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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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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 6th most commonly diagnosed cancer but the 3rd leading cancer killer worldwide, only after lung cancer and colorectal cancer[1].

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%[2]. 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[3]. Since 70% of them will experience recurrence within 5 years after resection[2], 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[4 5], 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[4].

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[6]. Despite this significant achievement, systemic treatment alone still can hardly cure HCC.

Taking these data together, a very straightforward ontology can be arrived at: If ICIs (mono- or combined with other systemic modalities) can be effectively applied to adjuvant and/or neoadjuvant therapies, significantly more HCC patients will be expected to experience long-term survival or even cure.

Meanwhile, the anti-tumor effect of radiation therapy (RT) has been attributed primarily to its enhancement of local control. RT also has an effect on tumor immunity and an additional anti-tumor effect can be expected if ICIs are administered simultaneously with RT.

Methods/design

Notable-HCC is a phase Ib study of neoadjuvant stereotactic body radiotherapy (SBRT) plus immune checkpoint inhibitor (ICI) prior to hepatic resection in adult patients (aged ⩾18 years) with HCC.

Tislelizumab (BGB-A317) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]) manufactured by BeiGene that inhibits the PD-1 receptor on cell surface. It is engineered with a nullified Fc portion of the antibody to minimize binding to Fc γ R on macrophages in order to abrogate antibody-dependent phagocytosis, a mechanism of T-cell clearance and potential resistance to anti-PD-1 therapy[7].

Eligible patients will receive SBRT (8 Gy × 3 fractions, every other day) on day 1, day 3 and day 5; the first dose of Tislelizumab will be administrated concurrently on day 1, then the second on day 22 (the first day of week 4, ± 3 days). Then on day 50 (the first day of week 8, ± 7 days), curative liver resection of HCC will be scheduled.

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 ≥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 ≥3,000/mcL

2) absolute neutrophil count ≥1,500/mcL

3) platelets ≥100,000/mcL

4) total bilirubin ≤ 2 × institutional upper limit of normal (ULN)

5) AST (aspartate aminotransferase)/ALT(alanine aminotransferase) ≤ 3 × institutional ULN

6) creatinine ≤ 1.5 × institutional ULN OR

7) estimated glomerular filtration rate (GFR) ≥50 mL/min/1.73 m2 (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 IU/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.

11. Participants with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

12. Female patient of childbearing potential should have a negative serum pregnancy test within 24 h of her first dose of IMP (Investigational Medicinal Product)

13. Women of childbearing potential must be willing to use a highly effective method of contraception for the course of the study through 5 months after the last dose of IMP. Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the patient.

14. Sexually active males must agree to use an adequate method of contraception starting with the first dose of IMP through 7 months after the last dose of study therapy. Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the patient.

Exclusion Criteria:

1. Extrahepatic metastasis

2. Prior systemic anticancer treatment for HCC, including an anti-PD-1, anti-PD-L1 or anti-CTLA-4 antibody

3. Prior orthotopic liver transplantation

4. Prior abdominal irradiation

5. Any major surgery within the 3 weeks prior to enrolment

6. Hepatic encephalopathy

7. Ascites that is refractory to diuretic therapy

8. Is currently receiving anti-cancer therapy (chemotherapy, radiation therapy, immunotherapy or biologic therapy) or has participated or is participating in a study of an IMP or used an investigational device within 4 weeks of the first dose of IMP

9. Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy

10. Known history of active Bacillus Tuberculosis (TB)

11. History of known hypersensitivity to any monoclonal antibody or any of their excipients

12. Known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy, or in situ cervical cancer

13. Active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment

14. Active infection requiring systemic therapy, with exceptions relating to Hepatitis B and C virus infection

15. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or is not in the best interest of the patient to participate, in the opinion of the treating Principal Investigator (PI)

16. Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial

17. Pregnant or breastfeeding

18. Known history of Human Immunodeficiency Virus (HIV; HIV 1/2 antibodies)

19. Received a live vaccine within 30 days of first dose of IMP administration.

Study procedures

Patients will undergo baseline tumour imaging including computed tomography (CT) scan of the chest, abdomen and pelvis, and by contrast enhanced magnetic resonance imaging (MRI) scan of the liver at screening. At post-treatment time-points prior to surgery (on Day 50), 4 weeks after surgery and then every 3 months after the surgery, tumour imaging will be repeated using contrast enhanced MRI. A triple-phase CT of the liver is an acceptable alternative for intrahepatic staging in patients with contraindications to MRI. Baseline CT/MRI scans do not need to be repeated if

obtained within 35 days of first SBRT. The same method used for assessment at baseline must then be used at all subsequent time points.

Participants will require a full hepatitis serology screen prior to enrolment into the study, this includes Hepatitis B and Hepatitis C Virus serology. In patients with positive serology for either virus, baseline HBV DNA and HCV quantitative RNA levels will be requested. Participants who are confirmed to have chronic and active hepatitis B and/or C (i.e. with detectable HBV DNA or HCV RNA at baseline) will have their viral load (HCV RNA and/or HBV DNA as appropriate) monitored at each cycle and at the end of treatment follow-up visit.

