Study protocol of a multicenter phase Ib/II clinical study on the safety and efficacy of selective internal radiation therapy (SIRT) with Yttrium-90 microspheres in combination with nivolumab, ipilimumab, and lenvatinib in patients with unresectable hepatocellular carcinoma

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A multicenter phase Ib/II clinical study on the safety and efficacy of selective internal radiation therapy (SIRT) with Yttrium-90 microspheres in combination with nivolumab, ipilimumab, and lenvatinib in patients with unresectable hepatocellular carcinoma

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Background Despite recent advances in the combination of systemic therapy and local treatment for patients with advanced unresectable hepatocellular carcinoma, limitations remain, including poor response rates and the lack of translation of short-term progression-free survival to long-term overall survival. The use of selective internal radiation therapy (SIRT) with Yttrium-90 microspheres combined with nivolumab, ipilimumab, and lenvatinib may overcome these shortcomings. This phase 1b/II clinical trial evaluates the safety and efficacy of this protocol in the treatment of patients with unresectable hepatocellular carcinoma.

Methods/design This multicenter, single-arm, prospective trial enrolls patients with unresectable hepatocellular carcinoma. Patients receive Yttrium-90 selective internal radiation therapy (Y90-SIRT) in combination with nivolumab, ipilimumab, and lenvatinib. The phase Ib portion of the trial explores the incidence of dose-limiting toxicity (DLT) in the quadruple therapeutic regimen. Three weeks after receiving Y90-SIRT, the patients are assigned to one of three dose exploration cohorts: (1) nivolumab 1 mg/kg IV every 3 weeks (Q3W) + ipilimumab 1 mg/kg IV Q3W for up to 4 cycles; (2) nivolumab 1 mg/kg IV Q3W + ipilimumab 2 mg/kg IV Q3W for up to 4 cycles; (3) nivolumab 1 mg/kg IV Q3W + ipilimumab 3 mg/kg IV Q3W for up to 4 cycles. After completion of ipilimumab administration, nivolumab is continued at 480 mg IV every 4 weeks (Q4W) until disease progression, unacceptable toxicity, withdrawal of informed consent, or a maximum treatment duration of two years. Lenvatinib is then administered after discontinuation of ipilimumab, in combination with nivolumab, at a dose of 8 mg (body weight <60 kg) or 12 mg (body weight >60 kg) orally once daily (PO QD), taken at a fixed time each day, with or without food. The phase II portion represents a single-arm trial using the dose selected in phase Ib. After completion of all treatments, patients will be followed up for 24 months. The primary endpoints are the incidence of DLT in phase Ib for the determination of the treatment

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regimen, and the objective response rate in the experimental group in the phase II trial.

Discussion This trial aims to establish a safe and effective strategy that combines local treatment with systemic therapy for patients with unresectable hepatocellular carcinoma, integrating local Y90-SIRT with systemic immunotherapy and targeted therapy. The results may provide guidance for future phase III clinical trials.

Trial registration This study has been approved by the Ethics.Committee of West China Hospital of Sichuan University (IRB No.).The trial was prospectively registered at ClinicalTrial Registry () on February 17, 2025.

Keywords: unresectable hepatocellular carcinoma, Yttrium-90 microsphere selective internal radiation therapy (Y90-SIRT), nivolumab, ipilimumab, lenvatinib, phase Ib/II study

Background

Hepatocellular carcinoma (HCC) is one of the most prevalent malignancies in the world. According to data released by the National Cancer Center of China, there were 367,700 new diagnoses of primary liver cancer in China in 2022, with the disease currently ranked fourth among all newly diagnosed cancers (lung, colorectal, thyroid, and liver), and fifth in incidence rate (lung, female breast, thyroid, colorectal, and liver). In addition, 316,500 deaths due to primary liver cancer occurred in 2022, with both the number of deaths and the mortality rate ranking second (lung and liver). Most patients with HCC in China are diagnosed at an intermediate or advanced stage. Despite recent improvements in diagnostic and therapeutic techniques, the prognosis for patients with unresectable intermediate or advanced HCC remains poor, with a 5-year survival rate of only 14.1%. Therefore, the exploration of more effective treatment strategies, particularly combination therapies, for unresectable intermediate or advanced HCC is of great clinical significance.

