoadjuvant therapies are recommended by major HCC guidelines<sup>4,5</sup>, because they have not been proven to improve the outcome of patients treated with resection to reduce the risk of recurrence, but EASL Clinical Practice Guidelines has encouraged further clinical trials with new agents for these applications<sup>4</sup>.

In the recent decade, systemic treatment of HCC with targeted therapies and immune checkpoint inhibitors (ICIs) has achieved great progress. In the real-world scenario, sequential systemic therapy has been able to prolong median OS (overall survival) in selected advanced HCC patients to over 3 years<sup>6</sup>. Despite this significant achievement, systemic treatment alone still can hardly cure HCC.



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4 Taking these data together, a very straightforward ontology can be arrived at: If ICIs (mono- or  
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6 combined with other systemic modalities) can be effectively applied to adjuvant and/or  
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8 neoadjuvant therapies, significantly more HCC patients will be expected to experience long-term  
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10 survival or even cure.  
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15 Meanwhile, the anti-tumor effect of radiation therapy (RT) has been attributed primarily to its  
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17 enhancement of local control. RT also has an effect on tumor immunity and an additional anti-  
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19 tumor effect can be expected if ICIs are administered simultaneously with RT.  
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### 23 24 **Methods/design**

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27 Notable-HCC is a phase Ib study of neoadjuvant stereotactic body radiotherapy (SBRT) plus  
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29 immune checkpoint inhibitor (ICI) prior to hepatic resection in adult patients (aged  $\geq 18$  years)  
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31 with HCC.  
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35  
36 Tislelizumab (BGB-A317) is a human monoclonal antibody (HuMAb; immunoglobulin G4  
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38 [IgG4]) manufactured by BeiGene that inhibits the PD-1 receptor on cell surface. It is engineered  
39  
40 with a nullified Fc portion of the antibody to minimize binding to Fc  $\gamma$  R on macrophages in order  
41  
42 to abrogate antibody-dependent phagocytosis, a mechanism of T-cell clearance and potential  
43  
44 resistance to anti-PD-1 therapy<sup>7</sup>.  
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50 Eligible patients will receive SBRT (8 Gy  $\times$  3 fractions, every other day) on day 1, day 3 and day  
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52 5; the first dose of Tislelizumab will be administrated concurrently on day 1, then the second on  
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54 day 22 (the first day of week 4,  $\pm 3$  days). Then on day 50 (the first day of week 8,  $\pm 7$  days),  
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56 curative liver resection of HCC will be scheduled.  
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### **Eligibility criteria**

In brief, Notable-HCC will recruit HCC patients who are candidate for hepatic resection, with a confirmed diagnosis of HCC by biopsy or by noninvasive diagnostic criteria of the American Association for the Study of the Liver (AASLD).

### **Inclusion Criteria:**

1. Written informed consent for the trial.
2. Aged  $\geq 18$  years
3. Willing to provide tissue from an excisional biopsy of a tumor lesion
4. Confirmed diagnosis of HCC. The diagnosis can be established radiographically by the criteria of the American Association for the Study of the Liver (AASLD), or by histologic diagnosis from the core biopsy.
5. Have measurable disease by Computed Tomography (CT)-scan or Magnetic Resonance Imaging (MRI) defined by RECIST (Response Evaluation Criteria In Solid Tumours) 1.1 criteria and HCC specific mRECIST (modified RECIST).
6. Medically fit to undergo surgery as determined by the treating medical and surgical oncology team
7. ECOG (Eastern Cooperative Oncology Group) performance status 0 or 1
8. Adequate organ and marrow function as defined below:

- 1) leukocytes  $\geq 3,000/\text{mcL}$
- 2) absolute neutrophil count  $\geq 1,500/\text{mcL}$
- 3) platelets  $\geq 100,000/\text{mcL}$
- 4) total bilirubin  $\leq 2 \times$  institutional upper limit of normal (ULN)
- 5) AST (aspartate aminotransferase)/ALT(alanine aminotransferase)  $\leq 3 \times$  institutional ULN
- 6) creatinine  $\leq 1.5 \times$  institutional ULN OR
- 7) estimated glomerular filtration rate (GFR)  $\geq 50 \text{ mL}/\text{min}/1.73 \text{ m}^2$  (according to the Cockcroft-Gault formula)
9. Overall Child-Pugh class A
10. Documented virology status of hepatitis, as confirmed by screening tests for HBV (hepatitis B virus) and HCV (hepatitis C virus)
  - 1) For patients with active HBV: HBV DNA  $< 2000 \text{ IU}/\text{mL}$  during screening, and have initiated anti-HBV treatment at least 14 days prior to SBRT and willingness to continue anti-HBV treatment during the study (per local standard of care; e.g., entecavir).
  - 2) Patients with HCV, either with resolved infection (as evidenced by detectable antibody and negative viral load) or chronic infection (as evidenced by detectable HCV RNA), are eligible.

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4 11. Participants with a prior or concurrent malignancy whose natural history or treatment  
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6 does not have the potential to interfere with the safety or efficacy assessment of the  
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9 investigational regimen are eligible for this trial.  
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13 12. Female patient of childbearing potential should have a negative serum pregnancy test  
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15 within 24 h of her first dose of IMP (Investigational Medicinal Product)  
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19 13. Women of childbearing potential must be willing to use a highly effective method of  
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21 contraception for the course of the study through 5 months after the last dose of IMP.  
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24 Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for  
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26 the patient.  
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30 14. Sexually active males must agree to use an adequate method of contraception starting  
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32 with the first dose of IMP through 7 months after the last dose of study therapy. Note:  
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35 Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the  
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38 patient.  
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42 **Exclusion Criteria:**  
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- 45 1. Extrahepatic metastasis  
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49 2. Prior systemic anticancer treatment for HCC, including an anti-PD-1, anti-PD-L1 or anti-  
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51 CTLA-4 antibody  
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55 3. Prior orthotopic liver transplantation  
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59 4. Prior abdominal irradiation  
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- 4 5. Any major surgery within the 3 weeks prior to enrolment
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- 8 6. Hepatic encephalopathy
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- 11 7. Ascites that is refractory to diuretic therapy
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- 14 8. Is currently receiving anti-cancer therapy (chemotherapy, radiation therapy,
- 15 immunotherapy or biologic therapy) or has participated or is participating in a study of an
- 16 IMP or used an investigational device within 4 weeks of the first dose of IMP
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- 23 9. Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form
- 24 of immunosuppressive therapy
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- 30 10. Known history of active Bacillus Tuberculosis (TB)
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- 33 11. History of known hypersensitivity to any monoclonal antibody or any of their excipients
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- 37 12. Known additional malignancy that is progressing or requires active treatment. Exceptions
- 38 include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has
- 39 undergone potentially curative therapy, or in situ cervical cancer
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- 45 13. Active autoimmune disease that has required systemic treatment in the past 2 years (i.e.
- 46 with use of disease modifying agents, corticosteroids or immunosuppressive drugs).
- 47
- 48 Replacement therapy (eg. thyroxine, insulin, or physiologic corticosteroid replacement
- 49 therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic
- 50 treatment
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4 14. Active infection requiring systemic therapy, with exceptions relating to Hepatitis B and C  
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6 virus infection  
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- 10 15. History or current evidence of any condition, therapy, or laboratory abnormality that  
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12 might confound the results of the trial, interfere with the patient's participation for the full  
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14 duration of the trial, or is not in the best interest of the patient to participate, in the  
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16 opinion of the treating Principal Investigator (PI)  
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- 20 21 16. Known psychiatric or substance abuse disorders that would interfere with cooperation  
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23 with the requirements of the trial  
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- 28 17. Pregnant or breastfeeding  
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- 31 18. Known history of Human Immunodeficiency Virus (HIV; HIV 1/2 antibodies)  
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- 35 19. Received a live vaccine within 30 days of first dose of IMP administration.  
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### 38 **Study procedures**