A baseline core tumor biopsy and PBMC (Peripheral Blood Mononuclear Cell) will be collected from participants at screening, and sample tumor tissue from the surgical specimen will be snap-frozen and stored for the future relevant studies.

Treatment will consist of 8 Gy × 3 fractions SBRT together with 2 cycles of tislelizumab 200mg administered intravenously with an interval of 3 weeks.

Patients will be reviewed following completion of SBRT and tislelizumab treatment (Follow-up visit 1; FU1) prior to surgery. Before surgery, Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1) and HCC-Specific mRECIST criteria will be used to determine patient response to treatment, including CR (complete response), PR (partial response) and ORR (objective response rate). PBMC will be collected again.

Hepatic resection will be performed as per standard of care. The safety FU2 will be conducted after the first dose of the post-resection tislelizumab. All AEs that occur prior to the visit will be

recorded. Participants with on-going AEs at the visit will be followed up by principal investigator (PI) or delegate until resolution or stabilization of the event. Following FU2, participants will be assessed every 3 months (±7 days) thereafter to collect information regarding disease status and survival. Long-term follow-up will continue, for each patient, for a total of 2 years.

Outcome measures and endpoints

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

Discussion

The effect of ICIs in the adjuvant therapeutic setting of HCC are being evaluated in serials of clinical trials[8], we are optimistic for the results to come in the near future. Compared to this, the possible roles of ICIs in the neoadjuvant setting of HCC remains a much less touched field[9]. The reason for this may arise from some concerns about the nature of neoadjuvant therapy itself before curative surgery. If patients do not respond to the therapy, they will suffer disease progression, some can even jeopardize the opportunity of curative surgery. Severe adverse effect from the neoadjuvant therapy can delay the resection or increase the risk of morbidity. For ICIs in

neoadjuvant therapy, immune-related adverse events (irAEs) and hyper-progression can potentially bring more danger to patients.

On the other hand, neoadjuvant therapy also has some advantages compared to adjuvant therapy. The existence of the target tumor permits the direct evaluation of the treatment, the recognition of the responders from non-responders, the validation of the surrogate predictors, the timely adjustment of treatment, etc.; and the resected specimen can provide pathologic evaluation of the treatment and facilitate translational studies.

In the context of cancer immunotherapy, neoadjuvant treatment may offer another very important additional advantage; immunotherapies enhance T-cell activation the moment antigen is encountered. Exposure to antigen during the period in which the major tumor mass is present may increase the breadth and durability of tumor-specific T-cell responses. While in adjuvant setting, the immunotherapy starts when the tumor, together with its antigens have been totally removed[10]. In melanoma, most recent data has showed the advantage of ICIs in neoadjuvant than in adjuvant therapies[11 12].

In a randomized, open label, perioperative phase II trial, effect of nivolumab alone or nivolumab plus ipilimumab in patients with resectable HCC were evaluated. The study was reported to reach its primary endpoint of safety. Importantly, it achieved a 40% pathologic response rate (pCR rate of 24%, and major necrosis rate of 16%) for resectable HCC after preoperative immunotherapy. The author argued that these findings may favor the perioperative treatment of resectable HCC by ICIs after future validation[13]. Another two similar clinical trials are still ongoing (NCT03222076, NCT03510871).

For patients with resectable HCC and portal vein tumor thrombus (PVTT), neoadjuvant 3-D conformal radiotherapy provided significantly better postoperative survival outcomes than surgery alone[14]. Mounting evidences are showing the synergistic effects on local and distant tumour control when radiation therapy is combined with immunotherapy[15].

The antitumor effect of radiation can be attributed to inducing tumour cell death through DNA damage, but radiotherapy also has immune modulatory effects and can stimulate the immune response through various mechanisms[15]. Although radiotherapy can enhance antitumor effects, its potential immunosuppressive effects can also restrain antitumor efficacy, including the up-regulation of co-inhibitory ligands such as PD-L1[16 17]. Combining radiotherapy with immune checkpoint blockade can overcome these immunosuppressive mechanisms and augment antitumor immunity.

In a recent single-center, randomised phase 2 trial in early-stage non-small-cell lung cancer (NSCLC), combination of stereotactic body radiotherapy (SBRT) to neoadjuvant durvalumab is well tolerated and associated with a high major pathological response rate[18].

Another important issue is the different sequence of RT and ICI, which may have differential effects on the outcomes of cancer patients. There is relative agreement in published work regarding the preclinical effects of sequencing, and various studies have shown that concurrent radiation and ICIs immunotherapy is better than sequential treatments； giving radiation before ICIs might result in antigen presentation in a tolerogenic environment with fully active checkpoints. Similarly, the efficacy of ICIs alone before radiation might be restricted as a result of diminished inflammatory cell death and reduced antigenic targets for the immune system to focus

on[15]. This schedule was also adopted by the above-mentioned neoadjuvant trials of SBRT plus ICIs in NSCLC [18]. In the recent animal model study of abscopal antitumor immune responses[19], as well as in the clinical study in melanoma brain metastases[20], ICIs start after radiation shows better outcome compare to the reverse sequence. Taking considerations of the experiences from the literature, as well as the possible unexpected side effects or additive toxicities could potentially occur in the combination therapy, in this planned trial, we also adopt concurrent PD-1 and SBRT as neoadjuvant therapy for resectable HCC.