To date, there has been some progress in the use of systemic therapy combined with local treatment for patients with unresectable intermediate or advanced HCC. The EMERALD-1[1]、LEAP-012[2] and CARES-005[3] studies indicate that although the combination of immunotherapy and targeted therapy with transarterial chemoembolization (TACE) has achieved a significant improvement in progression-free survival (PFS) compared to TACE alone, to date, overall survival (OS) has not reached significant thresholds and there is no evidence as yet of long-term survival benefits. Longer follow-up is needed, and certain limitations require addressing. Since most patients with liver cancer in China are diagnosed at an advanced stage, associated with high tumor burden and late staging, the increase in the 5-year survival has been less than 3% over the past decade, which is still far from the Healthy China 2030 goal. The efficacy of TACE is limited by incomplete embolization, increased VEGF levels leading to recurrence and metastasis, impaired liver function caused by repeated treatments, and post-embolization syndrome. On the other hand, immune-targeted combination regimens such as IMbrave150 (atezolizumab plus bevacizumab), CARES310 (camrelizumab plus apatinib), and ORIENT-32 (sintilimab plus bevacizumab) have all been approved in China as first-line treatments for advanced liver cancer. However, these regimens still have various issues, such as relatively unsatisfactory

objective response rates (ORRs), no published data on long-term survival (OS), and the unique adverse event profiles associated with anti-angiogenic therapy. For example, over 30% of patients receiving immunotherapy combined with bevacizumab experience hypertension, while over 40% experience proteinuria, and there is a 15% risk of bleeding. Therefore, there is an urgent need for an effective and safe systemic therapy combined with local treatment.

Yttrium-90 microsphere-selective internal radiation therapy (Y90-SIRT) relies on hepatic arterial catheterization for delivery of microspheres loaded with the radioactive isotope yttrium-90 (Y90) to the arterial vessels supplying the liver tumor. These microspheres remain in the terminal vascular network of the tumor, enabling precise coverage of the tumor and the continuous release of high-energy beta radiation in close proximity to tumor cells. This leads to irreversible damage to the tumor tissue, leading to necrosis and thereby achieving effective tumor control [4]. The beta radiation emitted by Y90 can damage cellular DNA either directly or indirectly and trigger immune responses in tumor cells, thereby inducing immunogenic cell death. Y90-SIRT offers several advantages, including marked shrinkage of the tumor, the promotion of compensatory hyperplasia of the contralateral healthy liver tissue (thus increasing the future liver remnant volume), regression of portal vein tumor thrombi, and improvement of the patient's quality of life.

International studies have confirmed the feasibility of using Y90 in a variety of liver cancer treatment scenarios, including radical treatment for early-stage disease, downstaging treatment for intermediate-stage liver cancer, palliative treatment for advanced-stage disease, and conversion therapy. Compared with TACE treatment, SIRT delivers high-dose radiation precisely to the capillary bed of the tumor, resulting in a greater degree of necrosis in specific scenarios[5]. This treatment has the dual advantages of direct contact with the tumor and continuous radiotherapy, which not only improve the ORR and disease control rate, but also significantly reduce the risk of damage to normal liver tissue. A recent meta-analysis published in 2025 retrieved 1749 potentially relevant papers, ultimately including 7 retrospective studies and 1 prospective study involving 1026 patients receiving TACE treatment and 358 patients receiving SIRT treatment. The results showed that compared with TACE, SIRT resulted in higher ORR (64.4% vs. 55.0%, P = 0.04) and disease control rate (89.5% vs. 79.3%, P = 0.003), longer survival benefit (1-year OS rate: 56.9% vs. 45.7%, P = 0.02), and lower adverse reactions in patients with HCC. This has led to the use of SIRT in preference to TACE in European and American countries, where it has become the preferred local treatment for intermediate and advanced liver cancer[6].

The liver itself is a unique organ with immune privilege, and the tumor microenvironment (TME) of HCC exhibits multiple immunosuppressive characteristics. In addition to the presence of immunosuppressive factors, such as PD-1 and CTLA-4, there is a significant increase in the number of regulatory T cells. The combination of these factors leads to immunosuppression and enables the tumor cells to evade immune surveillance. In this context, treatment with nivolumab combined with ipilimumab promotes the activation and proliferation of T cells, counteracts T-cell inhibition, and reduces T-cell exhaustion. These mechanisms work together to facilitate the differentiation of effector T cells into memory T cells, thereby enabling long-term immune surveillance. Thus, in the immunosuppressive HCC TME, these factors combine synergistically, transforming multiple

