# Envafolimab combined with chemoradiotherapy in the full neoadjuvant treatment of pMMR / MSS locally advanced rectal cancer

# Single-arm, single-center, exploratory, phase II, clinical study

## study protocol

**Protocol version number: V1.1**

**Version date: March 02, 2023**

**Study director: Chief Dr. Li Yunfeng**

**Associate Professor CAI Xinyi**

**Research unit: Yunnan Provincial Cancer Hospital**

# Scheme signature page

I, as the physician / statistical analyst involved in the study, have read the protocol for this study.

I have fully discussed the purpose of the study and the content of the protocol.

I agree to conduct the study under this protocol, to comply with the ethics requirements, and to conduct this clinical study under the guidance of Good Clinical Practice (GCP).

I agree that the contents of this protocol are confidential and will not be disclosed to third parties, and the contents of the protocol are only treatment for this study.

I understand that if the decision to prematurely terminate or suspend it is made at any time and for any reason, I will be informed in writing. Similarly, if I decide to withdraw from the study, I will immediately notify the study leader and the principal investigator.

Name: _____

Signature: _____

Date: _____

# Protocol summary

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| research topic | Single-arm, single-center, exploratory, phase II clinical study of envafolimab in full neoadjuvant treatment of pMMR / locally advanced rectal cancer with MSS |
| version number | V1.1 |
| Version date | March 02, 2023 |
| by stages | II designated time |
| Bid unit | And Yunnan Provincial Cancer Hospital |
| Principal investigator | Chief physician Li Yunfeng, Associate Professor CAI Xinyi |
| Participating in research units | Single center |
| subject investigated | Locally advanced rectal cancer |
| research design | This study is a single arm, single center, phase II, prospective clinical study to explore the efficacy and safety of envafolimab plus chemoradiotherapy in full neoadjuvant treatment of pMMR / MSS locally advanced rectal cancer. |
| Study duration | The study is scheduled to begin in March 2023. |
| Study objective / endpoint | <u>Main end point</u><br>Pathological complete response rate (pCR)<br><u>Secondary end point</u><br>1) R0 resection rate;<br>2) Objective response rate (ORR); clinical complete response rate (cCR);<br>3) Tumor downstaging rate (mrTRG); pathological downstaging rate; tumor regression grade (TRG);<br>4) Anal rate;<br>5) The rate of surgical complications;<br>6) The 2-year disease-free survival rate (DFS);<br>7) The 2-year overall survival rate (OS); |

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| | 8) Quality of life (including anal sphincter function, bladder function and sexual function);<br>9) Incidence of adverse reactions and serious adverse reactions. |
| study population | **Inclusion criteria:**<br>**1) Disease characteristics**<br>• Histological confirmation of rectal adenocarcinoma;<br>• Immunohistochemistry confirmed pMMR or / and pCR or / and NGS as MSS;<br>• The tumor location is within 12cm from the anal margin;<br>• Local advanced rectal cancer (stage II-III, cT 3-4 and / or N +);<br>* Preoperative staging method: pelvic MRI / transrectal ultrasound.<br>• No signs of intestinal obstruction; or obstruction relieved after proximal colostomy surgery;<br>• Preoperative thoracic, abdominal, and pelvic CT excluded distant metastases.<br>**2) Patient characteristics**<br>• Age: from 18 years old to 75 years old;<br>• Activity status score: ECOG 0-1;<br>• Life expectancy: greater than 2 years;<br>• Hematology: WBC> $350000^{6}$/L ; PLT>$100000\times10^{6}$/L ; Hb>10g/dL;<br>• Liver function: SGOT and SGPT were less than 1.5 times the normal value; bilirubin was less than 1.5 mg/dL;<br>• Renal function: creatinine was <1.8 mg/dL;<br>• 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.<br>• Patients or family members can understand the study protocol and are willing to participate in the study, and sign a written informed consent form;<br>• Patients had good compliance and volunteered for scheduled follow-up, treatment, laboratory tests, and other study procedures. |

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| | **3) Previous treatment**<br>• No previous rectal cancer surgery;<br>• No prior chemotherapy or radiotherapy;<br>• No previous biological treatment;<br>• Previous endocrine therapy: no restriction.<br>**Exclusion criteria:**<br>• CRC with highly unstable microsatellite (MSI-H) or defective mismatch repair protein expression (dMMR);<br>• Chronic hepatitis B or C (high-copy viral DNA) with a history of HIV infection or an active phase;<br>• AD;<br>• Other active clinical serious infections (> NCI-CTC version 3.0);<br>• Clinical stage I patients;<br>• There is already preoperative evidence of distant metastasis;<br>• Bad fluid mass, organ function decompensation;<br>• History of pelvic or abdominal radiotherapy;<br>• Multiple primary cancer;<br>• Patients with epileptic seizures (e. g., steroids or antiepileptic therapy);<br>• History of other malignancies within 5 years, except for cured cervical carcinoma in situ or basal cell carcinoma of the skin;<br>• Chronic inflammatory intestinal disease, intestinal obstruction;<br>• Drug abuse and medical, psychological, or social conditions may interfere with patient participation in research or influence the assessment of study outcomes;<br>• Known or suspected allergy to study drug or to any drug given related to this trial;<br>• Any unstable condition or conditions that may compromise patient safety and compliance; |
| The planned sample size | Statistical test efficacy was calculated with postoperative pathologic complete response rate (pCR) as the primary study endpoint.α 0.05, the test efficacy is 80%, the pathological complete response rate after conventional treatment is 15%, and the estimated pathological complete |

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| | response rate in the test group is 35%. Considering the loss of 10% of cases, the calculated sample size in the access group is 35 cases. |
| therapeutic regimen | 1. Induction phase: Treatment of chemotherapy combined with immunotherapy 2 cycles: Envafolimab: 200mg, subcutaneous injection, Q2W, 2 cycles; mFOLFOX6: Q2W, 2 cycles (envafolimab administered simultaneously on the first day of chemotherapy).<br><br>2. Synchronous chemoradiation phase: long-course chemoradiation plus immunotherapy for 3 cycles: radiotherapy: 50 Gy / 25f, 2 Gy per day, 5 days per week for 5 weeks; capecitabine: 825mg / m2, twice daily morning / evening orally (1650mg / m2 / d), concurrent with radiotherapy for a total of 25 days; Envafolimab: 200mg, subcutaneous, Q2W, 3 cycles (administration of envafolimab in radiotherapy on days 1,15 and 29).<br><br>3. Consolidation treatment phase: 2 cycles: Envafolimab: 200mg, subcutaneous injection, Q2W, 2 cycles; mFOLFOX6: Q2W, 2 cycles.(envafolimab was administered simultaneously on the first day of chemotherapy). |
| Safety evaluation criteria | Observe all subjects for any adverse events during the clinical study, including clinical symptoms and vital signs, abnormalities in laboratory tests, record their clinical presentation characteristics, severity, duration, duration, treatment methods and prognosis, and determine the correlation with the test drug. The safety of the drug was evaluated using the NCI-CTC AE 5.0 version criteria. |
| Effectiveness evaluation criteria | Tumor evaluation was performed throughout the study and analyzed using the Solid Tumor Efficacy Evaluation (RECIST) criteria (version 1.1,2009). Radiological imaging (CT, MRI) scans were performed, and the clinical complete response rate (cCR), objective response rate (ORR), and tumor staging rate (mrTRG) were determined and calculated for all patients. |
| statistical method | Statistical analysis was performed using SPSS23.0 or SAS software. For the PPS and FAS data, and safety indicators for the SS data. Most of the data presented in this study were descriptive. For continuous data, it is |

expressed by mean and standard deviation and percentage of index index.

