Prospective research project scheme of Union Hospital affiliated to Tongji Medical College of Huazhong University of Science and Technology

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Project name: The Efficacy and Safety of TACE, Lenvatinib and Camrelizumab in the Treatment of BCLC Stage B/C Hepatocellular Carcinoma: a Single-arm, Single-center, Open-label Study

Scheme number: 20201007

Main researcher: Xiongbin

Affiliated department:	radiology department
Start and end years:	2021.1.1-2022.12.1

Union medical college affiliated to Tongji medical college, Huazhong university of science and technology

October 6, 2020

1. research summary

1.1 summary

Research name:

The Efficacy and Safety of TACE, Lenvatinib and Camrelizumab in the Treatment of BCLC Stage B/C Hepatocellular Carcinoma: a Single-arm, Single-center, Open-label Study

Introduction to research:

This study is a single-center, single-arm, open-label prospective clinical trial. By recording the time to disease progression (PFS), overall survival time (OS) and tumor treatment response of the patients included in the trial, we intend to evaluate the survival benefit of patients with BCLC B/C stage hepatocellular carcinoma treated with TACE, Levatinib and Camrelizumab. Meanwhile, the immune indexes before and after treatment were detected,Optimize the dosage, explore the mechanism of combined treatment in liver cancer, and lay the foundation for screening more suitable treatment groups; Observe and evaluate the safety of combined therapy through laboratory detection indicators and adverse event records; Immunohistochemistry, pathology and cell were used.Biological, proteomic and imaging methods were used to comprehensively evaluate the changes after combined treatment.

Research purposes:

To evaluate the safety and clinical efficacy of TACE, lamivudine combined with Camrelizumab in the treatment of BCLC B/C hepatocellular carcinoma, focusing on the application value of anti-angiogenesis therapy combined with immunotherapy in the treatment of hepatocellular carcinoma.

Research object:	A total of 40 patients with BCLC B/C stage hepatocellular carcinoma were enrolled in this experiment. The patients were treated with TACE, Levatinib and Camrelizumab, and the maximum out-of-group rate was estimated to be 20%. Men and women, aged from 18 to 75.
Research unit/ place:	Union hospital affiliated to Tongji medical college, Huazhong university of science and technology.
Research intervention:	Patients included in the trial were treated with TACE, lamivudine combined with Camrelizumab.
Duration of study:	2021.1.1-2022.12.1
Participants' participation time:	Subjects from the initial visit to the end of follow-up or experiment.

2. Research background

2.1 research significance

At present, the treatment methods for advanced liver cancer mainly include local interventional therapy, targeted therapy and immunotherapy. This study focuses on patients with primary liver cancer diagnosed by clinical and imaging, histology or cytology, and liver cancer patients with B/C stage according to BCLC. To study the medium-and long-term efficacy of TACE, lenvartinib combined with carilizumab in the treatment of BCLC B/C stage liver cancer,And evaluate it effectively; To evaluate the safety and effectiveness of lamivudine combined with carilizumab in the treatment of liver cancer, and clarify the application value of combined treatment, so as to lay a foundation for evaluating the clinical efficacy of patients with advanced liver cancer.

2.2 research background

Immunocheckpoint inhibitors and cell-based cancer immunotherapy are widely used in a variety of advanced malignant tumors by regulating tumor immune response [1-3]. Studies have shown that programmed death receptor 1(PD-1) is an immune checkpoint molecule, which negatively regulates the immune function of T cells by interacting with its ligand PD-L1 [4, 5]. More and more evidence shows that,PD-1/PD-L1 interaction is one of the main cancer escape mechanisms of human beings [6, 7]. Tumor cells overexpress PD-L1 or PD-L2, and interact with PD-1 molecules expressed in activated T cells, which inhibits T cell receptor (TCR) signal transduction, and finally leads to inactivation and loss of proliferative ability of effector T cells, which leads to tumor immune escape. Based on this mechanism of tumor,The new immunotherapy that blocks the interaction between PD-1 and PD-L1 has changed the treatment strategies of many malignant tumors [8, 9]. By inhibiting the negative regulatory effect of PD-1/PD-L1 pathway on T cells, the anti-tumor immune response of the body is enhanced, the T cell reaction activity against tumors of patients is improved, and the proliferation of effective T lymphocytes is promoted.Finally, it provides patients with an important and lasting immune response to their malignant tumors.

Camrelizumab is a humanized anti-PD-1 monoclonal antibody with high affinity IgG4 independently developed by Suzhou Hengrui Pharmaceutical Co., Ltd., which can selectively prevent the activation of PD-1 and its downstream signal pathway, and restore immune function by activating effector T lymphocytes and cell-mediated immune response [10]. Some studies show that,The application of Camrelizumab in patients with advanced solid tumors has shown some clinical value [11-14], and predictive biomarkers such as PD-L1 expression level and tumor mutation load can screen out patients with high response to PD-1/PD-L1 monoclonal antibody [15, 16]. Even so, PD- 1/PD-L1 blocking therapy only brings clinical benefits to less than 20% of cancer patients [17].It indicated that patients who used these drugs only depended on their insufficient pre-existing endogenous anti-tumor specific T cells.

