Clinical Research Protocol

Study Title: Phase II Study of Anlotinib Combined with Sintilimab as First-Line Treatment for Advanced Non-Liver Metastatic Colorectal Cancer

Study ID: APICAL-CRC2

Version: 1.0

Date: 8 December 2025

Sponsoring Institution: Shanghai Changzheng Hospital

Principal Investigator: Yuan-sheng Zang

declaration of secrecy

Plan Signature Page

I agree:

This study was conducted with strict adherence to the protocol, clinical trial regulations, and all applicable laws and regulations. All resource information provided by Shanghai Changzheng Hospital was kept confidential in accordance with confidentiality requirements. When submitting these materials to the institutional review board or independent committee, it must be clearly indicated that the information is confidential.

I have read the full text of this plan and agree to all its contents.

Signature of the sponsor_____date_____

Statistician's signature_____date_____

Signature page of the plan

I have reviewed the attached document titled 'Phase II Study of Anlotinib Combined with Sintilimab as First-Line Therapy for Advanced Non-Hepatogenous Metastatic Colorectal Cancer' (dated December 8, 2025). I hereby confirm my consent to participate in this study in accordance with the protocol.

I agree to comply with the guidelines on Good Clinical Practice (GCP) and other applicable CFDA regulations/guidelines. I hereby declare that I am personally responsible for the overall implementation of this study. I consent to ensure that all assistants and colleagues involved in this study are fully aware of their responsibilities.

I hereby agree to guarantee that the confidential information contained in this document will not be used for any purpose other than the evaluation or implementation of this clinical study without prior written permission from the Changzheng Hospital affiliated to the Naval Medical University.

Name of the principal investigator at the sub-center:

Signature: Date: Year Month Day

Signature: Date: Year Month Day

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scenario summary	
scenario name	A phase Ⅱ study of anlotinib plus sintilimab as first-line treatment for advanced non-liver metastatic colorectal cancer
Program number	APICAL-CRC2
version number	1.0
date	2025-12-8
Sponsor	Shanghai Changzheng Hospital
indication	Advanced colorectal cancer
Estimated study duration	The study is scheduled from December 2025 to December 2026. Enrollment for this research project is planned to commence in December 2025 and is expected to conclude in December 2026. Data analysis will be completed in June 2026, with the total trial duration approximately 1.5 years.
purpose of research	The efficacy of anlotinib combined with sintilimab as first-line therapy for advanced non-hepatic metastatic colorectal cancer was evaluated using the investigator-assessed objective response rate (ORR).
Total number of cases	The sample size calculation was based on the margin of confidence compared with historical controls, assuming an ORR of 70% in this study and an ORR rate of 50% in the historical controls. In the ITT analysis set, according to the Simon two-stage design, with a one-sided α=0.05 and statistical power=0.8, the calculated sample size was 37 cases.
Case selection criteria	**Inclusion criteria:** • Patients with advanced colorectal adenocarcinoma confirmed by histology or cytology; • Patients without liver metastases who have explicitly refused chemotherapy; • Patients who have not received systematic therapy or have developed metastasis or recurrence more than 12 months after the completion of adjuvant therapy; • The patient has at least one measurable lesion (per RECIST 1.1 criteria); • Patients who have undergone local radiotherapy at least 3 weeks prior to initial drug therapy are eligible for enrollment; however, RECIST-evaluated

	lesions must not be within the radiotherapy field. • The patient must be at least 18 years of age; • Physical condition: ECOG score 0-1; •Life expectancy ≥12 weeks; •The patient must have the capacity to understand and voluntarily sign a written informed consent form; • Women of childbearing age must have a negative pregnancy test result within 7 days prior to initiating treatment. Both the patient and their spouse must use contraception during the study period. **Exclusion criteria:** • Patients who underwent major surgery or sustained severe trauma within 4 weeks prior to the initial medication administration; • Patients with hypersensitivity to any component of the study protocol; • Patients planning for pregnancy or already pregnant; • Patients with brain metastases who cannot accurately describe their condition; • Patients with autoimmune diseases or organ transplants; • Received immunosuppressive therapy within 2 weeks prior to treatment initiation (excluding inhaled corticosteroids or prednisone ≤10 mg/day, or other steroid hormones at physiologically equivalent doses); • Planning to receive a live attenuated vaccine within 4 weeks prior to study initiation or during the study period; • The patient has received anlotinib or anti-PD-1/PD-L1 monoclonal antibody therapy, or other treatments targeting T-cell co-stimulatory receptors or checkpoints; • Presence of the following conditions within 6 months prior to treatment initiation: myocardial infarction (MI), severe/unstable angina, NYHA class 2 or higher congestive heart failure, poorly controlled arrhythmias, etc.; • Abnormal laboratory findings: -Absolute neutrophil count (ANC) <1,500/mm^3; -Platelet count <75,000/mm^3;

	Total bilirubin>1.5 times the upper limit of normal Alanine aminotransferase (ALT) and aspartate aminotransferase (AST)>2.5 times the upper limit of normal; -Creatinine>1.5 times the upper limit of normal; • Patients with other cancers (excluding advanced colorectal cancer) within five years prior to the initiation of treatment in this study. Exclusions include cervical carcinoma in situ, cured basal cell carcinoma, and bladder epithelial tumors. • Patients with operable colorectal cancer (those who explicitly refuse surgery or are unsuitable for surgery may be enrolled); • History of drug abuse, substance use, or alcohol dependence •Lack of legal capacity or limited civil capacity; • Other circumstances deemed unsuitable for enrollment by the investigator. **Exit criteria:** • Withdrawal requested by the patient or their legal representative; •According to the investigator's opinion, the patient's continued participation in the study would be detrimental to their health; • Patients with severe non-adherence or serious protocol violations; • The patient is pregnant, and pregnancy should be reported as a serious adverse event; • When other diseases occur during the study and the investigator determines that the condition will significantly affect the assessment of the patient's clinical status, necessitating discontinuation of the protocol; • Presence of other malignant tumors requiring treatment; • Patients who were lost to follow-up; • Use of prohibited drugs or other medications that the investigator deems may cause toxic reactions or bias the study results; • Patient death. Note: Detailed records of the reasons and dates for withdrawal should be maintained for participants who withdraw during the study, and the withdrawal rate should be statistically analyzed upon study completion. Participants who withdraw from the study will receive appropriate treatment measures based on the judgment of the investigators at each center.