(1) Baseline demographic data and disease characteristics:

Characteristics of the observed patients were summarized by descriptive statistics, including age, sex, clinical stage, and ECOG scores, etc.

(2) Analysis method of the primary endpoint:

After the completion of the whole neoadjuvant treatment, two doctors in the pathology department jointly evaluated the pathological complete response rate (pCR).

(3) Secondary endpoints analysis method:

A. After the end of the whole neoadjuvant treatment, two doctors from the pathology department jointly evaluated the tumor withdrawal grade (TRG), and the pathological decline rate.

B. The imaging results were evaluated by RECIST 1.1 standard to calculate the objective response rate (ORR) and tumor descent rate (mr TRG);

C. Patient quality of life (QoL) was evaluated using the Chinese version of the Cancer Patient Quality of Life Scale [EORTC QLQ-C30] (V3.0);

D. Safety indicators: The evaluation is based on the SS set, using NCI-CTC AE v5.0 criteria, listing the incidence of adverse events and serious adverse events, their clinical presentation characteristics, severity, occurrence time, duration, treatment method, and prognosis.

E. The rate of tumor descent, the rate of anal preservation, incidence of surgical complications, incidence of adverse events and incidence of serious adverse events were all expressed in percentage.

F. Survival analysis was performed by Kaplan-Meier to estimate the 2-year overall survival (OS) and disease-free survival (DFS);

# Flow chart of the clinical trial

| 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 assay 9 | ■ | | | ■ | | | ■ | | ■ | ■ | | | |
| Thoracal 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** | | | | | | | | | | | | | ■ |

# Flow-chart description of the clinical trial

1. One period in this study was defined as 14 days. The inspection items should be completed within the time window listed in the test process. In case of statutory holidays, the reason for the overwindow can be recorded in advance and recorded in the CRF. In addition to the follow-up in the flow chart, the investigator may increase the examination items or increase the visit frequency based on the clinical condition of the subject.
2. The informed consent form for the screening period should be signed within 28 before treatment,Written informed consent must be obtained before performing any clinical study procedures, except for the existing tumor imaging examination and tumor tissue biopsy within the time limit specified before the first medication. This study allows previously failed subjects to re-screen, re-sign the informed consent form and re-register to obtain a new subject number.
3. Relevant examination of C1D1, such as relevant data within 7 days, does not have to be repeated. The treatment-phase follow-up program needs to be completed before each cycle of treatment.
4. Safety follow-up will be performed 28 ± 7 days after the last dose or before the start of a new antitumor therapy, whichever occurs first. All AEs occurring before the safety follow-up visit should be recorded until remission to level 0-1 or baseline, or follow-up is not required by the investigator for reasonable reasons (such as recovery or improvement) (whichever occurs first). SAEs occurring within 90 days of the last dose or before the subject started the new anticancer therapy (whichever occurred first) were followed up and recorded. If the patient is not due to disease progression, an imaging examination should be performed at this follow-up. If imaging data are available within the 4 weeks before this follow-up, the investigator can evaluate the need for a re-examination.
5. Survival follow-up began after the end of the safety visit period and was called every 3 months to record subject survival until the end of the last subject or the end of the trial.
6. Genetic tests should include routine tests for bowel cancer, such as MSI status (or MMR status), POLE / POLD 1 mutation status, PTEN mutation status, TMB status, RAS and BRAF mutation status, etc.
7. After height and weight screening period, only weight was measured in other stages to calculate body surface area.
8. Physical examination during treatment, with specified examination items according to clinical symptoms or clinical needs.
9. Peripheral blood tests include: CD3 +, CD4 +, and CD8 + T cell expression levels.
10. Adverse events were collected from the start of treatment, and once the subject had terminated trial treatment, only new or unresolved adverse events related to trial treatment should be recorded.
11. Concomitant medication records Concomitant medication within 28 days of the screening period and during the trial; once a subject interrupted trial treatment, only concomitant medication and concomitant treatment for new or unresolved adverse events related to trial treatment; no concomitant medication due to other disease should be recorded.
12. Quality of life was assessed using the Wexner rating scale, the EORTC QLQ-C30 scale, and the

EORTC-QLQ-CR29 scale.

# 1. research background

## 1.1 summary

Colorectal cancer (colorectal cancer, CRC) is one of the most common malignancies. According to the latest data released by the International Agency for Research on Cancer (International Agency for Research on Cancer, IARC), colorectal cancer is the third among all tumors and the second mortality rate, while China has the second incidence rate and the fifth mortality rate[1-2]. 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[1-2]。

The prognosis of rectal cancer is worse than colon cancer, one of the important reasons is the high local recurrence rate after rectal cancer. Surgical resection is the main treatment for rectal cancer. Due to the complex pelvic structure and small surgical space, local advanced rectal cancer (LocalIy Advanced Rectal Cancer, LARC) patients with complete surgical resection is difficult, low anal rate, local recurrence rate and high complications, including high postoperative recurrence rate is the most noteworthy cause of poor prognosis of LARC, its radical postoperative local recurrence rate of 5% -15%, distant metastasis rate of 30% -40%, is one of the main factors in patients. However, with the proposal and development of the concept of multidisciplinary comprehensive therapy (MDT), the perioperative neoadjuvant radiotherapy and chemotherapy have gradually received attention in the overall treatment of LARC. Studies have reported that total rectal series resection after neoadjuvant chemoradiotherapy for LARC reduced the local recurrence rate from 25% – 40% to 6%[3-4]。

According to the 2021 CSCO guidelines for the diagnosis and treatment of colorectal cancer: recommended for T3 / T4 or N + patients ± interval chemotherapy (reevaluation) + rectal cancer radical resection plus adjuvant chemotherapy (class 1A evidence)[5]. The National Comprehensive Cancer Network (National Comprehensive Cancer Network, NCCN) guidelines recommend "preoperative concurrent chemoradiotherapy + radical surgical ± adjuvant chemotherapy" as the standard treatment regimen for locally advanced rectal cancer (stages II, III), and recommend 6 months of perioperative treatment[6]. This treatment regimen

reduced the 5-year local recurrence rate of rectal cancer to 5% -10%, and the local control effect was significantly improved[7]. In the past decade, its mortality reduction has slowed due to its higher rate of distant metastasis (29% -39%)[8]. In addition, there are some locally advanced rectal cancer patients, even before the preoperative synchronous radiotherapy and chemotherapy, but still can not guarantee the tumor radical resection[9-10]。