Anti-angiogenic drugs can specifically bind to vascular endothelial growth factor (VEGF) and its receptor 2(VEGFR2), achieving the dual effects of enhancing cytotoxic chemotherapy and realizing molecular targeted therapy [18]. Some recent studies have shown that angiogenesis inhibitors can regulate tumor microenvironment and relieve hypoxia of tumor cells, which may promote tumor immune recovery [19, 20].Levatinib mesylate is a multi-target receptor tyrosine kinase inhibitor, which can block a series of regulatory factors such as VEGFR1-3, KIT and RET in tumor cells, and significantly inhibit angiogenesis in tumor tissues. At present, FDA approves its first-line treatment for unresectable hepatocellular carcinoma patients. In a phase III clinical study,The overall survival rate of lamivudine in the first-line treatment of unresectable hepatocellular carcinoma is no less than that of sorafenib (13.6 months vs 12.3 months) [21]. Another basic study shows that lenvartinib regulates cancer immunity in tumor microenvironment by reducing tumor-associated macrophages (TAM), and can enhance anti-tumor activity through IFN signaling pathway when combined with PD-1 inhibitor [22]. In addition, previous studies found that,Compared with TACE alone, transcatheter arterial chemoembolization (TACE) combined with anti-angiogenic agents showed a good response to tumor treatment, but the incidence of treatment-related adverse events was high, and the survival time of patients was not significantly improved [24]. Therefore,In this study, TACE, a powerful anti-angiogenic drug, and Camrelizumab, a new PD-1 inhibitor, were combined to treat patients with liver cancer, so as to improve their quality of life and improve their survival benefits.

The purpose of this study is to explore the clinical outcome of TACE, Lenvatinib combined with carilizumab in patients with BCLC B/C stage liver cancer, to monitor the complications and tumor treatment response of patients, to study the suitable population for combined treatment, and to evaluate the hepatorenal and cardiotoxicity of drugs to human body. Focus on exploring the mechanism and application value of anti-angiogenesis therapy combined with immunotherapy in the treatment of liver cancer.

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2.3 Expected results of research

① with enough sample size, explore the beneficiaries of TACE, Lenvatinib combined with Camrelizumab in the treatment of BCLC B/C stage liver cancer;

② To evaluate the efficacy and safety of TACE, Levatinib and Camrelizumab combined therapy, and provide theoretical and practical support for further research;

③ To study the incidence of adverse events of TACE, Levatinib and Camrelizumab, and provide practical support for further explaining the safety of drugs.

2.4 Risk/benefit assessment

2.4.1 Known potential risks

① Adverse drug reactions: including but not limited to (1) side effects of Camrelizumab zumab: Reactive Cutaneous Capillary Endothelial Proliferation, anemia, fever, fatigue, hypothyroidism, proteinuria, cough and loss of appetite. (2) Side effects of lamivudine:Fatigue, loss of appetite, joint and muscle soreness, weight loss, stomatitis, nausea and vomiting, abdominal pain and diarrhea, headache, hypertension, proteinuria, plantar erythema syndrome .
② Post-②TACE embolism syndrome: fever, abdominal pain, digestive tract reaction (nausea, vomiting), etc.

2.4.2 Known potential benefits

(1) relatively complete disease assessment; 2 Longer survival time and better quality of life; (3) Pay special attention to the illness and observe it closely; ④ Appropriate economic subsidies.

2.4.2 assessment of potential risks/benefits

At present, the treatment of advanced liver cancer is lacking, and the curative effect needs to be improved. Patients included in this study will receive advanced and perfect treatment programs, which will make it possible to get longer survival time and higher quality of life. The potential risks of this study are mainly adverse drug reactions. The research team includes chief physicians and attending physicians.With rich clinical experience and professional knowledge, once adverse events (including drug reactions and important adverse events) occur, researchers will fully evaluate whether the adverse events are related to drugs, actively take symptomatic measures, and keep follow-up observation in order to eliminate or reduce the impact of adverse events. At the same time, record it in detail on the case report form.In case of serious adverse events, fill in the serious adverse events form and report it to the applicant, ethics committee, CFDA safety supervision department and health administrative department within 24 hours.

