Clinical Study Protocol

Title of study	**Neoadjuvant chemotherapy combined with camrelizumab and apatinib in patients with locally advanced colon cancer: a single-arm, prospective study**
NCT number	**NCT04625803**
Institution	**The First Affiliated Hospital, Zhejiang University School of Medicine**
major investigators	**Weijia Fang** **Xiangming Xu**
Protocol No. **Version**	**MA-CRC-II-004** **1.3**
Version Date:	**07 November 2021**

PROTOCOL AGREEMENT

I confirm that I have read this protocol. I will comply with the protocol and the principles of Good Clinical Practice (GCP), any applicable laws and regulations, and the study protocol.

Protocol: MA-CRC-II-004, Version 1.3 (07 November 2021)

Protocol Title: Neoadjuvant chemotherapy combined with camrelizumab and apatinib in patients with locally advanced colon cancer: a single-arm, prospective study

Investigator Signature_____**Date**_____

Principal investigator protocol signature page

I will conscientiously perform my duties as a researcher according to ICH-GCP regulations and participate in or directly direct this clinical research. I have received the investigator's manual for the investigational drug in this clinical trial; I am aware of and have read the preclinical studies of the trial drug and the trial protocol. I agree to perform my duties in accordance with the ICH-GCP, the Declaration of Helsinki, any applicable laws and regulations, and the study protocol. Unless measures must be taken to protect the safety, rights, and interests of the subjects, I will modify the protocol only after the sponsor has been informed and consent has been obtained, and only after the ethics committee has agreed to implement it. I will be responsible for making clinically relevant medical decisions to ensure that subjects receive timely and appropriate treatment if adverse events occur during the study and that these adverse events are recorded and reported in accordance with relevant national regulations. I guarantee that the data will be true, accurate, complete and timely recorded. I will accept the monitoring by the sponsor or inspectors and the inspection by the drug regulatory department to ensure the quality of the clinical trial. I promise to keep the subject's personal information and related matters confidential. I agreed to disclose my full name and occupation to the sponsor, to disclose expenditures related to clinical research on request, and to prohibit any commercial or financial conduct related to the trial. I agree that the results of the study can be used for drug registration and public publication.

Institution **The First Affiliated Hospital, Zhejiang University School of Medicine**

Xiangming Xu		
Principal Investigator (In print)	Principal Investigator (Signature)	Signature Date
Weijia Fang		
Principal Investigator (In print)	Principal Investigator (Signature)	Signature Date

Neoadjuvant chemotherapy combined with camrelizumab and apatinib in patients with locally advanced colon cancer: a single-arm, prospective study

1.Background

Colorectal cancer (CRCs) is a heterogeneous disease with complex genetic and epigenetic changes. Tumors in different parts of the colon are clinically and molecular heterogeneous. The MOSAIC study established FOLFOX4 as an adjunct therapy for stage II and III colon cancer. Adjuvant therapy can improve relapse-free survival and overall survival time[1].

In the field of esophageal cancer, gastric cancer and rectal cancer, preoperative neoadjuvant chemotherapy and radiotherapy are more effective than postoperative treatment[2-4]. On the one hand, preoperative treatment can make the tumor shrink and reduce the probability of tumor cells falling off and incomplete resection during surgery[3, 5]. A positive surgical margin is strongly associated with local recurrence, which means that the tumor is very aggressive and poorly responsive to systemic therapy. On the other hand, preoperative treatment has the advantage of minimizing surgical procedures and allowing patients to return to normal activities earlier.

In 2012, FOxTROT enrolled 150 patients with T3/4 colon cancer and randomly divided them into two groups: one group received 3 cycles of oxaliplatin and fluorouracil-based chemotherapy before surgery and 9 cycles of chemotherapy after surgery; the other group received direct surgery and completed 12 cycles of chemotherapy after surgery. The results suggested that the rate of tumor regression was more significant in the preoperative chemotherapy group (p=0.04) with lower margin positive patients (4% vs. 20%) and higher tumor regression rate (31% vs.2%)[6]. The 2019 ASCO abstract reported the updated results of FOxTROT, a total of 1052 patients were enrolled. The incomplete resection rate of patients with preoperative neoadjuvant chemotherapy was reduced. In the neoadjuvant group, the 2-year recurrence rate was improved, although it did not reach statistical significance (14% vs 18%, P=0.11). For this reason, the NCCN recommends neoadjuvant therapy (FOLFOX or CAPEOX) for colon cancer patients with T4 or high tumor burden.