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41 Patients will undergo baseline tumour imaging including computed tomography (CT) scan of the  
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43 chest, abdomen and pelvis, and by contrast enhanced magnetic resonance imaging (MRI) scan of  
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45 the liver at screening. At post-treatment time-points prior to surgery (on Day 50), 4 weeks after  
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47 surgery and then every 3 months after the surgery, tumour imaging will be repeated using contrast  
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49 enhanced MRI. A triple-phase CT of the liver is an acceptable alternative for intrahepatic staging  
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51 in patients with contraindications to MRI. Baseline CT/MRI scans do not need to be repeated if  
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4 obtained within 35 days of first SBRT. The same method used for assessment at baseline must  
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6 then be used at all subsequent time points.  
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10 Participants will require a full hepatitis serology screen prior to enrolment into the study, this  
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12 includes Hepatitis B and Hepatitis C Virus serology. In patients with positive serology for either  
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14 virus, baseline HBV DNA and HCV quantitative RNA levels will be requested. Participants who  
15  
16 are confirmed to have chronic and active hepatitis B and/or C (i.e. with detectable HBV DNA or  
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18 HCV RNA at baseline) will have their viral load (HCV RNA and/or HBV DNA as appropriate)  
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21 monitored at each cycle and at the end of treatment follow-up visit.  
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27 A baseline core tumor biopsy and PBMC (Peripheral Blood Mononuclear Cell) will be collected  
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29 from participants at screening, and sample tumor tissue from the surgical specimen will be snap-  
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31 frozen and stored for the future relevant studies.  
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35 Treatment will consist of 8 Gy  $\times$  3 fractions SBRT together with 2 cycles of tislelizumab 200mg  
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37 administered intravenously with an interval of 3 weeks.  
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41 Patients will be reviewed following completion of SBRT and tislelizumab treatment (Follow-up  
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43 visit 1; FU1) prior to surgery. Before surgery, Response Evaluation Criteria in Solid Tumors,  
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45 version 1.1 (RECIST v1.1) and HCC-Specific mRECIST criteria will be used to determine patient  
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47 response to treatment, including CR (complete response), PR (partial response) and ORR  
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49 (objective response rate). PBMC will be collected again.  
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54 Hepatic resection will be performed as per standard of care. The safety FU2 will be conducted  
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56 after the first dose of the post-resection tislelizumab. All AEs that occur prior to the visit will be  
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4 recorded. Participants with on-going AEs at the visit will be followed up by principal investigator  
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6 (PI) or delegate until resolution or stabilization of the event. Following FU2, participants will be  
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8 assessed every 3 months ( $\pm 7$  days) thereafter to collect information regarding disease status and  
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10 survival. Long-term follow-up will continue, for each patient, for a total of 2 years.  
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### 15 **Outcome measures and endpoints**

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18 Primary study endpoints include: number of patients experiencing a surgery delay over 6 weeks or  
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20 later, ORR on pre-resection imaging according to the RECIST v1.1/ mRECIST criteria, pathologic  
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22 response rate on evaluation of the resected specimen, and determination of safety and tolerability  
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24 of the sequential SBRT/tislelizumab based on National Cancer Institute Common Terminology  
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26 Criteria for Adverse Events (NCI CTCAE) v5.0 criteria. Secondary endpoints are DFS and OS  
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28 rate every 3 or 6 months after the hepatic resection. Exploratory endpoints include patients'  
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30 immune response, morbidity and mortality of the surgery.  
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### 38 **Discussion**

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41 The effect of ICIs in the adjuvant therapeutic setting of HCC are being evaluated in serials of  
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43 clinical trials<sup>8</sup>, we are optimistic for the results to come in the near future. Compared to this, the  
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45 possible roles of ICIs in the neoadjuvant setting of HCC remains a much less touched field<sup>9</sup>. The  
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47 reason for this may arise from some concerns about the nature of neoadjuvant therapy itself before  
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49 curative surgery. If patients do not respond to the therapy, they will suffer disease progression,  
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51 some can even jeopardize the opportunity of curative surgery. Severe adverse effect from the  
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53 neoadjuvant therapy can delay the resection or increase the risk of morbidity. For ICIs in  
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4 neoadjuvant therapy, immune-related adverse events (irAEs) and hyper-progression can  
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6 potentially bring more danger to patients.  
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10 On the other hand, neoadjuvant therapy also has some advantages compared to adjuvant therapy.  
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12 The existence of the target tumor permits the direct evaluation of the treatment, the recognition of  
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14 the responders from non-responders, the validation of the surrogate predictors, the timely  
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16 adjustment of treatment, etc.; and the resected specimen can provide pathologic evaluation of the  
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18 treatment and facilitate translational studies.  
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24 In the context of cancer immunotherapy, neoadjuvant treatment may offer another very important  
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26 additional advantage; immunotherapies enhance T-cell activation the moment antigen is  
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28 encountered. Exposure to antigen during the period in which the major tumor mass is present may  
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30 increase the breadth and durability of tumor-specific T-cell responses. While in adjuvant setting,  
31  
32 the immunotherapy starts when the tumor, together with its antigens have been totally removed<sup>10</sup>.  
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35 In melanoma, most recent data has showed the advantage of ICIs in neoadjuvant than in adjuvant  
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37 therapies<sup>11 12</sup>.  
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44 In a randomized, open label, perioperative phase II trial, effect of nivolumab alone or nivolumab  
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46 plus ipilimumab in patients with resectable HCC were evaluated. The study was reported to reach  
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48 its primary endpoint of safety. Importantly, it achieved a 40% pathologic response rate (pCR rate  
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50 of 24%, and major necrosis rate of 16%) for resectable HCC after preoperative immunotherapy.  
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54 The author argued that these findings may favor the perioperative treatment of resectable HCC by  
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56 ICIs after future validation<sup>13</sup>. Another two similar clinical trials are still ongoing (NCT03222076,  
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58 NCT03510871).  
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4 For patients with resectable HCC and portal vein tumor thrombus (PVTT), neoadjuvant 3-D  
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6 conformal radiotherapy provided significantly better postoperative survival outcomes than surgery  
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8 alone<sup>14</sup>. Mounting evidences are showing the synergistic effects on local and distant tumour  
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10 control when radiation therapy is combined with immunotherapy<sup>15</sup>.  
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15 The antitumor effect of radiation can be attributed to inducing tumour cell death through DNA  
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17 damage, but radiotherapy also has immune modulatory effects and can stimulate the immune  
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19 response through various mechanisms<sup>15</sup>. Although radiotherapy can enhance antitumor effects, its  
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21 potential immunosuppressive effects can also restrain antitumor efficacy, including the up-  
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23 regulation of co-inhibitory ligands such as PD-L1<sup>16 17</sup>. Combining radiotherapy with immune  
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25 checkpoint blockade can overcome these immunosuppressive mechanisms and augment antitumor  
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27 immunity.  
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35 In a recent single-center, randomised phase 2 trial in early-stage non-small-cell lung cancer  
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37 (NSCLC), combination of stereotactic body radiotherapy (SBRT) to neoadjuvant durvalumab is  
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39 well tolerated and associated with a high major pathological response rate<sup>18</sup>.  
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44 Another important issue is the different sequence of RT and ICI, which may have differential  
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46 effects on the outcomes of cancer patients. There is relative agreement in published work  
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48 regarding the preclinical effects of sequencing, and various studies have shown that concurrent  
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50 radiation and ICIs immunotherapy is better than sequential treatments; giving radiation before  
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52 ICIs might result in antigen presentation in a tolerogenic environment with fully active  
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54 checkpoints. Similarly, the efficacy of ICIs alone before radiation might be restricted as a result of  
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56 diminished inflammatory cell death and reduced antigenic targets for the immune system to focus  
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4 on<sup>15</sup>. This schedule was also adopted by the above-mentioned neoadjuvant trials of SBRT plus  
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6 ICI in NSCLC <sup>18</sup>. In the recent animal model study of abscopal antitumor immune responses<sup>19</sup>, as  
7  
8 well as in the clinical study in melanoma brain metastases<sup>20</sup>, ICIs start after radiation shows better  
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10 outcome compare to the reverse sequence. Taking considerations of the experiences from the  
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12 literature, as well as the possible unexpected side effects or additive toxicities could potentially  
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14 occur in the combination therapy, in this planned trial, we also adopt concurrent PD-1 and SBRT  
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16 as neoadjuvant therapy for resectable HCC.  
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23 In general, we hope the results from this clinical trial can expand our knowledge about  
24  
25 neoadjuvant therapy of HCC, esp. by the combination of ICI and RT, thus improve the outcome of  
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27 HCC resection.  
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### 32 **Contributorship statement**

33  
34 LZ designs the clinical trial and applies the funding; LZ, BZ and XS are the chief liver surgeons  
35  
36 performing the surgery; JY is the chief radiation oncologist performing the radiotherapy; KC, LL,  
37  
38 CZ, PS, JZ, ZL are liver surgeons participating the surgery.  
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### 44 **Competing interests**

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47 LZ is on the speakers' bureau for BiGene, Bayer, MSD, Roche, Innovent, Hengrui Medicine. This  
48  
49 trial is partly funded by BeiGene.  
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# BMJ Open

## Protocol of Notable-HCC: A phase Ib study of neoadjuvant tislelizumab with stereotactic body radiotherapy in patients with resectable hepatocellular carcinoma

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<b>Primary Subject Heading</b>:	Gastroenterology and hepatology
Secondary Subject Heading:	Surgery
Keywords:	Clinical trials < THERAPEUTICS, Hepatobiliary tumours < ONCOLOGY, RADIOTHERAPY