3. Data of main researchers

3.1 Name, qualification and contact information of the main researcher

(full) name	Xiong bin	**gender**	man	**present incumbency**	Deputy director of radiology
place of work	Department of radiology, union hospital affiliated to Tongji medical college, Huazhong university of science and technology				
Address and zip code	Radiology Department, Union Hospital, No.1277 Jiefang Avenue, Wuhan City, Hubei Province 430022				

specialized subject	Radiointervention al radiology	**academic degree**	docto r
graduated institutions	Tongji Medical College, Huazhong University of Science and Technology	**Graduation time**	June, 2008
contact number	18627081029	**mailbox**	herr_xiong@126.com

Educational experience (university, other)

School name	From (time)	To (time)	specialized subject	degree
Wuhan Tongji Medical University	1993.9	1998.6	Clinical Medicine	bachelor
Tongji Medical College, Huazhong University of Science and Technology	2001.9	2004.6	Imaging medicine and nuclear science Medicine (intervention)	master
Tongji Medical College, Huazhong University of Science and Technology	2005.9	2008.6	Imaging medicine and nuclear science Medicine (intervention)	doctor

working situation

Work unit name	post	From (time)	To (time)

Wuhan union hospital radiology	Resident assistance teach	1998.7	2003.6
Radiology Hospital of Freiburg University, Germany	visiting scholar	2007.1	2008.9
Wuhan union hospital radiology	The attending physician said teacher	2003.7	2012.10
Wuhan union hospital radiology	associate chief physician	2012.11	2017.10
Wuhan union hospital radiology	Master tutor	2013.12	hitherto
Wuhan union hospital radiology	associate professor	2016.11	hitherto
Wuhan union hospital radiology	archiater	2017.11	hitherto
Wuhan union hospital radiology	Deputy director of teaching and research section	2018.12	hitherto
wuhan union hospital	doctoral supervisor	2018.12	hitherto

GCP and related training and participation in clinical trials

Clinical research projects hosted or participated in

（1） Multi-center randomized controlled study of portal vein irradiation stent implantation combined with hepatic arterial chemoembolization in the treatment of primary liver cancer complicated with portal vein tumor thrombus

（2） Intravascular brachytherapy combined with stent and transcatheter arterial chemoembolization in the treatment of hepatocellular carcinoma with portal vein tumor thrombus: a multicenter, randomized controlled study

（3） A multicenter, randomized controlled study of transcatheter arterial chemoembolization combined with sorafenib in the treatment of advanced liver cancer

（4） Scheme validation study of traditional Chinese medicine to reduce recurrence rate of stage I hepatitis B related liver cancer after comprehensive minimally invasive surgery, 2018ZX10303502- 001, under study, participating

（5）
Scheme validation study on improving clinical benefit rate of stage II hepatitis b-related liver cancer after comprehensive minimally invasive surgery with traditional Chinese medicine,

2018ZX10303502-002, under research, participating

（6）
A multicenter randomized controlled study on the effect of shunt left/right branch of portal vein on hepatic encephalopathy after TIPS operation.

3.2 Information on main participants

序号 serial number	姓名 (full) name	性别 gender	职称 professional title	专业 specialized subject	是否 GCP 培训 GCP training or not	研究中承担的角色 Role assumed in research （eg.PI、sub-I、CRC）
1	宋松林 Songsonglin	男 man	主治医师 attending physician	影像医学与 Imaging medicine and 核医学 nuclear medicine	否 no	sub-I
2	钱坤 Qian Kun	男 man	主治医师 attending physician	影像医学与 Imaging medicine and 核医学 nuclear medicine	否 no	sub-I
3	刘一鸣 Liu Yiming	男 man	主治医师 attending physician	影像医学与 Imaging medicine and 核医学 nuclear medicine	否 no	sub-I

4	袁峰 Yuanfeng	男 man	主治医师 attending physician	影像医学与 Imaging medicine and 核医学 nuclear medicine	否 no	sub-I [redacted]
5	周晨 Chen Zhou	男 man	住院医师 resident	影像医学与 Imaging medicine and 核医学 nuclear medicine	否 no	sub-I [redacted]
6	任衍乔 Ren Yanqiao	男 man	博士生 Doctor	影像医学与 Imaging medicine and 核医学 nuclear medicine	否 no	CRC
7	刘家成 Liu Jiacheng	男 man	博士生 Doctor	影像医学与 Imaging medicine and 核医学 nuclear medicine	否 no	CRC [redacted]
8	石钦 Shi Qin	男 man	硕士生 Postgraduat es	影像医学与 Imaging medicine and 核医学 nuclear medicine	否 no	CRC [redacted]
9	杨崇图 Yang chongtu	男 man	硕士生 Postgraduat es	影像医学与 Imaging medicine and 核医学 nuclear medicine	否 no	CRC [redacted]
10	黄松江 Huang Songjian g	男 man	硕士生 Postgraduat es	影像医学与 Imaging medicine and 核医学 nuclear medicine	否 no	CRC [redacted]

4.

research objective

In this study, the time to progression free (PFS), overall survival (OS) and response to tumor therapy were recorded in the included patients to evaluate the survival benefit of TACE combined with rivarotinib and carrerizumab;To detect the immune indexes before and after the combined treatment, optimize the dosage, and explore the application mechanism of combined therapy in liver cancer,To lay a foundation for screening more suitable treatment population;The safety of combined treatment was evaluated by laboratory test indexes and adverse event records;Immunohistochemistry, pathology, cell biology, proteomics and imaging were used to evaluate the changes after combined therapy.

