# Informed consent form for the clinical research project

Project name: Single arm, single center, exploratory, phase II clinical study of envafolimab in pMMR / MSS locally advanced rectal cancer

Scheme version number and date: V1.1, March 02,2023

Informed Consent Form Version Number and Date: V1.2, March 02,2023

Research institution: Yunnan Provincial Cancer Hospital

Principal investigator: Li Yunfeng

Subject Name: Subject Name is abbreviated:

Subjects address:

Subjects telephone:

We invite you to participate in a clinical study. This informed consent form provides you some information to help you decide whether to participate in this clinical study. Please use the time to read the following content carefully. If there are any unclear questions or terminology, you can discuss with the doctor concerned.

Your participation in this study is completely voluntary. This study has been reviewed by the Ethics Committee of Yunnan Cancer Hospital.

**research background:**

Colorectal cancer (colorectal cancer, CRC) is one of the most common malignancies. In recent years, with the continuous improvement of people's living standards, the change of dietary habits and structure, and the aging of the population, the incidence and mortality of CRC in China have been increased. Chinese rectal cancer patients in the overall CRC population, higher than 26% in the United States; middle and low rectal cancer is as high as 70% -80% in rectal cancer, and most rectal cancer patients are in local progression. For T3 / T4 or N + patients, guidelines recommend synchronous chemoradiotherapy + rectal cancer radical ± adjuvant chemotherapy, rectal cancer 5 years local recurrence rate to 5% -10%, local control effect has improved significantly, but there are some patients with locally advanced rectal cancer, even if the preoperative synchronous chemoradiotherapy, but still

cannot guarantee the radical resection of tumor.

In recent years, with the excellent performance of immune point inhibitors in various solid tumors, many researchers have also tried to apply them in patients with rectal cancer, expecting to get better results than the available treatment data. At present, some results have been made in some studies on immune checkpoint inhibitors. Immune checkpoint inhibitors may have great potential in the neoadjuvant treatment of rectal cancer. As the first subcutaneous PD-L1 mab, it may provide a safer and more convenient option for the treatment of locally advanced locally advanced rectal cancer.

In the Phase II clinical study (C N006) of envafolimab, 103 subjects were enrolled, including 65 CRC patients, confirmed ORR in advanced CRC; the median DOR was not met, late CRC 12-month DOR rate was 88.4%; advanced CRC, the median PFS was 7.2 months; median OS was not reached, and 12-month OS rate for late CRC subjects was 72.9%. The incidence of all-grade adverse events during treatment was 96%, the incidence of drug-related adverse events was 85.4%, 20 patients (19.4%) had grade 3 to 4 treatment-related adverse events (TEAEs) and no study drug-related grade 5 TEAEs. Three percent of the subjects permanently discontinued treatment due to drug-related TEAEs. Therefore, the incidence of grade immune-related adverse events was 43%, including grade 3 to 4 incidence was 8%, and no grade 5 immune-related adverse events occurred. It can be seen that envafolimab has good tolerability and safety.

Furthermore, ASCO-GI 2023 reported preliminary efficacy and safety data of envafolimab plus radiochemotherapy as neoadjuvant therapy in MSS rectal cancer. As of 31 December 2022,32 patients were enrolled in the study, where 28 had completed surgical treatment and 4 patients were still on treatment. Of the 28 operated patients, the pCR rate was 57.1% (16 / 28). TRAEs occurred in 96.9% (31 / 32) of the patients, with a grade 3 / 4 incidence of 6.2%. The study data suggest that in MSS / pMMR locally advanced rectal cancer, preoperative neoadjuvant therapy with sequential envafolimab + CAPEOX achieved good pathological response, good safety, and significantly improved the quality of life of patients.

This study will explore the efficacy and safety of envafolimab combined with chemoradiotherapy in neoadjuvant treatment of pMMR / MSS locally advanced rectal cancer, in order to bring good news to patients with locally advanced rectal cancer.

**purpose of research:**

To explore and analyze the efficacy and safety of envafolimab combined with chemoradiotherapy in the whole-course neoadjuvant treatment of pMMR / MSS locally advanced rectal cancer.