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4 **1 Protocol of Notable-HCC: A phase Ib study of neoadjuvant tislelizumab**  
5 **2 with stereotactic body radiotherapy in patients with resectable**  
6 **3 hepatocellular carcinoma**  
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55 18 **Potential conflicts of interests**  
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4 **24 Abstract**

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7 **25 Introduction** Liver resection is the mainstay of curative-intent treatment for hepatocellular  
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10 **26** carcinoma (HCC), but the postoperative 5-year recurrence rate reaches 70%, and there are no  
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13 **27** adjuvant or neoadjuvant therapies recommended by major HCC guidelines that can reduce the risk  
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16 **28** of recurrence. In the recent decade, significant progress has been achieved in the systemic  
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18 **29** treatment of HCC, mainly from immune checkpoint inhibitors (ICIs) and targeted therapy. In  
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21 **30** other malignancies, ICIs in the neoadjuvant setting have shown better outcomes than in the  
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24 **31** adjuvant setting. On the other hand, the addition of radiation to ICIs incrementally improves the  
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27 **32** systemic response to ICIs. Neoadjuvant therapy of ICIs plus stereotactic body radiotherapy  
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29 **33** (SBRT) has shown promising results in several types of solid tumours but not HCC. **Methods and**  
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31 **34 analysis** Here, we describe a phase Ib clinical trial of neoadjuvant SBRT plus PD-1 (tislelizumab)  
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34 **35** prior to hepatic resection in HCC patients. Prior to resection, eligible HCC patients will receive 8  
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37 **36** Gy × 3 fractions of SBRT together with 2 cycles of tislelizumab with an interval of 3 weeks. HCC  
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40 **37** resection is scheduled 4 weeks after the second dose of tislelizumab, followed by adjuvant  
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43 **38** tislelizumab for 1 year. We plan to enrol 20 participants in this trial. The primary study endpoints  
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46 **39** include the delay of surgery, tumour response, and safety and tolerability of the sequential  
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49 **40** SBRT/tislelizumab. Other endpoints are the disease-free survival (DFS) and overall survival (OS)  
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52 **41** rates every 3 or 6 months after the surgery. **Ethics and dissemination** This trial was approved by  
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55 **42** the Ethics Committee of Shandong Cancer Hospital and Institute (SDZLEC2022-021-01). The  
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58 **43** final results of this trial will be published in a peer-reviewed journal after completion. **Patient and**  
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4 44 **public involvement** No patients were involved. **Trial registration** ClinicalTrials.gov:

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6 45 NCT05185531.  
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10 46 **Strengths and limitations of this study**  
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14 47 • To examine the role of tislelizumab (PD-1 blocker) plus radiation as the neoadjuvant therapy  
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16 48 in resectable HCC.

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20 49 • Eligible patients will receive 8 Gy × 3 fractions of SBRT together with 2 cycles of  
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22 50 tislelizumab.  
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26 51 • Hepatic resection will be performed 4 weeks after the 2<sup>nd</sup> dose of tislelizumab.  
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30 52 • The delay of surgery, tumour response, safety and tolerability as well as DFS and OS will be  
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32 53 explored.  
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35 54 **Key words**  
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39 55 clinical trial, hepatocellular carcinoma (HCC), neoadjuvant therapy, immune checkpoint inhibitor  
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42 56 (ICI), stereotactic body radiotherapy (SBRT)  
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4 57 **Background and rationale**  
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7 58 Hepatocellular carcinoma (HCC) remains prevalent worldwide and accounts for 75% to 85% of  
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10 59 all primary liver cancers (PLCs). in 2020, PLC was the 6<sup>th</sup> most commonly diagnosed cancer but  
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13 60 the 3<sup>rd</sup> leading cause of cancer death worldwide, only after lung cancer and colorectal cancer[1].  
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16 61 Surgical therapies (hepatic resection, liver transplantation and ablation in well-selected patients)  
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19 62 remain the backbone of curative therapies for HCC. In patients who meet guidelines and undergo  
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22 63 resection, the 5-year survival rate with these modalities is over 60%[2]. However, the global HCC  
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25 64 BRIDGE study that covered 8656 newly diagnosed HCC patients from 20 leading worldwide liver  
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28 65 centres showed that less than 10% of HCC patients were “ideal” candidates for liver resection, and  
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31 66 only 27% underwent resection in the real-world scenario[3]. Since 70% of resected patients will  
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34 67 experience recurrence within 5 years after resection[2], theoretically, only less than 10% of  
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37 68 patients can be cured by surgery. To date, neither adjuvant nor neoadjuvant therapies are  
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40 70 outcome of patients treated with resection in terms of reducing the risk of recurrence, but the  
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43 71 European Association for the Study of the Liver (EASL) Clinical Practice Guidelines have  
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46 72 encouraged further clinical trials with new agents for these applications[4].  
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49 73 In the recent decade, systemic treatment of HCC with targeted therapies and immune checkpoint  
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52 74 inhibitors (ICIs) has achieved great progress. In the real-world scenario, sequential systemic  
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55 75 therapy has been able to prolong median overall survival (OS) in selected advanced HCC patients  
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58 76 to over 3 years[6]. Despite this significant achievement, systemic treatment alone rarely cures  
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60 77 HCC.

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4 78 Considering these data together, a very straightforward ontology can be arrived at: If ICIs (alone  
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7 79 or combined with other systemic modalities) can be effectively applied to adjuvant and/or  
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9 80 neoadjuvant therapies, significantly more HCC patients will be expected to experience long-term  
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12 81 survival or even cure.

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15 82 Meanwhile, the antitumor effect of radiation therapy (RT) has been attributed primarily to its  
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18 83 enhancement of local control. RT also has an effect on tumour immunity, and an additional  
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21 84 antitumour effect can be expected if ICIs are administered simultaneously with RT.

#### 22 23 24 85 **Methods/design**

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28 86 Notable-HCC is a phase Ib study of neoadjuvant stereotactic body radiotherapy (SBRT) plus an  
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31 87 ICI prior to hepatic resection in adult patients (aged  $\geq 18$  years) with HCC. Twenty participants are  
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34 88 planned to be enrolled in this trial. The study has started on March 1, 2022, and is anticipated to be  
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37 89 completed on December 31, 2024.

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39 90 Tislelizumab (BGB-A317) is a human monoclonal antibody (HuMAb; immunoglobulin G4  
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42 91 [IgG4]) manufactured by BeiGene that inhibits the PD-1 receptor. It is engineered with a nullified  
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45 92 Fc portion of the antibody to minimise binding to Fc  $\gamma$  R on macrophages in order to abrogate  
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48 93 antibody-dependent phagocytosis, a mechanism of T-cell clearance and potential resistance to  
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51 94 anti-PD-1 therapy[7].

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54 95 Eligible patients will receive SBRT (8 Gy  $\times$  3 fractions, every other day) on day 1, day 3 and day  
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57 96 5; the first dose of tislelizumab will be administered concurrently on day 1, then the second dose  
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4 97 will be administered on day 22 (the first day of week 4,  $\pm$  3 days). Then on day 50 (the first day of  
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6 98 week 8,  $\pm$  7 days), curative liver resection of HCC will be scheduled.  
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10 99 **Patient and public involvement**  
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14 100 No patients were involved.  
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17 101 **Eligibility criteria**  
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20 102 In brief, Notable-HCC will recruit HCC patients who are candidates for hepatic resection, with a  
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22 103 confirmed diagnosis of HCC by biopsy or by the noninvasive diagnostic criteria of the American  
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24 104 Association for the Study of the Liver Diseases(AASLD).  
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29 105 **Inclusion criteria:**  
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33 106 1. Written informed consent for the trial.  
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36 107 2. Aged  $\geq$ 18 years  
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39 108 3. Willing to provide tissue from an excisional biopsy of a tumour lesion  
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43 109 4. Confirmed diagnosis of HCC. The diagnosis can be established radiographically by the  
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45 110 criteria of the American Association for the Study of the Liver (AASLD), or by histologic  
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47 111 diagnosis from a core biopsy.  
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52 112 5. Measurable disease by computed tomography (CT)-scan or magnetic resonance imaging  
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54 113 (MRI) defined by the Response Evaluation Criteria In Solid Tumours ( RECIST) 1.1  
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57 114 criteria and HCC-specific modified RECIST ( mRECIST).  
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6 116 oncology team  
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13 118 8. Adequate organ and marrow function as defined below:  
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20 120 2) absolute neutrophil count  $\geq 1,500/\text{mcL}$   
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23 121 3) platelets  $\geq 100,000/\text{mcL}$   
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26 122 4) total bilirubin  $\leq 2 \times$  institutional upper limit of normal (ULN)  
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29 123 5) aspartate aminotransferase ( AST )/ alanine aminotransferase ( ALT )  $\leq 3 \times$  institutional  
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31 124 ULN  
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34 125 6) creatinine  $\leq 1.5 \times$  institutional ULN or  
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37 126 7) estimated glomerular filtration rate (GFR)  $\geq 50 \text{ mL}/\text{min}/1.73 \text{ m}^2$  (according to the  
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39 127 Cockcroft-Gault formula)  
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43 128 9. Overall Child-Pugh class A  
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47 129 10. Documented virology status of hepatitis, as confirmed by screening tests for hepatitis B  
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49 130 virus ( HBV ) and hepatitis C virus ( HCV )  
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53 131 1) For patients with active HBV: HBV DNA  $< 2000 \text{ IU}/\text{mL}$  during screening, and have  
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55 132 initiated anti-HBV treatment at least 14 days prior to SBRT and willingness to continue  
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57 133 anti-HBV treatment during the study (per local standard of care; e.g., entecavir).  
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4 134 2) Patients with HCV, either with resolved infection (as evidenced by detectable antibody  
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6 135 and negative viral load) or chronic infection (as evidenced by detectable HCV RNA),  
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9 136 are eligible.  
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13 137 11. Participants with a prior or concurrent malignancy whose natural history or treatment  
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15 138 does not have the potential to interfere with the safety or efficacy assessment of the  
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18 139 investigational regimen are eligible for this trial.  
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21 140 12. Female patients of childbearing potential should have a negative serum pregnancy test  
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24 141 within 24 h of their first dose of Investigational Medicinal Product ( IMP )  
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27 142 13. Women of childbearing potential must be willing to use a highly effective method of  
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30 143 contraception for the course of the study through 5 months after the last dose of IMP.  
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33 144 Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for  
34  
35 145 the patient.  
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38  
39 146 14. Sexually active males must agree to use an adequate method of contraception starting  
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41  
42 147 with the first dose of IMP through 7 months after the last dose of study therapy. Note:  
43  
44 148 Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the  
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46  
47 149 patient.  
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50 150 **Exclusion criteria:**