## 1.2 significance of studying

Preoperative radiotherapy combined with 5-fluorouracil / capecitabine is the current standard treatment for locally advanced rectal cancer. Although this strategy is effective in reducing the risk of local recurrence, it fails to effectively improve the overall survival rate of patients[11-12]. The underlying reason is the failure of 5-fluorouracil / capecitabine-based local radiotherapy to effectively control the potential micrometastases. Therefore, many studies have tried to use more intense chemotherapy and targeted drugs on the basis of preoperative radiotherapy, as well as induction chemotherapy and then consolidation chemotherapy before preoperative radiotherapy, in order to achieve better efficacy. However, several studies have shown that increasing cytotoxic drugs is not effective in improving pathological complete response rates (pCR) and long-term survival rates, and significantly increases treatment toxicity[13-16]. Therefore, the idea of trying to improve the efficacy by adding up the cytotoxic drugs does not work.

In recent years, the tumor immunotherapy represented by PD-1 / PD-L1 antibody has achieved remarkable results, and has become an important means to break through the current ceiling of tumor treatment. However, tumors with high immunogenicity can benefit from anti-PD-1 / PD-L1 treatment[17-18]. In the case of colorectal cancer, colorectal cancer with high microsatellite degree instability (MSI-H) can benefit from anti-PD-1 / PD-L1 therapy[19]. This population accounts for 10 – 15% of all colorectal cancers, while only 5% of patients with advanced disease are MSI-H. Therefore, how to improve the immunogenicity of the tumor and transform the "cold tumor" into the "hot tumor" is the key to the success of the tumor immunotherapy. Radiotherapy is able to activate the core elements of the immune system associated with immunotherapy resistance. Upregulation of tumor-associated antigens in tumor cells expressing no or low MHC class I molecules; and radiotherapy can also enhance immune responses in causing immunogenic cell death, activating dendritic cells, and reducing regulatory T cells in tumors. Therefore, radiotherapy is possible to be a completely non-immunogenic tumor or low immunogenic tumor into immunogenic tumor, thus lay the

foundation for the combination of radiotherapy and immunotherapy, continue to improve local tumor control, and tumor control of the body (distal effect), induce the memory effect of specific anti-tumor immunity. Meanwhile, the resistance to PD-1 inhibition can be overcome when PD-1 / PD-L1 is up-regulated by radiotherapy. Extensive data show that local radiotherapy stimulates the systemic immune response. Specifically, radiation to tumors results in tumor-associated antigens and damage-related molecular patterns (DAMPs) that can produce an immune response, a process called in situ vaccination. Radiotherapy has also been found to improve the expression and diversity of tumor-associated antigens, with their draining lymph nodes leading to immune responses, potentially increasing tumor recognition and antitumor activity.

In June 2019, the American Annual Oncology Conference (ASCO) reported a phase II clinical study of PD-1 antibody combined with CTLA-4 antibody and radiotherapy for locally advanced rectal cancer[20], The results showed that although all patients failed with at least two lines of chemotherapy, 17.5% of patients had disease control, 7.5% had tumor reduction, and the regimen was safe without increased adverse effects associated with radiation (e. g., radiation proctitis). In 2020, a phase II clinical study from Japan (VOLTAGE)[21], Administration of sequential PD-1 antibody therapy after neoadjuvant chemoradiotherapy for locally advanced rectal cancer showed a pCR rate of 30% in the MSS cohort. In 2021, a phase II / III clinical study from the United States (NRG-GI002)[22], After neoadjuvant induction chemotherapy, the pCR rate was 31.9% in the pablizumab group, whereas the pCR rate was only 9.4% in the control group without immunotherapy. In the same year, Professor Zhang Tao from the Cancer Center of Union Hospital affiliated to Tongji Medical College of Huazhong University of Science and Technology reported a phase II study on delayed surgical treatment of locally advanced rectal cancer after short-course radiotherapy combined with CAPOX and Carrelizumab[23], The results showed that in 27 subjects undergoing surgery, the postoperative pathological complete response (pCR) rate was 48%, with 26 subjects having pMMR type with a pCR rate of 46%, one dMMR type and a pCR rate of 100%. In 2022, the preliminary results of "multi-center and phase clinical study of tireliizumab combined with concurrent chemotherapy and neoadjuvant treatment of locally advanced medium and low rectal cancer" conducted by Professor Zhang Zhongtao and Professor Yao Hongwei of Beijing Friendship Hospital, Capital Medical University also demonstrated the efficacy of immune combined chemoradiotherapy, Evaluation of data from 20 subjects enrolled from June 2021 to February 2022 showed, Twelve MSS subjects completed neoadjuvant therapy and underwent TME surgery, Both the sphincter-sparing resection and

R0 resection rates were 100%, Of which the pCR rate reached 58.3%, The ORR reached 100%, In this subset of patients with Non-pCR, According to the AJCC criteria, Three patients achieved tumor withdrawal grade 1, Two patients reached tumor withdrawal grade 2. In terms of safety, 3 (16.7%) of immune-related adverse events and 1 (8.3%) had anastomotic fistula (Grade Clavien-Dindo II) with no treatment-related death. Based on the above data, although the number of reported cases is limited, it has shown the superior prospect of immunochemotherapy combined with radiochemotherapy in patients with locally advanced rectal cancer.

Envafolimab (Envafolimab, R & D code: KN 035) is the world's first recombinant humanized PD-L1 nanoantibody entered into clinical development. It is independently developed by Corning Jerry and commercialized by Xindi Pharmaceutical, Corning Jerry and Pioneer Pharmaceutical. Compared with the PD- (L) 1 antibody already marketed and under development, it has obvious advantages: first, the molecular weight of envafolimab is about 80 kDa, which is only half that of conventional antibodies. It can quickly and uniformly spread to the whole body, and is suitable for a variety of administration routes; second, envafolimab has good tissue penetration and can evenly penetrate well in tumor tissue compared with ordinary mab; third, nanoantibody VHH replaces hydrophobic residues in FR 2 by hydrophilic residues, so the nanoantibody is more water soluble than ordinary mab, and can still maintain activity under extreme conditions such as high pressure or acid. Preclinical studies showed that the high protein concentration of envafolimab could effectively induce cytokine secretion in T cells. At similar doses, the anti-tumor activity of envafolimab was stronger than that of Durvalumab. The affinity of Envafolimab and durvalumab and PD-L1-muFc was studied and compared by ELISA analysis, and the results showed that the relative binding activity of PD-L1 and envafolimab was 1.45 times that of durvalumab. And in its clinical research, nworizab is administered by subcutaneous injection, is currently listed PD-(L) 1 antibody only a subcutaneous injection preparation, convenient, comfort is relatively high, can meet the treatment needs of patients with intravenous infusion, also can improve drug compliance, improve the quality of life, to achieve the tumor as chronic long-term management goal has important value.