5.
research design

5.1
overall design

5.1.1
Research staging

January 2021 to June 2021

10-15 patients were enrolled, and the basic characteristics of the study population and relevant research information were recorded.

2021 年 6 月～2021 年 12 月

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10-15 patients were enrolled, and the basic characteristics and related research information of the study population were recorded, and the previous study population was followed up regularly.

December 2021 to June 2022

10-15 patients were enrolled, and the basic characteristics and related research information of the study population were recorded, and the previous study population was followed up regularly.

June 2022 to December 2022

Regular follow-up of the previous study population, collation of research data, data analysis, statistics and summary, write research

Research Report and published papers.

5.1.2 。

This study is a single center clinical trial.

5.1.3

Research intervention settings

1. TACE treatment: the patients were selected according to the inclusion criteria. The HBV-DNA titer of the patients with positive detection of HBV-DNA was 10 ^ 4. Antiviral treatment was required for 1-2 weeks. TACE could be performed after the HBV-DNA titer decreased.

(1) Hepatic arteriography: Seldinger's method was used, femoral artery cannula was punctured through skin, and catheter was placed in celiac trunk or common hepatic artery for angiography;We should pay attention to find the collateral artery of tumor;Indirect portal venography should be done through splenic artery to understand the blood flow of portal vein.

(2)

Hepatic arterial chemoembolization (TACE):

① Chemotherapeutic drug used: epirubicin (≤60mg);

② embolic materials used: lipiodol (≤20ml), gelatin sponge particles or microspheres. (3) Technical operation requirements: use microcatheter to superselective intubate the blood supply artery branch of tumor, and inject embolic materials containing chemotherapy drugs, and the dosage should be controlled according to the size of tumor, blood supply and the number of blood supply arteries of tumor.After treatment, common hepatic arteriography was performed again to understand the immediate effect of transcatheter arterial chemoembolization. If liver cancer is complicated with arterioportal fistula, the fistula should be blocked with granular embolic agent with appropriate diameter, and then embolic materials should be added for embolization chemotherapy.

The treatment method of levatinib: taking levatinib from the fourth day after TACE; Oral

lamivudine dose: 8mg/d for patients below 60Kg; Patients over 60Kg were taken at 12mg/d .. For patients with adverse reactions related to lamivudine, symptomatic treatment and treatment can be given to alleviate the adverse reactions of patients. If the patient has gastrointestinal bleeding, stop taking the medicine.Take it after the bleeding has improved.

The usage of Camrelizumab: Intravenous infusion was started on the fourth day after TACE, and the dose was 200mg once every three weeks. Provisions on dose suspension: If the patient has intolerable adverse reactions during taking Lenvatinib and Camrelizumab, they can temporarily suspend Lenvatinib or Camrelizumab to alleviate the adverse reactions, but the continuous suspension time shall not exceed one month.If the dose suspension is not carried out as required during the research process, it will be rejected.

5.2 Define the study endpoint

Patient death, tumor progression, tumor progression beyond TACE treatment, and the trial was closed on December 1, 2022.

5.3 Determine the sample size

A total of 40 patients with BCLC B/C stage liver cancer were enrolled in this experiment, and were treated with TACE, Levatinib and Camrelizumab. It is estimated that the maximum out-of-group rate is 20%.

6. Research objects

6.1 Entry criteria

1. 18 -75 years old, male or female, with a pre-survival period of more than 12 weeks;
2. Primary liver cancer confirmed by clinical and imaging, histology or cytology;
3. Patients with liver cancer in B/C stage according to BCLC;
4. Never used molecular targeted therapy drugs or immune checkpoint inhibitors before;

5. The behavioral state score of the American Eastern Cancer Cooperative Group (ECOG) is 0 or 1;

6. The main organs function normally, and there are no serious abnormalities of blood, heart, lung, liver and kidney function and immunodeficiency diseases. Laboratory examination

Meet the following requirements: a. hemoglobin (HGB)≥90g/L; B. neutrophil count (ANC)≥1.5×109/L; C. platelet count (PLT)≥100×109/L; D.ALT and AST≤2.5×ULN; Liver metastasis, ALT and AST≤5×ULN; E. total bilirubin (TBIL)≤1.5 times the upper limit of normal value (ULN); F. serum Cr ≤ 1 ′ uln, endogenous creatinine clearance rate > 50ml/min(Cockcroft-Gault formula); G. urine routine is normal, or urine protein < (++), or 24-hour urine protein amount < 1.0 g;

7.Coagulation function is normal, there is no active bleeding and thrombotic disease: a. international standardized ratio INR≤1.5×ULN; B. partial thromboplastin time APTT≤1.5×ULN; C. prothrombin time PT≤1.5×ULN;