layers of suppression into potent activation and overcoming the efficacy bottleneck of previous immunotherapy regimens. In the phase II CheckMate 040 study, the optimal dosing regimen was found to be nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg every 3 weeks (Q3W) for up to four cycles, followed by nivolumab 480 mg every 4 weeks (Q4W) until disease progression, the development of unacceptable toxicity, or a maximum treatment duration of two years. The CheckMate-9DW study[7] is a global, randomized, open-label phase III clinical study that investigated the efficacy and safety of nivolumab combined with ipilimumab versus sorafenib/lenvatinib as first-line treatment for advanced HCC. Analysis of the primary endpoint showed that nivolumab plus ipilimumab significantly improved OS compared to sorafenib/lenvatinib in first-line HCC patients, with a median OS of 23.7 months, notably higher than that of 20.6 months observed in the control group (HR=0.79, p=0.018). Importantly, 38% of patients treated with nivolumab plus ipilimumab survived for longer than 3 years (3-year OS rate: 38% vs 24%), highlighting the long-term survival advantage of dual immunotherapy. The secondary endpoint, the ORR, reached 36%, higher than that found in all previous similar phase III studies (20.1–27.3%), indicating that over one-third of patients achieved significant tumor shrinkage. Notably, 7% of patients in the combination group achieved complete response (CR), and, among patients with evaluable target lesions, 37% showed over 50% shrinkage of target lesions, while nearly 20% of patients experienced shrinkage of over 75%, indicating that nivolumab plus ipilimumab induces deep responses and significantly reduces the tumor burden. In terms of safety, the incidence of treatment-related grade 3/4 adverse events was 41% versus 43% in the control group, with the most common adverse events being hepatitis, colitis, rash, and thyroid dysfunction, and no new safety signals were observed. Currently, the dual immunotherapy regimen has been approved both in China and by the US FDA for first-line treatment of adult patients with unresectable or advanced HCC. Compared to the combination of targeted therapy and immunotherapy, dual immunotherapy offers advantages in terms of higher ORR (36%), significant long-term survival benefit (3-year OS rate: 38%), and a manageable safety profile. The combination of lenvatinib with dual immunotherapy aims to address the early crossing of survival curves seen with dual immunotherapy alone, with the goal of achieving short-term benefits in both progression-free survival (PFS) and ORR, as well as long-term OS benefits.

Iparomlimab and Tuvonralimab (QL1706) is a dual combination antibody that targets PD-1/CTLA-4. The phase II portion of the DUBHE-H-308 study presented at the 2025 ESMO conference evaluated the efficacy and safety of three regimens, namely QL1706 plus Bevacizumab Biosimilar plus XELOX, QL1706 plus Bevacizumab Biosimilar, and QL1706 plus XELOX, in comparison with Sintilimab plus Bevacizumab Biosimilar as the first-line treatment for advanced HCC. After a median follow-up of 15.2 months, the ORR reached 40% in both the QL1706 plus Bevacizumab Biosimilar plus XELOX group and the QL1706 plus Bevacizumab Biosimilar group, which was double that of the 20.7% ORR found in the control group. This indicates that dual-immunotherapy combinations can induce tumor shrinkage in a higher proportion of patients. Comparison of the QL1706 plus Bevacizumab Biosimilar group and the control group showed PFS values of 8.1 months vs. 5.9 months, respectively, while the 12-month OS rates were 65.5% and 62.1%, respectively, with both showing an increase. In terms of safety, the incidence of adverse events (AEs) of grade 3 or above was

53.3% in the QL1706 plus Bevacizumab Biosimilar group vs. 44.8% in the control group. The proportion of treatment discontinuations resulting from treatment-related adverse events (TRAE) was 23.3% vs. 10.3%. Tolerable toxicity was observed in the QL1706 combination group, and the primary AE of grade 3 or above was hypertension[8].

Studies have shown that radiotherapy (RT), including Y90-SIRT, acts synergistically with immunotherapy. Firstly, RT can promote the release of tumor antigens and increase the number and enhance the maturation of antigen-presenting dendritic cells, and the resulting increases in antigen presentation help stimulate T-cell activation and strengthen the anti-tumor immune response [9]. Secondly, immune-mediated mechanisms can occasionally induce tumor responses at sites distant from the irradiated area, a phenomenon termed the "abscopal effect" [10]. Thirdly, RT can activate the downstream activation of stimulator of interferon genes (STING), resulting in increased production of type I interferons (IFN-I), which is crucial for immune cell recruitment, particularly of dendritic cells or CD8+ T cells, thereby inducing antigen presentation and promoting the transformation of the TME from "cold" to "hot"[11]. Compared to patients who received either TACE or no preoperative treatment, those treated with Y90-SIRT showed significantly increased levels of tumor-infiltrating lymphocytes, CD4+ and CD8+ T cells, as well as increased expression of granzyme B in tumor tissues[12].

The hypoxic microenvironment caused by abnormalities in the tumor vasculature is an important factor contributing to radioresistance. Inhibition of vascular endothelial growth factor (VEGF) inhibitors can normalize tumor blood vessels and alleviate hypoxia, thereby increasing tumor radiosensitivity. Clinical studies have also confirmed that RT combined with anti-VEGF agents can enhance the anti-tumor response. Although VEGF inhibitors may prevent further tumor angiogenesis, which could potentially favor radioresistance, many clinical studies have shown that the combination of RT and anti-VEGF agents can enhance the anti-tumor response[13]. Blockade of VEGF has been found in both preclinical models and clinical trials to synergize with RT and immunotherapy in various ways. In summary, SIRT in combination with molecular-targeted therapy and the application of immune checkpoint inhibitors has a synergistic effect; the anti-angiogenic agents can normalize the tumor vasculature, thereby not only increasing radiosensitivity but also improving the TME and enhancing the efficacy of immunotherapy.