Envafolimab Phase I studies (US001, CN001, and JP001) explored the maximum tolerated dose (MTD), Phase II recommended dose (RP2D), safety profile, PK, pharmacodynamics (PD), and antitumor activity of envafolimab monotherapy in subjects with advanced solid tumors.In the phase II clinical study of envafolimab (CN006), 103 subjects were enrolled in 65 CRC patients, the confirmed ORR in advanced CRC was 43.1%;

median DOR was not achieved, late CRC 12-month DOR rate was 88.4%; median PFS was 7.2 months; median OS was not achieved and the 12-month OS rate 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 drug-related adverse events (TEAEs), no study drug related grade 5 TEAEs; 3% of subjects had permanent treatment discontinuation due to drug-related TEAEs; so the incidence of grade immune-related adverse events was 43%, grade 3 to 48%, no grade 5 immune-related adverse events. The overall safety summary data for envafolimab were obtained from four clinical trials involving 453 patients who had received at least one envafolimab monotherapy, including US001 28, CN001 287, JPO01 35, and CN006 103. A total of 36 subjects with different tumors were included, including 112 cases (24.7%) of colorectal cancer. In the above studies, In the 453 patients who had received at least one administration of envafolimab, One patient received 0.01mg / kg QW, one received 0.03 mg / kg QW, 3 received 0.1mg / kg Q W, 5 received 0.3 mg / kg QW, 9 received 1.0mg / kg Q W, 7 received 2.5 mg / kg Q2W, 254 received 2.5 mg / kg Q W, 1 03 received 150mg Q W, 9 received 5.0 mg / kg Q2W, 36 received 5.0 mg / kg Q W, and 6 received 10. 0mg/kg Q W, 19 patients received 300mg Q4W. In the all subject (n=453) population, the median treatment time was 12.00 weeks (range: 1.0-120.0 weeks), and the proportion of subjects with treatment time> 6,9 and 12 months was 28.9%, 23.0% and 18.8%, respectively. The incidence of 453 patients with all grades receiving at least one envafolimab was 90.5%, with> 10% of adverse events, including elevated aspartate aminotransferase, alanine aminotransferase, anemia, increased blood bilirubin, rash, hypothyroidism, body weight reduction, decreased white blood cell count, and fatigue. The incidence of grade 3 and above was 34.4%, and the incidence of grade 3 and above was 1% of the incidence from high to low, in order, including: aspartate aminotransferase, blood bilirubin, anemia, alanine aminotransferase, γ -glutamate transferase, hyponatremia, decreased lymphocyte count, lung infection, hypokalemia and diarrhea. It can be seen that envafolimab has good tolerability and safety.

Furthermore, the 2023 ASCO-GI 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.

We explored the usage of PD-1 / PD-L1 antibody in colorectal cancer and other solid tumors, referring to the regimen of PD-1 / PD-L1 antibody combined with radiotherapy in other solid tumors, and added envafolimab to radiotherapy in locally advanced rectal cancer, in order to further improve the pCR rate and long-term survival of patients.

Therefore, we plan to conduct a phase II clinical study to explore the efficacy and safety of envafolimab and chemotherapy neoadjuvant chemotherapy in the treatment of locally advanced rectal cancer in pMMR / MSS.

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## 2. research contents

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.

### 2.1 fundamental purpose

- Pathological complete response rate (pCR)

### 2.2 Secondary purpose

- Objective response rate (ORR);
- Clinical complete response rate (cCR);
- Tumor downstaging rate (mrTRG);
- Downstaging rate of tumor pathology;
- Grade of tumor regression (TRG);
- R0 resection rate;
- Anal rate;
- The rate of surgical complications;
- 2-year disease-free survival rate (2-year DFS);
- 2-year overall survival rate (2-year OS);
- Quality of life (including anal sphincter function, bladder function and sexual function);
- Incidence of adverse reactions and serious adverse reactions.

The safety and tolerability of the study protocol will be evaluated according to the incidence and severity of adverse events and graded according to the NCI CTC AE 5.0 standard.

## 3. The research plan

This topic is a single-arm, single-center, prospective phase II clinical study.

## 3.1 Whole-course neoadjuvant therapy regimen:

### 3.1.1 Induction treatment phase (chemotherapy plus immunotherapy for 2 cycles)

1 Envafolimab: 200mg, subcutaneous injection, Q2W, 2 cycles (concurrent administration on the first day of chemotherapy).

2 mFOLFOX6: Q2W, 2 cycles: oxaliplatin 85mg / m2 intravenous infusion for 2h, 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).

### 3.1.2 Synchronous chemoradiotherapy phase (3 cycles of long-range chemoradiotherapy combined with immunotherapy)

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

Body position fixation: using prone position, bladder filling, body fixation frame or vacuum bag fixation;

CT scan: before scanning, intravenous injection of contrast agent to develop the intestine, fill the bladder, empty the intestine, collect two sets of CT images of plain scan and enhanced phase (people with contrast allergy can only collect plain scan images);

Radiotherapy equipment: linear accelerator;

Target area and irradiation field: The target area includes rectal primary and lymphatic drainage area. The treatment plan is IMRT radiotherapy design, and the target coverage and normal tissue limit are determined by the radiotherapy doctor according to the specific situation of the patient.

2 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.

3 Envafolimab: 200mg, subcutaneous, Q2W, 3 cycles (administered on radiotherapy days 1,15,29).

### 3.1.3 Consolidation treatment phase (2 cycles of chemotherapy plus immunotherapy)

1 Envafolimab: 200mg, subcutaneous injection, Q2W, 2 cycles, administered simultaneously on the first day of chemotherapy.

2 mFOLFOX6: Q2W, 2 cycles: oxaliplatin 85mg / m2 intravenous infusion for 2h, 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).

## 3.2 Surgical treatment protocol

Time to surgery: 6 weeks after completion of last neoadjuvant radiotherapy / 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.

## 3.3 Postoperative adjuvant treatment regimen

The 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.