Research Phase and Steps	1) December 2025 – January 2026: Obtain ethical review approval, screen and identify patients clinically diagnosed with advanced non-hepatic metastatic colorectal cancer; 2) February 2026 – June 2026: Informed consent was obtained from the selected population meeting inclusion/exclusion criteria, followed by treatment and evaluation. 3) July 2026 – December 2026: Complete enrollment of study cases; collect efficacy and safety data from patients who signed informed consent forms; 4) January 2027 – June 2027: Refine the data, correct errors, and perform statistical analysis.
statistical analysis	**sample size estimation** The sample size calculation was based on the margin of confidence compared with historical controls, assuming an ORR of 70% in this study and an ORR rate of 50% in the historical controls. In the ITT analysis set, according to the Simon two-stage design, with a one-sided α=0.05 and statistical power=0.8, the calculated sample size was 37 cases. **Statistical analysis of research data** Statistical analysis was performed using SPSS software. Between-group and within-group comparisons were conducted using t-tests, with statistical significance defined as $p<0.05$.

Abbreviations
Table

abbreviation	definition
AE	adverse event
ANC	Absolute neutrophil count
BID	twice daily
CBC	CBC
CI	confidence interval
CR	complete remission
CRR	complete remission rate
CT	computerized tomographic scanning
DOR	Duration of relief
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
FDA	U.S. Food and Drug Administration
HBcAb	HBcAb
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	HCV
IEC	independent ethics committee
IHC	immunohistochemical

IRB	institutional review board
FOLFIRI	5-FU, Iletixan, Lysine Folate
NCI-CTCAE v5.0	National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0
NYHA	New York Heart Association
ORR	overall remission rate
OS	overall survival
PD	PD
PET	Positron Emission Tomography
PFS	progression-free survival
PR	partial remission
PT	Preferred term
QTc	Calibrated QT interval
SAE	Serious adverse events
SD	The disease is stable.
TEAE	Adverse events occurring during treatment
TRAE	adverse events related to treatment
ULN	ULN

catalogue

1. Introduction

Colorectal cancer (CRC) is the third most common malignant tumor globally and the second leading cause of cancer-related mortality [1]. Despite recent advances in CRC research, approximately 15%-30% of patients present with metastatic lesions at initial diagnosis, and an additional 20%-50% of patients with locally advanced CRC will eventually develop metastatic disease [2]. The standard first-line treatment for metastatic colorectal cancer (mCRC) is fluorouracil-based chemotherapy combined with anti-EGFR/VEGF targeted agents, yet the prognosis remains poor, with a median overall survival of only about 2 years [3,4]. Moreover, some mCRC patients may be ineligible for standard doublet or triplet chemotherapy combined with targeted therapy due to factors such as advanced age, poor physical status, comorbidities, or personal preferences [5]. Exploring novel, highly effective, and low-toxicity treatment regimens holds significant clinical importance for these patients. In recent years, immune checkpoint inhibitors have emerged as a promising treatment option for mCRC, particularly for patients with DNA mismatch repair (dMMR) or high microsatellite instability (MSI-H) characteristics [6-8]. However, most pMMR/MSS mCRC patients exhibit primary resistance to immune checkpoint inhibitors due to the presence of immune deserts or immune rejection microenvironments [9]. To enhance the efficacy of immune checkpoint inhibitors in pMMR/MSS patients, a highly promising research direction is the combination of immunomodulatory antineoplastic agents with immunotherapy [10]. Anti-angiogenic drugs can directly or indirectly transform an immunosuppressive microenvironment into an immunostimulatory one, suggesting that the combination of immune checkpoint inhibitors with anti-angiogenic agents may produce synergistic antitumor effects [11,12]. For instance, the REGONIVO trial demonstrated that the combination of regorafenib and nivolumab exhibited controllable safety and encouraging antitumor activity in patients with refractory colorectal cancer [13]. However, in the LEAP-017 study, which compared lenvatinib plus pembrolizumab versus regorafenib or TAS-102 in previously treated, chemotherapy-resistant metastatic colorectal cancer patients, the primary endpoint was not met [14]. Patient characteristics (e.g., prior treatment history), treatment modalities (e.g., subsequent regimens), and performance of the control group may have influenced the results of the LEAP-017 trial. Although the clinical value of this regimen in subsequent treatments remains questionable, its potential to provide clinical benefits for immunocompetent first-line patients warrants further exploration.

Anlotinib is an oral tyrosine kinase inhibitor (TKI) that targets vascular endothelial growth factor receptors 1/2/3, epidermal growth factor receptors 1/2/3, FDGFR, and c-Kit,

demonstrating broad-spectrum antitumor activity in various cancers [15-17]. Multiple clinical trials have shown therapeutic potential in patients with metastatic colorectal cancer (mCRC) [18,19]. A retrospective study evaluated the feasibility and tolerability of anlotinib combined with a PD-1 inhibitor in chemotherapy-resistant mCRC patients, revealing significant efficacy and favorable safety profile in this patient population [20]. Sintilimab, a fully humanized IgG4 monoclonal antibody, has demonstrated clinical benefits in non-small cell lung cancer (NSCLC) and hepatocellular carcinoma (HCC) by blocking the interaction between PD-1 and its ligand [21,22]. Previous studies have confirmed that the combination of sintilimab and anlotinib forms a novel chemotherapy-free regimen applicable to diseases such as cervical cancer and lung cancer [23,24]. Additionally, the combination of sintilimab and furquintinib has shown promising prospects in patients with refractory colorectal cancer, further suggesting its potential value when combined with anti-angiogenic TKIs [25].

Based on the aforementioned findings, the combination of immune checkpoint inhibitors and anti-angiogenic TKIs is expected to generate potent synergistic antitumor effects. This strategy opens a new avenue for "chemotherapy-free" treatment of mCRC when the immune system is functional, particularly worthy of exploration in first-line therapy for mCRC. To preliminarily evaluate the efficacy and safety of anlotinib combined with sintilimab in first-line treatment of mCRC patients, we conducted the APICAL-CRC study [26], enrolling a total of 30 patients. The clinical objective response rate (ORR) was 48.3%, the disease control rate was 89.7%, with median progression-free survival (mPFS) and median overall survival (mOS) of 8.6 months and 22.9 months, respectively. Subgroup analysis revealed that the ORR in patients without liver metastases reached 70%, with mPFS of 14.9 months, whereas the ORR in patients with liver metastases was only 36.8%, significantly lower than that in patients without liver metastases. These results are consistent with previous studies (in the LEAP-017 study, the ORR for lenvatinib combined with pembrolizumab in patients with liver metastases was only 4.8% [14], while in the REGONIVO (USA) study, the ORR in patients with liver metastases was 0% [27]). Patients with better physical performance scores (ECOG PS $0-1$) achieved an ORR of 66.7%, superior to those with ECOG PS 2 (21.4%). Patients carrying ARID1A mutations or those predicted to have a higher ORR (100% vs. wild-type 40%) also demonstrated better outcomes. In terms of safety, the incidence of treatment-related adverse events (TRAEs) of grade ≥ 3 with anlotinib plus sintilimab was only 13.3% (significantly lower than the 50%-70% observed with standard chemotherapy regimens). Adverse events such as hand-foot

syndrome and hypertension were manageable, with no treatment-related deaths. This regimen provides a new option for chemotherapy-free treatment in patients with advanced colorectal cancer. Based on the preliminary results of the APICAL-CRC study, we plan to further screen the optimal patient population for subsequent research in advanced colorectal cancer patients. The enrolled patients will be limited to those without liver metastases and with a PS score of 0-1. Additionally, molecular biomarker analysis will be conducted, particularly stratified analysis based on ARID1A mutation status, to provide new strategies and methods for precision treatment of advanced colorectal cancer.