8.
The subjects voluntarily joined the study and signed the informed consent form.

6.2 Exclusion criteria

1 within five years or at the same time suffering from other active malignant tumors except liver cancer. Cured localized tumors, such as skin basal cell carcinoma, skin squamous cell carcinoma, superficial bladder cancer, prostate cancer in situ, cervical cancer in situ, breast cancer in situ, etc., can be grouped;

2. The tumor size of liver cancer is ≥ 70% of liver parenchyma or there is extrahepatic metastasis;

3.
Pregnant or lactating women;

4.
It is known to be allergic to carilizumab, lenvartinib or pharmaceutical excipients;

5.
After other anti-tumor treatments, including surgical treatment, local treatment and systemic treatment, within 4 weeks before entering the group;

6.
Having received organ or allogeneic bone marrow transplantation;

7. ;
Suffering from any active autoimmune disease or history of autoimmune disease (including but not limited to interstitial pneumonia, uveitis, enteritis, hepatitis, hypophysitis, vasculitis, myocarditis, nephritis, hyperthyroidism and hypothyroidism (which can be included after hormone replacement therapy));

8.
Use immunosuppressive drugs within 14 days before the first use of the study drug, excluding nasal spray and inhaled corticosteroids or systemic steroid hormones with physiological dose (i.e., prednisolone or other corticosteroids with the same physiological dose);

9.
Vaccinate live attenuated vaccine within 4 weeks before the first administration or during the study period;

10.
Severe infection (such as intravenous drip of antibiotics, antifungal or antiviral drugs) occurred within 4 weeks before the first administration, or fever of unknown origin > 38.5° C occurred during the screening period/before the first administration;

11.
Known history of allogeneic organ transplantation or allogeneic hematopoietic stem cell transplantation;

12.
There is objective evidence to show that there have been or are currently suffering from pulmonary fibrosis, interstitial pneumonia, pneumoconiosis, radiation pneumonia, drug-related pneumonia, and severe impairment of lung function;

13. Patients with hypertension, but still unable to drop to normal range after 3 months of antihypertensive drug treatment (systolic blood pressure ≤140 mmHg/diastolic blood pressure ≤ 90 mmHg);

14.
Suffering from uncontrollable clinical symptoms or diseases of the heart, including but not limited to congestive heart failure (NYHA grade > II grade); Unstable or severe angina pectoris; Acute myocardial infarction occurred within 6 months; Patients with clinically significant supraventricular or ventricular arrhythmia who need clinical intervention; Left ventricular ejection fraction (LVEF)<50%;

15.
Patients with active bleeding or patients with severe bleeding risk caused by various reasons, including but not limited to severe bleeding (bleeding within 3 months > 30 ml), hemoptysis (bleeding within 4 weeks > 5 ml) and thromboembolic events (including stroke events and/or transient ischemic attacks) within 12 months;

16.
Participate in other clinical trials or participate in any other drug clinical research within 4 weeks, or take no more than 5 drugs from the last study

Half-life;

17.
Other circumstances that the researcher thinks are not suitable for inclusion.

6.3 Recruitment of subjects

Recruitment targets are outpatients and inpatients who come to our department for diagnosis and treatment, and patients who have been transferred to our department from other hospitals or departments, which must meet the inclusion and exclusion criteria of this study. Recruitment sites are outpatient and inpatient departments of our department. During the follow-up visit, the subjects will be reimbursed for travelling expenses or given appropriate financial subsidies.

7. Research intervention

7.1 give research intervention

7.1.1 Description of research intervention

Patients included in the trial were treated with TACE, lamivudine combined with Camrelizumab. The specific operation is described in the above intervention measures.

7.1.2 Dosage and Administration Method

① treatment mode of levatinib: taking levatinib from the fourth day after TACE; Oral lamivudine dose: 8mg/d for patients below 60Kg; Patients over 60Kg were taken at 12mg/d ..

② Usage of Camrelizumab: Intravenous infusion was started on the fourth day after TACE, once every three weeks, with a dose of 200mg.

7.1.3 Items and times of clinical and laboratory examinations to be conducted

Clinical treatment: the number of TACE is determined by the researcher according to the patient's condition. Lenvatinib and Camrelizumab were used until the patients reached the study endpoint.

Laboratory examination: items include blood routine, urine routine, stool routine+occult blood, liver function, kidney function and tumor markers (AFP, CA19-9, CEA, CA125), immunological index examination, etc. 4-6 weeks after the first TACE

treatment, all subjects were reexamined for liver CT plain scan+enhancement or MRI plain scan+enhancement, tumor markers, blood routine, liver and kidney function, coagulation function, urine routine, stool routine+occult blood and other laboratory tests, whether there is hepatic encephalopathy and ECOG score; If the initial review is CR, it will be reviewed every 2- 3 months;If the initial reexamination is not CR, reexamine every 4-6 weeks and perform TACE treatment in time

7.2 Preparation/Disposal/Storage/Responsibility

7.2.1 Responsibility

Related drugs are purchased by patients from hospitals.