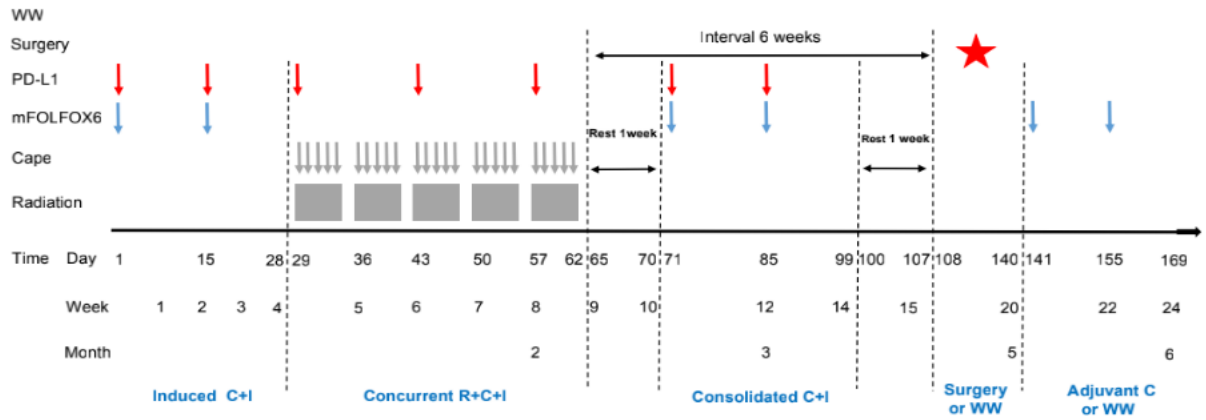
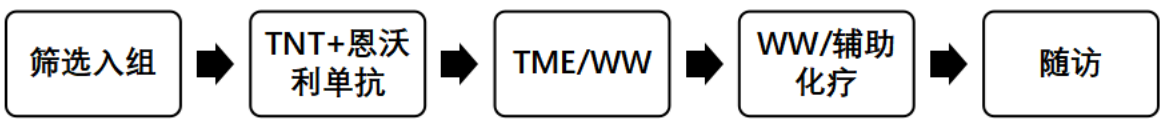



Figure. Study flow chart of TNT with PD-L1 in MSS LARC

The flow of the study is shown below:



## 3.4 The Watch Wait policy

A "watchful wait" strategy (non-radical surgery) for patients whose tumor withdrawal achieved clinical complete remission (cCR) (watch-and-wait policy). Specific strategies include: digital rectal examination, tumor markers every 1 to 2 months for 2 years, thoracic, abdominal and pelvic CT, pelvic MRI, endorectal ultrasound, colonoscopy and biopsy, and even PET-CT every 3 months.

## 3.5 therapeutic review

1 Effectiveness: objective efficacy evaluation according to RECIST1.1 standard evaluation, divided into CR, PR, SD and PD (see 4.7 for details);

After the end of induction therapy (available), after the completion of concurrent chemoradiotherapy (available), after the end of consolidation therapy / before surgery (required) can be evaluated after neoadjuvant treatment, according to the following conditions:

1) The patient evaluation is CR: if anal preservation surgery is feasible, direct surgical resection; if anal preservation is impossible, after full communication and informed consent, wait for observation (wait and watch);
2) Patients were evaluated as PR or SD, with direct surgical resection;
3) The patient was evaluated as PD, but there was still possible R0 resection in preoperative evaluation, and surgical resection was performed;
4) If the patient is evaluated as PD and cannot be removed by R0, the replacement treatment plan should be discussed according to MDT;
5) If distant metastases during neoadjuvant therapy are treated in accordance with the guidelines for diagnosis and treatment of metastatic colorectal cancer.

* After completion of neoadjuvant therapy, patients must receive efficacy evaluation of the same means in the same center.

2 Surgical resection rate: R0, R1, R2 (R0 no residual tumor; R1 microscopic tumor residue; R2 gross tumor residue);

3 Safety: Observation and graded according to NCI CTC AE 5.0 toxicity criteria. Tumor markers, blood routine, blood biochemistry, and liver and kidney function were checked every 2 weeks. In the course of treatment, the occurrence of adverse reactions should be closely monitored, including edema, gastrointestinal reaction, leukopenia, anemia, hand and foot syndrome, rash, muscle spasm, diarrhea, etc., and the time,

degree, treatment methods and treatment results of adverse reactions should be recorded.

## 3.6 Dose adjustment and adverse reaction treatment

Hematological toxicity dose adjustment

All dose changes should be documented and treated with the most adequate supportive therapy. If the symptoms resolve immediately after supportive care and continued study treatment is considered appropriate and the investigator believes the treatment is beneficial to the patient, consider continuing the same dose of study treatment plus appropriate continued supportive care. If the reduction is medically required, the reduction of chemotherapy is allowed. Adjust this cycle dose according to the lowest blood count after last dose (refer to the table below):

| low | | The next cycle dose |
|---|---|---|
| Neutrophil number (109 / L) | Platelet count (109 / L) | |
| ≥0.5 | And oneself 50 | invariant |
| ＜0.5 | Or <50 | The subsequent dose of chemotherapy will be reduced by 20% at the discretion of the investigator |

After two reductions, another 4 degrees of neutropenia or III degree grain deficiency with fever (> 38.5℃) or above 3 degrees occurred, without the third reduction, the investigator will discuss whether to continue the trial according to the specific situation.

Non-hematologic toxicity including diarrhea, dermatitis, myxitis mucositis and peripheral neuritis

For non-haematological toxicity (except vomiting and alopecia), the subsequent dose of chemotherapy should be reduced by 20% at the discretion of the investigator;

Periperipheral nerve toxicity above 3 degrees was reduced by 20% at the discretion of the investigator. If the peripheral nerve toxicity does not decrease or continues to worsen, the investigator will discuss whether to continue using oxaliplatin in adjuvant chemotherapy according to the specific situation.

hepatotoxicity

- Bilirubin: If the bilirubin levels are abnormal in the study, the next cycle should be delayed. If 4 weeks, the trial;
- Liver enzymes: AST and / or ALT and / or alkaline phosphatase levels abnormal in the absence of disease progression, liver protection treatment, within 2 weeks, not returning to normal, dose can be adjusted according to the table below.

If the liver function recovers in the next cycle, the dose should be increased to the previous level.

| AST/ALT price | Alkaline phosphatase values | dose titration |
|---|---|---|
| ＜1.5×ULN | ＜5×ULN | No dose adjustment is required |
| > 1.5 ULN to <2.5 ULN | ＜2.5×ULN | No dose adjustment is required |
| 2.5 ULN to <5 ULN | ＜2.5×ULN | Subsequent dose reduction of chemotherapy was 20-25% as determined by the investigator |
| > 1.5 ULN to <5 ULN | ＞2.5×ULN＜5×ULN | |
| > 5 ULN and / or> 5 ULN | | Delay by up to two weeks, if still not Recovery, at the discretion of the investigator, Ill Whether the person withdrew from the study. |

Immune-related adverse effects

Based on the mechanism of action, patients receiving its treatment may develop immune-related adverse reactions, including severe and fatal cases. Most immune-related adverse effects are reversible and can be managed by suspension or cessation of the treatment and administering corticosteroid therapy and / or supportive therapy. Depending on individual patient safety and tolerability, dose suspension or permanent discontinuation may be required. Increase or dose reduction is not recommended. See the table below for recommended envafolimab.

