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

Informed Consent Form

(Version 1.0, 3 December 2025)

Subject Name: _____

Contact address: _____

Contact number: _____

Research Center Name: Shanghai Changzheng Hospital

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Dear Mr./Ms._____,

We sincerely invite you to participate in the "Phase II Study of Anlotinib Combined with Sintilimab as First-Line Treatment for Advanced Non-Hepatogenous Metastatic Colorectal Cancer". This study is conducted by the Department of Oncology at Shanghai Changzheng Hospital. Before you agree to participate in this study, please carefully read this informed consent form, which will provide you with information regarding the background, purpose, methods, benefits and potential risks or changes during the trial, as well as your rights and protections. The information provided in this informed consent form will assist you in deciding whether to participate in this study. If you have any questions, you may consult the study investigators to ensure you fully understand the relevant content. If you agree to participate in this study, please sign the informed consent form and retain a copy signed by both parties. This study protocol has been approved by the Biomedical Ethics Committee of Shanghai Changzheng Hospital.

1. Why should you participate in this study?

Colorectal cancer (CRC) is the third most common malignant tumor globally and the second leading cause of cancer-related mortality. Despite recent advances in CRC research, approximately 15%-30% of patients present with metastatic lesions at initial diagnosis, while an additional 20%-50% of patients with primary localized CRC will eventually develop metastatic disease. The conventional treatment for first-line metastatic colorectal cancer (mCRC) is fluorouracil-based chemotherapy combined with anti-EGFR/VEGF targeted agents. However, some mCRC patients may not be eligible for standard dual-or triple-chemotherapy combined with targeted therapy due to factors such as advanced age, poor physical status, comorbidities, or personal preferences. Therefore, exploring novel, highly effective, and low-toxicity treatment regimens holds significant clinical importance. The combination of immune checkpoint inhibitors and anti-angiogenic TKIs is expected to generate potent synergistic antitumor effects. This strategy opens a new approach for treating mCRC with a "chemotherapy-free" regimen when immune system function is intact. In our earlier APICAL-CRC study, a total of 30 patients were enrolled, achieving an objective response rate (ORR) of 48.3% and a disease control rate of 89.7%. The median progression-free survival (mPFS) and median overall survival (mOS) were 8.6 months and 22.9 months, respectively. Subgroup analysis revealed that the ORR in patients without liver metastases reached 70%, with an mPFS of 14.9 months, significantly higher than that in patients with liver metastases (ORR 36.8%). Additionally, patients with a better physical status score (ECOG PS 0−1) had an ORR of 66.7%, superior to those with an ECOG PS of 2 (21.4%). In terms of safety, the incidence of treatment-related adverse events (TRAEs) of grade ≥3 with anlotinib plus sintilimab was only 13.3%. Based on the preliminary results of the APICAL-CRC study, we plan to further screen for optimal patient populations in advanced colorectal cancer for subsequent research. The enrolled patients will be limited to those without liver metastases and with an ECOG PS of 0−1, aiming to provide new strategies and methods for precision treatment of advanced colorectal cancer.

The purpose 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 study was conducted at Shanghai Changzheng Hospital. The study drugs included anlotinib and sintilimab, both of which are marketed drugs in China.

2. Who is eligible to participate in this study?

（1）Inclusion criteria (who is eligible to participate in the study?)

• 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.

(2) Exclusion Criteria (Who is ineligible to participate in the study?)

• 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/mm³;

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.

3. How many participants were enrolled in this study?

This study is expected to enroll 37 eligible subjects, all of whom will receive the anlotinib and sintilimab combination regimen.

4. How was the study conducted?

Within 28 days prior to initiating the study drug: Informed consent must be obtained; an electrocardiogram (ECG) examination must be performed; baseline tumor assessment must be conducted, including at least CT or MRI scans of the target lesion. The tumor stage at the time of diagnosis must be recorded/confirmed, and the patient's demographic information, complete medical history, and surgical history, including prior anticancer therapy, must be collected. A comprehensive physical examination must be performed, including a general condition score, height, weight, and detailed systemic examination, with documentation of all comorbidities and concomitant medications and their indications. Complete blood, urine, and stool routine tests, as well as blood biochemical tests, must be performed.

During the treatment period, anlotinib was administered orally at a dose of 12 mg once daily, from day 1 to day 14 of each cycle, with each cycle lasting 3 weeks. Sintilimab was administered intravenously at a dose of 200 mg over 1 hour ± 5 minutes, once every 3 weeks, until disease progression or intolerable adverse reactions occurred.

The patient undergoes regular follow-up examinations of blood parameters and imaging markers to evaluate the efficacy and safety of the treatment. The treatment continues until disease progression or intolerance is observed. If imaging indicates disease progression but the study physician determines that the patient has clinical benefit, the treatment may be continued.

5. Potential Risks and Adverse Reactions of Participation in This Study

(1) Study of potential adverse effects and side effects of the investigational drug: Common adverse reactions of anlotinib include hand-foot syndrome, diarrhea, fatigue, decreased appetite, hypertension, stomatitis, hoarseness, weight loss, infection, headache, and rash. Common adverse reactions of sintilimab include rash, hypothyroidism, hyperthyroidism, pruritus, fatigue, anemia, thrombocytopenia, leukopenia, elevated AST, elevated ALT, anemia, decreased lymphocyte count, pneumonia, elevated lipase, and

proteinuria. If any discomfort, new changes in the condition, or any unexpected events occur, regardless of whether they are related to the drug, the study physician should be promptly notified. The study physician will make a judgment and provide medical intervention.