In general, we hope the results from this clinical trial can expand our knowledge about neoadjuvant therapy of HCC, esp. by the combination of ICI and RT, thus improve the outcome of HCC resection.

Contributorship statement

LZ designs the clinical trial and applies the funding; LZ, BZ and XS are the chief liver surgeons performing the surgery; JY is the chief radiation oncologist performing the radiotherapy; KC, LL, CZ, PS, JZ, ZL are liver surgeons participating the surgery.

Competing interests

LZ is on the speakers' bureau for BiGene, Bayer, MSD, Roche, Innovent, Hengrui Medicine. This trial is partly funded by BeiGene.

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Abstract

Introduction Liver resection is the mainstay of curative-intent treatment for hepatocellular carcinoma (HCC), but the postoperative 5-year recurrence rate reaches 70%, and there are no adjuvant or neoadjuvant therapies recommended by major HCC guidelines that can reduce the risk of recurrence. In the recent decade, significant progress has been achieved in the systemic treatment of HCC, mainly from immune checkpoint inhibitors (ICIs) and targeted therapy. In other malignancies, ICIs in the neoadjuvant setting have shown better outcomes than in the adjuvant setting. On the other hand, the addition of radiation to ICIs incrementally improves the systemic response to ICIs. Neoadjuvant therapy of ICIs plus stereotactic body radiotherapy (SBRT) has shown promising results in several types of solid tumours 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 of 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 for 1 year. We plan to enrol 20 participants in this trial. The primary study endpoints include the delay of surgery, tumour response, and safety and tolerability of the sequential SBRT/tislelizumab. Other endpoints are the disease-free survival (DFS) and overall survival (OS) rates every 3 or 6 months after the surgery. **Ethics and dissemination** This trial was 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 patients were involved. **Trial registration** ClinicalTrials.gov: NCT05185531.

Strengths and limitations of this study

- To examine the role of tislelizumab (PD-1 blocker) plus radiation as the neoadjuvant therapy in resectable HCC.
- Eligible patients will receive 8 Gy × 3 fractions of SBRT together with 2 cycles of tislelizumab.
- Hepatic resection will be performed 4 weeks after the 2nd dose of tislelizumab.
- The delay of surgery, tumour response, safety and tolerability as well as DFS and OS will be explored.

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 and accounts for 75% to 85% of all primary liver cancers (PLCs). in 2020, PLC was the 6th most commonly diagnosed cancer but the 3rd leading cause of cancer death worldwide, only after lung cancer and colorectal cancer[1].

Surgical therapies (hepatic resection, liver transplantation and ablation in well-selected patients) remain the backbone of curative therapies for HCC. In patients who meet guidelines and undergo resection, the 5-year survival rate with these modalities is over 60%[2]. However, the global HCC BRIDGE study that covered 8656 newly diagnosed HCC patients from 20 leading worldwide liver centres showed that less than 10% of HCC patients were "ideal" candidates for liver resection, and only 27% underwent resection in the real-world scenario[3]. Since 70% of resected patients will experience recurrence within 5 years after resection[2], theoretically, only less than 10% of patients can be cured by surgery. To date, neither adjuvant nor neoadjuvant therapies are recommended by major HCC guidelines[4, 5], because they have not been proven to improve the outcome of patients treated with resection in terms of reducing the risk of recurrence, but the European Association for the Study of the Liver (EASL) Clinical Practice Guidelines have encouraged further clinical trials with new agents for these applications[4].

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 overall survival (OS) in selected advanced HCC patients to over 3 years[6]. Despite this significant achievement, systemic treatment alone rarely cures HCC.

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

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

Methods/design

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

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

Eligible patients will receive SBRT (8 Gy × 3 fractions, every other day) on day 1, day 3 and day 5; the first dose of tislelizumab will be administered concurrently on day 1, then the second dose

will be administered on day 22 (the first day of week 4, ± 3 days). Then on day 50 (the first day of week 8, ± 7 days), curative liver resection of HCC will be scheduled.

Patient and public involvement

No patients were involved.

Eligibility criteria

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

Inclusion criteria:

1. Written informed consent for the trial.
2. Aged ≥18 years
3. Willing to provide tissue from an excisional biopsy of a tumour 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 a core biopsy.
5. Measurable disease by computed tomography (CT)-scan or magnetic resonance imaging (MRI) defined by the Response Evaluation Criteria In Solid Tumours (RECIST) 1.1 criteria and HCC-specific modified RECIST (mRECIST).