2. Research Objective

To evaluate the efficacy and safety of anlotinib combined with sintilimab as first-line treatment for non-hepatic metastatic advanced colorectal cancer.

Primary efficacy endpoint: ORR (objective response rate).

Secondary efficacy endpoints: safety, PFS (progression-free survival), OS (overall survival), and DPR (depth of tumor response).

3. Research Content

3.1 Research Design and Planning

This study is a prospective, single-center clinical trial employing anlotinib combined with sintilimab. Based on preliminary research findings and statistical analysis of prior literature, the planned enrollment number is 37 patients.

3.2 Control

Eligible subjects will receive treatment according to the aforementioned protocol, with historical controls as the reference.

3.3 Selection of Study Population

According to the study protocol definition, all subjects were untreated advanced non-hepatic metastatic colorectal cancer.

3.3.1 Eligibility Criteria

- patients with advanced colorectal adenocarcinoma confirmed by histology or cytology;
- patients without liver metastases and who have explicitly refused chemotherapy;
- those who have not received systematic therapy or have developed metastasis or recurrence 12 months after the end of adjuvant therapy;
- The patient has at least one measurable lesion (according to RECIST 1.1 criteria);

- Patients who had received local radiotherapy at least 3 weeks prior to initial drug therapy were eligible for enrollment; however, RECIST-evaluated lesions must not be within the radiotherapy field.
- The patient must be ≥18 years of age;
- The ECOG physical status score was 0-1;
- Life expectancy ≥12 weeks;
- Patients must be able to understand and voluntarily sign a written informed consent form;
- Women of childbearing age must have a negative pregnancy test result within 7 days prior to initiating treatment. Both the patient and their spouse must use contraception during the study period.

3.3.2 Exclusion Criteria

- patients who have undergone major surgery or severe trauma within 4 weeks prior to the first dose of the medication;
- patients with hypersensitivity to the components in the study protocol;
- patients who are planning to conceive or who are pregnant;
- patients with brain metastases who cannot accurately describe their condition;
- patients with autoimmune diseases or organ transplants;
- treatment within 2 weeks prior to study;
- Study of planned vaccination with live attenuated vaccines within 4 weeks before study initiation or during the study;
- The patient has received anlotinib or anti-PD-1/PD-L1 monoclonal antibody therapy, or other treatments targeting T-cell co-stimulatory targets or checkpoints.
- Within 6 months prior to the initiation of the study, the following conditions were present: myocardial infarction (MI), severe/unstable angina pectoris, NYHA class 2 or higher congestive heart failure, poorly controlled arrhythmias, etc.
- Abnormal laboratory test results:

-Absolute neutrophil count (ANC) <1,500/mm^3;

-Platelet count <75,000/mm^3;

Total bilirubin>1.5 times the upper limit of normal

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST)>2.5 times the upper limit of normal;

-Creatinine>1.5 times the upper limit of normal;

- Patients with other cancers (excluding advanced colorectal cancer) within five years prior to the initiation of treatment in this study. Excluded: cervical carcinoma in situ, cured basal cell carcinoma, and bladder epithelial tumors.
- Patients with operable colorectal cancer (those who explicitly refuse surgery or are unsuitable for surgery may be enrolled);
- history of drug abuse, substance use, or alcohol dependence;
- lack of legal capacity or limited civil capacity;
- Other circumstances deemed unsuitable for enrollment by the investigators.

3.4 Study Duration

Based on an estimated enrollment of approximately 5 patients per month, the enrollment period would require approximately 8 months. The total study duration is estimated to be around 12 months.

3.5 Subject Withdrawal from the Study

Discontinued cases refer to patients who cease medication for various reasons during clinical studies. Patients meeting the following criteria will be withdrawn from the study:

- The patient or their legal representative requests withdrawal;
- According to the investigators 'opinion, continued participation in the study would be harmful to the patient's health.
- patients with severe non-adherence or serious protocol violations;
- The patient is pregnant, and pregnancy should be reported as a serious adverse event.
- When other diseases occur concurrently during the study, and based on the investigator's assessment that the disease will significantly affect the evaluation of the patient's clinical condition, and when discontinuation of the current treatment regimen is required;
- other malignancies requiring treatment;
- lost to follow-up;

- Use of prohibited drugs or other drugs that the investigator judges may cause toxic reactions or bias the results of the study;
- The patient died.

All patients who withdraw from the study should have the reason for withdrawal recorded in the case report form and the patient's medical record.

All patients who withdrew due to adverse events or abnormal laboratory findings should be followed up until the adverse event resolved or stabilized, with subsequent outcomes recorded. If a patient died during the trial or within 30 days after trial completion, the investigator must be notified by the researchers. The cause of death must be documented in detail on the Serious Adverse Event (SAE) report form within 24 hours.

3.6 Treatment Plan

3.6.1 Treatment Arrangements

Treatment regimen: Anlotinib, orally, 12 mg once daily, administered from day 1 to day 14 of each cycle, with each cycle lasting 3 weeks; Sintilimab, 200 mg, intravenous infusion for 1 hour ± 5 minutes, administered every 3 weeks until disease progression or intolerable adverse reactions occur.

Treatment should be continued until disease progression or intolerance is achieved. Due to the inherent limitations of the RECIST criteria used for efficacy evaluation, if imaging suggests disease progression but the study physician determines that the patient has clinical benefit, treatment may still be continued.

The efficacy was evaluated every 6 weeks.

3.6.2 Delay in Drug Administration and Dose Adjustment

Patients' toxic reactions should be closely monitored, and dosage adjustments should be made based on their tolerance. It is recommended to adjust the dosage according to the most severe toxic reaction or laboratory abnormalities observed during the previous treatment course or the current treatment course. The severity of toxic reactions should be graded according to NCI CTC AE 5.0. If multiple toxic reactions occur, the dosage should be adjusted based on the most severe toxic reaction.

Medication may be reduced or suspended at any stage of the study due to adverse events.

All adverse events should be graded according to the criteria of NCI CTCAE 5.0.

3.6.2.1 Dose Adjustment

During the treatment phase of this study, the dose of the relevant drug should be

reduced or the medication should be suspended if any of the drug-induced severe toxic reactions occurs.