NCCN guidelines and CSCO guidelines recommend immunotherapy as the first-line treatment for patients with advanced MSI-H or dMMR colon cancer. The PICC study[7] published in The Lancet Gastroenterology and Hepatology by Professor Yanhong Deng revealed that the pCR rate of colon cancer patients with locally advanced MSI-H using immunotherapy reached 76%. Immunotherapy has brought light to the treatment of MSI-H patients. Nowadays, everal clinical studies are exploring the neoadjuvant study of immunotherapy combined with chemotherapy for colon cancer.

The combination of antivascular therapy and immunotherapy has shown advantages in liver cancer, kidney cancer and other tumors.Appropriate doses of anti-angiogenic drugs such as apatinib (VEGFR2-TKI) can regulate the tumor immunosuppressive microenvironment and alleviate resistance to anti-PD-1 /PD-L1 therapy[8].

The purpose of this study is to determine the efficacy and safety of camrelizumab and apatinib combined with chemotherapy (mFOLFOX6) for MSS/pMMR locally advanced colon cancer.

2 Endpoint

2.1 Primary Endpoint

Tumor regression rate of MSS/pMMR patients (Pathological response, percentage of TRG2-4 to all MSS patients, Dworak criteria)

2.2 Secondary Endpoint

The secondary endpoints included the tumor pathological downstage rate, defined as the percentage of patients with a lower postoperative stage than baseline stage, pCR rate, R0 resection rate, 2-year DFS, 2-year EFS and OS for MSS/pMMR colon cancer. The pathological response rate and pCR rate for MSI-H/dMMR patients. Perioperative complication rate, mortality and Adverse events (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE], version 5.0).

3.1 Experiment Design

This is a single-institution, single-arm phase II clinical trial. Patients with histopathologically or cytologically confirmed colon adenocarcinoma without distant metastases (T4 or T3 with extramural depth ≥5 mm, $N_{0\text{-}2}$, M_0, AJCC 8th) were enrolled.

Patients with microsatellite-stable or proficient mismatch repair (pMMR) received 5 cycles of mFOLFOX6 and camrelizumab (200 mg intravenously on day 1, every 2 weeks) and apatinib (250 mg orally once daily, 2 months). mFOLFOX6 consisted of oxaliplatin 85 mg/m2 on day 1, leucovorin 400 mg/m2 on day 1, fluorouracil 400 mg/m2 bolus on day 1, followed by fluorouracil 2,400 mg/m2 continuous infusion over 46 hours, repeated once every 2 weeks. Surgery was scheduled within 4-6 weeks after the last cycle of therapy. 7 cycles of adjuvant camrelizumab plus mFOLFOX6 were administered after surgery.

For patients with microsatellite-instability-high (MSI-H) or deficiency in mismatch repair (dMMR), 5 cycles of camrelizumab (200 mg intravenously on day 1, every 2 weeks) plus apatinib (250 mg orally once daily, 2 months) were given preoperatively and 7 cycles of camrelizumab plus apatinib were given postoperatively.

Tissue samples and peripheral blood samples were collected for further multiomics analysis. The sampling points were: (1) Peripheral blood and colonoscopy tumor tissue at baseline; (2) Peripheral blood before operation; (3) surgical tumor tissue; (4) Peripheral blood 1 month after surgery (5) Peripheral blood after adjuvant chemotherapy

3.2 Sample Size

To determine the sample size, we used the Simon 2 stage optimum design with unilateral alpha 0.05 to achieve the power of 0.8, the pathological response rate (TRG 2-4) is expected to increase from 22.5% to 40%. Considering a 10% shedding rate, it is estimated that 64 patients will need to be enrolled.

3.3 Surveillance

Chemotherapy combined with anti-PD-1 antibodies was used every 14 days for 5 cycles, while apatinib treatment was used for 2 months. Chemotherapy, immunotherapy, and apatinib need to be discontinued for 4-6 weeks before surgery. After surgery, 7 cycles of chemotherapy combined with PD-1 antibody were completed. During chemotherapy, patients should be followed up for the quality of life and the toxic and side effects of chemotherapy. Imaging examination should be done to evaluate the tumor size after 5 courses of treatment. Imaging examinations were required before and after postoperative adjuvant chemotherapy.

Imaging reviews were performed every 12 weeks for 1 year after the end of medication and every 6 months after 1 year. Telephone follow-up was conducted every 12 weeks after the end of

treatment, and the total follow-up time was from enrollment to death.