6. Medically fit to undergo surgery as determined by the treating medical and surgical oncology team

7. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1

8. Adequate organ and marrow function as defined below:

1) leukocytes ≥3,000/mcL

2) absolute neutrophil count ≥1,500/mcL

3) platelets ≥100,000/mcL

4) total bilirubin ≤ 2 × institutional upper limit of normal (ULN)

5) aspartate aminotransferase (AST)/ alanine aminotransferase (ALT) ≤ 3 × institutional ULN

6) creatinine ≤ 1.5 × institutional ULN or

7) estimated glomerular filtration rate (GFR) ≥50 mL/min/1.73 m2 (according to the Cockcroft-Gault formula)

9. Overall Child-Pugh class A

10. Documented virology status of hepatitis, as confirmed by screening tests for hepatitis B virus (HBV) and hepatitis C virus (HCV)

1) For patients with active HBV: HBV DNA <2000 IU/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.

11. Participants with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

12. Female patients of childbearing potential should have a negative serum pregnancy test within 24 h of their first dose of Investigational Medicinal Product (IMP)

13. Women of childbearing potential must be willing to use a highly effective method of contraception for the course of the study through 5 months after the last dose of IMP. Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the patient.

14. Sexually active males must agree to use an adequate method of contraception starting with the first dose of IMP through 7 months after the last dose of study therapy. Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the patient.

Exclusion criteria:

1. Extrahepatic metastasis.

2. Prior systemic anticancer treatment for HCC, including an anti-PD-1, anti-PD-L1 or anti-CTLA-4 antibody.

3. Prior orthotopic liver transplantation.

4. Prior abdominal irradiation.

5. Any major surgery within the 3 weeks prior to enrolment.

6. Hepatic encephalopathy.

7. Ascites that is refractory to diuretic therapy.

8. Currently receiving anticancer therapy (chemotherapy, radiation therapy, immunotherapy or biologic therapy) or has participated or is participating in a study of an IMP or used an investigational device within 4 weeks of the first dose of IMP.

9. Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy.

10. Known history of active Bacillus tuberculosis (TB) infection.

11. History of known hypersensitivity to any monoclonal antibody or any of their excipients.

12. Known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

13. Active autoimmune disease that has required systemic treatment in the past 2 years (i.e. use of disease-modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.

14. Active infection requiring systemic therapy, with exceptions relating to Hepatitis B and C virus infection.

15. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or is not in the best interest of the patient to participate, in the opinion of the treating Principal Investigator (PI).

16. Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial

17. Pregnant or breastfeeding

18. Known history of human immunodeficiency virus (HIV; HIV 1/2 antibodies)

19. Received a live vaccine within 30 days of the first dose of IMP administration.

Study procedures

The consent form will be signed by a liver surgeon with the participant or his delegate. Patients will undergo baseline tumour imaging including CT scans of the chest, abdomen and pelvis, and

by contrast-enhanced MRI scans of the liver at screening. At posttreatment time points prior to surgery (on Day 50), 4 weeks after surgery and then every 3 months after surgery, tumour imaging will be repeated using contrast-enhanced MRI. Triple-phase CT of the liver is an acceptable alternative for intrahepatic staging in patients with contraindications to MRI. Baseline CT/MRI scans do not need to be repeated if obtained within 35 days of the first SBRT. The same method used for assessment at baseline must then be used at all subsequent time points.

Participants will require a full hepatitis serology screen prior to enrolment in the study, which includes HBV and HCV serology. In patients with positive serology for either virus, baseline HBV DNA and HCV quantitative RNA levels will be requested. Participants who are confirmed to have chronic and active hepatitis B and/or C (i.e., with detectable HBV DNA or HCV RNA at baseline) will have their viral load (HCV RNA and/or HBV DNA as appropriate) monitored at each cycle and at the end of the treatment follow-up visit.

A baseline core tumour biopsy and Peripheral Blood Mononuclear Cell (PBMC) will be collected from participants at screening, and sample tumour tissue from the surgical specimen will be snap-frozen and stored for the future relevant studies.

Treatment will consist of 8 Gy × 3 fractions SBRT together with 2 cycles of tislelizumab 200mg administered intravenously with an interval of 3 weeks.

Patients will be reviewed following the completion of SBRT and tislelizumab treatment (Follow-up visit 1; FU1) prior to surgery. Before surgery, RECIST v1.1 and HCC-specific mRECIST

criteria will be used to determine patient response to treatment, including complete response (CR), partial response (PR) and objective response rate (ORR). PBMCs will be collected again.

Hepatic resection will be performed as per the standard of care. Safety FU2 will be conducted after the first dose of the postresection tislelizumab. All adverse events (AEs) that occur prior to the visit will be recorded. Participants with ongoing AEs at the visit will be followed up by the PI or delegated until resolution or stabilisation of the event. Following resection, participants will be assessed every 3 months (±7 days) thereafter to collect information regarding disease status and survival. Long-term follow-up will continue for a total of 2 years for each patient.

All personal information of the enrolled participants will be maintained and protected in the hospital information system, and be accessible only to the authorized medical staffs to protect the confidentiality. PIs of the trial have access to the final entire trial dataset.