The dose adjustment for the next cycle will be based on the toxic reactions observed in the previous cycle.

In the event of any severe hypersensitivity reaction to the relevant medication during treatment, the injection should be immediately discontinued and documented.

If a patient develops a severe hypersensitivity reaction on day 1 of the first treatment course, the patient should be excluded from the study.

Imaging evaluation should be performed even if the patient has developed hypersensitivity to the drug, provided that at least two cycles of chemotherapy have been completed.

The specific dose adjustment was implemented according to the chemotherapy-related adverse event management guidelines and drug instructions.

3.6.3 Adjunctive Therapy

3.6.3.1 Therapies Not Permitted

- No other anticancer drug therapy is permitted except for the prescribed treatment regimen.
- Experimental drugs (e.g. experimental antibiotics, antiemetics, etc.)
- Any herbal medicine with antitumor indication during the treatment process.
- Radiotherapy, excluding palliative radiotherapy for existing bone metastases.

3.6.3.2 Permitted Therapies

- Unconventional therapies (e.g., non-cancer-related herbal treatments or acupuncture) and vitamins/microelements may also be administered at the discretion of the investigator, provided they do not interfere with the observation of the study endpoint.
- Patients may receive palliative and supportive care for their underlying condition, such as bisphosphonate therapy.
- Radiation therapy for existing bone lesions (bone metastases present at baseline) with the aim of symptom relief.
- Patients with known bone metastases at baseline who require radiotherapy should complete radiotherapy prior to the first administration of the investigational drug.

- Patients with pre-existing bone metastases at baseline who did not require radiotherapy prior to the first administration of the investigational drug but subsequently required radiotherapy during the study were permitted to receive radiotherapy.
- Patients who received radiotherapy for bone metastases at baseline and require subsequent radiotherapy during the study may undergo additional radiation therapy.
- Topical corticosteroids for the treatment of rash or cutaneous reactions of the hands and feet.

3.6.4 Treatment Compliance

The dosage and administration time of each medication used in each treatment course for every subject should be recorded in the CRF form. Reasons for delayed administration, dose reduction, or missed doses should also be documented in the CRF.

Subject compliance with treatment and protocol includes voluntary adherence to all aspects of the protocol, including compliance with all blood draws required for safety assessment. Subjects who fail to return for follow-up visits or administer medications on time may be excluded from the study based on the opinion of the principal investigator or sponsor.

3.7 Research Indicators

The objective of this study was to evaluate the efficacy and safety of anlotinib combined with sintilimab as first-line treatment for non-hepatic metastatic advanced colorectal cancer. The primary efficacy endpoint was overall response rate (ORR), while secondary efficacy endpoints included safety (assessed using CTCAE 5.0), progression-free survival (PFS), overall survival (OS), and disease progression rate (DPR). Concurrent biomarker analysis was performed.

3.7.1 Efficacy Indicators

Objective response rate (ORR) refers to the proportion of patients whose tumors shrink to a certain extent and sustain this reduction for a specified duration (primarily for solid tumors). It encompasses cases of complete response (CR) and partial response (PR).

Deepness of response (DpR): This refers to the percentage of maximum tumor shrinkage achieved during treatment compared to baseline. If a complete response (CR) is observed, the DpR is 100%.

Tumor response and disease progression will be assessed by investigators according to the RECIST criteria.

Progression-free survival (PFS) refers to the time from enrollment until tumor progression or death.

Overall survival (OS) refers to the time from randomization to death from any cause.

The duration of response maintenance was calculated for all patients who achieved confirmed RECIST-standardized PR or CR. The response maintenance period was defined as the time from the first recorded PR or CR until death or disease progression (whichever occurred first). For patients who were still alive and disease-free as of the analysis date, the cutoff date was set as the date of their last radiological assessment.

This study also explores the relationship between molecular markers and therapeutic efficacy and safety.

3.7.2 Safety Indicators

All patients who have received at least one dose of the investigational drug will be included in the safety analysis as the valid population. The physical examination results, vital signs, adverse events, and abnormal laboratory test values of the patients will be summarized. All adverse events should be reported and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

3.7.3 Evaluation Period

The study was started on the date of signing the informed consent form.

3.7.3.1 Research Visits

- Screening visit should be conducted within 28 days prior to initiation of study drug therapy.
- The treatment period refers to the duration from the initiation of the first study drug administration until the patient discontinues the study drug therapy.
- Patients were evaluated every 8 weeks after discontinuation of study drug therapy due to non-progressive conditions. If disease progression was confirmed, they would enter the follow-up period. During this period, contact with patients should be maintained every 3 months until the patient's death was recorded, to collect data on overall survival.

3.7.3.2 Imaging Evaluation

- Screening period: A CT or MRI scan of the chest and abdomen must be performed at least 28 days prior to enrollment, and tumor measurements must be recorded in the CRF according to RECIST criteria.
- Treatment phase: CT or MRI scans should be performed at least every 6 weeks ±

5 days to evaluate the lesion, and tumor measurements should be recorded in the CRF according to RECIST criteria. Additional examinations should be conducted based on symptomatic indications.

- At the end of the study: CT or MRI scans were performed to evaluate the lesions, and tumor measurements were recorded in the CRF according to the RECIST criteria. Additional examinations were conducted based on symptomatic indications.

3.8 Research Process

3.8.1 Screening Period

within 28 days prior to initiating the study drug

- Sign an informed consent form before any research-related procedure is performed;
- baseline 12-lead electrocardiogram (ECG) examination;
- Brain CT or MRI scans should only be performed when neurological symptoms are present (indicating brain metastases).
- Tumor assessment at baseline: At least one CT or MRI scan of the target lesion, which can be performed within 28 days prior to initiating the investigational drug.

Screening period – within 7 days prior to initiating study drug therapy

- Record/confirm the tumor stage at the time of diagnosis.
- Demographic information, complete medical history, and surgical history, including previous anticancer treatments.
- A complete physical examination (PE), including the ECOG general condition score, height, weight, and a detailed systemic examination.
- Signs and symptoms (including heart rate, blood pressure, respiratory rate, and body temperature).
- Record all comorbidities and concomitant medications with their indications.
- Complete blood count (CBC): hemoglobin, platelet count, white blood cell count and differential, including absolute counts of neutrophils and lymphocytes.
- Complete blood biochemistry panel: including blood glucose, calcium, phosphorus, sodium, potassium, chloride, creatinine, blood urea nitrogen

(BUN), total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, etc.