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54 151 1. Extrahepatic metastasis.  
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4 152 2. Prior systemic anticancer treatment for HCC, including an anti-PD-1, anti-PD-L1 or anti-  
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6 153 CTLA-4 antibody.  
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10 154 3. Prior orthotopic liver transplantation.  
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14 155 4. Prior abdominal irradiation.  
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16  
17 156 5. Any major surgery within the 3 weeks prior to enrolment.  
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21 157 6. Hepatic encephalopathy.  
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23  
24 158 7. Ascites that is refractory to diuretic therapy.  
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28 159 8. Currently receiving anticancer therapy (chemotherapy, radiation therapy, immunotherapy  
29  
30 or biologic therapy) or has participated or is participating in a study of an IMP or used an  
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32 160 investigational device within 4 weeks of the first dose of IMP.  
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34 161  
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36 162 9. Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form  
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39 163 of immunosuppressive therapy.  
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43 164 10. Known history of active Bacillus tuberculosis (TB) infection.  
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46 165 11. History of known hypersensitivity to any monoclonal antibody or any of their excipients.  
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49  
50 166 12. Known additional malignancy that is progressing or requires active treatment. Exceptions  
51  
52 167 include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has  
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55 168 undergone potentially curative therapy or in situ cervical cancer.  
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4 169 13. Active autoimmune disease that has required systemic treatment in the past 2 years (i.e.  
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6 170 use of disease-modifying agents, corticosteroids or immunosuppressive drugs).  
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9 171 Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement  
10  
11 172 therapy for adrenal or pituitary insufficiency) is not considered a form of systemic  
12  
13 173 treatment.  
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18 174 14. Active infection requiring systemic therapy, with exceptions relating to Hepatitis B and C  
19  
20 175 virus infection.  
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23  
24 176 15. History or current evidence of any condition, therapy, or laboratory abnormality that  
25  
26 177 might confound the results of the trial, interfere with the patient's participation for the full  
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28 178 duration of the trial, or is not in the best interest of the patient to participate, in the  
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30 179 opinion of the treating Principal Investigator (PI).  
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35 180 16. Known psychiatric or substance abuse disorders that would interfere with cooperation  
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37 181 with the requirements of the trial  
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42 182 17. Pregnant or breastfeeding  
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45 183 18. Known history of human immunodeficiency virus (HIV; HIV 1/2 antibodies)  
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49 184 19. Received a live vaccine within 30 days of the first dose of IMP administration.  
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52 185 **Study procedures**

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56 186 The consent form will be signed by a liver surgeon with the participant or his delegate. Patients  
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58 187 will undergo baseline tumour imaging including CT scans of the chest, abdomen and pelvis, and  
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4 188 by contrast-enhanced MRI scans of the liver at screening. At posttreatment time points prior to  
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6 189 surgery (on Day 50), 4 weeks after surgery and then every 3 months after surgery, tumour imaging  
7  
8  
9 190 will be repeated using contrast-enhanced MRI. Triple-phase CT of the liver is an acceptable  
10  
11 191 alternative for intrahepatic staging in patients with contraindications to MRI. Baseline CT/MRI  
12  
13  
14 192 scans do not need to be repeated if obtained within 35 days of the first SBRT. The same method  
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16  
17 193 used for assessment at baseline must then be used at all subsequent time points.  
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20 194 Participants will require a full hepatitis serology screen prior to enrolment in the study, which  
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22  
23 195 includes HBV and HCV serology. In patients with positive serology for either virus, baseline  
24  
25  
26 196 HBV DNA and HCV quantitative RNA levels will be requested. Participants who are confirmed  
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28  
29 197 to have chronic and active hepatitis B and/or C (i.e., with detectable HBV DNA or HCV RNA at  
30  
31  
32 198 baseline) will have their viral load (HCV RNA and/or HBV DNA as appropriate) monitored at  
33  
34 199 each cycle and at the end of the treatment follow-up visit.  
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36  
37 200 A baseline core tumour biopsy and Peripheral Blood Mononuclear Cell (PBMC) will be collected  
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39  
40 201 from participants at screening, and sample tumour tissue from the surgical specimen will be snap-  
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42  
43 202 frozen and stored for the future relevant studies.  
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46 203 Treatment will consist of 8 Gy  $\times$  3 fractions SBRT together with 2 cycles of tislelizumab 200mg  
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48  
49 204 administered intravenously with an interval of 3 weeks.  
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52 205 Patients will be reviewed following the completion of SBRT and tislelizumab treatment (Follow-  
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55 206 up visit 1; FU1) prior to surgery. Before surgery, RECIST v1.1 and HCC-specific mRECIST  
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4 207 criteria will be used to determine patient response to treatment, including complete response (CR),  
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6  
7 208 partial response (PR) and objective response rate (ORR). PBMCs will be collected again.  
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9  
10 209 Hepatic resection will be performed as per the standard of care. Safety FU2 will be conducted  
11  
12 210 after the first dose of the postresection tislelizumab. All adverse events (AEs) that occur prior to  
13  
14 211 the visit will be recorded. Participants with ongoing AEs at the visit will be followed up by the PI  
15  
16 212 or delegated until resolution or stabilisation of the event. Following resection, participants will be  
17  
18 213 assessed every 3 months ( $\pm 7$  days) thereafter to collect information regarding disease status and  
19  
20 214 survival. Long-term follow-up will continue for a total of 2 years for each patient.  
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26 215 All personal information of the enrolled participants will be maintained and protected in the  
27  
28 216 hospital information system, and be accessible only to the authorized medical staffs to protect the  
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30 217 confidentiality. PIs of the trial have access to the final entire trial dataset.  
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### 35 218 **Outcome measures and endpoints**

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39 219 The primary study endpoints include the number of patients experiencing a surgery delay of over  
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41 220 6 weeks or later, ORR on preresection imaging according to the RECIST v1.1/mRECIST criteria,  
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43 221 pathologic response rate on evaluation of the resected specimen, and determination of safety and  
44  
45 222 tolerability of the sequential SBRT/tislelizumab based on the National Cancer Institute Common  
46  
47 223 Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 criteria. The secondary endpoints  
48  
49 224 are DFS and OS rates every 3 or 6 months after the hepatic resection. Exploratory endpoints  
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51 225 include patients' immune response and morbidity and mortality of the surgery.  
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### 59 226 **Statistical analysis**