7.2.2 Composition, appearance, packaging and labeling of drugs

① Camrelizumab: General name: Camrelizumab for injection; Trade name: Erica; English name: Camrelizumab for Injection. Drug composition: active ingredient: Camrelizumab zumab (humanized anti-PD-1 monoclonal antibody); Adjuvant ingredients: α-trehalose dihydrate, polysorbate 20, glacial acetic acid, sodium hydroxide and water for injection. outside Appearance: white to off-white powder or block. Packaging: injection bottled with neutral borosilicate glass tube, 200 mg/ bottle x 1 bottle/ Box.

② Lenvatinib: General name: Lenvatinib mesylate capsule; Trade name: Leweima; English name: Lenvatinib Mesilate Capsules. Composition of medicine: the active ingredient is lamivudine mesylate. Appearance: white to white granular. Packing: 4mg/ capsule *30 capsules/box.

7.2.3 Storage and Stability of Products

(1) Carrilizumab was stored and transported at 2-8℃ away from light.

② Lenvatinib was stored and transported in a ventilated place at room temperature.

7.2.4 preparation

① Carrilizumab was administered by trained health professionals, and reconstituted and diluted by aseptic technique. Infusion is completed within 30-60 minutes. Intravenous injection or rapid intravenous injection should not be used.

② Lenvatinib is a capsule preparation, which should be taken orally. It should be taken at a fixed time every day, either on an empty stomach or with food. It should be swallowed as a whole, or it can be mixed with one tablespoon of water or apple juice in a glass to form a suspension. The capsule must stay in the liquid for at least 10 minutes and stir for at least 3 minutes to dissolve the capsule shell.Then swallow the suspension. After drinking, you must add the same amount of water or apple juice (one tablespoon) to the glass 中，搅拌数次，然后喝完玻璃杯中所有的液体。
Stir several times, then drink all the liquid in the glass.

7.3 Follow-up and Compliance

4-6 weeks after the first TACE treatment, all subjects were reexamined for liver CT plain scan+enhancement or MRI plain scan+enhancement, tumor markers, blood routine, liver and kidney function, coagulation function, urine routine, stool routine+occult blood and other laboratory tests, whether there is hepatic encephalopathy and ECOG score; If the initial review is CR, it will be reviewed every 2-3 months; If the initial reexamination is not CR, reexamine every 4-6 weeks and timely perform TACE treatment.

7.5 research intervention commitment

All treatment measures and means used for patients will be strictly registered on the case report form by special personnel and recorded in the hospital routine medical records.

8.1 Suspension of research intervention

(1) Patients who have any serious adverse events during the trial need to stop treatment;

(2) Patients or clients withdraw informed consent or request to stop treatment;

(3) Patient lost follow-up;

(4) Patient is pregnant;

(5) Patients should also be followed up after termination of treatment or withdrawal of treatment, to understand the disease state until death or the end of research.

8.2 suspension/withdrawal of subjects

(1) Those who do not conform to the test plan are found during the test;

(2) During the trial, other anti-tumor treatments, such as ablation, radiotherapy, chemotherapy and traditional Chinese medicine treatment, were carried out besides TACE, Lenvatinib and Camrelizumab, so that the curative effect could not be evaluated. The reasons for the rejected cases should be explained in writing;

（3） Those who stop treatment due to serious adverse reactions are not included in the curative effect analysis, but should be included in the statistics of adverse reactions.

8.3 Lost visits

When the subject stops the scheduled study follow-up, fails to complete the prescribed procedure, or the researcher cannot contact the subject, it is regarded as lost follow-up. The researcher will record and describe the patient's lost follow-up, and the main researcher and relevant personnel will evaluate it to decide whether to include the experimental results.

9. Evaluation of research outcome

Evaluation of primary and secondary outcomes

9.1.1 leading indicator

Progression free survival, PFS). Definition of PFS: It refers to the period from the beginning of treatment to the progression of tumor or death for any reason.

9.1.2 Secondary indicators:

(1) Total survival time (OS); OS definition: the time from the patient's enrollment to the last follow-up or death.

(2) Time-Time-to-tumor progression, TTP); TTP definition: It refers to the period from the beginning of treatment to the observation of disease progression.

(3) TACE-to-unaccessible progression ttup; TTUP definition: refers to the period from the time when patients with tumor diseases receive treatment to the time when they are unsuitable for TACE treatment (unable to receive or benefit from TACE treatment).

The patients who can't accept TACE further include: the liver function deteriorated to Child-Pugh C grade, extrahepatic diffusion including inferior vena cava invasion, complete embolism of portal vein trunk, tumor volume exceeding 70% of liver volume, ECOG score ≥2 points; The failure to benefit from TACE treatment include: 1-3 months aft full selective TACE, re-evaluating that response after tumor treatment with enhanced CT/MRI,There are still two or more consecutive poor responses (active lesions > 50%), or two or more consecutive intrahepatic tumor progression (compared with the number

of tumors before TACE treatment, the number of tumors after TACE treatment increases)

(4) The time of extrahepatic metastasis; That is, from the time of the first visit to the time of extrahepatic metastasis in the follow-up.