Outcome measures and endpoints

The primary study endpoints include the number of patients experiencing a surgery delay of over 6 weeks or later, ORR on preresection imaging according to the RECIST v1.1/mRECIST criteria, pathologic response rate on evaluation of the resected specimen, and determination of safety and tolerability of the sequential SBRT/tislelizumab based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 criteria. The secondary endpoints are DFS and OS rates every 3 or 6 months after the hepatic resection. Exploratory endpoints include patients' immune response and morbidity and mortality of the surgery.

Statistical analysis

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

All participants who receive at least one dose of tislelizumab and one fraction of SBRT will be included in the safety analysis. All participants who receive at least one dose of the tislelizumab and all 3 fractions of SBRT and complete HCC resection will be included in the efficacy analysis. RECIST 1.1/mRECIST response rates (CR, PR and ORR) and pathologic response rates (MPR, pCR, etc.) will be presented descriptively. Progression-free survival (PFS) and OS rates will be presented with Kaplan–Meier plots using the full timespan from the completion of HCC resection to the date of recurrence or death from any cause. The proportions of participants who do not experience recurrence and who are alive at 3-monthly time-points thereafter will also be estimated, and the appropriate descriptive analysis will be conducted.

Discussion

The effect of ICIs in the adjuvant therapeutic setting of HCC is being evaluated in several clinical trials[8]. In contrast, the possible role of ICIs in the neoadjuvant setting of HCC has not been adequately explored[9]. The reason for this may arise from some concerns about the nature of neoadjuvant therapy itself before curative surgery. If patients do not respond to the therapy, they will suffer disease progression, and some can even jeopardize the opportunity of curative surgery.

Severe adverse effects from the neoadjuvant therapy can delay the resection or increase the risk of morbidity. For ICIs in neoadjuvant therapy, immune-related adverse events (irAEs) and hyperprogression can potentially bring more danger to patients.

However, neoadjuvant therapy also has some advantages compared to adjuvant therapy. The existence of the target tumour permits the direct evaluation of the treatment, the recognition of the responders from nonresponders, the validation of the surrogate predictors, the timely adjustment of treatment, etc.; and the resected specimen be used for the pathologic evaluation of the treatment and can facilitate translational studies.

In the context of cancer immunotherapy, neoadjuvant treatment may offer another very important additional advantage; immunotherapies enhance T-cell activation the moment antigen is encountered. Exposure to antigen during the period in which the major tumour mass is present may increase the breadth and durability of tumour-specific T-cell responses. In the adjuvant setting, the immunotherapy starts when the tumour, together with its antigens have been totally removed[10]. In melanoma, the most recent data have shown the advantage of ICIs in neoadjuvant therapies compared with adjuvant therapies[11, 12].

In a randomised, open-label, perioperative phase II trial, the effect of nivolumab alone or nivolumab plus ipilimumab in patients with resectable HCC was evaluated. The study was reported to reach its primary endpoint of safety. Importantly, it achieved a 40% pathologic complete response (pCR) rate (pCR rate of 24%, and major necrosis rate of 16%) for resectable HCC after preoperative immunotherapy. The author suggested that these findings may favour the

perioperative treatment of resectable HCC by ICIs after future validation[13]. Another two similar clinical trials are still ongoing (NCT03222076, NCT03510871).

More recently, the neoadjuvant application of another anti-PD-1, cemiplimab, in HCC patients was evaluated and reported. Twenty-one HCC patients were enrolled in this study, all received neoadjuvant cemiplimab and 20 patients underwent successful resection. Four (20%) had significant tumour necrosis, three (15%) had a partial response, and all other patients maintained stable disease. Seven patients had grade 3 AEs, and no grade 4 or 5 AEs were observed. One patient developed pneumonitis, which led to a delay in surgery by 2 weeks[14].

For patients with resectable HCC and portal vein tumour thrombus (PVTT), neoadjuvant 3-D conformal radiotherapy provided significantly better postoperative survival outcomes than surgery alone[15]. Mounting evidence shows the synergistic effects on local and distant tumour control when RT is combined with immunotherapy[16].

The antitumor effect of radiation can be attributed to the induction of tumour cell death through DNA damage, but radiotherapy also has immunomodulatory effects and can stimulate the immune response through various mechanisms[17, 18]. Although radiotherapy can enhance antitumor effects, its potential immunosuppressive effects can also restrain antitumor efficacy, including the upregulation of coinhibitory ligands such as PD-L1[19, 20]. Combining radiotherapy with immune checkpoint blockade can overcome these immunosuppressive mechanisms and augment antitumor immunity.

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

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

Contributorship statement

LZ designed the clinical trial and applied for funding; LZ, BZ and XS are the chief liver surgeons performing the surgeries; JY is the chief radiation oncologist performing the radiotherapy; and KC, LL, CZ, PS, JZ and ZL are liver surgeons participating in the surgeries.

Competing interests

LZ is on the speakers' bureau for BeiGene, Bayer, MSD, Roche, Innovent and Hengrui Medicine.