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4 227 Statistical analyses will include an intent to treat (ITT) analysis including all participants enrolled  
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6 228 and a per-protocol analysis including all participants who complete the study without major  
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9 229 protocol violations. The baseline demographic and clinicopathological variables will be presented  
10  
11 230 by descriptive analyses. Data analysis will be performed when the study is complete. Interim  
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14 231 analyses of safety data will be conducted at the end of FU1 and at the end of FU2. The  
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17 232 comprehensive statistical analysis plan will be finalised prior to the final analysis.  
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21 233 All participants who receive at least one dose of tislelizumab and one fraction of SBRT will be  
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23 234 included in the safety analysis. All participants who receive at least one dose of the tislelizumab  
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25  
26 235 and all 3 fractions of SBRT and complete HCC resection will be included in the efficacy analysis.  
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28 236 RECIST 1.1/mRECIST response rates (CR, PR and ORR) and pathologic response rates (MPR,  
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31 237 pCR, etc.) will be presented descriptively. Progression-free survival (PFS) and OS rates will be  
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33  
34 238 presented with Kaplan–Meier plots using the full timespan from the completion of HCC resection  
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36  
37 239 to the date of recurrence or death from any cause. The proportions of participants who do not  
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39 240 experience recurrence and who are alive at 3-monthly time-points thereafter will also be  
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42 241 estimated, and the appropriate descriptive analysis will be conducted.  
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## 45 242 **Discussion**

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49 243 The effect of ICIs in the adjuvant therapeutic setting of HCC is being evaluated in several clinical  
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51 244 trials[8]. In contrast, the possible role of ICIs in the neoadjuvant setting of HCC has not been  
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54 245 adequately explored[9]. The reason for this may arise from some concerns about the nature of  
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57 246 neoadjuvant therapy itself before curative surgery. If patients do not respond to the therapy, they  
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59 247 will suffer disease progression, and some can even jeopardize the opportunity of curative surgery.  
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4 248 Severe adverse effects from the neoadjuvant therapy can delay the resection or increase the risk of  
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6 249 morbidity. For ICIs in neoadjuvant therapy, immune-related adverse events (irAEs) and  
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9 250 hyperprogression can potentially bring more danger to patients.  
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11  
12 251 However, neoadjuvant therapy also has some advantages compared to adjuvant therapy. The  
13  
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15 252 existence of the target tumour permits the direct evaluation of the treatment, the recognition of the  
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18 253 responders from nonresponders, the validation of the surrogate predictors, the timely adjustment of  
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21 254 treatment, etc.; and the resected specimen be used for the pathologic evaluation of the treatment and  
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23 255 can facilitate translational studies.  
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27 256 In the context of cancer immunotherapy, neoadjuvant treatment may offer another very important  
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30 257 additional advantage; immunotherapies enhance T-cell activation the moment antigen is  
31  
32 258 encountered. Exposure to antigen during the period in which the major tumour mass is present  
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35 259 may increase the breadth and durability of tumour-specific T-cell responses. In the adjuvant  
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38 260 setting, the immunotherapy starts when the tumour, together with its antigens have been totally  
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41 261 removed[10]. In melanoma, the most recent data have shown the advantage of ICIs in neoadjuvant  
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43 262 therapies compared with adjuvant therapies[11, 12].  
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46 263 In a randomised, open-label, perioperative phase II trial, the effect of nivolumab alone or  
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49 264 nivolumab plus ipilimumab in patients with resectable HCC was evaluated. The study was  
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52 265 reported to reach its primary endpoint of safety. Importantly, it achieved a 40% pathologic  
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55 266 complete response (pCR) rate (pCR rate of 24%, and major necrosis rate of 16%) for resectable  
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57 267 HCC after preoperative immunotherapy. The author suggested that these findings may favour the  
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4 268 perioperative treatment of resectable HCC by ICIs after future validation[13]. Another two similar  
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6 269 clinical trials are still ongoing (NCT03222076, NCT03510871).  
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9  
10 270 More recently, the neoadjuvant application of another anti-PD-1, cemiplimab, in HCC patients  
11  
12 271 was evaluated and reported. Twenty-one HCC patients were enrolled in this study, all received  
13  
14 272 neoadjuvant cemiplimab and 20 patients underwent successful resection. Four (20%) had  
15  
16 273 significant tumour necrosis, three (15%) had a partial response, and all other patients maintained  
17  
18 274 stable disease. Seven patients had grade 3 AEs, and no grade 4 or 5 AEs were observed. One  
19  
20 275 patient developed pneumonitis, which led to a delay in surgery by 2 weeks[14].  
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26 276 For patients with resectable HCC and portal vein tumour thrombus (PVT), neoadjuvant 3-D  
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28 277 conformal radiotherapy provided significantly better postoperative survival outcomes than surgery  
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30 278 alone[15]. Mounting evidence shows the synergistic effects on local and distant tumour control  
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32 279 when RT is combined with immunotherapy[16].  
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38 280 The antitumor effect of radiation can be attributed to the induction of tumour cell death through  
39  
40 281 DNA damage, but radiotherapy also has immunomodulatory effects and can stimulate the immune  
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42 282 response through various mechanisms[17, 18]. Although radiotherapy can enhance antitumor  
43  
44 283 effects, its potential immunosuppressive effects can also restrain antitumor efficacy, including the  
45  
46 284 upregulation of coinhibitory ligands such as PD-L1[19, 20]. Combining radiotherapy with  
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48 285 immune checkpoint blockade can overcome these immunosuppressive mechanisms and augment  
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50 286 antitumor immunity.  
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4 287 In a recent single-centre, randomised phase 2 trial in early-stage non-small cell lung cancer  
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6 288 (NSCLC), the combination of SBRT and neoadjuvant durvalumab was well tolerated and  
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8  
9 289 associated with a high major pathological response rate[21].  
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11  
12 290 In general, we hope the results of this clinical trial can expand our knowledge about neoadjuvant  
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15 291 therapy of HCC, especially by the combination of ICI and RT, thus improving the outcome of  
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17  
18 292 HCC resection.  
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### 20 21 293 **Contributorship statement**

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24  
25 294 LZ designed the clinical trial and applied for funding; LZ, BZ and XS are the chief liver surgeons  
26  
27  
28 295 performing the surgeries; JY is the chief radiation oncologist performing the radiotherapy; and  
29  
30  
31 296 KC, LL, CZ, PS, JZ and ZL are liver surgeons participating in the surgeries.  
32

### 33 34 297 **Competing interests**

35  
36  
37 298 LZ is on the speakers' bureau for BeiGene, Bayer, MSD, Roche, Innovent and Hengrui Medicine.  
38  
39  
40 299 This trial is partly funded by BeiGene.  
41

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44  
45  
46  
47 301 LZ received funding from the Key Research and Development Program of Shandong (Major  
48  
49  
50 302 Science & Technology Innovation Project), 2021SFGC0501  
51

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The Lancet Oncology, 2021. **22**(6): p. 824-835.

For peer review only



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

Section/item	ItemNo	Description	Page/ li
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1/1-3
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3/41-42
	2b	All items from the World Health Organization Trial Registration Data Set	4/44-45
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	27/297-298
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1/4-9
	5b	Name and contact information for the trial sponsor	1/11-13
	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	17/290-2
	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)	N/A

**Introduction**

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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	5/58-76
	6b	Explanation for choice of comparators	6/77-83
Objectives	7	Specific objectives or hypotheses	6/77-83
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)	3/34-41
<b>Methods: Participants, interventions, and outcomes</b>			
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	6/85-88
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)	7/104-118
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12/201-212
	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)	13/208-212
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13/211-212
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A

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4	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	13/215-2
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9	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)	11/184
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12	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	6/86-88
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16	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
17				
18	<b>Methods: Assignment of interventions (for controlled trials)</b>			<b>N/A</b>
19				
20	Allocation:			
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22	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	
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27	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	
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30	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	
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34	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	
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37		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	
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4 **Methods: Data collection, management, and analysis**

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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	13/223-2
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14/226-2
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14/229-2
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14/233-2
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14/235-2

27 **Methods: Monitoring**

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Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13/208

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4	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
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7	<b>Ethics and dissemination</b>			
8				
9	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	3/41-43
10				
11	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)	N/A
12				
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14	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11/185
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17		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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20	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	13/214
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24	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17/294-2
25				
26	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	13/214
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29	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	13/210-2
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32	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	3/43
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37		31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
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39		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
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**Appendices**

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	submitte
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	12/199

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\*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.

peer review only

# BMJ Open

## Protocol of Notable-HCC: A phase Ib study of neoadjuvant tislelizumab with stereotactic body radiotherapy in patients with resectable hepatocellular carcinoma

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-060955.R2
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<b>Primary Subject Heading</b>:	Gastroenterology and hepatology
Secondary Subject Heading:	Surgery
Keywords:	Clinical trials < THERAPEUTICS, Hepatobiliary tumours < ONCOLOGY, RADIOTHERAPY

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4 **1 Protocol of Notable-HCC: A phase Ib study of neoadjuvant tislelizumab**  
5 **2 with stereotactic body radiotherapy in patients with resectable**  
6 **3 hepatocellular carcinoma**  
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37  
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40  
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44 15 3,975 words  
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48 16 **Number of figures and tables**  
49  
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51 17 none  
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55 18 **Potential conflicts of interests**  
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For peer review only