(5) Objective reaction rate (ORR): (ratio of Cr+PR);

(6) Disease control rate (DCR): (ratio of Cr+PR+SD);

According to the modified response evaluation criteria in solid tumors,

M resistance), the curative effect is defined as CR (complete remission), PR (partial remission), SD (stable) and PD (progress);

(7) The times of TACE treatment in the two groups;

(8) Incidence, category and severity of adverse events of advanced liver cancer in two groups.

9.2 Safety and other evaluations

(1) Blood routine, electrolyte, urine routine and stool routine;

(2) Electrocardiogram, chest DR, liver function, kidney function and heart function;

(3) Coagulation function test;

(4) Incidence of clinical adverse events: record in detail at any time.

Patients with abnormal safety test indexes after medication must be followed up and recorded in detail.

9.3 Adverse Events and serious adverse events

9.3.1 Adverse event (AE) definition

Adverse events: injuries caused by medical treatment, contrary to the natural outcome of diseases, prolong the hospital stay of patients, and all events leading to disability, including preventable and preventable adverse events. Unpreparable adverse events refer to preventable injuries caused by correct medical behavior;Preventable adverse events refer to injuries caused by errors or equipment failures that cannot be prevented in medical treatment.

9.3.2 Serious adverse events (SAE) definition

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Serious adverse events (SAE) refers to events such as hospitalization, prolonged hospitalization, disability, affecting working ability, endangering life or death, and leading to congenital malformation.

9.3.3 Classification of adverse events

9.3.3.1 Event severity

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Severity classification (NCI-CTCAE version 4.0, National Cancer Institute): Grade I: mild, asymptomatic or mild, only seen in clinic or diagnosis, without treatment;

Grade 2: Moderate, requiring minor, local or non-invasive treatment, or limited instrumental activities of daily living of the same age; Grade III: serious or medically significant but not immediately life-threatening, or leading to hospitalization or prolonged hospitalization, or disability, or serious limitation of personal daily activities;

Grade 4: life threatening, requiring emergency treatment. Grade 5: Death related to adverse events.

9.3.3.2 Correlation with research intervention

Relationship with research	describe

intervention	
Definitely	Clinical events (including laboratory test abnormalities) that have a reasonable time relationship with the use of the test drug and cannot be explained by basic diseases or other drugs.The adverse events disappeared after drug withdrawal;The AE must be a known reaction in pharmacology or Phenomenology: the result of provocation test is positive.
Probably relevant	It has a reasonable time relationship with drug use and is unlikely to be attributed to the use of underlying diseases or other drugs Clinical events with reasonable withdrawal reaction (including abnormal laboratory tests).There is no need to confirm the excitation test results.
May be relevant	es) that have a reasonable time relationship with drug use but may also be explained by underlying diseases or other drugs.Information on withdrawal reactions may be "None" Or "unknown.".
Probably not	There is no reasonable time relationship with drug use and can be explained by basic diseases or other drugs Events (including laboratory test abnormalities).
irrelevant	Clinical events (including laboratory test abnormalities) unrelated to drug use.

9.3.3.3

Anticipation

The team of researchers includes clinicians with rich clinical experience and professional knowledge. Once an adverse event occurs, the researcher will confirm that the adverse event is expected or unexpected. If the nature, severity or frequency of the adverse event does not match the risk information described in previous studies, it will be considered as unexpected.

9.3.4 time, frequency, follow-up and outcome of adverse event assessment

All AE including local and systemic reactions were collected using case report form (CRF). The information collected included the description of the event, the time of occurrence, the doctor's assessment of the severity, the relationship with the research product, and the time from the event to resolution / stabilization.All AE will be fully resolved.At each study follow-up, the investigator will ask about the AE / SAE that has occurred since the last follow-up,AE / SAE will be followed up until it is resolved or stabilized.

9.3.5 adverse event reporting

The potential clinical adverse events during treatment were evaluated according to nci-ctcae 4.0.Once adverse events (including major adverse events) occur, researchers will fully evaluate whether the adverse events are related to drugs, actively take symptomatic measures, and maintain follow-up observation,In order to eliminate or reduce the impact of adverse events.At the same time, record in detail on the case report form, fill in the serious adverse event form in case of serious adverse event, and report to the sponsor, ethics committee, CFDA safety supervision department and health administrative department within 24 hours.

9.3.6 serious adverse event reporting

The investigator will immediately report any SAE to the sponsor, whether or not related to the study intervention.