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

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

Section/item	ItemNo	Description	Page/ li
Administrative information			
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			

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
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	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)	7/104-18
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12/201-2
	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)	13/208-2
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13/211-2
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A

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
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
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
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
Methods: Assignment of interventions (for controlled trials)			**N/A**
Allocation:			
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	
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	
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	

Methods: Data collection, management, and analysis			
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
Methods: Monitoring			
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

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
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	3/41-43
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
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
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17/294-2
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
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
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
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A

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

*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.

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

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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Potential conflicts of interests

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Abstract

Introduction Liver resection is the mainstay of curative-intent treatment for hepatocellular carcinoma (HCC), but the postoperative 5-year recurrence rate reaches 70%, and there are no adjuvant or neoadjuvant therapies recommended by major HCC guidelines that can reduce the risk of recurrence. In the recent decade, significant progress has been achieved in the systemic treatment of HCC, mainly from immune checkpoint inhibitors (ICIs) and targeted therapy. In other malignancies, ICIs in the neoadjuvant setting have shown better outcomes than in the adjuvant setting. On the other hand, the addition of radiation to ICIs incrementally improves the systemic response to ICIs. Neoadjuvant therapy of ICIs plus stereotactic body radiotherapy (SBRT) has shown promising results in several types of solid tumours 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 of 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 for 1 year. We plan to enrol 20 participants in this trial. The primary study endpoints include the delay of surgery, tumour response, and safety and tolerability of the sequential SBRT/tislelizumab. Other endpoints are the disease-free survival (DFS) and overall survival (OS) rates every 3 or 6 months after the surgery. **Ethics and dissemination** This trial was 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 patients were involved. **Trial registration** ClinicalTrials.gov: NCT05185531.

Strengths and limitations of this study

- The pilot exploration of ICIs plus radiotherapy as the neoadjuvant therapy for HCC.
- Single-armed, non-randomised design of the trial.
- Relatively long waiting time before the curative resection is scheduled.

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 and accounts for 75% to 85% of all primary liver cancers (PLCs). in 2020, PLC was the 6th most commonly diagnosed cancer but the 3rd leading cause of cancer death worldwide, only after lung cancer and colorectal cancer[1].

Surgical therapies (hepatic resection, liver transplantation and ablation in well-selected patients) remain the backbone of curative therapies for HCC. In patients who meet guidelines and undergo resection, the 5-year survival rate with these modalities is over 60%[2]. However, the global HCC BRIDGE study that covered 8656 newly diagnosed HCC patients from 20 leading worldwide liver centres showed that less than 10% of HCC patients were "ideal" candidates for liver resection, and only 27% underwent resection in the real-world scenario[3]. Since 70% of resected patients will experience recurrence within 5 years after resection[2], theoretically, only less than 10% of patients can be cured by surgery. To date, neither adjuvant nor neoadjuvant therapies are recommended by major HCC guidelines[4, 5], because they have not been proven to improve the outcome of patients treated with resection in terms of reducing the risk of recurrence, but the European Association for the Study of the Liver (EASL) Clinical Practice Guidelines have encouraged further clinical trials with new agents for these applications[4].

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 overall survival (OS) in selected advanced HCC patients to over 3 years[6]. Despite this significant achievement, systemic treatment alone rarely cures HCC.

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

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

Methods/design

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

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

Eligible patients will receive SBRT (8 Gy × 3 fractions, every other day) on day 1, day 3 and day 5; the first dose of tislelizumab will be administered concurrently on day 1, then the second dose

will be administered on day 22 (the first day of week 4, ± 3 days). Then on day 50 (the first day of week 8, ± 7 days), curative liver resection of HCC will be scheduled.

Patient and public involvement

No patients were involved.

Eligibility criteria

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

Inclusion criteria:

1. Written informed consent for the trial.
2. Aged ≥18 years
3. Willing to provide tissue from an excisional biopsy of a tumour 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 a core biopsy.
5. Measurable disease by computed tomography (CT)-scan or magnetic resonance imaging (MRI) defined by the Response Evaluation Criteria In Solid Tumours (RECIST) 1.1 criteria and HCC-specific modified RECIST (mRECIST).

6. Medically fit to undergo surgery as determined by the treating medical and surgical oncology team

7. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1

8. Adequate organ and marrow function as defined below:

1) leukocytes ≥3,000/mcL

2) absolute neutrophil count ≥1,500/mcL

3) platelets ≥100,000/mcL

4) total bilirubin ≤ 2 × institutional upper limit of normal (ULN)

5) aspartate aminotransferase (AST)/ alanine aminotransferase (ALT) ≤ 3 × institutional ULN

6) creatinine ≤ 1.5 × institutional ULN or

7) estimated glomerular filtration rate (GFR) ≥50 mL/min/1.73 m2 (according to the Cockcroft-Gault formula)

9. Overall Child-Pugh class A

10. Documented virology status of hepatitis, as confirmed by screening tests for hepatitis B virus (HBV) and hepatitis C virus (HCV)

1) For patients with active HBV: HBV DNA <2000 IU/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.