**Study entry and discharge criteria:**

**Selection criteria:**

**1) Disease characteristics**

- Histological confirmation of rectal adenocarcinoma;
- Immunohistochemistry confirmed as pMMR or / and pCR or / and NGS detection as MSS;
- The tumor location is within 12cm from the anal margin;
- Local advanced rectal cancer (stage II-III, cT 3-4 and / or N +);

* Preoperative staging method: pelvic MRI / transrectal ultrasound.

- No signs of intestinal obstruction; or obstruction relieved after proximal colostomy surgery;
- Preoperative thoracic, abdominal, and pelvic CT excluded distant metastases.

**2) Patient characteristics**

- Age: from 18 years old to 75 years old;
- Activity status score: ECOG 0-1;
- Life expectancy: greater than 2 years;
- Hematology: WBC> 350010$^6$/L ； PLT>100000×10$^6$/L ； Hb>10g/dL;
- Liver function: SGOT and SGPT were less than 1.5 times the normal value; bilirubin was less than 1.5 mg/dL;
- Renal function: creatinine was <1.8 mg/dL;

- Other: non-pregnant or lactating women; no other malignant disease (except non-melanoma or carcinoma of the cervix) within 5 years or concurrent; no mental illness that prevents informed consent; no other serious disease that leads to shortened survival.
- Patients or family members can understand the study protocol and are willing to participate in the study, and sign a written informed consent form;
- Patients had good compliance and volunteered for scheduled follow-up, treatment, laboratory tests, and other study procedures.

**3) Previous treatment**

- No previous rectal cancer surgery;
- No prior chemotherapy or radiotherapy;
- No previous biological treatment;
- Previous endocrine therapy: no restriction.

**Exclusion criteria:**

- CRC of microsatellite instability (MSI-H or dMMR);
- Chronic hepatitis B or C (high-copy viral DNA) with a history of HIV infection or an active phase;
- AD;
- Other active clinical serious infections (> NCI-CTC version 3.0);
- Clinical stage I patients;
- There is already preoperative evidence of distant metastasis;
- Bad fluid mass, organ function decompensation;
- History of pelvic or abdominal radiotherapy;
- Multiple primary cancer;
- Patients with epileptic seizures (e. g., steroids or antiepileptic therapy);
- History of other malignancies within 5 years, except for cured cervical carcinoma in situ or basal cell carcinoma of the skin;
- Chronic inflammatory intestinal disease, intestinal obstruction;
- Drug abuse and medical, psychological, or social conditions may interfere with patient participation in research or influence the assessment of study outcomes;

- Known or suspected allergy to study drug or to any drug given related to this trial;
- Any unstable condition or condition that may compromise patient safety and compliance.

**Research process:**

**Main research contents:**

This study used a single-arm, single-center study design. To evaluate the efficacy and safety of envafolimab combined with chemoradiotherapy in the full-course neoadjuvant treatment of pMMR / MSS locally advanced rectal cancer. Pathological complete response rate (pCR) was used as the primary endpoint, objective response rate (ORR), clinical complete response rate (cCR), tumor downstaging rate (mr TRG), pathological staging rate, R0 resection rate, tumor regression grade (TRG), anal preservation rate, surgical complication rate, 2-year disease-free survival rate (2-year DFS), 2-year overall survival rate (2-year OS); patient quality of life and safety were used as secondary study endpoints.

**Number of subjects expected to attend: 35 patients**

**Process and Term:**

You may choose not to participate in this study or to withdraw at any stage of the trial without any reason. Your medical treatment and interests will not be affected. If you decide to withdraw from the study, the study doctor will stop collecting your data, but your previously collected data and samples will be saved and used to ensure the validity of the study and managed according to regulatory requirements, and then the study doctor will invite you to conduct the end of the study visit to check your health status. Once you decide to participate in this study, you should sign this informed consent form indicating your consent. Before entering the study, the physician will screen you to confirm if you are the right candidate.

If you volunteer to participate in this study, you need to follow the protocol with the study doctor or his team; If you have questions about the treatment, refer to your study doctor.

（1） Screening period (-28~ -1 day): screened for inclusion / exclusion criteria and enrolled after qualification.