As recommended for envafolimab

| Immune-related adverse effects | order of severity ‡ | Treatment adjustment protocol |
|---|---|---|
| pneumonia | Level 2 | Sucontinue until adverse effects return to grade 0-1 |

| | | |
|---|---|---|
| | Grade 3 or 4 or recurrent grade 2 | Permanent withdrawal of drugs |
| Diarrhea and colitis | Level 2 or 3 | Sucontinue until adverse effects return to grade 0-1 |
| | Level 4 | Permanent withdrawal of drugs |
| hepatitis | Grade 2, aspartate aminotransferase (AST) or alanine aminotransferase (ALT)> 3 to 5 times the upper limit of normal (ULN); and / or total bilirubin (TBIL)> 1.5 to 3 times ULN | Suuse until adverse effects return to grade 0-1 and prednisone 10mg / day or equivalent dose |
| | Grade 3, AST or ALT> 5 x ULN, and / or TBIL> 3 x ULN | Permanent withdrawal of drugs |
| Nephritis and renal dysfunction | Grade 2, creatinine> 2-3 times ULN | Sucontinue until adverse effects return to grade 0-1 |
| | Grade 3, creatinine> 3 times ULN or> 4.0 mg/dL, with indication for hospitalization; life-threatening, indication for dialysis treatment | Permanent withdrawal of drugs |
| endocrine disease | Grade 2 hyperthyroidism | Suspension until symptom improvement or adverse response remission to grade 0-1 |
| | Grade 2 hypothyroidism | Continue the medication, by standard therapy, by hormone replacement therapy[a]Control |
| | Grade 2 hyperglycaemia or type 1 diabetes mellitus | Suuse until adverse reactions return to grade 0-1. Start insulin replacement therapy as clinically indicated, and use hypoglycemic drugs for hyperglycemia |
| | Grade 2 pituitary inflammation | Suused until the subject is clinically stable |

| | | |
|---|---|---|
| | Grade 3 or 4 hypophysitis | Suspend until hormone replacement therapy[a]To when the subject was clinically stable |
| | Grade 2 adrenal insufficiency | Suused until the subject is clinically stable |
| Skin adverse effects | Grade 3, or suspected Stevens-Johnson syndrome (Stevens Johnson syndrome, SJS) or toxic epidermal necrolysis (Toxic Epidermal Necrolysis, TEN) | Sucontinue until adverse effects return to grade 0-1 |
| | Level 4, or to confirm the SJS or TEN | Permanent withdrawal of drugs |
| carditis | Level 1 | Suspension of dosing |
| | Adventitia level 2 | Permanent withdrawal of drugs |
| thrombocytopenia | Level 3 | Sucontinue until adverse effects return to grade 0-1 |
| | Level 4 | Permanent withdrawal of drugs |
| Other immune-related adverse effects | Grade 1 encephalitis<br>Grade 2 or 3 pancreatitis<br>Grade 2 myasthenia gravis<br>Grade 3 or 4 with elevated blood amylase or elevated lipase<br>Other immune-related adverse reactions that first occurred in grade 2 or 3 include dermatitis, etc | The administration should be suspended until the adverse reaction returns to grade 0-1, and the encephalitis should decide whether to continue the medication based on clinical judgment |
| | Adventitia grade 2 encephalitis<br>Grade 4 pancreatitis<br>Grade 3 or 4 myasthenia gravis | Permanent withdrawal of drugs |

| | | |
|---|---|---|
| | Guillain Barre Syndrome (Guillain-Barresyndrome, GBS)<br>Other immune-related adverse reactions first occurring in grade 4 include dermatitis | |
| Recurrent or persistent adverse effects | Recurrent Grade 3 or Grade 4 (except for endocrine disorders)<br>Within 12 weeks after the last dose: Grade 2 or 3 adverse effects did not improve to Grade 0-1 (except endocrine disease) or the corticosteroid dose was not reduced to prednisone 10mg daily, or equivalent dose | Permanent withdrawal of drugs |
| Injection site reaction | Level 2 | cont.rem |
| | Level 3-4 | Permanent withdrawal of drugs |
| hypersensitivity | Level 2 | Stop the drug administration immediately. Depending on the observed intensity of response, antihistamines should be given in advance in the next cycle of treatment and the subcutaneous injection is slowed. |
| | Level 3-4 | Immediately continue immediately with subsequent permanent withdrawal |

Toxicity grading was determined using the National Cancer Institute Common Terminology Assessment Criteria for Adverse Events version 4.03 (NCICTCAE v4.03).

[a]For advice on hormone replacement therapy, see the envafolimab insert [Notes].

Adverse reactions related to radiotherapy

Gastrointestinal reaction: nausea, vomiting and other gastrointestinal to reaction after radiotherapy, can be antivomiting, promote gastrointestinal peristalsis drug treatment;

Bone marrow suppression: if white blood cells, red blood cells and platelets decrease after radiotherapy, the recombinant human granulocyte colony stimulating factor, recombinant human thrombopoietin, blood transfusion and other treatments can be given accordingly;

Radioactive dermatitis: after radiotherapy, the perianal skin appears itching, erythema, ulcer and other symptoms, and the skin protective agent can be applied;

Radioactive proctitis: after radiotherapy, abdominal pain and diarrhea, emergency, hematochezia and other symptoms, can be spasmodic, diarrhea, antidiarrhea, sitting basin, dexamethasone enema treatment;

Tumor hemorrhage: tumor rupture after radiotherapy, causing massive bleeding of blood vessels, endoscopic hemostasis or interventional embolization should be performed in emergency department, and radiotherapy should be terminated.

Treatment of the adverse reactions

The treatment of other adverse reactions can refer to the drug instructions or the routine treatment principles of the test center.

## 3.7 fl.up

1) Before treatment

All patients participating in this trial should sign an informed consent form and receive a copy of the informed consent form. If the patient agrees to participate in the trial, the participation form should be completed and signed immediately, and thereafter the patient can be enrolled. Within 28 days prior to initiation of treatment, the investigator should evaluate the following clinical and laboratory indicators.

1 Past history, including: age, sex, tumor location, disease stage, histological stage, history of perforation or obstruction, duration of surgery, and the procedure

2 Physical strength status score (see Appendix)

3 Clinical examination, height (pre-treatment measurement only), body weight

4 electrocardiogram

5 Collection of clinical laboratory data:

Routine blood indicators: hemoglobin, white blood cells, platelets and neutrophils;

Blood biochemical indexes: creatinine, alkaline phosphatase, total bilirubin, SGOT, SGPT;

Coagulation function: prothrombin time (PT), activated partial thromboplastin time (APTT) and international standardized ratio (INR);

Thyroid function: thyroid-stimulating hormone (TSH), free T3, free T4;

Urine routine: including urine specific gravity, pH value, white blood cells, red blood cells, protein, glucose, ketone body, and tube type. Two consecutive routine urine testing of urine protein + +, it is recommended to test 24 hours of urine protein quantification as soon as possible (such as within 72 hours);

Subactive blood examination;

HIV check;

HBV infection: including hepatitis B five and HBV DNA;

HCV-infected persons: including HCV RNA.