11. Participants with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

12. Female patients of childbearing potential should have a negative serum pregnancy test within 24 h of their first dose of Investigational Medicinal Product (IMP)

13. Women of childbearing potential must be willing to use a highly effective method of contraception for the course of the study through 5 months after the last dose of IMP. Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the patient.

14. Sexually active males must agree to use an adequate method of contraception starting with the first dose of IMP through 7 months after the last dose of study therapy. Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the patient.

Exclusion criteria:

1. Extrahepatic metastasis.

2. Prior systemic anticancer treatment for HCC, including an anti-PD-1, anti-PD-L1 or anti-CTLA-4 antibody.

3. Prior orthotopic liver transplantation.

4. Prior abdominal irradiation.

5. Any major surgery within the 3 weeks prior to enrolment.

6. Hepatic encephalopathy.

7. Ascites that is refractory to diuretic therapy.

8. Currently receiving anticancer therapy (chemotherapy, radiation therapy, immunotherapy or biologic therapy) or has participated or is participating in a study of an IMP or used an investigational device within 4 weeks of the first dose of IMP.

9. Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy.

10. Known history of active Bacillus tuberculosis (TB) infection.

11. History of known hypersensitivity to any monoclonal antibody or any of their excipients.

12. Known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

13. Active autoimmune disease that has required systemic treatment in the past 2 years (i.e. use of disease-modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.

14. Active infection requiring systemic therapy, with exceptions relating to Hepatitis B and C virus infection.

15. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or is not in the best interest of the patient to participate, in the opinion of the treating Principal Investigator (PI).

16. Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial

17. Pregnant or breastfeeding

18. Known history of human immunodeficiency virus (HIV; HIV 1/2 antibodies)

19. Received a live vaccine within 30 days of the first dose of IMP administration.

Study procedures

The consent form will be signed by a liver surgeon with the participant or his delegate. Patients will undergo baseline tumour imaging including CT scans of the chest, abdomen and pelvis, and

by contrast-enhanced MRI scans of the liver at screening. At posttreatment time points prior to surgery (on Day 50), 4 weeks after surgery and then every 3 months after surgery, tumour imaging will be repeated using contrast-enhanced MRI. Triple-phase CT of the liver is an acceptable alternative for intrahepatic staging in patients with contraindications to MRI. Baseline CT/MRI scans do not need to be repeated if obtained within 35 days of the first SBRT. The same method used for assessment at baseline must then be used at all subsequent time points.

Participants will require a full hepatitis serology screen prior to enrolment in the study, which includes HBV and HCV serology. In patients with positive serology for either virus, baseline HBV DNA and HCV quantitative RNA levels will be requested. Participants who are confirmed to have chronic and active hepatitis B and/or C (i.e., with detectable HBV DNA or HCV RNA at baseline) will have their viral load (HCV RNA and/or HBV DNA as appropriate) monitored at each cycle and at the end of the treatment follow-up visit.

A baseline core tumour biopsy and Peripheral Blood Mononuclear Cell (PBMC) will be collected from participants at screening, and sample tumour tissue from the surgical specimen will be snap-frozen and stored for the future relevant studies.

Treatment will consist of 8 Gy × 3 fractions SBRT together with 2 cycles of tislelizumab 200mg administered intravenously with an interval of 3 weeks.

Patients will be reviewed following the completion of SBRT and tislelizumab treatment (Follow-up visit 1; FU1) prior to surgery. Before surgery, RECIST v1.1 and HCC-specific mRECIST

criteria will be used to determine patient response to treatment, including complete response (CR), partial response (PR) and objective response rate (ORR). PBMCs will be collected again.

Hepatic resection will be performed as per the standard of care. Safety FU2 will be conducted after the first dose of the postresection tislelizumab. All adverse events (AEs) that occur prior to the visit will be recorded. Participants with ongoing AEs at the visit will be followed up by the PI or delegated until resolution or stabilisation of the event. Following resection, participants will be assessed every 3 months (±7 days) thereafter to collect information regarding disease status and survival. Long-term follow-up will continue for a total of 2 years for each patient.

All personal information of the enrolled participants will be maintained and protected in the hospital information system, and be accessible only to the authorized medical staffs to protect the confidentiality. PIs of the trial have access to the final entire trial dataset.

Outcome measures and endpoints

The primary study endpoints include the number of patients experiencing a surgery delay of over 6 weeks or later, ORR on preresection imaging according to the RECIST v1.1/mRECIST criteria, pathologic response rate on evaluation of the resected specimen, and determination of safety and tolerability of the sequential SBRT/tislelizumab based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 criteria. The secondary endpoints are DFS and OS rates every 3 or 6 months after the hepatic resection. Exploratory endpoints include patients' immune response and morbidity and mortality of the surgery.