4. Inclusion and Exclusion Criteria:

4.1Inclusion Criteria:

1. Age ≥ 18 years, ≤75 years
2. Histologically confirmed colon cancer (tumor penetrated of muscularis propria depth ≥5mm of T3 , T4, N0-2, M0) without distant metastasis (AJCC 8th).
3. ECOG 0-1
4. Surgical treatment is planned after completion of neoadjuvant therapy
5. Patients can swallow pills normally
6. Expected overall survival ≥12 months
7. Blood routine: no blood transfusion or blood products usage within 14 days, G-CSF or other hematopoietic stimulator was not used. WBC counts > 3000/μl, Absolute neutrophil count (ANC) ≥ 1500 cells/μl, Platelet count ≥ 100,000/μl, Hemoglobin ≥ 9.0 g/dL.
8. AST, ALT and alkaline phosphatase ≤ 2.5 times the upper limit of normal (ULN), Serum bilirubin ≤ 1.5 x ULN, creatinine<ULN
9. Prothrombin time (PT), international standard ratio (INR) ≤1.5 × ULN
10. Patients who have not received systemic chemotherapy or immunotherapy
11. Women of childbearing age must be willing to use adequate contraceptives during the study period of drug treatment;
12. Informed consent has been signed.

4.2 Exclusion Criteria:

1. Patients have received any prior systemic antitumor therapy;
2. Active bleeding within 3 months; Occurrence of arterial/venous thrombosis within 6 months; Hereditary or acquired bleeding (e.g., clotting dysfunction) or thrombotic tendencies; Full dose oral or injectable anticoagulants or thrombolytic drugs for therapeutic purposes are currently being used or have been used recently (10 days prior to the commencement of study treatment); Surgery (except for biopsy) was performed within 4 weeks prior to the study or the surgical incision was not fully healed; Aspirin (> 325 mg/ day) or dipyridamole, ticlopidine, clopidogrel, and silotazole are currently being used or have recently been used (10 days prior to the study).
3. Systemic corticosteroids or other systemic immunosuppressive drugs were used within 2 weeks prior to treatment. Immunosuppressive drugs were started or expected to be used during the trial. Inhaled corticosteroids, physiologic replacement doses of glucocorticoids are allowed.
4. Certain or suspected distant metastases.
5. The patient has a history of autoimmune disease.
6. Serious uncontrolled systemic diseases, such as severe active infections;
7. A person is known to be infected with the immunodeficiency virus (HIV) or known to be HIV-positive;
8. Patients have suffered from other malignancies in the past 5 years except cervical carcinoma in situ or basal cell carcinoma of the skin
9. Untreated chronic hepatitis B or chronic hepatitis B virus (HBV) carriers (HBV DNA >500

IU/mL) or active HCV carriers with HCV RNA can be detected. Remarks: Inactive hepatitis B surface antigen (HBsAg) carriers, treated and stable hepatitis B patients (HBV DNA < 500 IU/mL) may be enrolled

10. Anti-infective therapy was not discontinued 14 days before the study;
11. A prior history of interstitial lung disease, drug-induced interstitial lung disease, radiation pneumonia, and symptomatic interstitial lung disease or the presence of active pneumonia on a chest CT scan within 4 weeks prior to the study.
12. Patients have a history of intestinal obstruction within six months. Patients with incomplete obstruction syndrome of ileus at the time of initial diagnosis may be enrolled in the study if they have received definitive (surgical) treatment to resolve the symptoms, as assessed by the investigator.
13. Patients have non-resectable factors, including surgical contraindications
14. Patients Have high blood pressure that cannot be well controlled by antihypertensive medication (systolic ≥140 mmHg or diastolic ≥90 mmHg)
15. Urine routine indicated urinary protein ≥++ and confirmed 24-hour urinary protein >1.0g;
16. Known to be allergic to any study drug;
17. Patients have participated in other drug clinical studies within 4 weeks before enrollment;
18. Lactating women
19. According to the judgment of the researcher, the patient may have other factors that may affect the results of the study or cause the study to be terminated, such as alcohol abuse, drug abuse, other serious diseases (including mental diseases) requiring combined treatment. Patients have severe laboratory abnormalities, which will affect the safety of the patient.

5 Clinical Assessments

5.1 Evaluation Method

Full abdominal enhanced CT, chest CT, pathology assessment, tests (blood routine, biochemistry, coagulation function, tumor markers, thyroid function, urine stool routine, electrocardiogram)

5.2 Tumor Assessments

Disease assessments are to be performed as scheduled according to the calendar, regardless of treatment delays resulting from toxicity. Care must be taken in scheduling disease assessments to prevent the introduction of bias based on treatment delays.

Disease assessments will be performed at baseline (Screening) and after 5 courses of treatment. Imaging studies will include a CT scan of the chest, abdomen, and pelvis. Radiographic confirmation of disease progression (appearance of distant metastasis) will be based on RECIST 1.1. Pathological assessment was evaluated after operation.