- Urinary pregnancy tests should be performed for all women of childbearing age. Women who have been postmenopausal for at least 1 year or have undergone sterilization procedures are not required to undergo pregnancy testing.
- Urinalysis: Includes urine leukocytes, urine red blood cells, urine glucose, urine protein, and occult blood
- Routine stool examination

3.8.2 Treatment Period

The treatment period is defined as a 21-day cycle. Therapeutic efficacy is evaluated every 2 cycles. Laboratory tests and imaging assessments during the treatment phase are detailed in the flowchart.

3.8.3 Post-treatment

After treatment (non-progression end of treatment), examinations should be performed every 3 months until disease progression (see flowchart).

3.8.4 Temporary Visits

Temporary visits should be conducted based on clinical needs. Corresponding clinically significant laboratory test abnormalities and adverse events should be recorded in the CRF and original documentation. If multiple laboratory tests are performed on the same day, only one set of test values needs to be recorded in the CRF. However, all abnormal values from repeated laboratory tests should be documented in the CRF.

3.8.5 Follow-up after disease progression

Contact patients every 3 months (via in-person visits or telephone calls) to obtain data on overall survival and post-study chemotherapy. Follow-up should be conducted every 3 months until the patient's death. During each follow-up visit, the following information should be collected:

- Patient survival status.
- Disease status and progress date (if applicable).
- Date of death (if applicable).
- Record all new anticancer therapies.

Note: Patients with tumor progression should be treated as other patients with advanced colorectal cancer.

3.9 Data Quality

In compliance with the guidelines of Good Clinical Practice (GCP), monitors will conduct regular visits to each center to ensure adherence to the study protocol, GCP, and relevant regulations. The visits will include on-site inspections of the completeness and clarity of Case Report Forms (CRFs), cross-verification with original documents, and clarification of management-related matters.

3.10 Archive

The data entered into the Case Report Form (CRF) must be consistent with the original documents or recorded directly in the CRF. In cases of direct recording in the CRF, the recorded content shall be considered as the original data. The parameters of the original data must be validated, and the source information of the data must be documented. Both the study documents and all original data should be retained until the investigator issues a notice for destruction.

4. Ethical and Legal Considerations

4.1 Ethics Committee (EC) or Institutional Review Board (IRB)

In accordance with Good Clinical Practice (GCP), Chinese laws and regulations, and requirements of relevant organizations, all participating centers must obtain approval documents from the corresponding ethics committee/institutional review board prior to the initiation of the study. When necessary, extensions, amendments, or re-evaluations of the ethics committee approval must be obtained and forwarded to the investigators.

4.2 Ethical Guidelines for This Study

The procedures for operations, evaluations, and documentation in this research protocol are designed to ensure that researchers adhere to the guidelines of clinical practice standards and the principles detailed in the Declaration of Helsinki. The implementation of this study will also comply with relevant laws and regulations in China.

Researchers are not permitted to modify the study protocol without prior consent. However, in emergency situations to eliminate risk factors for subjects, researchers may deviate from or alter the protocol without obtaining approval or support from the Ethics Committee/Institutional Review Board/Principal Investigator. Any deviations or modifications made, along with their rationale, must be promptly reported to the Ethics Committee/Institutional Review Board/Principal Investigator. Where appropriate, a proposal for protocol amendment should also be submitted. Researchers are required to provide a comprehensive explanation and justification for all deviations or modifications to the study protocol.

4.3 Subjects' Instructions and Informed Consent

The subject must be provided with the key information of the study and the informed consent form. Prior to the initiation of the study, the investigator must provide the subject with written approval from the ethics committee/institutional review board (IRB) or endorsement of the informed consent form, along with all other written information. The ethics committee/institutional review board approval and the approved informed consent form must be archived together in the study documentation.

Informed consent must be obtained prior to the implementation of any specific study procedure. The date of participant enrollment and signing of the informed consent form shall be recorded in the corresponding subject documentation.

4.4 Confidentiality

All records relating to the identity of the patient are kept confidential and will not be made publicly available to the extent permitted by applicable laws and/or regulations.

The names of participants will not be provided. Case report forms only record the participant's number and the initials of their name. If the participant's name appears in any other documents (e.g., pathology reports), copies of such documents must be redacted. Computer-stored research reports must comply with local data protection laws. When research results are published, participant identities will also be kept confidential.

The investigators will keep a list to identify the records of the subjects.

5. Statistical Methods

5.1 Statistical and Analysis Plan

5.1.1 Study Population Analysis

The efficacy analysis will be conducted in the intention-to-treat (ITT) population, defined as all patients who received at least 2 cycles of study drug therapy. The safety analysis population includes all patients who received at least one dose of study drug therapy. The response rate analysis population refers to all patients in the ITT population who achieved partial or complete response as determined by the RECIST criteria.

5.1.2 Baseline and Demographic Characteristics

Summarize the baseline, demographic characteristics, baseline tumor characteristics, medical history, previous anticancer therapy, concomitant medications, vital signs, and trial discontinuation of all patients who underwent randomization according to different treatment groups. For continuous assessments, calculate the mean, standard deviation, range, and median; also calculate absolute values, frequencies, and percentages.

5.1.3 Efficacy Analysis

The efficacy analysis will be performed in the ITT population.

5.1.3.1 Primary Efficacy Analysis

The primary endpoint was the objective response rate (ORR). The objective response rate refers to the proportion of patients who achieved tumor shrinkage of a certain size and maintained it for a specified duration, including cases with complete response (CR) or partial response (PR). The Kaplan-Meier method was used to derive the expected survival curves for patients in the treatment group.

5.1.3.2 Secondary Efficacy Analysis

The depth of response (DpR) is defined as the percentage of maximum tumor shrinkage achieved during treatment compared to baseline. If a complete response (CR) is observed, the DpR is recorded as 100%.

Tumor response and disease progression will be assessed by investigators according to the RECIST criteria.

Progression-free survival (PFS) is defined as the time from randomization to tumor progression or death, with tumor progression recorded promptly.

Overall survival (OS) is defined as the time from randomization to death from any cause.

5.1.3.3 Safety Analysis

Adverse events and their most severe reaction levels will be summarized according to the criteria of the 5th edition of the NCI CTCAE. Additionally, adverse events will be summarized based on their severity and relationship with the investigational drug. Descriptive summaries of laboratory test values primarily focus on abnormal values. Laboratory test abnormalities will also be summarized according to the most severe level specified in the 5th edition of the NCI CTCAE.

6. Adverse Events

6.1 Precautions/Warnings

Treatment must be administered under the supervision and guidance of a specialized oncologist with experience in the use of relevant medications. Appropriate management of complications is only possible when adequate diagnostic and therapeutic equipment is readily available. Common adverse events include cutaneous reactions of the hands and feet, fatigue, rash, fever, stomatitis, diarrhea, anorexia, hoarseness, arthromuscular pain, abnormal liver function, leukopenia, and thrombocytopenia.