（2） Treatment phase:

Induction treatment phase: 2 cycles of chemotherapy plus immunotherapy:

envafolimab: 200mg, subcutaneous injection, Q2W, 2 cycles (simultaneous administration on the first day of chemotherapy);

mFOLFOX6: Q2W, 2 cycles, oxaliplatin 85mg / m2 intravenous infusion for 2h on day 1. Linovorin calcium 400mg / m2 was infusion for 2h on day 1. Fluoruracil 400mg / m2, day 1, then 1200mg / (m2 · d) 2d, continuous intravenous infusion (total 2400mg / m2,46 to 48 h).

Synchronous chemoradiation stage: 3 cycles of long-range chemoradiation combined with immunotherapy:

Radiotherapy: 50 Gy / 25f, 2 Gy per day, 5 days per week for 5 weeks;

Capecitabine: 825mg / m2, administered orally twice daily, morning and evening (1650mg / m2 / d), 5 days per week, concurrent with radiotherapy for a total of 25 days; 200mg, subcutaneous, Q2W, 3 cycles.

envafolimab: 200mg, subcutaneous, Q2W, 3 cycles (concurrent administration on radiotherapy days 1,15,29).

Consolidation treatment phase: 2 cycles of chemotherapy combined with immunotherapy:

envafolimab: 200mg, subcutaneous injection, Q2W, 2 cycles (simultaneous administration on the first day of chemotherapy);

mFOLFOX6: Q2W, 2 cycles, oxaliplatin 85mg / m2 intravenous infusion for 2h on day 1. Linovorin calcium 400mg / m2 was infusion for 2h on day 1. Fluoruracil 400mg / m2, day 1, then 1200mg / (m2 · d) 2d, continuous intravenous infusion (total 2400mg / m2,46 to 48 h).

Surgical regimen: surgical time: 6 weeks after completion of the last

neoadjuvant radiotherapy or 3 weeks after consolidation immunotherapy. Surgical method: According to the surgical principle of total mesorectal resection (TME), the specific procedure is decided by the surgeon according to the center team.

Postoperative adjuvant treatment regimen: Postoperative treatment regimen includes adjuvant chemotherapy or waiting observation strategy, which will be discussed by the investigator team. Postoperative adjuvant chemotherapy regimen: starting about 3 weeks after R0 resection, 2 cycles of mFOLFOX6 regimen, and about 6 months of perioperative treatment. For patients who failed to receive preoperative treatment, determine whether to change the treatment regimen based on the discussion results of the MDT team.

**fl.up:**

You need to come to the hospital according to the protocol and continue until the end of the study. The purpose of the follow-up is to understand your treatment effect, any adverse reactions and treatment accordingly.

Visit follow-up time included: screening period, dosing period (once per cycle), preoperative follow-up, postoperative first month, postoperative follow-up every three months, safety follow-up within 28 days after the last dose, and survival follow-up every three months after disease progression.

Your doctor may also recommend to you to adjust or increase the follow-up program or frequency based on your condition.

**Items to be inspected:**

（1） MMR status testing by immunohistochemistry (by the Department of Pathology, Yunnan Cancer Hospital) or MSI status testing by pCR or / and NGS (by the Molecular Diagnostic Center of Yunnan Cancer Hospital).

（2） General examination: medical history, vital signs, physical examination, height, weight, ECOG physical status score, 12-lead electrocardiogram, cardiac ultrasound examination, etc. (conducted by the Department of Colorectal Surgery of

Yunnan Cancer Hospital).

（3） Blood routine, blood chemistry, urine routine, coagulation function, thyroid function, myocardial enzyme spectrum, lymphatic immunity ten, tumor markers, etc. (by the laboratory of Yunnan Cancer Hospital).

（4） Tumor imaging examination (CT, MRI) (performed by Radiography Department of Yunnan Cancer Hospital) colonoscopy (performed by gastroenteroscopy room of Yunnan Cancer Hospital), B ultrasound (performed by ultrasound Department of Yunnan Cancer Hospital, etc.);

（5） Your doctor may also recommend that you have other tests based on your condition.