In a comparative study of Y90-SIRT combined with targeted immunotherapy, Amel et al. conducted a retrospective analysis of 35 patients, of whom 27 had received Y90-SIRT alone, and 8 had undergone Y90-SIRT combined with atezolizumab plus bevacizumab. At the time of publication, the median OS had not yet been reached in the group receiving Y90-SIRT combined with atezolizumab plus bevacizumab, while the median OS for patients treated with Y90-SIRT alone was 14 months. The median PFS was higher in the group receiving Y90-SIRT combined with atezolizumab plus bevacizumab compared to treatment with Y90-SIRT alone (87% vs 60%). Eight patients achieved tumor downstaging (23%), while four underwent surgical resection (one in the Y90-SIRT combined with atezolizumab plus bevacizumab group), and four were treated with liver transplantation (one in the Y90-SIRT combined with atezolizumab plus bevacizumab group). No grade 3 or above AEs occurred after treatment. These findings suggest that, for unresectable HCC, administration of atezolizumab plus bevacizumab before and after SIRT may help improve OS and PFS

compared to SIRT alone[14][15]. However, the design of this study was retrospective, with potential intergroup imbalances and a small sample size, which may have led to confounding bias.

The combination of Y90-SIRT and dual immunotherapy is a major focus of ongoing investigation. However, there are no reports on the use of the more complex triple therapy, involving Y90-SIRT, dual immunotherapy, and targeted agents. Therefore, exploring the feasibility, safety, and synergistic mechanisms of triple therapy will be an important direction for future research.

In terms of dose exploration, previous phase I/II studies on dose exploration have shown that the safety profile of nivolumab is similar for different tumor types and dose levels (0.1–10 mg/kg) [16]. The incidence of AEs with ipilimumab is clearly dose-dependent. The CA184-022 study evaluated the anti-tumor activity, OS, and safety of ipilimumab at doses of 0.3, 3, and 10 mg/kg. The results showed that ipilimumab efficacy was positively correlated with dose, and the incidence of immune-related adverse events (irAEs) increased with higher doses. Most AEs were grade 1–2, and mainly affected the skin and gastrointestinal tract [17]. Study 117 investigated dose-limiting toxicity and identified the dose combination of nivolumab 240 mg Q2W with lenvatinib 8 mg or 12 mg/day [18]. Therefore, in the phase Ib part of the present study, we incorporated a dose escalation for ipilimumab to identify the optimal dose combination.

Based on this background, this clinical trial was designed to evaluate the safety and efficacy of Y90-SIRT combined with nivolumab, ipilimumab, and lenvatinib in patients with unresectable HCC. In addition to assessing short-term efficacy endpoints, such as ORR and PFS, this trial places particular emphasis on the OS benefit for patients. This study is therefore both novel and innovative.

2 Methods and design

This investigator-initiated phase Ⅰb/Ⅱ trial adopts a multicenter, single-arm, prospective design to evaluate the safety and efficacy of Y90-SIRT combined with nivolumab, ipilimumab, and lenvatinib in patients with unresectable HCC. Enrollment is planned from January 2026 to June 2026, with a 24-month follow-up period initiated after inclusion of the final participant. Recognizing the potential biases inherent in single-arm trials, we have implemented the following measures: (1) blinded adjudication of the ORR(iRecist and mRecist) by an independent review facility (IRF); (2) propensity score-adjusted sensitivity analysis compared with historical control groups; (3) transparent screening logs documenting reasons for exclusion. The structure of the protocol and assessment timelines are detailed in Figure 1 and Table 1, respectively.

Figure 1: Flowchart of the study protocol.

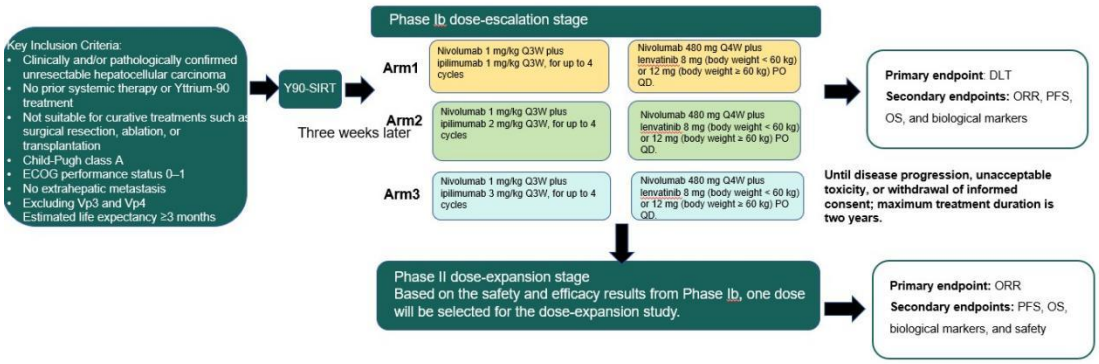

Table 1: Schedule of clinical assessments for enrolled patients.