6.2 Detection of Adverse Events

Close monitoring of adverse events occurring in subjects must be conducted. This monitoring includes clinical laboratory tests. The evaluation should be based on the severity, seriousness, and relationship to the investigational drug of the adverse event.

The investigator is responsible for evaluating the relationship between all adverse events and the investigational drug. However, the principal investigator may delegate this judgment to other investigators participating in the study, while remaining accountable for the outcome. The investigator must provide a list of qualified personnel who have been authorized to perform this task.

6.3 Definition of Adverse Events

6.3.1 Adverse Events

Adverse events refer to any adverse medical events occurring in patients or subjects receiving investigational drug therapy. Adverse events do not necessarily have a causal relationship with the treatment. Therefore, adverse events may include any adverse and nonspecific signs (including abnormal laboratory test results), symptoms, or diseases temporarily associated with the investigational drug, regardless of whether the event is considered drug-related.

Adverse events occurring in humans (whether or not drug-related) include the following:

- adverse events that occur during the use of a drug by a professional;
- adverse events caused by drug overdose (whether intentional or accidental);
- adverse events caused by drug abuse;
- adverse events caused by discontinuation of medication;
- Adverse events that may be purely study-related (e.g., those caused by discontinuation of antihypertensive drugs during the washout period or serious adverse events) must be reported as adverse events, even if they are unrelated to the study medication.

Clinical pharmacological effects that do not occur or do not meet the expected outcomes, and are already recorded in the corresponding section of the CRF, shall not be recorded as adverse events. However, if they meet the criteria for a 'serious' adverse event, they must also be recorded and reported as serious adverse events. In this study, the progression or deterioration of existing tumors that meet the 'serious' criteria must also be reported as serious adverse events (SAEs). Investigators should also report symptoms and

signs arising from the progression or deterioration of existing cancers.

6.3.2 Serious Adverse Events

A serious adverse event refers to any adverse medical event occurring under any medication condition that meets one of the following criteria:

- leading to death;
- threat to life ;
- resulting in hospitalization or longer hospital stays for patients;
- resulting in permanent or significant loss of the ability to work or disability;
- congenital malformation or congenital defect;
- Major medical events.

Life-threatening: The term 'life-threatening' is defined as 'severe', indicating that the subject is at risk of death when the adverse event occurs. It does not refer to adverse events that may lead to death under more severe hypothetical conditions.

Hospitalization: Any adverse event that results in a patient being hospitalized or that prolongs the length of hospitalization is considered serious, unless one of the following exceptions applies:

- Stay in hospital for no more than 12 hours;
- perhaps
- Admission was pre-planned (i.e. pre-scheduled surgery or elective surgery prior to the start of the study);
- perhaps
- Hospitalization was not associated with adverse events (e.g. hospitalization for convalescence purposes).
- Note: Any invasive treatment performed during hospitalization may meet the criteria for a 'major medical event' and may therefore require reporting as a serious adverse event based on clinical judgment. Furthermore, if local regulatory authorities require a more stringent definition, the local regulations shall prevail.

Disability: means that a person has a severely impaired ability to perform daily activities.

Major Medical Event: Any adverse event that may endanger the subject and may require intervention to prevent more serious conditions is considered a serious adverse

event. The determination of major medical events should be based on the "WHO Adverse Event Terminology – Main List of Terms". These terms refer to serious disease states or descriptions of serious disease states.

These events are reported as serious adverse events (SAEs) because they may be associated with serious disease conditions and, compared to other reporting methods, reporting them as SAEs ensures heightened attention and facilitates necessary actions.

6.3.3 Unintended Adverse Events

An unexpected adverse event refers to any adverse drug reaction (ADR) whose characteristics or severity differ from those described in the package insert of the marketed product. Supplementary information regarding the characteristics or severity of known or documented adverse events also constitutes part of the unexpected adverse event report. For instance, events that are more specific or severe than those described in the package insert should be classified as "unexpected." Specific examples include: (a) acute renal failure, which has been previously reported as an adverse event, subsequently complicated by interstitial nephritis; and (b) hepatitis initially reported as acute liver necrosis.

6.3.4 Relationship Between Adverse Events and Study Drug

The evaluation of the relationship between a adverse event and the investigational drug is a comprehensive clinical judgment made based on all available information when completing the case report form.

"Not relevant" may include:

1. There are clear alternative explanations, such as traumatic bleeding at the surgical site;

perhaps

2. Unreasonable, such as when a subject is hit by a car, but there is no indication that the event was caused by the drug-induced disorientation; or cancer developing just days after the start of the drug.

A 'yes' evaluation indicates that there are reasonable grounds to suggest a potential association between the adverse event and the study medication.

The following factors should be considered when assessing the relationship between adverse events and the investigational drug:

- Short-term occurrence after drug administration: This adverse event should occur after administration. The duration between medication and the occurrence of the event should be considered during clinical evaluation.

- The event disappeared after discontinuation of administration (cessation of stimulation) and reappeared after resumption of administration (repeated stimulation): When analyzing the clinical course of a suspected event, the response after discontinuation of administration (cessation of stimulation) or after resumption of administration (repeated stimulation) should be fully considered.
- Underlying, comorbid and comorbid conditions: Assess the natural course of the disease, the treatment process and all other conditions the patient may have in each report;
- Concomitant medications or treatments: The other medications taken by the subject or other treatments received by the subject should be examined to determine whether any of them may have caused the adverse event.
- Known response patterns of a specific class of drugs: clinical/preclinical
- Pharmacology and Pharmacokinetics of the Investigational Drug: The pharmacokinetic characteristics (absorption, distribution, metabolism, and excretion) of the investigational drug should be considered in conjunction with the individual pharmacodynamic response of each subject.

6.3.5 Recording of Adverse Events

All adverse events occurring after the subject signs the informed consent form must be fully documented in the subject's case report form.

Records must be supported by original documentation. Laboratory test abnormalities deemed clinically relevant (e.g., those leading to early study withdrawal, requiring treatment, or causing significant clinical manifestations, or those considered clinically relevant by investigators) should be reported as adverse events. Each event must be described in detail, including the start and end dates, severity, relationship to the investigational product, measures taken, and the outcome of the event.

6.4 Reporting of Serious Adverse Events

From the time of informed consent signing until 30 days after the completion of the last dose, any defined serious adverse event (SAE), including laboratory test abnormalities meeting the SAE definition, must be immediately reported to the designated personnel in the study documents (within 24 hours of the investigator's knowledge). The SAE report form must also be completed and submitted to the designated personnel in the study documents within 24 hours of the investigator's knowledge.