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4 **24 Abstract**

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7 **25 Introduction** Liver resection is the mainstay of curative-intent treatment for hepatocellular  
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10 **26** carcinoma (HCC), but the postoperative 5-year recurrence rate reaches 70%, and there are no  
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13 **27** adjuvant or neoadjuvant therapies recommended by major HCC guidelines that can reduce the risk  
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16 **28** of recurrence. In the recent decade, significant progress has been achieved in the systemic  
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18 **29** treatment of HCC, mainly from immune checkpoint inhibitors (ICIs) and targeted therapy. In  
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21 **30** other malignancies, ICIs in the neoadjuvant setting have shown better outcomes than in the  
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24 **31** adjuvant setting. On the other hand, the addition of radiation to ICIs incrementally improves the  
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27 **32** systemic response to ICIs. Neoadjuvant therapy of ICIs plus stereotactic body radiotherapy  
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29 **33** (SBRT) has shown promising results in several types of solid tumours but not HCC. **Methods and**  
30  
31 **34 analysis** Here, we describe a phase Ib clinical trial of neoadjuvant SBRT plus PD-1 (tislelizumab)  
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34 **35** prior to hepatic resection in HCC patients. Prior to resection, eligible HCC patients will receive 8  
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37 **36** Gy × 3 fractions of SBRT together with 2 cycles of tislelizumab with an interval of 3 weeks. HCC  
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40 **37** resection is scheduled 4 weeks after the second dose of tislelizumab, followed by adjuvant  
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43 **38** tislelizumab for 1 year. We plan to enrol 20 participants in this trial. The primary study endpoints  
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46 **39** include the delay of surgery, tumour response, and safety and tolerability of the sequential  
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49 **40** SBRT/tislelizumab. Other endpoints are the disease-free survival (DFS) and overall survival (OS)  
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52 **41** rates every 3 or 6 months after the surgery. **Ethics and dissemination** This trial was approved by  
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55 **42** the Ethics Committee of Shandong Cancer Hospital and Institute (SDZLEC2022-021-01). The  
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58 **43** final results of this trial will be published in a peer-reviewed journal after completion. **Patient and**  
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4 44 **public involvement** No patients were involved. **Trial registration** ClinicalTrials.gov:

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6 45 NCT05185531.  
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10 46 **Strengths and limitations of this study**  
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13 47 • The pilot exploration of ICIs plus radiotherapy as the neoadjuvant therapy for HCC.  
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16 48 • Single-armed, non-randomised design of the trial.  
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19 49 • Relatively long waiting time before the curative resection is scheduled.  
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23  
24 50 **Key words**  
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27 51 clinical trial, hepatocellular carcinoma (HCC), neoadjuvant therapy, immune checkpoint inhibitor  
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30 52 (ICI), stereotactic body radiotherapy (SBRT)  
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4 53 **Background and rationale**  
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7 54 Hepatocellular carcinoma (HCC) remains prevalent worldwide and accounts for 75% to 85% of  
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10 55 all primary liver cancers (PLCs). In 2020, PLC was the 6<sup>th</sup> most commonly diagnosed cancer but  
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13 56 the 3<sup>rd</sup> leading cause of cancer death worldwide, only after lung cancer and colorectal cancer[1].  
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16 57 Surgical therapies (hepatic resection, liver transplantation and ablation in well-selected patients)  
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18  
19 58 remain the backbone of curative therapies for HCC. In patients who meet guidelines and undergo  
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22 59 resection, the 5-year survival rate with these modalities is over 60%[2]. However, the global HCC  
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25 60 BRIDGE study that covered 8656 newly diagnosed HCC patients from 20 leading worldwide liver  
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28 61 centres showed that less than 10% of HCC patients were “ideal” candidates for liver resection, and  
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31 62 only 27% underwent resection in the real-world scenario[3]. Since 70% of resected patients will  
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34 63 experience recurrence within 5 years after resection[2], theoretically, only less than 10% of  
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37 64 patients can be cured by surgery. To date, neither adjuvant nor neoadjuvant therapies are  
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40 65 recommended by major HCC guidelines[4, 5], because they have not been proven to improve the  
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43 66 outcome of patients treated with resection in terms of reducing the risk of recurrence, but the  
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46 67 European Association for the Study of the Liver (EASL) Clinical Practice Guidelines have  
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49 68 encouraged further clinical trials with new agents for these applications[4].  
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52 69 In the recent decade, systemic treatment of HCC with targeted therapies and immune checkpoint  
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55 70 inhibitors (ICIs) has achieved great progress. In the real-world scenario, sequential systemic  
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58 71 therapy has been able to prolong median overall survival (OS) in selected advanced HCC patients  
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61 72 to over 3 years[6]. Despite this significant achievement, systemic treatment alone rarely cures  
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64 73 HCC.

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4 74 Considering these data together, a very straightforward ontology can be arrived at: If ICIs (alone  
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6 75 or combined with other systemic modalities) can be effectively applied to adjuvant and/or  
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9 76 neoadjuvant therapies, significantly more HCC patients will be expected to experience long-term  
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12 77 survival or even cure.

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15 78 Meanwhile, the antitumor effect of radiation therapy (RT) has been attributed primarily to its  
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18 79 enhancement of local control. RT also has an effect on tumour immunity, and an additional  
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21 80 antitumour effect can be expected if ICIs are administered simultaneously with RT.

### 22 23 24 81 **Methods/design**

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27 82 Notable-HCC is a phase Ib study of neoadjuvant stereotactic body radiotherapy (SBRT) plus an  
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30 83 ICI prior to hepatic resection in adult patients (aged  $\geq 18$  years) with HCC. Twenty participants are  
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33 84 planned to be enrolled in this trial. The study has started on March 1, 2022, and is anticipated to be  
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36 85 completed on December 31, 2024.

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39 86 Tislelizumab (BGB-A317) is a human monoclonal antibody (HuMAb; immunoglobulin G4  
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42 87 [IgG4]) manufactured by BeiGene that inhibits the PD-1 receptor. It is engineered with a nullified  
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45 88 Fc portion of the antibody to minimise binding to Fc  $\gamma$  R on macrophages in order to abrogate  
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48 89 antibody-dependent phagocytosis, a mechanism of T-cell clearance and potential resistance to  
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51 90 anti-PD-1 therapy[7].

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53 91 Eligible patients will receive SBRT (8 Gy  $\times$  3 fractions, every other day) on day 1, day 3 and day  
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56 92 5; the first dose of tislelizumab will be administered concurrently on day 1, then the second dose