(2) Risks of blood draw: These include transient mild pain, localized cyanosis, and a minority of individuals may experience mild dizziness.
or extremely rare needlestick infections.

(3) Other risks: There may also be some currently unpredictable risks, adverse reactions, drug interactions, or
Adverse reactions.

6. What are the benefits of participating in this study?

You may not directly benefit from this study, but your participation will provide substantial support for frontline research on the treatment of advanced colorectal cancer, contributing to the ultimate conquest of tumor diseases. Your involvement will facilitate more accurate diagnosis of your condition, offer essential recommendations for your treatment, or provide valuable information for disease research.

Potential benefits: This study may potentially cure the disease or halt/slow its progression, but we cannot guarantee this outcome. Although participation in this study may not provide you with direct benefits, your involvement could benefit future patients who may suffer from similar conditions.

7. If you do not participate in this study, are there any alternative treatment options available?

If you decide not to participate in this study, you will receive other standardized treatments (e.g., fluorouracil, oxaliplatin, irinotecan ± bevacizumab or cetuximab), and your investigator will propose a treatment regimen tailored to your condition. Your investigator will also be pleased to explain the potential benefits and risks of alternative therapies for your disease.

8. Costs of Participation in This Study

The study provides free anlotinib and sintilimab treatment for up to 12 months to participants in the trial group. For treatment exceeding 12 months, the participant is responsible for the costs of anlotinib and sintilimab. Participants are required to bear their own expenses for other treatments, nursing care, and diagnostic tests. Participants in this study will not receive any compensation or remuneration.

9. Management of research-related injuries

All investigational drugs have been officially marketed in China and are in clinical use, with related adverse reactions managed as per standard procedures.

10. Voluntary participation and withdrawal from the trial

You may opt out of this study or withdraw from it at any time by notifying the investigators without facing discrimination or retaliation, and your medical treatment and rights will not be affected.

If you cannot make a decision immediately, you have plenty of time to consider it. If necessary, you can consult with relatives, friends, and other trusted people before making a decision.

If additional diagnosis/treatment is required, if you fail to comply with the study protocol, or if any other reasonable reason arises, the investigator may terminate your participation in the study.

If you decide to withdraw from the study early, it is crucial to consult the investigator and understand the required procedures. Throughout the trial, you may access relevant information pertaining to your involvement at any time.

11. Your personal information will be strictly protected

If you decide to participate in this study, your participation and personal data during the study will be kept confidential. The study physicians and other researchers will use your medical information for the study. This information may include your name, address, telephone number, medical history, and any information obtained during your study visit. To ensure the study is conducted in accordance with regulations, the sponsor, regulatory authorities, or members of the ethics review committee may, when necessary, access your personal data at the study site as required. When the results of this study are published, no personal information about you will be disclosed.

12. Others

1. In the following circumstances, for the sake of your health, the investigator may withdraw you from the trial without your consent:

Continuing to participate in this trial may result in a greater risk than benefit for you.

You did not participate in the trial in accordance with the protocol as instructed by the investigator.

The trial was terminated prematurely.

2. We recommend that you take necessary contraceptive measures during the trial. If you or your spouse becomes pregnant during the trial, please immediately inform the investigator or your physician.

13. Who should I contact if I have any questions or difficulties?

You may access relevant information and updates regarding this study at any time. If you have questions related to this study or experience any discomfort or injury during the research process, please contact your study physician at: Tel: 021-66540109-8007.

If you have any questions regarding your rights and interests during the study, please contact the Biomedical Ethics Committee of Shanghai Changzheng Hospital at 021-81885046.

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Informed Consent Statement of the Subject

I have read and fully understand the informed consent form.
I had the opportunity to ask questions and all of them were answered.

I understand that participation in this study is voluntary.

I am aware of other treatment options available (including but not limited to chemotherapy, anti-VEGF monoclonal antibodies or anti-EGFR monoclonal antibodies, surgery, etc.), but I do not opt for the aforementioned alternative treatments. I hereby choose to participate in this study.
I may opt out of this study, and my medical benefits and entitlements will not be affected by this decision.
If I require additional treatment, fail to adhere to the study protocol, sustain study-related injuries, or for any other reason, the study physician may terminate my participation in this study.

I will receive a signed copy of the informed consent form.

Subject Name: _____ Legal Representative Signature: _____

Subject's signature: _____Relationship with the subject: _____

Subject's phone: _____ Legal representative's phone: _____

Date: __/__/____ (DD/MM/YYYY)

(Note: If the subject is incapacitated, the signature of the legal representative is required.)

Statement of Informing the Researcher

I have provided the subject or their legal representative with a detailed explanation of the study's purpose, methods, procedures, as well as the associated risks and benefits. I have given them sufficient time to review the informed consent form, discuss it with others, and answer all their questions. I have also informed the subject of the contact information available for any inquiries. Additionally, I have made it clear to the subject or their legal representative that they may withdraw from the study at any time during the study period without any reason.

Researcher's Name: _____

Researcher's signature: _____

Researcher's phone: _____

Date: __/__/____ (DD/MM/YYYY)