Imaging examinations were required before and after postoperative adjuvant chemotherapy. Imaging reviews were performed every 12 weeks after the end of all treatments and every six months after 1 year.

5.3 Primary Study Endpoint

Tumor regression rate of MSS/pMMR patients (Pathological response, percentage of TRG2-4 to all MSS patients, Dworak criteria)

TRG Dworak criteria: Grade 0: no regression; Grade 1: dominant tumor mass with obvious

fibrosis and/or vasculopathy; Grade 2: dominantly fibrotic changes with few tumor cells or groups (easy to find); Grade 3: very few (difficult to find microscopically) tumor cells in fibrotic tissue with or without mucous substance; Grade 4: no tumor cells, only fibrotic mass (total regression or response).

5.4 Secondary Study Endpoint

The secondary endpoints included the tumor pathological downstage rate, defined as the percentage of patients with a lower postoperative stage than baseline stage, pCR rate, R0 resection rate, 2-year DFS, 2-year EFS and OS for MSS/pMMR colon cancer. The pathological response rate and pCR rate for MSI-H/dMMR patients. Perioperative complication rate, mortality and Adverse events (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE], version 5.0).

6. Safety Evaluation

6.1 Safety Measurements

6.1.1 Vital Signs

Body temperature, blood pressure, pulse and respirations will be performed after resting for 5 minutes at Screening and every subsequent clinic visit.

6.1.2 Performance Status

The Eastern Cooperative Oncology Group (ECOG) performance status scale will be used (Appendix 3) and will be assessed at Screening and every subsequent clinic visit.

6.1.3 Laboratory Measurements

Blood and urine will be obtained at the time points described in the Schedule of Activities and sent to a central lab for hematology, blood chemistry profile, and urinalysis, respectively. After enrollment, blood routine, liver function and renal function were reviewed weekly, and blood routine, biochemistry, thyroid function, myocardial enzyme profile, troponin and cytokine were reviewed every treatment cycle.

6.1.4 Electrocardiogram (ECG)

A standard12-lead ECG (with a 10-second rhythm strip) will be collected at Screening and as clinically indicated. ECG results were recorded during the screening period, before each cycle of chemotherapy and before surgical treatment.

6.2 Adverse Events

6.2.1 Chemotherapy-related Adverse Events

1) Oxaliplatin

The most common adverse events observed during the combination of oxaliplatin and 5-fluorouracil/folin were gastrointestinal (diarrhea, nausea, vomiting, and mucositis), hematological (neutropenia, thrombocytopenia), and neurological reactions (acute, dose accumulation, peripheral sensory neuropathy).

2) fluorouracil

Nausea, loss of appetite or vomiting; oral mucositis or ulcers, abdominal discomfort or diarrhea;

Leukopenia is common, most of them reach the lowest point within 2-3 weeks after the start of treatment, and return to normal within 3-4 weeks. Thrombocytopenia. Rarely cough, shortness of breath, or cerebellar ataxia; Hair loss or intravenous hyperpigmentation with drug injection; Extravasation at the intravenous drip may cause local pain, necrosis, or cellulitis. Long-term application can cause neurological toxicity. Occasionally, myocardial ischemia.

6.2.2 Camrelizumab-related Adverse Events

Adverse reactions with an incidence of > 10% included reactive cutaneous capillary endothelial proliferation, anemia, fever, weakness, hypothyroidism, proteinuria, cough, and decreased appetite. Incidence > 1% included: hyponatremia, pulmonary infection, elevated aspartate aminotransferase, elevated γ-glutamyltransferase, elevated blood bilirubin, elevated bound bilirubin, abnormal liver function, neutropenia, decreased white blood cell count, thrombocytopenia, decreased lymphocyte count, hypokalemia, elevated propionate aminotransferase, and lipase increased.

6.2.2.1 Suggestions for symptomatic management of common adverse reactions

The toxicity of immune checkpoint inhibitors (ICPi) is different from other types of antineoplastic drugs, and its severity and duration have their particularity. It can be divided into infusion reactions and immune-related adverse events (irAE). Camrelizumab belongs to this class of drugs, so it is necessary to identify and treat adverse events caused by camrelizumab early to reduce the occurrence of serious toxic events.

Immune-related adverse events are defined as specific events (including pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, and endocrine lesions) for which the subject requires treatment with an immunosuppressive drug.

6.2.2.2 Safety management rules

Safety management rules and relevant guidelines (e.g., ESMO Clinical practice guidelines for the diagnosis, treatment, and follow-up of immunotherapy) for similar products on the market abroad can be referred to assist investigators in the evaluation and management of adverse events in the following systems: gastrointestinal, renal, pulmonary, hepatic, endocrine, cutaneous, and neurological.