| **Study Step / Visit 1** | **Screening period** | **Treatment period 3** | | | | | | | **Preoperative** | **Postoperative follow-up** | | **Safety follow-up 4** | **Survival follow-up 5** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **inductive treatment** | | **Synchronous chemoradiotherapy** | | | **after treatment** | | **After completion of consolidation treatment / before surgery** | **One month after surgery** | **Once every 3 months after surgery** | **And 28 days after the last dose** | **Once every 3 months** |
| **Visit time** | **-28~0** | **C1 D1** | **C2 D1** | **C3 D1** | **C4 D1** | **C5 D1** | **C6 D1** | **C7 D1** | | | | | |

| Window time | 0 | ± 3 days | ± 3 days | ± 3 days | ± 3 days | ± 3 days | ± 3 days | ± 3 days | ± 7 days | ± 7 days | ± 7 days | ± 7 days | ± 7 days |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Signed the informed consent form 2 | ■ | | | | | | | | | | | | |
| Demographic data | ■ | | | | | | | | | | | | |
| history of past illness | ■ | | | | | | | | | | | | |
| Tumor diagnosis | ■ | | | | | | | | | | | | |
| Genetic testing 6 | ■ | | | | | | | | | | | | |
| Height, weight 7 | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | |
| vital sign | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | |
| Physical examination 8 | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | |
| ECOG PS Score | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | |
| And a 12-lead ECG | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | |
| CEA | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | | |
| routine blood test | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | |
| Blood biochemical | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | |
| coagulation function | ■ | | | | | | | | ■ | | | ■ | |
| Fecal hidden blood | ■ | | | | | | | | | | | | |
| routine urine test | ■ | | | | | | | | ■ | | | ■ | |
| thyroid function | ■ | | | ■ | | | ■ | | ■ | | | ■ | |
| HIV、HBV、HCV | ■ | | | | | | | | ■ | | | | |
| Peripheral blood detection | ■ | | | ■ | | | ■ | | ■ | ■ | | | |
| Thoracal \ abdominal \ pelvic enhanced CT | ■ | | | ■ | | | ■ | | ■ | | ■ | ■ | |
| pelvic cavity MRI | ■ | | | ■ | | | ■ | | ■ | Was performed as clinically required | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **enteroscopy** | ■ | | | | | | | | ■ | **Once a year** | | | |
| **Ctoluminal ultrasound** | ■ | | | | | | | | ■ | | | | |
| **Abdominal B ultrasound** | ■ | | | | | | | | ■ | | | | |
| **Whole-course neoadjuvant therapy** | | ■ | ■ | ■ | ■ | ■ | ■ | ■ | | | | | |
| **Adverse events 10** | | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | |
| **Concomitant medication 11** | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | |
| **Quality of life assessment 12** | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | |
| **survival condition** | | | | | | | | | | | | | ■ |

**Study flow chart:**

**Risk and discomfort of study:**

**<u>The possible adverse effects of envafolimab are as follows:</u>**

Very common (above 10%):

- Elevated aspartate aminotransferase (18.3%)
- Alanine aminotransferase increased (17.1%)
- Blood bilirubin increased (14.0%)
- Rash (11.4%)

Common (incidence rate> 1% - <10%):

- Hypothyroidism (9.4%)
- Anaemia (7.7%)
- White BC count decreased (5.4%)
- Weak (5.4%)
- Fever (4.9%)
- Loss of appetite (4.6%)
- Platelet count decreased (4.3%)
- Proteinuria (4.3%)
- Hyperthyroidism (3.7%)
- Injection site reaction (3.4%)

- Diarrhoea (2.9%)

Uncommon ((incidence> 0.1% - <1%)):

- Elevated blood sugar
- Hypoalbuminemia
- elevation of blood pressure
- carditis
- dermatitis
- cerebritis
- pancreatitis
- asthenic bulbar paralysis
- Elevated blood amylase or elevated lipase
- Other immune-related adverse reactions occurring for the first time

**When using any drug, side effects can occur.** Your study doctor will ask if you have any side effects. When treatment with the study drug, side effects may be previously observed with drugs we consider similar to the study drug, which may vary from person to person. In addition, there may be currently unpredictable adverse reactions or risks.

**Risk of chemoradiotherapy:**

Adverse reactions related to radiotherapy and chemotherapy include: gastrointestinal reactions (decreased appetite, nausea, vomiting, abdominal distension, diarrhea, etc.), bone marrow suppression (decreased white blood cell count, thrombocytopenia, anemia, etc.), infection, etc. You can see more about the possible adverse reactions related to chemoradiotherapy through your attending doctor. Rademoradiotherapy may also have some currently unpredictable risks and adverse reactions.