6 Detection of tumor markers: CEA

7 Enteroscopy and pathological diagnosis

8 Enhanced CT scans of the chest, abdominal, and pelvic areas

9 Abdominal B ultrasound

10 pelvic cavity MRI

11 Ctoluminal ultrasound

12 Genetic testing: MSI status (or MMR status assessed by immunohistochemistry), POLE / POLD 1, PTEN mutation status, TMB status, RAS and BRAF gene mutation testing

13 Peripheral tumor blood: CD3 +, CD4 +, and CD8 + T cell

14 Concomitant medication: collect medication within the 3 months before treatment

15 Quality of life assessment

Note: The relevant examinations involved in this institute were conducted by the Department of Clinical Laboratory of Yunnan Cancer Hospital, Department of Pathology, Department of Cardiac function, Gastroenteroscopy room, molecular Diagnosis Center and Yunnan Cancer Institute;

2) During the treatment process

During the treatment process, the investigator may increase the follow-up content or increase the frequency of follow-up as needed. The treatment-phase follow-up program needs to be completed before each cycle of treatment.

The follow-up content of the trial plan is as follows:

1 Body weight: during induction treatment, synchronous treatment, consolidation treatment, before and after surgery

2 Physical examination: performed during induction treatment, during synchronous treatment, during consolidation treatment, and before and after surgery

3 ECOG PS Score: during induction treatment, during synchronous treatment, during consolidation treatment, and before and after surgery

4 12-lead ECG: performed during induction treatment, during synchronous treatment, during consolidation treatment, and before and after surgery

5 Blood routine: during induction treatment, synchronous treatment, consolidation treatment, before and after surgery

6 Blood biochemistry: during induction treatment, during synchronous treatment, during consolidation treatment, before and after surgery

7 Detection of tumor markers: during induction treatment, during synchronous treatment, during consolidation treatment, and before and after surgery

8 Thyroid function: after the end of induction therapy / before synchronous chemoradiotherapy, after completion / before consolidation therapy and before surgery

9 Peripheral blood test: after induction treatment / before synchronous chemoradiotherapy, after synchronous chemoradiotherapy / before consolidation treatment, before and after surgery

10 Enhanced CT scans of chest, abdominal and pelvic areas: after completion of induction therapy / before concurrent chemoradiotherapy, after completion of concurrent chemoradiotherapy / before consolidation therapy, and before and after surgery

11 Pelvic MRI: after completion of induction therapy / before concurrent chemoradiotherapy, after completion of concurrent chemoradiotherapy / before consolidation therapy

12 Adverse events: Adverse events after initiation of treatment.

13 Concomitant medication: Continuous collection.

14 Quality of life assessment: collected per cycle

3) After the completion of the treatment

After completion of treatment, patients should be reviewed at the items and time in the table below; until tumor recurrence or at least 2 years. Review beyond the time of the following table can be conducted according to the habits of different centers, with PET / CT if necessary.

| project | After the first_moon | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1 / | 3 / | 6 / | 9 / | 12 / | 15 / | 18 / | 21 / | 24 / |
| symptom | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| check-up | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| routine blood test | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| Blood biochemical | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| CEA | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| Peripheral blood detection | √ | | | | | | | | |
| Chest / abdominal / pelvic CT | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| colonoscope * | | | | | √ | | | | √ |
| Assessment of QoL | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| Observe the efficacy | √ | √ | √ | √ | √ | √ | √ | √ | √ |

* If the lesion is found by colonoscopy, the colonoscopy period can be shortened according to the specific situation.

4) Safety follow-up

Safety follow-up was performed 28 days after the last dose and the trial planned follow-up is as follows:

1 weight
2 check-up
3 ECOG PS Score
4 And a 12-lead ECG
5 routine blood test
6 Blood biochemical
7 routine urine test
8 coagulation function
9 thyroid function
10 Enhanced thoracic, abdominal, and pelvic CT scans: Patients who are discontinued due to disease progression do not need further follow-up enhancement

11 Adverse events: Continuous follow-up until adverse event recovery or further observation is not required by the investigator.

12 Concomitant medication: Continuous collection until treatment for the adverse event is completed or the investigator.

13 Quality of life assessment

5) Survival follow-up

After disease progression, patient survival status was collected every 3 months allowing telephone follow-up.

5) Patient compliance observation

The investigator's responsibility to ensure patient compliance with the trial will be examined by itinerant representatives.

## 3.8 data collection

All data shall be timely, truthfully and detailed in the medical record register (Case Report Form, CRF) or CRF software. The medical record form should be filled in by special personnel and signed by the project leader. The medical records (CRFs) shall be checked and collected regularly, and recorded according to the time node required by the clinical trial management center of the hospital.

After the clinical trial, the unit shall write the clinical summary report according to the standard requirements.

## 3.9 Clinical safety assessment

1) Adverse events

Definition of the adverse events

Adverse event (or adverse experience, AE): any adverse medical event occurring in a subject or clinical subject, not necessarily causally related to treatment.

The AE can therefore be any bad or non-intended signs (e. g., including abnormal laboratory results), symptoms, or transient drug-related disease, which should be considered for medication involvement.

Adverse events occurring both before and after treatment were considered as adverse events according on management needs. Therefore, safety monitoring (reporting adverse events or serious adverse events) should be performed from subject enrollment to the end of

the study. Therefore, adverse events occurring during signing the informed consent and initiation of study treatment were also considered as AEs.

Adverse drug reactions (ADRs): All toxicities and non-intended reactions to the drug related to any dose should be considered as adverse drug reactions (ADRs).

Response to the drug means that there is at least a reasonable possibility of a causal relationship between the drug and the AE, meaning that this relationship cannot be excluded.

Serious Adverse Event (SAE): means all adverse medical events occurring at any drug dose:

- Lead to death
- life-threatening

Note: "serious" and "life threatening" are defined as an adverse event when the subject has the adverse event; rather than an adverse event that the more serious may lead to death.

- Patients require hospitalization or extension of existing hospitalization
- Leading in persistent or significant incapacity / disability
- Congenital malformations or birth defects

Important medical events: important medical events, do medical and scientific appraisal to decide whether to report is appropriate, these important medical events may not immediately life threat or cause death or hospitalization, but may harm subjects or may need interference to prevent the occurrence of the other results, usually should also be considered serious. For example, some adverse events require severe treatment in the emergency room, or management of allergic bronchial asthma at home; malignant fluid or convulsions without hospitalization; drug dependence and abuse, or malignant tumors histologically different from the primary tumor.