The general principle is to first make a differential diagnosis according to standard medical practice, then consider a noninflammatory cause and manage it appropriately. After excluding other causes (e.g., disease progression, infection, or other medications), immune-related adverse events were considered and immunosuppressive agents were used. Testing for autoantibodies is often helpful, and the role of tissue biopsies in diagnosing immune-related adverse events is unclear. Consultation with a medical or surgical specialist is recommended, especially before invasive diagnostic or therapeutic procedures are performed.

Corticosteroids are the mainstay of treatment. Subjects with low grade toxicity who are ambulatory may be considered for the oral equivalent of the recommended intravenous dose. The lower bioavailability of oral corticosteroids should be taken into account when changing to an equivalent dose of oral corticosteroids.

6.2.2.3 infusion reaction

Camrelizumab is a fully human monoclonal antibody, which is less likely to cause infusion reactions and generally does not require prophylactic medication before infusion.

Once the infusion reaction occurs, the infusion should be slowed down or interrupted according to the situation, and clinical supportive treatment should be given, and preventive medication should be given before future medication.

Acute infusion reactions usually develop associated symptoms and signs at the time of or shortly after drug infusion and usually resolve within 24 hours after completion of the infusion. Signs and symptoms include: Anaphylaxis/hypersensitivity (including drug-induced fever), cough, chills, chills/chills, dizziness, headache, fatigue (fatigue, lethargy), rash, itchy/itchy skin, joint pain, muscle pain, low or high blood pressure, nausea, vomiting, sweating (sweating), tachycardia, urticaria (wheals), dyspnea (shortness of breath), or bronchospasm.

All grade 3-4 infusion reactions were reported according to the SAE if they met the SAE criteria. Management of anaphylaxis should be based on institutional medical practice and guidelines. Management of delayed anaphylaxis (e.g., pruritus that develops more than 1 week after the end of the infusion) should be managed with symptomatic treatment (e.g., oral antihistamines or corticosteroids).

6.2.2.4 Grading criteria and treatment recommendations for reactive cutaneous capillary endothelial proliferation (RCCEP)

Table1 Grading criteria and treatment recommendations for RCCEP

Grade	Clinical manifestation	Recommendations
Grade 1	Multiple or single nodules, maximum diameter ≤10mm, with or without ulceration and hemorrhage	Study drug was continued, and topical treatment was strengthened for those with ulceration and bleeding to prevent infection
Grade 2	Multiple or single nodules, >10mm in diameter, with or without ulceration	Study drug should be continued, observation or local treatment measures should be taken, such as laser or surgical resection, and topical treatment should be strengthened for those with ulceration and bleeding to prevent infection
Grade 3	Multiple nodules were found throughout the body and complicated by skin infection	study drug should be held until the severity of the toxicity decreases to Grade 1 or returns to baseline. Observation or topical treatment measures such as laser or surgical resection were taken, and anti-infection treatment shouled be given to concurrent infection

Grade 4 life-threatening and grade 5 deaths have not yet occurred and are therefore not specified

6.2.3 Apatinib-related Adverse Events

Elevated blood pressure: Most patients with elevated blood pressure occur about 2 weeks after taking medicine, and most patients can generally be well controlled by combined use of antihypertensive drugs.

Proteinuria: Proteinuria generally occurs about 3 weeks after administration of the drug and can be relieved by dose interruption or dose reduction.

Hand-foot syndrome: Hand-foot syndrome usually occurs about 3 weeks after taking medicine, and can be alleviated by symptomatic treatment.

Bleeding: The observed bleeding symptoms included gastrointestinal bleeding, hematemesis, hemoptysis, positive fecal occult blood, positive urinary occult blood, skin bleeding spots, and

rupture of liver metastases. Patients in whom fecal occult blood developed generally developed within the first cycle after taking the drug.

Cardiotoxicity: electrocardiographic abnormalities, including sinus bradycardia, partial ST-T changes, slowing heart rate, QT prolongation, and acute myocardial infarction.

Liver toxicity: transaminase, bilirubin, alkaline phosphatase, lactate dehydrogenase increased, liver enzyme abnormalities mostly occurred at the initial of the second cycle.

6.3 Dose Modifications

6.3.1 Recommendations for Chemotherapy Dose Modifications

During the treatment, the patient's blood routine was monitored. After the first occurrence of grade III-IV neutropenia, the use of G-CSF was recommended after active treatment. In cases of grade IV neutropenia, grade III neutropenia with fever (>38.5°C) despite prophylactic colony-stimulating factor treatment, or grade III or higher thrombocytopenia and increased creatinine during treatment that could not be tolerated after treatment, each dose reduction of oxaliplatin and fluorouracil was allowed at the discretion of the investigator if toxicity occurred. There were two levels of dose adjustment. If a reduction of more than two dose levels was required, treatment was discontinued.