During the study, you may not experience any adverse effects or some adverse effects, classified as mild, moderate or severe. If an adverse event occurs, your study doctor will actively symptomatic treatment based on the severity of your adverse event, including recommending you use certain drugs to reduce the side effects in some of them.

**The Benefits of Study Participation:**

Participation in this study may have a direct medical benefit, but may not benefit. Your disease may be remission, but it may not achieve the desired effect, or even disease progression. We hope that the information from your participating study will be instructive in the future for patients with the same condition as your condition.

**Cost associated with the study:**

① If you agree to participate in this study, you will receive free medication for the study drug, envafolimab.② Radiotherapy, chemotherapy and other treatments and tests that may be required involved in the study are routine medical items for rectal cancer and will be paid at your own expense.③ Throughout the study, additional costs such as transportation, accommodation and accommodation will be at your expense.

**Compensation and compensation related to the study:**

① From the beginning of the study to the safety follow-up, whether the adverse event is related to the study drug should be judged by the investigator. If you are caused by the drug-related adverse event, the Sponsor will bear certain economic compensation in accordance with Chinese laws and regulations. The sponsor initiating this study project has purchased drug clinical trial liability insurance for this study.

Injury resulting from adverse events does not include injuries occurring in the following circumstances:

You did not comply with the study requirements or the instructions of the study doctor;

You failed to inform the study doctor and treat as recommended by the study doctor;

Is the result of the natural development of the disease or its accompanying complications;

It was intentionally caused;

Treatment that you will not receive in this study.

The informed consent form that you have signed will not affect all your legal rights.

If you have an adverse reaction related to the trial, you should give active treatment. You can get compensation through settling the claims, and the insurance company is responsible for the compensation within the agreed compensation limit according to the provisions of the insurance contract.

② The study did not involve subsidies, so the transportation and accommodation costs incurred during treatment and follow-up were self-borne.

**Alternative treatment:**

In addition to participating in this study, you have the following options:

1. Standard treatment regimen recommended by current guidelines or used in clinical practice
2. Participate in other studies
3. Other possible treatment options

You will not necessarily participate in this study. You can promise or refuse. Your routine medical care will not be affected. If you do not participate in this study, your doctor will discuss with you the other treatment options suitable for you.

**Privacy and confidentiality issues:**

If you decide to participate in this study, the personal data, biological samples and examination data you participated in the trial and collected in the trial are kept confidential. During the study, your name, gender and other personal data will be replaced by code names or numbers, and kept strictly confidential. Only the relevant doctor knows your information, and your privacy will be well protected. The results may be published in a journal, but will not disclose any of your personal information.

If you agree to participate in this study, your relevant medical information will be reviewed by the relevant personnel of the research and development unit initiating the study, or by an independent ethics committee to check whether the study is being properly conducted. If you sign the informed consent form, you agree to accept the above personnel.

**How to get help in the study:**

You can always know the information and progress of the study. If you have questions related to this study, please contact you_____take part in____ contact. Ethics Committee of Yunnan Cancer

Hospital_____。

**Informed consent signature page**

If you fully understand the content of this research project and agree to participate in this study, you will sign this informed consent form in duplicate, each retained by the investigator and the subject or the client.

Signed by the subject himself or his legal representative:

Consent statement:

1、 I confirm that I have read and understood the informed consent for this study, that possible problems and solutions during the study have been explained to me, and that I have the opportunity to raise my own questions.

2、 I have made it clear that participation in the study is voluntary and refusal to participate in the study will not harm my due interests.

3、 I have learned that the physicians involved in the study, the person in charge of this work and the medical ethics Committee have the right to review the study records and case data. I agree that the above personnel can directly obtain my study records and understand that the above information will be kept confidential.

4、 I agree to take part in this study

Subjects signed:_____ date:_____

Subject contact details:_____

(Note: If the subject is incompetent / limited capacity, guardian signature and signature date)

Signature of guardian:_____date:_____

Contact information of the guardian:_____Guardian and subject relationship:_____

(Note: If the subject cannot read the consent form, an independent witness is required to prove that the investigator has informed the subject of all contents of the consent form and the independent witness needs signature and signature date)

Signature of the Independent Witness:_____date:_____

Contact Information of the Independent Witness:_____

Signature of the investigator:_____date:_____

Investigator Contact Information:_____