Each serious adverse event should be followed up until resolution or stabilization,

with an updated report submitted to the designated personnel. A simple Level 4 laboratory test abnormality (according to the CTCAE 5.0 criteria) should not be reported as a serious adverse event unless the investigator determines that the abnormality meets the International Conference on Harmonisation (ICH) criteria for serious adverse events (as defined in Section 6.3.2). A Level 4 laboratory test abnormality that occurs at baseline and is a manifestation of the disease according to the CTCAE 5.0 criteria should not be reported as a serious adverse event, particularly if the abnormality is present but the patient is still allowed to enroll or is not excluded from enrollment. If there is any doubt about whether the abnormality should be reported as a serious adverse event, the investigator may consult the study monitor. A Level 4 laboratory test abnormality should be recorded on the "Laboratory Data" page and regularly cross-checked by the medical monitor.

According to the requirements of local laws and regulations, serious adverse events must be reported to the ethics committee and the drug regulatory authority.

7. Appendix

7.1 General Status (ECOG Score)

classify	description
0	Full capacity to perform all pre-disease behaviors without restriction. (Karnofsky 90-100 points)
1	Significant limitation of physical activity, but able to walk and perform light physical or sedentary work (e.g., housework and office work). (Karnofsky score 70-80)
2	Capable of walking and performing basic self-care activities, but unable to complete any work-related activities. The time spent on ambulation and alertness exceeds 50% of the total. (Karnofsky score 50-60)
3	Only limited self-care is possible. More than 50% of the waking time requires bed rest or sitting. (Karnofsky score 30-40)
4	Complete disability with loss of mobility. No ability for self-care. Completely bedridden or sedentary. (Karnofsky score 10-20)

7.2 TNM staging

International Standard for Staging Colorectal Cancer

The American Joint Committee on Cancer (AJCC) stipulates that the staging of colorectal cancer is performed according to the TNM staging system.

1. Definition of TNM

primary tumor (T)

- TX: The primary tumor cannot be evaluated.
- T0: No evidence of primary tumor.
- Tis: Carcinoma in situ. Limited to the epithelium or invading the mucosal lamina propria.
- T1: Tumor invasion into the submucosa.
- T2: Tumor invasion of the muscularis propria.
- T3: The tumor penetrates the muscularis propria layer to reach the subserosal layer, or invades the perirectal tissues without peritoneal coverage.
- T4a: Tumor penetrates the visceral peritoneum.
- T4b: The tumor directly invades or adheres to other organs or structures.

Regional lymph nodes (N)

- NX: Regional lymph nodes cannot be evaluated.
- N0: No regional lymph node metastasis.
- N1: Metastasis to 1-3 regional lymph nodes.
- N1a:1 regional lymph node metastasis
- N1b: There are 2−3 regional lymph node metastases.
- N1c: Tumor deposits (TD) in the subserosal, mesenteric, and peritoneally uncovered perirectal tissues, without regional lymph node metastasis.
- N2: Metastasis to more than 4 regional lymph nodes.
- N2a: Metastasis to 4-6 regional lymph nodes.
- N2b: Metastasis to 7 or more regional lymph nodes.

distant metastasis (M)

- MX: The distant metastasis status is unknown.
- M0: No distant metastasis.
- M1: distant metastasis.
- M1a: Distant metastasis is confined to a single organ or site (e.g., liver, lung, ovary, non-regional lymph nodes) but without peritoneal metastasis
- M1b: distant metastases are present in more than one organ, but without peritoneal metastases.
- M1c: Peritoneal metastasis with or without metastasis to other organs.

American Joint Committee on Cancer (AJCC) staging

Stage 0 Tis, N0, M0 Stage 0 Tis, N0, M0

Stage IA, T1, N0, M0 Stage IA, T1, N0, M0

Stage IB, T2, N0, M0 Stage IB, T2, N0, M0

Stage IIIA, T3, N0, M0 Stage IIIA, T3, N0, M0

Stage IIB, T4a, N0, M0 Stage IIB, T4a, N0, M0

Stage IIIC, T4b, N0, M0

Stage IIIIA, T1-2, N1/N1c, M0 Stage IIIIA, T1-2, N1/N1c, M0

T1, N2a, M0

Stage IIIIB, T3-4a, N1, M0 Stage IIIIB, T3-4a, N1, M0

T2-3, N2a, M0

T1-2, N2b, M0	
Stage IIIIC, T4a, N2a, M0	Stage IIIIC, T4a, N2a, M0
T3-4a, N2b, M0	
T4b, N1-2, M0	
Stage IVA, any T, any N, M1a	Stage IVA, any T, any N, M1a
Stage IVB: Any T, Any N, M1b	Stage IVB: Any T, Any N, M1b
Stage IVC: Any T, Any N, M1c	Stage IVC: Any T, Any N, M1c

7.3 RECIST Tumor Assessment Criteria

In this study, the new international standard proposed by the RECIST (Response Evaluation Criteria in Solid Tumors) committee will be used to evaluate tumor response and progression. The only change in the RECIST criteria is the application of the maximum diameter of the tumor lesion (one-dimensional measurement).

Measurable lesions: Measurable lesions are defined as those that can be accurately measured in at least one dimension (with the longest diameter recorded), with a maximum diameter ≥ 20 mm measured using conventional techniques (PE, CT, XR, MRI) or ≥ 10 mm using spiral CT scanning. Spiral CT scans for tumor response evaluation must be reconstructed with a slice thickness of 5 mm. All tumor measurements must be recorded in millimeters (or tenths of centimeters).

Unmeasurable lesions: All other lesions (or disease sites) excluding measurable lesions, including small lesions (measured by conventional techniques with a maximum diameter <20mm or by spiral CT with a maximum diameter <10mm), are considered unmeasurable. Lesions in bones, meninges, ascites, pleural/pericardial effusions, cutaneous lymphangitis/pneumonia, inflammatory breast diseases, abdominal masses (unfollowable by CT or MRI), and bladder lesions are all deemed unmeasurable.

Target lesions: A maximum of 2 lesions from each organ's measurable lesions may be selected as target lesions, with up to 5 representative lesions from all affected organs eligible for selection. All target lesions must be recorded and measured during the baseline phase. These 5 lesions should be chosen based on their size (longest diameter of the lesion) and the reproducibility of their precise measurements (whether via imaging techniques or clinical measurements). The sum of the longest diameters (LD) of all target lesions will serve as the baseline total LD. The baseline total LD will be used as a reference value to

objectively evaluate tumor response by measuring the size of subsequent lesions. If more than 5 measurable lesions are available, those not selected as target lesions will be classified as non-target lesions along with unmeasurable lesions.

Non-target lesions: include all non-measurable lesions (or disease sites) and all measurable lesions outside the selected 5 target lesions. These lesions do not require measurement but should be recorded as "present" or "absent" at baseline and at each follow-up.

Efficacy Evaluation: All patients will undergo one of the following efficacy evaluations:

Complete remission (CR): All clinical and imaging evidence of the tumor (including target and non-target lesions) is eliminated.

