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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-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 two 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 and overall survival 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.

Trial registration number NCT05185531.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The pilot exploration of immune checkpoint inhibitors plus radiotherapy as the neoadjuvant therapy for hepatocellular carcinoma.
⇒ Single-armed, non-randomised design of the trial.
⇒ Relatively long waiting time before the curative resection is scheduled.

BACKGROUND AND RATIONALE

Hepatocellular carcinoma (HCC) remains prevalent worldwide and accounts for 75%–85% of all primary liver cancers (PLCs). In 2020, PLC was the sixth most commonly diagnosed cancer but the third 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 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 1 March 2022, and is anticipated to be completed on 31 December 2024.

Tislelizumab (BGB-A317) is a human monoclonal antibody (HuMAb; 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 FcγR 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 non-invasive 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 AASLD, or by histological diagnosis from a core biopsy.
5. Measurable disease by CT-scan or 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 performance status 0 or 1.
8. Adequate organ and marrow function as defined below:
    1. Leucocytes ≥3×10^9/L.
    2. Absolute neutrophil count ≥1.5×10^9/L.
    3. Platelets ≥100×10^9/L.
    4. Total bilirubin ≤2×institutional upper limit of normal (ULN).
    5. Aspartate aminotransferase/alanine aminotransferase ≤3×institutional ULN.
    6. Creatinine ≤1.5×institutional ULN.
    7. Estimated glomerular filtration rate ≥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; eg, 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 hours 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, RT, immunotherapy or biological 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 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 (ie, use of disease-modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin or physiological 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 HBV and HCV 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 post-treatment 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 (ie, 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 two cycles of tislelizumab 200 mg 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 authorised 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, pathological 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 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 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 three 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 pathological response rates (MPR, pCR, etc) will be presented descriptively. Progression-free survival 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 jeopardise 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 AEs and hyperprogression can potentially bring more danger to patients.

However, neoadjuvant therapy also has some advantages compared with adjuvant therapy. The existence of the target tumour 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 be used for the pathological 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% pathological 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, 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 antitumour 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 antitumour effects, its potential immunosuppressive effects can also restrain antitumour 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 antitumour immunity.

In a recent single-centre, randomised phase II trial in early-stage non-small cell lung cancer, 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.

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Contributors 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. KC, LL, CZ, PS, JZ and ZL are liver surgeons participating in the surgeries.

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

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

Patient consent for publication Consent obtained from next of kin.

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