Assessments	Pre-enrollment baseline (≤ 7 days)	Cycle initiation c	Post-treatment evaluation (≤ 4 weeksafterfinal PD-L1 inhibitor dose)	Follow-up schedule
Enrollment: Eligibility screen a and Informed consent b	√			
Baseline characteristics#	√			
Pathological assessment#	√			
Laboratory tests#	√	√	√	✓ (Year 1: quarterly; Years 2 and 3: biannual)
Imaging examination#	√	√	√	✓ (Year 1: quarterly; Years 2 and 3: biannual)
Toxicity/adverse event monitoring		√	√	✓ (Year 1: quarterly; Years 2 and 3: biannual)
Quality of life	√	√	√	✓ (Year 1: quarterly; Years 2 and 3: biannual)

Relapse		**√**	**√**	**✓ (Year 1: quarterly; Years 2 and 3: biannual)**
Survival		**√**	**√**	**✓(Year 1: quarterly; Years 2 and 3: biannual)**

2.1 Main inclusion criteria

Eligible participants must meet the following key criteria: (1) Unresectable HCC confirmed by clinical and/or pathological diagnosis; The term "unresectable hepatocellular carcinoma" refers to a clinical state in which radical surgical resection is precluded because the tumor extent or an inadequate anticipated future liver remnant would prevent R0 removal, or because the procedural risk is prohibitively high, and where surgical intervention is not expected to yield a survival advantage over non‐surgical therapies. (2) No prior systemic therapy or treatment with Y90; (3) Not suitable for curative treatments, such as surgical resection, ablation, or transplantation; (4) Child-Pugh class A; (5) ECOG performance status 0–1; (6) No extrahepatic metastasis; (7) Excluding Vp3 and Vp4; (8) Estimated life expectancy ⩾3 months. The complete inclusion and exclusion criteria are detailed in Table 2.

Table 2 Study eligibility criteria.

Inclusion criteria	Exclusion criteria
1. HCC confirmed as unresectable by imaging or histology, or patients who refuse surgery. Eligible for Y90-SIRT, with no evidence of extrahepatic disease on any available imaging. Lymph node involvement is permitted. The term "unresectable hepatocellular carcinoma" refers to a clinical state in which radical surgical resection is precluded because the tumor extent or an inadequate anticipated future liver remnant would prevent R0 removal, or because the procedural risk is prohibitively high, and where surgical intervention is not expected to yield a survival advantage over non‐surgical therapies.	1. Diffuse HCC or presence of vascular invasion or extrahepatic spread, with the following exceptions: invasion of segmental portal vein or hepatic vein.
2. Aged between 18 and 80 years at the time of enrollment	2. Patients with Child-Pugh class C cirrhosis.
3. Participants with Child-Pugh class A.	3. Any contraindication to hepatic arterial

	embolization: Known hepatic arterial reflux; known portosystemic shunt; coagulopathy (platelet count < 50 × 10^9/L, INR > 1.5); renal failure/insufficiency requiring hemodialysis or peritoneal dialysis; known severe arteriosclerosis; complete thrombosis or complete invasion of the main portal vein.
4. Participants with an ECOG performance status of 0 or 1 at the time of enrollment	4. History of heart disease: congestive heart failure > New York Heart Association (NYHA) class II; active coronary artery disease (CAD) (myocardial infarction ⩾ 6 months prior to study initiation is permitted); arrhythmias that are difficult to control with antiarrhythmic drugs or require a pacemaker (NCI-CTCAE v5.0 > grade 2); uncontrolled hypertension; clinically significant gastrointestinal bleeding within 4 weeks prior to initiation of study drugs.
5. Participants with a lung dose threshold of 30 Gy for yttrium-90 microspheres (each treatment dose ⩽ 30 Gy), and an anticipated future liver remnant volume (FLRV) ⩾ 30% of the total liver volume.	5. Thrombotic or embolic events, such as cerebrovascular accident (including transient ischemic attack), deep vein thrombosis, or pulmonary embolism, occurring within 6 months prior to the first administration of study drug, except for segmental portal vein thrombosis.
6. Participants with one or more measurable lesions; for those with segmental or right anterior/posterior portal vein invasion (Vp1/Vp2), the disease is confined to a single lobe and suitable for Y90 microsphere treatment.	6. Receipt of systemic anticancer therapy, radiotherapy, endocrine therapy, immunotherapy, or other investigational drugs within 4 weeks prior to study initiation.
7. If the patient is co-infected with hepatitis B virus (HBV) or hepatitis C virus (HCV), the following criteria must be met: HBV or HCV viral levels should be monitored during study participation. Patients with detectable hepatitis B surface antigen (HBsAg) or HBV DNA should have HBV DNA < 100 IU/ml and be managed according to local treatment guidelines. Most patients with advanced HCC and HCV have not received treatment for HCV infection. However, if antiviral therapy has been completed prior	7. Current or prior use of immunosuppressive drugs within 28 days before the first administration of nivolumab or ipilimumab. Exceptions to this criterion include: intranasal, inhaled, topical steroids or local steroid injections (e.g., intra-articular injection); physiological doses of systemic corticosteroids not exceeding 10 mg/day of prednisone or equivalent; steroids used for the prevention of allergic reactions (e.g., premedication for CT scan).