Table 2 Dose modifications of oxaliplatin and fluorouracil: hematologic toxicity, nonhematologic toxicity

Dose Level		Drug	Dose
0	-	Oxaliplatin	85mg/m2
		Fluorouracil	400 mg/m2 (intravenous infusion), 2400 mg/m2 (continuous infusion)
-1	Grade III and IV hematologic toxicity, non-hematologic toxicity (excluding peripheral neurotoxicity	Oxaliplatin	75mg/m2
		Fluorouracil	0 mg/m2 (intravenous infusion), 1900 mg/m2 (continuous infusion)
-2	Grade IV hematologic toxicity after 1 dose level reduction of oxaliplatin or fluorouracil	Oxaliplatin	55mg/m2
		Fluorouracil	0 mg/m2 (intravenous infusion), 1400 mg/m2 (continuous infusion)

Peripheral neurotoxicity: As far as possible, the neurological examination of the subjects was performed by the same investigator, before each cycle of treatment, and the subjects should be reviewed regularly if they develop symptoms or signs of peripheral neurological disease. The administration dose was adjusted according to Table 3

Table 3 Oxaliplatin dose adjustment: Peripheral neurotoxicit

AE	Peripheral neurotoxicity		
	time of duration		
	≤7 days	8-13days	⩾14days
Hypoesthesia	No change	No change	No change
Hypoesthesia without cold pain	No change	No change	After recovery, the dose was reduced 1 dose
Hypoesthesia with cold pain	No change	1 dose reduction	2 dose reduction
Hypoesthesia with functional impairment	1 dose reduction	2 dose reduction	Discontinued oxaliplatin

6.3.2 Recommendations for Modifications of Apatinib

Table 4 Recommendations for modifications of apatinib

AE		Grade	Drug held or not	Drug resumed	modification	permanently discontinued
Apatinib related toxicity	hematologic toxicities	Grade 1/2	No	—	—	—
		Grade 3	Yes (except a decreased lymphocyte count)	until toxicity grade decreases to Grade 2	The first time: the original dose; Second time: 5 days on, 2 days off; Third time: medication on alternate days	Grade 3 or higher hematologic toxicity after two dose modification
		Grade 4	Yes	until the severity of the toxicity decreases to Grade 2	The first time: 5 days on, 2 days off; Second time: medication on alternate days	
	Other nonhematologic toxicities *	Grade 1	No	—	—	—
		Grade 2 (lasting more than 7 days)	Yes	until toxicity grade decreases to Grade 1	Original dose	—
		Grade 3	Yes	until toxicity grade decreases to Grade 1	The first time: 5 days on, 2 days off; Second time: medication on alternate days	Grade 3 or higher nonhematologic toxicity after two dose modification
	hypertension	Grade 3 (after treatment)	Yes	until toxicity grade decreases to Grade 1	The first time: the original dose; Second time: 5 days on, 2 days off; Third time: medication on alternate days	After two adjustments, grade 3 hypertension recurred
		hypertensive crisis	Yes	—	permanently discontinued	permanently discontinued
	Proteinuria (without a significant increase in serum creatinine)	Grade 3	Yes	until toxicity grade decreases to Grade 2	The first time:5 days on, 2 days off; Second time: medication on alternate days	After two adjustments, grade 3 proteinuria recurred
	hand-foot	Grade 3	Yes	until	The first time:5	After two

	syndrome			toxicity grade decreases to Grade 1	days on, 2 days off; Second time: medication on alternate days	adjustments, grade 3 hand-foot syndrome recurred
	headache	Grade 2 headache lasting ≥7 days after symptomatic treatment, or grade 3 headache	Yes	until toxicity grade decreases to Grade 1	The first time: 5 days on, 2 days off; Second time: medication on alternate days	After two adjustments, grade 3 headache recurred

* : In the event of cerebral hemorrhage, ≥ grade 2 pulmonary hemorrhage, ≥ grade 3 other hemorrhage, arterial thrombosis, leukoencephalopathy syndrome, gastrointestinal perforation, and nephrotic syndrome during the trial, apatinib administration and active symptomatic treatment were terminated, and whether to continue camrelizumab treatment was determined depending on the recovery of toxicity of the subjects

6.3.3 Recommendations for Modifications of Camrelizumab

No dose adjustment is allowed, only suspension of administration is allowed. The withdrawal criteria can be referred to the NCCN Guidelines for immune-related Adverse Reactions

7. Adverse Event

7.1 Definition

An adverse event (AE) is an adverse medical event that occurs after a clinical trial subject receives a drug, but is not necessarily causally related to the treatment. An AE can be any adverse and undesired symptom, sign, laboratory abnormality, or disease, including at least the following:

1) The pre-existing medical condition/disease (prior to entry into the clinical trial) is only recorded as an adverse event if it worsens (including worsening of symptoms, signs, and abnormalities in laboratory tests) after initiation of the investigational drug;

2) Any newly occurring AE: any newly occurring adverse medical condition (including symptoms, signs, and newly diagnosed diseases);

3) Abnormal clinically significant laboratory test results.