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4 93 will be administered on day 22 (the first day of week 4,  $\pm$  3 days). Then on day 50 (the first day of  
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6 94 week 8,  $\pm$  7 days), curative liver resection of HCC will be scheduled.  
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10 95 **Patient and public involvement**  
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13 96 No patients were involved.  
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17 97 **Eligibility criteria**  
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20 98 In brief, Notable-HCC will recruit HCC patients who are candidates for hepatic resection, with a  
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22 99 confirmed diagnosis of HCC by biopsy or by the noninvasive diagnostic criteria of the American  
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24 100 Association for the Study of the Liver Diseases(AASLD).  
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29 101 **Inclusion criteria:**  
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33 102 1. Written informed consent for the trial.  
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36 103 2. Aged  $\geq$ 18 years  
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39 104 3. Willing to provide tissue from an excisional biopsy of a tumour lesion  
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43 105 4. Confirmed diagnosis of HCC. The diagnosis can be established radiographically by the  
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45 106 criteria of the American Association for the Study of the Liver (AASLD), or by histologic  
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47 107 diagnosis from a core biopsy.  
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52 108 5. Measurable disease by computed tomography (CT)-scan or magnetic resonance imaging  
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54 109 (MRI) defined by the Response Evaluation Criteria In Solid Tumours ( RECIST) 1.1  
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56 110 criteria and HCC-specific modified RECIST ( mRECIST).  
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4 1 1 1 6. Medically fit to undergo surgery as determined by the treating medical and surgical  
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6 1 1 2 oncology team  
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10 1 1 3 7. Eastern Cooperative Oncology Group ( ECOG ) performance status 0 or 1  
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13 1 1 4 8. Adequate organ and marrow function as defined below:  
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17 1 1 5 1) leukocytes  $\geq 3,000/\text{mcL}$   
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20 1 1 6 2) absolute neutrophil count  $\geq 1,500/\text{mcL}$   
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23 1 1 7 3) platelets  $\geq 100,000/\text{mcL}$   
24  
25  
26 1 1 8 4) total bilirubin  $\leq 2 \times$  institutional upper limit of normal (ULN)  
27  
28  
29 1 1 9 5) aspartate aminotransferase ( AST )/ alanine aminotransferase ( ALT )  $\leq 3 \times$  institutional  
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31 1 2 0 ULN  
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34 1 2 1 6) creatinine  $\leq 1.5 \times$  institutional ULN or  
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37 1 2 2 7) estimated glomerular filtration rate (GFR)  $\geq 50 \text{ mL}/\text{min}/1.73 \text{ m}^2$  (according to the  
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39 1 2 3 Cockcroft-Gault formula)  
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43 1 2 4 9. Overall Child-Pugh class A  
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47 1 2 5 10. Documented virology status of hepatitis, as confirmed by screening tests for hepatitis B  
48  
49 1 2 6 virus ( HBV ) and hepatitis C virus ( HCV )  
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53 1 2 7 1) For patients with active HBV: HBV DNA  $< 2000 \text{ IU}/\text{mL}$  during screening, and have  
54  
55 1 2 8 initiated anti-HBV treatment at least 14 days prior to SBRT and willingness to continue  
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57 1 2 9 anti-HBV treatment during the study (per local standard of care; e.g., entecavir).  
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4 130 2) Patients with HCV, either with resolved infection (as evidenced by detectable antibody  
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6 131 and negative viral load) or chronic infection (as evidenced by detectable HCV RNA),  
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9 132 are eligible.  
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13 133 11. Participants with a prior or concurrent malignancy whose natural history or treatment  
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15 134 does not have the potential to interfere with the safety or efficacy assessment of the  
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17 135 investigational regimen are eligible for this trial.  
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21 136 12. Female patients of childbearing potential should have a negative serum pregnancy test  
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23 137 within 24 h of their first dose of Investigational Medicinal Product ( IMP )  
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27 138 13. Women of childbearing potential must be willing to use a highly effective method of  
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29 139 contraception for the course of the study through 5 months after the last dose of IMP.  
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33 140 Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for  
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35 141 the patient.  
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39 142 14. Sexually active males must agree to use an adequate method of contraception starting  
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41 143 with the first dose of IMP through 7 months after the last dose of study therapy. Note:  
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43 144 Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the  
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45 145 patient.  
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51 146 **Exclusion criteria:**  
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- 54 147 1. Extrahepatic metastasis.  
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4 148 2. Prior systemic anticancer treatment for HCC, including an anti-PD-1, anti-PD-L1 or anti-  
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6 149 CTLA-4 antibody.  
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10 150 3. Prior orthotopic liver transplantation.  
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14 151 4. Prior abdominal irradiation.  
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17 152 5. Any major surgery within the 3 weeks prior to enrolment.  
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21 153 6. Hepatic encephalopathy.  
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24 154 7. Ascites that is refractory to diuretic therapy.  
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28 155 8. Currently receiving anticancer therapy (chemotherapy, radiation therapy, immunotherapy  
29  
30 156 or biologic therapy) or has participated or is participating in a study of an IMP or used an  
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32 157 investigational device within 4 weeks of the first dose of IMP.  
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36 158 9. Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form  
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38 159 of immunosuppressive therapy.  
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42 160 10. Known history of active Bacillus tuberculosis (TB) infection.  
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46 161 11. History of known hypersensitivity to any monoclonal antibody or any of their excipients.  
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50 162 12. Known additional malignancy that is progressing or requires active treatment. Exceptions  
51  
52 163 include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has  
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54 164 undergone potentially curative therapy or in situ cervical cancer.  
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4 165 13. Active autoimmune disease that has required systemic treatment in the past 2 years (i.e.  
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6 166 use of disease-modifying agents, corticosteroids or immunosuppressive drugs).  
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9 167 Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement  
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11 168 therapy for adrenal or pituitary insufficiency) is not considered a form of systemic  
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13  
14 169 treatment.
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18 170 14. Active infection requiring systemic therapy, with exceptions relating to Hepatitis B and C  
19  
20 171 virus infection.  
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24 172 15. History or current evidence of any condition, therapy, or laboratory abnormality that  
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26 173 might confound the results of the trial, interfere with the patient's participation for the full  
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28 174 duration of the trial, or is not in the best interest of the patient to participate, in the  
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30 175 opinion of the treating Principal Investigator (PI).  
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35 176 16. Known psychiatric or substance abuse disorders that would interfere with cooperation  
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37 177 with the requirements of the trial  
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42 178 17. Pregnant or breastfeeding  
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45 179 18. Known history of human immunodeficiency virus (HIV; HIV 1/2 antibodies)  
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49 180 19. Received a live vaccine within 30 days of the first dose of IMP administration.  
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52 181 **Study procedures**

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56 182 The consent form will be signed by a liver surgeon with the participant or his delegate. Patients  
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58 183 will undergo baseline tumour imaging including CT scans of the chest, abdomen and pelvis, and  
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3  
4 184 by contrast-enhanced MRI scans of the liver at screening. At posttreatment time points prior to  
5  
6 185 surgery (on Day 50), 4 weeks after surgery and then every 3 months after surgery, tumour imaging  
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8  
9 186 will be repeated using contrast-enhanced MRI. Triple-phase CT of the liver is an acceptable  
10  
11 187 alternative for intrahepatic staging in patients with contraindications to MRI. Baseline CT/MRI  
12  
13  
14 188 scans do not need to be repeated if obtained within 35 days of the first SBRT. The same method  
15  
16  
17 189 used for assessment at baseline must then be used at all subsequent time points.  
18  
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20  
21 190 Participants will require a full hepatitis serology screen prior to enrolment in the study, which  
22  
23 191 includes HBV and HCV serology. In patients with positive serology for either virus, baseline  
24  
25  
26 192 HBV DNA and HCV quantitative RNA levels will be requested. Participants who are confirmed  
27  
28  
29 193 to have chronic and active hepatitis B and/or C (i.e., with detectable HBV DNA or HCV RNA at  
30  
31 194 baseline) will have their viral load (HCV RNA and/or HBV DNA as appropriate) monitored at  
32  
33  
34 195 each cycle and at the end of the treatment follow-up visit.  
35  
36  
37 196 A baseline core tumour biopsy and Peripheral Blood Mononuclear Cell (PBMC) will be collected  
38  
39  
40 197 from participants at screening, and sample tumour tissue from the surgical specimen will be snap-  
41  
42  
43 198 frozen and stored for the future relevant studies.  
44  
45  
46 199 Treatment will consist of 8 Gy  $\times$  3 fractions SBRT together with 2 cycles of tislelizumab 200mg  
47  
48  
49 200 administered intravenously with an interval of 3 weeks.  
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51  
52 201 Patients will be reviewed following the completion of SBRT and tislelizumab treatment (Follow-  
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54  
55 202 up visit 1; FU1) prior to surgery. Before surgery, RECIST v1.1 and HCC-specific mRECIST  
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4 203 criteria will be used to determine patient response to treatment, including complete response (CR),  
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6  
7 204 partial response (PR) and objective response rate (ORR). PBMCs will be collected again.  
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9  
10 205 Hepatic resection will be performed as per the standard of care. Safety FU2 will be conducted  
11  
12 206 after the first dose of the postresection tislelizumab. All adverse events (AEs) that occur prior to  
13  
14  
15 207 the visit will be recorded. Participants with ongoing AEs at the visit will be followed up by the PI  
16  
17  
18 208 or delegated until resolution or stabilisation of the event. Following resection, participants will be  
19  
20  
21 209 assessed every 3 months ( $\pm 7$  days) thereafter to collect information regarding disease status and  
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23  
24 210 survival. Long-term follow-up will continue for a total of 2 years for each patient.  
25  
26  
27 211 All personal information of the enrolled participants will be maintained and protected in the  
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30 212 hospital information system, and be accessible only to the authorized medical staffs to protect the  
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32  
33 213 confidentiality. PIs of the trial have access to the final entire trial dataset.

#### 34 35 36 214 **Outcome measures and endpoints**

37  
38  
39 215 The primary study endpoints include the number of patients experiencing a surgery delay of over  
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42 216 6 weeks or later, ORR on preresection imaging according to the RECIST v1.1/mRECIST criteria,  
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44  
45 217 pathologic response rate on evaluation of the resected specimen, and determination of safety and  
46  
47  
48 218 tolerability of the sequential SBRT/tislelizumab based on the National Cancer Institute Common  
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50  
51 219 Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 criteria. The secondary endpoints  
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53  
54 220 are DFS and OS rates every 3 or 6 months after the hepatic resection. Exploratory endpoints  
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56  
57 221 include patients' immune response and morbidity and mortality of the surgery.