to the first administration of study drugs, these patients are considered eligible for inclusion.	
8. No prior systemic therapy or transarterial radioembolization (Y90 glass microsphere TARE).	8. Receipt of live attenuated vaccines within 30 days prior to the first administration of study drug (IP). Note: If the patient is enrolled, live vaccines should not be administered during the study drug treatment period and within 30 days after the last dose of the study drug.
9. No active autoimmune disease and no history of chronic or recurrent autoimmune disease.	9. Major surgery within 4 weeks prior to study initiation, and the patient must have recovered from the effects of major surgery.
10. Adequate hematological, liver, and renal function as follows: (1) Absolute neutrophil count ⩾ 1,500/mm³ (2) Hemoglobin level ⩾ 9.0 g/dL (3) Platelet count ⩾ 75,000/mm³ (4) Total bilirubin ⩽ 1.5 × ULN (5) AST ⩽ 2.5 × ULN (6) ALT ⩽ 2.5 × ULN (7) International normalized ratio (INR) ⩽ 1.25 (8) Albumin ⩾ 31 g/L (9) 24-hour urine collection creatinine clearance (CL) > 40 mL/min or calculated creatinine clearance (CL) > 40 mL/min.	10. Patients with a second primary malignancy, apart from adequately treated basal cell carcinoma of the skin or carcinoma in situ of the cervix, unless disease-free for more than 3 years.
11. Not pregnant and no intention to conceive before or during treatment.	11. Uncontrolled comorbidities, including but not limited to persistent or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina, arrhythmia, interstitial lung disease, severe chronic gastrointestinal disease associated with diarrhea, or psychiatric/social conditions that limit compliance with study requirements, significantly increase the risk of adverse events, or impair the patient's ability to provide written informed consent.
12. Written informed consent from the patient.	12. Active infections, including tuberculosis (clinical assessment including medical history, physical examination, and imaging, as well as tuberculosis testing according to local practice), hepatitis B (known positive HBV surface antigen [HBsAg]), and hepatitis

	C. Patients with past or resolved HBV infection (defined as presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients who are HCV antibody-positive are eligible only if HCV RNA measured by PCR is negative.
13. Expected survival of at least 12 weeks.	13. History of allogeneic organ transplantation.
	14. Psychiatric disorders or altered mental status that interfere with understanding the informed consent process and/or compliance with the study protocol.
	15. Symptomatic brain metastases. If symptoms are present, imaging is required to confirm the absence of brain metastases.
	16. Pregnant or breastfeeding women.
	17. Immunocompromised patients, such as those known to be serologically positive for human immunodeficiency virus (HIV).
	18. Active or previously documented autoimmune or inflammatory diseases (including inflammatory bowel disease [such as colitis or Crohn's disease], diverticulitis [excluding diverticulosis], systemic lupus erythematosus, sarcoidosis, or Wegener's granulomatosis [granulomatosis with polyangiitis], Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, among others).
	19. Known allergy or hypersensitivity to any study drug or its components.
	20. Currently participating in or previously participated in a study involving an investigational drug, or use of an investigational device within 4 weeks prior to the first administration of study treatment.