Invasive (e.g., surgery), non-invasive procedures that are diagnostic or therapeutic should not be reported as AE, but should be reported when the disease conditions that led to the procedure meet the definition of AE, such as acute appendicitis that developed during the reporting period of AE should be reported as AE, and appendectomy performed as a result should be recorded as the treatment for that AE.

The investigator should record in detail any AE that occurred in the subject, including the name of the AE, time of occurrence and end, severity (graded according to NCI CTCAE <5.0>), correlation between the AE and the trial drug, duration, measures taken on the trial drug due to the AE, outcome of the AE, and whether it was a serious adverse event.

7.2 Recording and Management

Researchers should observe any adverse events that occur during the study, and require subjects to truthfully report changes in their condition after receiving treatment and avoid leading questions. Watch for adverse events or unanticipated clinical manifestations and adverse events (including symptoms, signs, and laboratory tests) while observing efficacy. Adverse events, whether related to the investigational drug or not, should be recorded in detail in the CRF, and the combination of drugs should be recorded in detail to analyze the relevance of adverse events to clinical procedures and drugs, and the record should be signed and dated.

Medical treatment of subjects: When adverse events are found, the investigator may take necessary treatment measures according to the condition, such as surgical intervention, adjustment of chemotherapy dose, temporary interruption of treatment, etc., and decide whether to terminate the trial. In the event of serious adverse events, necessary treatment measures should be taken immediately to protect the safety of subjects.

7.3 AE Severity Grading

Table 5 AE Severity Grading

Severity (Toxicity Grade)	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting ageappropriate instrumental activities of daily living (ADL)
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

7.4 The Relationship Between AEs and Experimental Drugs

The investigator shall conduct a comprehensive evaluation to determine whether the investigational drug has a reasonable probability of causing or contributing to AE, including whether there is a reasonable time sequence between the occurrence of AE and the administration of the investigational drug, the characteristics of the investigational drug, the toxicological and pharmacological effects of the investigational drug, the use of combined drugs, the subject's underlying disease, medical history, and other factors. Family history and deactivation and reactivation responses. The possible association between adverse events and the investigational drug was evaluated according to a five-level classification of "definitely relevant, probably relevant,

probably irrelevant, definitely irrelevant, and undetermined".

7.5 SAE Reporting

7.5.1 SAE Definition

SAE is an adverse event that occurs during the study that meets one or more of the following criteria:
events leading to death;
life-threatening (the term "life-threatening" means that the subject is at risk of death at the time of the event/reaction; It is not assumed that an increase in illness may lead to death);
Events requiring hospitalization or prolonged hospitalization;
events resulting in permanent or serious disability/loss of function;
congenital abnormalities or birth defects;
Other medically important events.

7.5.2 SAE Reporting

In the event of an SAE, whether first report or follow-up report, the investigator must immediately complete, sign and date the Serious Adverse Event Report Form and report it to the appropriate authorities within 24 hours of the investigator becoming aware of it. If SAE occurs after initiation of study drug use, it should also be reported to Hengrui Drug Safety Department (hengrui_drug_safety@hrglobe.cn).

All SAEs should record in detail the symptoms, severity (refer to NCI-CTCAE 5.0), correlation with each investigational drug, occurrence time, treatment time, measures taken by SAE for each investigational drug, follow-up time and method, and outcome. If the investigator considers an SAE unrelated to the investigational drug, but potentially related to study conditions (such as discontinuation of the original treatment, or comorbidities during the trial), this relationship should be detailed in the narrative section of the SAE report form. If the intensity of an ongoing SAE or its relationship to the investigational drug changes, a follow-up report should be submitted immediately. If an investigator believes that a previously reported SAE contains false positives, corrections, retractions, or downgrades may be made in the follow-up report and reported in accordance with SAE reporting procedures.

Any serious adverse event that occurs during the study, regardless of whether it is related to the study, should be dealt with promptly. The researcher should promptly study the serious adverse event and take necessary measures to ensure the safety and rights of the subjects. Researchers must complete a Serious Adverse Event Reporting Form, which should record in the original data when, how, and to whom the serious adverse event was reported.