10. Statistical analysis

10.1 一般方法
10.1 general methods

The target value of PFS was 9.2 months, and the difference was statistically significant (P<0.05). The secondary curative effect index OS was tested with the target value of 15 months, and the difference was statistically significant (P<0.05). The other secondary curative effect indexes TTP, TTUP, time of extrahepatic metastasis, objective response rate (ORR) and disease control rate (DCR) were mainly descriptive statistics.Paired T-test was performed on immunological indexes and biochemical indexes before and after treatment, and the difference was statistically significant (P<0.05).

10.2

Analysis of primary and secondary study endpoints

10.2.1

leading indicator

Definition of PFS: It refers to the period from the beginning of treatment to the progression of tumor or death for any reason.

10.2.2

Secondary indicators

（1）。

Total survival time (OS); OS definition: the time from the first visit to the last follow-up or death after enrollment.

（2）

Time-Time-to-tumor progression, TTP);

TTP definition: It refers to the period from the beginning of treatment to the observation of disease progression.

（3）

TACE-to-unaccessible progression ttup;

TTUP definition: refers to patients with tumor diseases from the beginning of receiving treatment to unsuitable for TACE treatment (unable to receive further or from TACE)
Benefit from treatment).

The patients who can't accept TACE further include: the liver function deteriorated to Child-Pugh C grade, extrahepatic diffusion including inferior vena cava invasion, complete embolism of portal vein trunk, tumor volume exceeding 70% of liver volume, ECOG score ≥2 points;

Failure to benefit from TACE treatment includes: 1-3 months after full selective TACE, re-evaluating the response of tumor after treatment with enhanced CT/MRI, and still having two or more consecutive poor responses (active lesions > 50%), or still having two or more consecutive intrahepatic progression of tumor (compared with the number of tumors before TACE treatment, the number of tumors after TACE treatment increased)

(4) Time of extrahepatic metastasis

(5) Objective reaction rate (ORR): (ratio of Cr+PR);

(6) Disease control rate (DCR): (ratio of Cr+PR+SD);

According to the modified response evaluation criteria in solid tumors,

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M resistance), the curative effect is defined as CR (complete remission), PR (partial remission), SD (stable) and PD (progress);

(7) The times of TACE treatment in the two groups;

(8) Incidence, category and severity of adverse events of advanced liver cancer in two groups.

10.3 safety analysis

The researcher will fully evaluate the patient's condition in the whole process, and once serious adverse events occur, such as hepatic encephalopathy, upper gastrointestinal bleeding, hepatorenal syndrome, hepatopulmonary syndrome and serious laboratory examination abnormality, they will be given treatment such as drug withdrawal and symptomatic treatment, and keep close follow-up until the patient's symptoms or laboratory examination abnormality are alleviated or disappeared.

10.4
10.4 baseline descriptive analysis

Descriptive statistics were used to compare the demographic characteristics, BCLC stages, Child-
Pugh grades and laboratory indicators at baseline among the groups.

11.
11. Supporting documents and precautions

11.1
11.1 informed consent process

Informed consent will be completed before the subjects agree to participate in the research, and will continue throughout the whole research process. Informed consent is approved by the Ethics Committee, and the subjects should read the informed consent. The researcher will explain the research process and answer the questions raised by the research object; And inform the subjects of possible risks and their rights.Subjects can discuss with their families or guardians before agreeing to participate. The researcher must inform the research object that it is voluntary to participate in the research and can withdraw from the research at any time. Copies of informed consent can be provided to the subjects for preservation. The rights and welfare of research subjects will be protected,And stressed that the quality of their medical care will not be affected by refusing to participate in the research.

11.2 隐私保护

11.2 privacy protection

In this experiment, the personal information and condition of the subjects will be kept strictly confidential, and only open to the subjects and those whom the subjects are willing to make known.

11.3 collection and use of specimens and data

Specimens collected during normal diagnosis and treatment of patients and used for blood routine, urine routine, liver and kidney function in hospitals will not be recycled, but will be tested or kept by a third party. The testing unit and address will be indicated, and after testing, they will be taken back and stored in the refrigerator of the laboratory. These data will be kept until the end of the experiment.

11.4

11.4 quality control and quality assurance

1) The experimental scheme will be scrutinized repeatedly by the research team and the opinions of relevant personnel will be widely collected.

2) Selected patients will be evaluated by blind method.

3) The efficacy and safety analysis will be evaluated by blind method.

4) The establishment and modification of each project of CRF can be traced back to the specific implementers.

5)

A corresponding mechanism will be established to regularly review and review the collected information and data.

11.5 data processing and record keeping

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11. 5.1 data collection and management

Paper materials include CRF and informed consent; PACS system data include medical records, imaging examinations, laboratory results, etc. These materials will be sorted and stored by the research team. All data should be clear to ensure its traceability.

11.5.2 research data retention

The collected data will be kept for 3 years after the end of the whole experiment, so as to facilitate retrospective analysis, and will be approved by the main researcher and relevant institutions before destruction.

11.6 publishing and data sharing agreements are fair, just and open

11.7 conflict of interest statement There is no potential conflict of interest.