2.2 Treatment

Assessment of the incidence of dose-limiting toxicity (DLT) in the phase IB exploratory quadruple regimen:

Enrolled patients will receive the quadruple regimen, starting with selective internal radiation therapy using Y90-SIRT. Three weeks after Y90-SIRT intervention, patients will be assigned to one of three dose exploration cohorts:

(1) Nivolumab 1 mg/kg IV Q3W + Ipilimumab 1 mg/kg IV Q3W dual immunotherapy for up to 4 cycles;
(2) Nivolumab 1 mg/kg IV Q3W + Ipilimumab 2 mg/kg IV Q3W dual immunotherapy for up to 4 cycles;
(3) Nivolumab 1 mg/kg IV Q3W + Ipilimumab 3 mg/kg IV Q3W dual immunotherapy for up to 4 cycles.
After completion of the dual immunotherapy treatment, nivolumab 480 mg IV Q4W will be administered until disease progression, development of unacceptable toxicity, withdrawal of informed consent, or a maximum treatment duration of 2 years. Lenvatinib will be administered in combination with nivolumab after discontinuation of ipilimumab, at a dose of 8 mg (body weight < 60 kg) or 12 mg (body weight ≥ 60 kg) PO QD, taken at a fixed time each day, either fasting or with food. Dose adjustment or temporary interruption of lenvatinib will be permitted during treatment (refer to the prescribing information for adjustment), with a maximum interruption period of 30 days. Treatment will continue until disease progression, the development of unacceptable toxicity, or withdrawal of informed consent. If any drug is discontinued for any reason during treatment, continuation of the other drugs is allowed.

The phase II study is designed as a single-arm trial, using the dose regimen selected in phase IB.

2.3 Criteria for study discontinuation

The trial should be stopped immediately in the following cases:
1. The patient requests to terminate the trial, the Ethics Committee demands termination of the trial, or the drug regulatory department requires termination of the trial.
2. The investigators confirm that the disease has progressed or that continuing treatment would be of no therapeutic benefit.
3. Participant- or clinician-reported unacceptable AEs.
4. The patient fails to adhere strictly to the treatment protocol.
All withdrawal rationales will be systematically documented in the clinical records of the trial.

2.4 Data collection

1. Baseline patient characteristics:
a. Age, year
b. Sex, male/female
c. Body mass index, kg/m2
d. Personal history of smoking, alcohol consumption, and medication usage
e. Comorbidities
f. ECOG performance status
g. Child-Pugh class
h. Hepatitis B status
i. Hepatitis C status

2. Laboratory examinations:

a. CA19-9, U/mL
b. CEA, ng/mL
c. Hemoglobin (g/dL)
d. White blood cell count, × 10^9 cells/L
e. Absolute neutrophil count,× 10^9 cells/L
f. Platelet count, × 10^9/L
g. Glomerular filtration rate, mL/min
h. Aspartate aminotransferase, U/L
i. Alanine aminotransferase, U/L
j. Bilirubin, μmol/L
k. Creatinine, μmol/L
i. Thyroid function indices

3. Imaging examinations:
a. Liver MRI/CT scans
b. Chest CT scans
c. Isotope bone scans
d. Liver ultrasound
e. Electrocardiography

2.5 Outcome measures

Primary Objectives:

(1) In phase Ib, determination of the incidence of dose-limiting toxicity (DLT) of the treatment regimen.
(2) In phase II, the primary objective is the ORR (iRecist and mRecist)in the experimental group.

Secondary Objectives:

Assessment of PFS, OS, disease control rate (DCR) (iRecist and mRecist), duration of response (DoR), and safety in the experimental group. Additionally, to explore and evaluate the relationship between biomarkers in tumor tissue and peripheral blood and the treatment efficacy.

AEs will be systematically classified and documented in compliance with the National Cancer Institute's Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE 5.0)

2.6 Sample size

(1) All statistical tests will be two-sided, and P-values ⩽ 0.05 will be considered statistically significant. Continuous data will be described using mean, median, standard deviation, maximum, minimum, and 25th and 75th percentiles; categorical or ordinal data will be presented as frequency and percentage.
(2) Statistical analyses will be performed using SAS 8.2 statistical software.
(3) All statistical tests will be two-sided, and P-values ⩽ 0.05 will be considered statistically

significant.

(4) Sample size determination:

Phase IB: Three predefined dose levels of dual immunotherapy will be explored (see dosing regimen for details). To ensure the reliability of safety assessment and efficiently determine the recommended phase II dose (RP2D), a "3+3" dose-escalation design will be adopted. At least 3 evaluable patients for DLT will be enrolled at each dose level. The sample size for this stage will be 9 patients.

Phase II: All patients will receive treatment at the RP2D determined in phase IB. According to Simon's two-stage design, and based on historical data from the HIMALAYA study in hepatocellular carcinoma, the maximum response rate for ineffective treatment is assumed to be 21%, and the minimum response rate for effective treatment is estimated to be 45%. Using a two-sided test with $\alpha=0.05$ and power $(1-\beta)=0.8$, the Minimax two-stage design is selected. In the first stage, 11 patients will be enrolled; if $\leqslant 2$ responses are observed, the study will be terminated early. If the study proceeds to the second stage, an additional 13 patients will be enrolled, for a total sample size of 24. At the end of the study, if the total number of responses is $\leqslant 8$, the treatment regimen will be rejected.