Statistical analysis

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

All participants who receive at least one dose of tislelizumab and one fraction of SBRT will be included in the safety analysis. All participants who receive at least one dose of the tislelizumab and all 3 fractions of SBRT and complete HCC resection will be included in the efficacy analysis. RECIST 1.1/mRECIST response rates (CR, PR and ORR) and pathologic response rates (MPR, pCR, etc.) will be presented descriptively. Progression-free survival (PFS) and OS rates will be presented with Kaplan–Meier plots using the full timespan from the completion of HCC resection to the date of recurrence or death from any cause. The proportions of participants who do not experience recurrence and who are alive at 3-monthly time-points thereafter will also be estimated, and the appropriate descriptive analysis will be conducted.

Ethics and dissemination

This trial has been approved by the Ethics Committee of Shandong Cancer Hospital and Institute (SDZLEC2022-021-01). An abstract of the interim results will be prepared for academic conferences such as American Society of Clinical Oncology Annual Meeting. The final results of this trial will be published in a peer-reviewed journal after completion.

Discussion

The effect of ICIs in the adjuvant therapeutic setting of HCC is being evaluated in several clinical trials[8]. In contrast, the possible role of ICIs in the neoadjuvant setting of HCC has not been adequately explored[9]. The reason for this may arise from some concerns about the nature of neoadjuvant therapy itself before curative surgery. If patients do not respond to the therapy, they will suffer disease progression, and some can even jeopardize the opportunity of curative surgery. Severe adverse effects from the neoadjuvant therapy can delay the resection or increase the risk of morbidity. For ICIs in neoadjuvant therapy, immune-related adverse events (irAEs) and hyperprogression can potentially bring more danger to patients.

However, neoadjuvant therapy also has some advantages compared to adjuvant therapy. The existence of the target tumour permits the direct evaluation of the treatment, the recognition of the responders from nonresponders, the validation of the surrogate predictors, the timely adjustment of treatment, etc.; and the resected specimen be used for the pathologic evaluation of the treatment and can facilitate translational studies.

In the context of cancer immunotherapy, neoadjuvant treatment may offer another very important additional advantage; immunotherapies enhance T-cell activation the moment antigen is encountered. Exposure to antigen during the period in which the major tumour mass is present may increase the breadth and durability of tumour-specific T-cell responses. In the adjuvant setting, the immunotherapy starts when the tumour, together with its antigens have been totally removed[10]. In melanoma, the most recent data have shown the advantage of ICIs in neoadjuvant therapies compared with adjuvant therapies[11, 12].

In a randomised, open-label, perioperative phase II trial, the effect of nivolumab alone or nivolumab plus ipilimumab in patients with resectable HCC was evaluated. The study was reported to reach its primary endpoint of safety. Importantly, it achieved a 40% pathologic complete response (pCR) rate (pCR rate of 24%, and major necrosis rate of 16%) for resectable HCC after preoperative immunotherapy. The author suggested that these findings may favour the perioperative treatment of resectable HCC by ICIs after future validation[13]. Another two similar clinical trials are still ongoing (NCT03222076, NCT03510871).

More recently, the neoadjuvant application of another anti-PD-1, cemiplimab, in HCC patients was evaluated and reported. Twenty-one HCC patients were enrolled in this study, all received neoadjuvant cemiplimab and 20 patients underwent successful resection. Four (20%) had significant tumour necrosis, three (15%) had a partial response, and all other patients maintained stable disease. Seven patients had grade 3 AEs, and no grade 4 or 5 AEs were observed. One patient developed pneumonitis, which led to a delay in surgery by 2 weeks[14].

For patients with resectable HCC and portal vein tumour thrombus (PVTT), neoadjuvant 3-D conformal radiotherapy provided significantly better postoperative survival outcomes than surgery alone[15]. Mounting evidence shows the synergistic effects on local and distant tumour control when RT is combined with immunotherapy[16].

The antitumor effect of radiation can be attributed to the induction of tumour cell death through DNA damage, but radiotherapy also has immunomodulatory effects and can stimulate the immune response through various mechanisms[17, 18]. Although radiotherapy can enhance antitumor effects, its potential immunosuppressive effects can also restrain antitumor efficacy, including the

upregulation of coinhibitory ligands such as PD-L1[19, 20]. Combining radiotherapy with immune checkpoint blockade can overcome these immunosuppressive mechanisms and augment antitumor immunity.

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

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

Contributorship statement

LZ designed the clinical trial and applied for funding; LZ, BZ and XS are the chief liver surgeons performing the surgeries; JY is the chief radiation oncologist performing the radiotherapy; and KC, LL, CZ, PS, JZ and ZL are liver surgeons participating in the surgeries.

Competing interests

LZ is on the speakers' bureau for BeiGene, Bayer, MSD, Roche, Innovent and Hengrui Medicine.

This trial is partly funded by BeiGene.

Funding

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

Section/item	ItemNo	Description	Page/ li
Administrative information			
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			

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
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	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)	7/104-18
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12/201-2
	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)	13/208-2
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13/211-2
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A

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
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
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
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
Methods: Assignment of interventions (for controlled trials)			**N/A**
Allocation:			
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	
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	
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	

Methods: Data collection, management, and analysis			
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
Methods: Monitoring			
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

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
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	3/41-43
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
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
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17/294-2
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
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
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
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A

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

*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.