Partial response (PR): A reduction of at least 30% in the sum of LD values at the target lesion compared to baseline total LD.

Stable Disease (SD): A stable state of the disease. The lesion has not met the PR criteria for shrinkage or has not met the PD criteria for progression.

Disease progression (PD): Referring to the minimum total LD value recorded from the start of treatment, the sum of LD in the measured lesions increases by at least 20% or one or more new lesions appear. The emergence of any new lesions indicates disease progression. In special cases, unmeasurable lesions with clear progression may also be accepted as evidence of disease progression.

Evaluation of therapeutic efficacy for target lesions versus non-target lesions

Target lesion	**Non-target lesions**	**New lesion**	**Overall response**	**This type of optimal response also requires**
CR	CR	not have	CR	Confirm after 4 weeks
CR	Non-CR/Non-PD	not have	PR	Confirm after 4 weeks
PR	Non-PD	not have	PR	
SD	Non-PD	not have	SD	At least 4 weeks from the baseline period
PD	any	Present or absent	PD	No SD, PR, or CR had occurred previously.
any	PD	Present or absent	PD	

any	any	have	PD	

Patients with an overall deterioration in health status requiring treatment discontinuation should be reported as 'symptom exacerbation' if there is no objective evidence of disease progression at this time. Objective disease progression should be observed and documented as closely as possible even after treatment cessation.

Relief time

The duration of remission should be calculated from the time of the first meeting of the criteria for CR or PR (whichever is recorded first) until the date of the first recorded disease recurrence or progression.

disease stable time

The duration of disease stability should be calculated from the start of treatment until disease progression is achieved, with the minimum measured lesion size after treatment initiation serving as the reference.

measuring method

The same evaluation criteria and measurement techniques should be used to describe and report each designated lesion during both the baseline and follow-up periods.

Clinical lesions — Clinical lesions are considered measurable only when located on the body surface (e.g., skin nodules, palpable lymph nodes). For dermatological lesions, it is recommended to document them with color photographs including the lesion and the measuring ruler used.

Chest X-ray — When the lesion has well-defined margins and is surrounded by air-filled lung tissue, the lesion observed on chest X-ray may be considered measurable. However, CT should still be the preferred modality.

CT/MRI — CT and MRI are currently the most feasible and reproducible methods for measuring target lesions selected for response evaluation. Conventional CT and MRI should be performed with continuous scanning at a slice thickness of 10 mm or less. Spiral CT should be performed with continuous scanning at a slice thickness of 5 mm and reconstruction. This method is suitable for the chest, abdomen, and pelvis. Scanning of the head, neck, and limbs often has specific requirements.

When measurable tumor lesions meet the criteria for remission and disease stability, cytological examination must be performed for any effusion that occurs or worsens during

treatment to confirm whether it is tumor-induced (the effusion may be a side effect of treatment), thereby distinguishing between disease remission/stability and disease progression.

7.4 New York Heart Association (NYHA) Classification of Heart Function

	New York Heart Association (NYHA) functional classification
I level	The patient has a history of heart disease but no restrictions on physical activity. Normal physical activity does not lead to excessive fatigue, palpitations, dyspnea, or angina pectoris.
II level	The patient's cardiac condition results in mild limitation of physical activity. No discomfort is observed at rest. Even mild physical exertion may lead to fatigue, palpitations, dyspnea, or angina pectoris.
III level	The patient's cardiac condition results in significantly restricted physical activity. No discomfort is observed during rest. Even mild physical exertion may lead to fatigue, palpitations, dyspnea, or angina pectoris.
IV level	The patient's cardiac condition renders them incapable of any physical activity. Even at rest, symptoms of heart failure or angina may occur. Any physical exertion exacerbates the discomfort.

7.5 Research Process Table

Flowchart of Therapy Process

	pretherapy	Each 3-week period constitutes one cycle.			Post-treatment follow-up visit	Follow-up after treatment discontinuation due to non-progressive conditions until disease progression	Follow-up after progression 9
		Cycle 1	Cycle 2	The 4th and subsequent cycles until disease progression or treatment discontinuation			
Operation item	Filter period	Day 1	Day 1	Day 1	Within 7 days	Every 8 weeks	Every 3 months
Informed Consent Form	X (within 28 days)						Every 2 months, telephone follow-up or outpatient visit is conducted to collect the following information: 1. Patient survival information; 2. Changes in cancer treatment modalities, including all new therapies
Medical History 1	X (within 7 days)						
Complete physical examination 2	X (within 7 days)						
Inclusion/Exclusion Criteria	X						
stochastic	X						
Life signs and ECOG score	X	X	X	X	X	X	
12-lead electrocardiogram	X (within 28 days)		X	X	X		
Brain CT or MRI scan 3	X (within 28 days)						
Imaging Evaluation 4	X (within 28 days)	X (every 6 weeks) ----------					
Hematological examination 5	X (within 7 days)		X	X	X		
Complete Set of Biochemical Tests 6	X (within 7 days)		X	X	X		
Urine test 7	X (within 7 days)		X	X	X		
Fecal Test 8	X (within 7 days)	X (every 6 weeks) ----------					
Serum pregnancy test	X (within 7 days)						
Study of drug use		X	X	X	X		
Evaluation of Adverse Events (AEs)	----------(						
comorbidities and concomitant medications	----------(						

1. Complete medical history, demographic data, surgical history, concomitant medications, comorbidities, allergy history, and smoking history.
2. Complete physical examination, ECOG performance status score, height, weight, vital signs, and detailed examinations of all body systems.

3. Head CT/MRI scans are only required for patients with baseline neurological symptoms to exclude brain metastases.
4. Tumor assessment during the treatment phase is required every 6 weeks. After treatment completion, imaging evaluations are required every 8 weeks until disease progression occurs. If a patient withdraws from the study due to disease progression, no additional CT scans are required during the final follow-up at study completion.
5. Hematological tests include: hemoglobin, hematocrit, platelets, white blood cells, absolute neutrophil count, and absolute lymphocyte count, which can be performed 1 day prior to the start of each treatment course.
6. The complete biochemical panel includes: blood glucose, calcium, phosphorus, sodium, potassium, chloride, creatinine, blood urea nitrogen, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin. These tests can be performed one day prior to the start of each treatment course.
7. Urinalysis includes: urine specific gravity, pH value, urine glucose, urine protein, and occult blood. Screening requires laboratory urinalysis, followed by urine test strips during subsequent treatment courses. Urinalysis can be performed one day before the start of each treatment course.
8. Fecal examination, also known as routine stool test, includes fecal occult blood, white blood cells, and red blood cells. It is performed once during the screening phase and can be conducted concurrently with each subsequent tumor assessment.
9. Follow-up should be conducted every 3 months after disease progression until 1 year after progression or death.

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