2.7 Data management and monitoring plan

Data will be collected by trained evaluators using a validated case report form (CRF), ensuring timeliness, completeness, and accuracy. Two independent investigators responsible for data entry will input the raw data from the completed CRFs into Epidata (V3.1). An independent monitoring committee, comprising multidisciplinary experts in oncology, interventional radiology, pharmacology, and biostatistics, will oversee the integrity of the trial data and ensure adherence to the protocol. The committee will have the prerogative to halt the trial prematurely if necessary. Following study closure, all CRFs will undergo archival storage for a minimum of five years, with the implementation of read-only access to prevent post-hoc alterations.

2.8 Confidentiality

All research-related data will be stored in a highly secure environment at the study site. The personal information of the participants will be safeguarded in encrypted digital databases with restricted access. To maintain participant confidentiality, any identifiable data, such as laboratory results, questionnaires, data analysis outcomes, and administrative records, will be labeled solely with anonymous identification codes.

2.9 Patient and public involvement

No participants or the public will be involved in the development of the protocol or design of the study. The results of the study will be presented at peer-reviewed journals and international meetings.

3 Discussion

Most Chinese patients with HCC are diagnosed at an intermediate or advanced stage. While there has been some progress in the use of systemic therapy combined with local treatment for patients with unresectable intermediate or advanced HCC, significant

differences in short-term PFS rates have been observed, and, to date, positive results have not translated into long-term OS benefits, indicating the limitations of this approach. The exploration of more effective treatment strategies, especially combination therapies for unresectable intermediate or advanced HCC, is of great clinical significance. Therefore, this single-arm, multicenter, prospective phase 1b/II study is designed to evaluate the safety and efficacy of selective internal radiation therapy (SIRT) with Yttrium-90 microspheres in combination with nivolumab, ipilimumab, and lenvatinib in patients with unresectable HCC, aiming to address the unmet needs of these patients.

The quadruple therapy strategy of Y90-SIRT combined with nivolumab, ipilimumab, and lenvatinib integrates three evidence-based therapeutic approaches: (1) the synergistic advantages of dual immunotherapy using PD-1/CTLA-4 inhibitors, the synergy of immunotherapy and targeted therapy, and the advantages of immunotherapy combined with Y90-SIRT; (2) the combination of guideline-recommended first-line treatment regimens; (3) dose exploration and optimization of treatment strategies. The sequential design of the trial, in which SIRT is given first, followed by administration of PD-1 and CTLA-4 inhibitors combined with lenvatinib, not only leverages the cytoreductive effect on micrometastases and increases immunogenicity, but also mitigates synergistic toxicities. To the best of our knowledge, this is the first phase II clinical trial to investigate a quadruple modality (SIRT sequential PD-1/CTLA-4 inhibitors and lenvatinib) for treating patients with unresectable HCC.

One limitation of this study is that, due to the single-arm design, there may be biases in patient selection and outcome assessment. However, this approach is necessary as the use of Y90-SIRT in patients with unresectable HCC is rare, and it is not ethically possible to set up an inactive control group. The pre-planned comparative analyses with propensity score adjustment partially mitigate this limitation. In addition, this study is expected to yield exciting results and lay the foundation for subsequent phase III clinical trials. Furthermore, this clinical trial will be conducted at multiple clinical centers, enabling relatively easy achievement of the predefined sample sizes, thereby enhancing the statistical reliability of the study outcomes.

Abbreviations

AE Adverse Event
AUC Area Under Curve
CTLA-4 Cytotoxic T-Lymphocyte Antigen 4
CI Confidence Interval
CR complete response
DoR Duration of response
DCR Disease control rate
ECOG PS Eastern Cooperative Oncology Group – performance status
ORR Objective Response Rate
OS Overall survival
PD-L1/PD-1 Programmed death-1/ligand 1
PFS Progression-free survival
PR partial response

QoL quality of life
RECIST Response Evaluation Criteria in Solid Tumors
SD stable disease
SCC small cell carcinoma
SCLC small cell lung carcinoma

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Author contributions
Rui-Hong Dai and Chang Liu designed the study and wrote the original protocol. Rui-Hong Dai and Fa-Cheng Lu drafted the manuscript. All the other authors directly contributed, read, and approved the final manuscript.

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Data availability
The original contributions presented in the study are included in the article or Supplementary Material. Further inquiries can be directed to the corresponding author

Ethics statement
The ethics committee on Biomedical Research of West China Hospital of Sichuan University approved this study All participants will sign written informed consent prior to participation in any study activities.

Conflict of interest
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement
The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

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