#### 58 59 222 **Statistical analysis**

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4 223 Statistical analyses will include an intent to treat (ITT) analysis including all participants enrolled  
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6 224 and a per-protocol analysis including all participants who complete the study without major  
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9 225 protocol violations. The baseline demographic and clinicopathological variables will be presented  
10  
11 226 by descriptive analyses. Data analysis will be performed when the study is complete. Interim  
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14 227 analyses of safety data will be conducted at the end of FU1 and at the end of FU2. The  
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17 228 comprehensive statistical analysis plan will be finalised prior to the final analysis.

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21 229 All participants who receive at least one dose of tislelizumab and one fraction of SBRT will be  
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23 230 included in the safety analysis. All participants who receive at least one dose of the tislelizumab  
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25  
26 231 and all 3 fractions of SBRT and complete HCC resection will be included in the efficacy analysis.  
27  
28 232 RECIST 1.1/mRECIST response rates (CR, PR and ORR) and pathologic response rates (MPR,  
29  
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31 233 pCR, etc.) will be presented descriptively. Progression-free survival (PFS) and OS rates will be  
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33  
34 234 presented with Kaplan–Meier plots using the full timespan from the completion of HCC resection  
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36  
37 235 to the date of recurrence or death from any cause. The proportions of participants who do not  
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39  
40 236 experience recurrence and who are alive at 3-monthly time-points thereafter will also be  
41  
42 237 estimated, and the appropriate descriptive analysis will be conducted.

#### 43 44 45 238 **Ethics and dissemination**

46  
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49 239 This trial has been approved by the Ethics Committee of Shandong Cancer Hospital and Institute  
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51 240 (SDZLEC2022-021-01). An abstract of the interim results will be prepared for academic  
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54 241 conferences such as American Society of Clinical Oncology Annual Meeting. The final results of  
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57 242 this trial will be published in a peer-reviewed journal after completion.  
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4 243 **Discussion**  
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7 244 The effect of ICIs in the adjuvant therapeutic setting of HCC is being evaluated in several clinical  
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10 245 trials[8]. In contrast, the possible role of ICIs in the neoadjuvant setting of HCC has not been  
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12 246 adequately explored[9]. The reason for this may arise from some concerns about the nature of  
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15 247 neoadjuvant therapy itself before curative surgery. If patients do not respond to the therapy, they  
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18 248 will suffer disease progression, and some can even jeopardize the opportunity of curative surgery.  
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20 249 Severe adverse effects from the neoadjuvant therapy can delay the resection or increase the risk of  
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23 250 morbidity. For ICIs in neoadjuvant therapy, immune-related adverse events (irAEs) and  
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26 251 hyperprogression can potentially bring more danger to patients.  
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29 252 However, neoadjuvant therapy also has some advantages compared to adjuvant therapy. The  
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32 253 existence of the target tumour permits the direct evaluation of the treatment, the recognition of the  
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34 254 responders from nonresponders, the validation of the surrogate predictors, the timely adjustment of  
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37 255 treatment, etc.; and the resected specimen be used for the pathologic evaluation of the treatment and  
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40 256 can facilitate translational studies.  
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43 257 In the context of cancer immunotherapy, neoadjuvant treatment may offer another very important  
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46 258 additional advantage; immunotherapies enhance T-cell activation the moment antigen is  
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49 259 encountered. Exposure to antigen during the period in which the major tumour mass is present  
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52 260 may increase the breadth and durability of tumour-specific T-cell responses. In the adjuvant  
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54 261 setting, the immunotherapy starts when the tumour, together with its antigens have been totally  
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57 262 removed[10]. In melanoma, the most recent data have shown the advantage of ICIs in neoadjuvant  
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60 263 therapies compared with adjuvant therapies[11, 12].

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4 264 In a randomised, open-label, perioperative phase II trial, the effect of nivolumab alone or  
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6 265 nivolumab plus ipilimumab in patients with resectable HCC was evaluated. The study was  
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9 266 reported to reach its primary endpoint of safety. Importantly, it achieved a 40% pathologic  
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12 267 complete response (pCR) rate (pCR rate of 24%, and major necrosis rate of 16%) for resectable  
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14 268 HCC after preoperative immunotherapy. The author suggested that these findings may favour the  
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17 269 perioperative treatment of resectable HCC by ICIs after future validation[13]. Another two similar  
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20 270 clinical trials are still ongoing (NCT03222076, NCT03510871).  
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23 271 More recently, the neoadjuvant application of another anti-PD-1, cemiplimab, in HCC patients  
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26 272 was evaluated and reported. Twenty-one HCC patients were enrolled in this study, all received  
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29 273 neoadjuvant cemiplimab and 20 patients underwent successful resection. Four (20%) had  
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32 274 significant tumour necrosis, three (15%) had a partial response, and all other patients maintained  
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34 275 stable disease. Seven patients had grade 3 AEs, and no grade 4 or 5 AEs were observed. One  
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36 276 patient developed pneumonitis, which led to a delay in surgery by 2 weeks[14].  
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40 277 For patients with resectable HCC and portal vein tumour thrombus (PVTT), neoadjuvant 3-D  
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43 278 conformal radiotherapy provided significantly better postoperative survival outcomes than surgery  
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45  
46 279 alone[15]. Mounting evidence shows the synergistic effects on local and distant tumour control  
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48 280 when RT is combined with immunotherapy[16].  
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51 281 The antitumor effect of radiation can be attributed to the induction of tumour cell death through  
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54 282 DNA damage, but radiotherapy also has immunomodulatory effects and can stimulate the immune  
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57 283 response through various mechanisms[17, 18]. Although radiotherapy can enhance antitumor  
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59 284 effects, its potential immunosuppressive effects can also restrain antitumor efficacy, including the  
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4 285 upregulation of coinhibitory ligands such as PD-L1[19, 20]. Combining radiotherapy with  
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6 286 immune checkpoint blockade can overcome these immunosuppressive mechanisms and augment  
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9 287 antitumor immunity.

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12 288 In a recent single-centre, randomised phase 2 trial in early-stage non-small cell lung cancer  
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15 289 (NSCLC), the combination of SBRT and neoadjuvant durvalumab was well tolerated and  
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18 290 associated with a high major pathological response rate[21].

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21 291 In general, we hope the results of this clinical trial can expand our knowledge about neoadjuvant  
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24 292 therapy of HCC, especially by the combination of ICI and RT, thus improving the outcome of  
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26  
27 293 HCC resection.

#### 30 294 **Contributorship statement**

31  
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33  
34 295 LZ designed the clinical trial and applied for funding; LZ, BZ and XS are the chief liver surgeons  
35  
36 296 performing the surgeries; JY is the chief radiation oncologist performing the radiotherapy; and  
37  
38  
39 297 KC, LL, CZ, PS, JZ and ZL are liver surgeons participating in the surgeries.

#### 40 41 42 298 **Competing interests**

43  
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45  
46 299 LZ is on the speakers' bureau for BeiGene, Bayer, MSD, Roche, Innovent and Hengrui Medicine.  
47  
48  
49 300 This trial is partly funded by BeiGene.

#### 50 51 52 301 **Funding**

53  
54  
55  
56 302 LZ received funding from the Key Research and Development Program of Shandong (Major  
57  
58 303 Science & Technology Innovation Project), 2021SFGC0501

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The Lancet Oncology, 2021. **22**(6): p. 824-835.

For peer review only



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

Section/item	ItemNo	Description	Page/ li
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1/1-3
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3/41-42
	2b	All items from the World Health Organization Trial Registration Data Set	4/44-45
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	27/297-298
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1/4-9
	5b	Name and contact information for the trial sponsor	1/11-13
	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	17/290-2
	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)	N/A

**Introduction**

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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	5/58-76
	6b	Explanation for choice of comparators	6/77-83
Objectives	7	Specific objectives or hypotheses	6/77-83
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)	3/34-41
<b>Methods: Participants, interventions, and outcomes</b>			
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	6/85-88
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)	7/104-118
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12/201-212
	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)	13/208-212
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13/211-212
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A

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4	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	13/215-2
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9	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)	11/184
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12	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	6/86-88
13				
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16	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
17				
18	<b>Methods: Assignment of interventions (for controlled trials)</b>			<b>N/A</b>
19				
20	Allocation:			
21				
22	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	
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27	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	
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30	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	
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34	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	
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37		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	
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4 **Methods: Data collection, management, and analysis**

5	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	13/223-2
6		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A
7	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14/226-2
8	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14/229-2
9		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14/233-2
10		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14/235-2

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27 **Methods: Monitoring**

28	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
29		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
30	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13/208

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4	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
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7	<b>Ethics and dissemination</b>			
8				
9	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	3/41-43
10				
11	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)	N/A
12				
13				
14	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11/185
15				
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17		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
18				
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20	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	13/214
21				
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23	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17/294-2
24				
25	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	13/214
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29	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	13/210-2
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32	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	3/43
33				
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37		31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
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39		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
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**Appendices**

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	submitte
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	12/199

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