Investigators must report all AEs, SAEs, and other safety events that occur after informed consent is signed, but before enrollment, if they result in exclusion from the study or are the result of protocol-mandated interventions (including, but not limited to, washout or discontinuation of usual treatment, diet, or procedures).

7.6 Pregnancy

If a female subject becomes pregnant during the study, the subject shall immediately terminate the use of the experimental drug and be discharged from the group; if a male subject's partner becomes pregnant during the clinical study, the subject shall continue the clinical study.

8 End of Treatment

A patient may be discontinued from study treatment at any time if the patient, the investigator, feels that it is not in the patient's best interest to continue on study. If a patient's study treatment must be discontinued, this will not result in automatic withdrawal of the patient from the study.

The following is a list of possible reasons for early discontinuation of study treatment:

Disease progression (patients should be highly encouraged to stay on study treatment until there is confirmed radiographic progression)

Any episode of seizure

Any other adverse event that cannot be adequately managed with dose modifications, including dose interruption for ≥ 28 days may require study drug discontinuation, which must be discussed with the Sponsor.

Protocol violation requiring discontinuation of study treatment

Patient is not compliant with study procedures

Lost to follow-up

Patient withdrawal of consent

9 Protocol Violations

A protocol violation occurs when the patient or Investigator fails to adhere to significant protocol requirements affecting the inclusion, exclusion, patient safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria [no waivers will be granted to meet the eligibility criteria]
- Use of a prohibited concomitant medication
- Dose modifications that are not within the protocol specifications
- Any other deviation that presents significant risk or safety concerns to the patient

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The Sponsor, in consultation with the Investigator, will determine if a protocol violation should result in withdrawal of a patient.

10 Statistic Method

10.1 Analysis Set

Full Analysis Set (FAS) : Patients who met the enrollment criteria and were treated with the study protocol.

Per Protocol Set (PPS) : This analysis set is defined as subjects with no significant protocol deviations during the study or no protocol deviations that have a significant impact on the study results.

Safety Set (SS) : Participants enrolled and receiving at least one cycle of treatment with at least one safety evaluation record constitute the safety set of the study.

The efficacy evaluation of this study will be based on FAS and PPS, in which FAS is the main analysis set. Secfety analysis will be based on SS.

10.2 Statistic Method

The statistical analysis plan is determined before the database is locked, and the statistical analysis is carried out in strict accordance with the statistical analysis plan.

All statistical analysis will be calculated using SAS9.4 or above version of statistical analysis

software. All confidence intervals (CI) are applied with 95% confidence. For measurement data, mean ± standard deviation or median (minimum value, maximum value) will be used for statistical description; Frequency (rate) was used for statistical description of counting data. The Kaplan-Meier method was used to calculate the median value and 95%CI for time event data, and the survival curve was plotted.

10.2.1. Subject Distribution

Descriptive analysis of subject distribution, including but not limited to enrollment, withdrawal, and major protocol violations. The reasons for screening failure and the reasons for quitting the test were summarized.

10.2.2. Demographic and Other Disease Characteristics

Descriptive statistics were performed on sociodemographic characteristics and other disease characteristics. Sociodemographic characteristics include age, sex, etc. Other characteristics include tumor history and past medical history.

10.2.3. Analysis of Primary Study Endpoint

The primary endpoint of this study is pathological response rate, which will be aggregated and its 95%CI.

10.2.4. Secondary Study Endpoint Analysis

For the temporal event data (DFS, OS) in the secondary endpoints, Kaplan-Meier was used to estimate the median value, estimate the 95%CI of the median DFS/OS, plot a survival curve, and estimate the 2-year disease-free survival and its 95%CI.

Statistical rates and 95%CI were pooled for binary data in secondary endpoints (tumor pathological downphase rate, pCR rate, and R0 removal rate).

10.2.5. Safety Analysis

10.2.5.1. Adverse event analysis

Adverse events will be coded using MedDRA (v23.0 or higher) as low-level terms, preferred terms, and major System organ Class (SOC).

An adverse event occurring during treatment (TEAE) is defined as any adverse event that occurs after initiation of the investigational drug. Data on AE, SAE, grade ≥3 AE, grade ≥3 SAE, drug-related AE, drug-related AE, incidence ≥5%, incidence ≥5%, AE leading to dose adjustment, AE leading to termination of treatment, and AE related to surgery were statistically summarized.

10.2.5.2. Surgical safety

Perioperative complication rate, mortality rate and 95%CI need to be collected.

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