Other events that should be addressed as SAEs: Drug exposure during pregnancy / lactation: In principle, pregnancy and lactation are under the exclusion criteria. If a pregnancy occurs during the study, the patient should immediately withdraw from the study and inform the investigator immediately and follow up the patient throughout the pregnancy and postpartum. Even if the mother and child are completely normal without any adverse events, the consequences should be recorded. Even if the pregnancy is not a SAE, use the SAE report form.

Events that should be handled as SAEs: disease progression.

2) Record and evaluation methods of adverse events

All AEs should be recorded in the appropriate part of the Medical Record Report Form (CRF). SAE report forms (including initiation or follow-up reports) should also be completed.

The following aspects of each event should be recorded in the CRF:

- AEs in medical terms, not as a subject;
- Date of occurrence (start date);
- Octime (start time);
- Recovery date (end date);
- Recovery time (end time).

The grading was assessed by the investigator as defined by NCI-CTC version 5.0.

- Level 1 = mild;
- Level 2 = moderate;
- Level 3 = Heavy;
- Grade 4 = life-threatening or disabling;
- Level 5 = death.

The investigator should assess the causal relationship between the adverse events and the study drug; the decisive factor assessed in the record is the temporal correlation between the AEs and the study drug. The causal relationship between the adverse event and the study drug or study protocol is judged as follows:

- Uncorrelation = no temporal relationship with the study drug (too early, too late or not medication), or a reasonable causal relationship between the AE and another drug, associated disease or environment;
- Impossible = a temporal relationship with study drug, but no reasonable causal relationship between AE and study drug;
- Probably = a reasonable causal relationship between AE and study drug. Lack of withdrawal information (withdrawal information) or unclear;
- It is likely that there is a reasonable causal relationship between AE and study drug. Discontinuation (withdrawal from the drug study) had an effect on the response. No redose to prove;
- Clear / definite = a reasonable causal relationship between AE and study drug. Discontinuation has an effect on response and can occur if readministered when clinically feasible.

Measures taken for this study treatment (none, discontinuation, dose reduction, delayed treatment, slowing of intravenous infusion) and other measures (no, concomitant medication,

need for hospitalization, or prolonged hospitalization, surgery, delayed chemotherapy, discontinuation of chemotherapy, chemotherapy reduction) were defined as follows:

- Recovery with sequelae
- Healing without sequelae
- Not healed, but no treatment is needed
- Not healed and need treatment
- die

Toxicity grade / severity was changed

- Serious: Yes or No;
- If the patient has the same AE several times, each must be recorded and re-evaluated.

3) Reporting procedures for serious adverse events

Any serious or medically significant clinical adverse event or laboratory abnormality occurring during the study obligates the investigator to report every serious adverse event to the ADR by telephone or email within 24 hours.

After the telephone report, the written information should be sent by fax. The report shall provide the information of the reporter and recipient including name, address, telephone and fax number, and indicate that the report is "preliminary" report or "follow-up" report. If necessary, the report form shall be accompanied by the relevant medical record report form.

The investigator shall guarantee to the public ethics committee or competent authority any additional information regarding the death of the subject.

All forms must be dated and signed by the responsible person, or signed by an authorized colleague of the responsible person.

4) Monitoring of the adverse events of the subjects

Any adverse events occurring during the study were monitored and followed up until the end of the study. In addition, the SAEs must be reported through the SAE table.

5) Laboratory index evaluation

All laboratories in the hospital for clinical evaluation should meet the basic principles of Good Laboratory Practice (GLP) and the requirements of their hospital.

6) Clinical safety assessment

Version NCI-CTCAE 5.0 will be used to evaluate the clinical safety of the treatment in the study. The occurrence of adverse events will be assessed at each clinical visit.

## 3.10 statistical analysis

statistical analysis technique

Using computer (SPSS or R) software package, count data adoption rate, mean and 95% credible interval for measurement data; t-test for measurement data when comparing two groups, chi-square test for count data, Kaplan-Meier and Log Rank methods for survival analysis, and Cox proportional risk model for prognosis analysis. The probability P-value was used at any stage, and the statistical significant difference bound was used at 0.05.

Safety analysis: The toxicity evaluation criteria were evaluated according to the NCI-CTC 5.0 criteria. Specific statistical methods are the same as above.

Type of analysis

Prior to database lock, the following three datasets were identified.

The primary efficacy analysis will be performed in all enrolled populations (the intent-to-treat population or the ITT population) and the per-protocol population (PP). Secondary efficacy analysis and exploratory analysis will be performed in the intention-to-treat population. Non-inferiority analysis will be performed in the per-protocol population.

1. Intention-to-treat population

The intention-to-treat population consists of all patients randomized to any of the two treatment arms. Analysis will be performed according to the treatment groups randomassigned by the patients.

2. Population conforming to the protocol

Patients who have not received any dose of chemotherapy or chemoradiotherapy, or those who have suffered a serious violation of the inclusion or exclusion criteria. Analysis will be performed according to the treatment groups randomassigned by the patients.

3. Safety population

The safety population includes all patients who have received at least one dose of chemotherapy or radiotherapy. The Safety population was used to analyze all safety parameters. Patients were assigned to the treatment group based on the medication they actually received.

4. The data that should be excluded during the analysis

There were no excluded data available.

Medium-term analysis

An interim analysis of the efficacy endpoints is not performed in this study. An independent data security monitoring team will monitor the safety data throughout the study. All safety data descriptive analysis will be performed after study treatment for all patients enrolled in this study. This analysis will be strictly limited to the safety data and will not include any efficacy endpoints.

# 4. research contents

## 4.1 Sample size of the study

Sample size estimation (by single group)

Statistical test efficacy was calculated with postoperative pathologic complete response rate (pCR) as the primary study endpoint.α 0.05, the test efficacy is 80%, the postoperative pathological complete response rate after conventional treatment is 15%, and the estimated postoperative pathological complete response rate in the test group is 35%. Considering the loss of 10% of cases, the calculated sample size of the access group is 35 cases.

## 4.2 subject investigated

The study subjects of this project were obtained from 35 patients with pMMR / MSS locally advanced rectal cancer initially diagnosed in Yunnan Cancer Hospital (the Third Affiliated Hospital of Kunming Medical University) from September 2022 to March 2024.

## 4.3 Enrollment criteria

**1) Disease characteristics**

- Histological confirmation of rectal adenocarcinoma;
- Immunohistochemistry confirmed pMMR or / and pCR or / and NGS 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.

## 4.4 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 conditions that may compromise patient safety and compliance;

## 4.5 Exit standard

- The subject withdrew his informed consent and requested his withdrawal;
- Poor compliance, not administered according to the study protocol;
- After enrollment from the study, the patient requests withdrawal from the investigator or fails to complete the study schedule for any reason;
- Other circumstances deemed necessary to conclude the study.

## 4.6 Termination of treatment

- Serious adverse events or serious adverse reactions (SAEs) during the study;
- Delay treatment for more than 4 weeks for any reason (meaning all drugs in the delayed regimen).

## 4.7 Evaluation of the study findings

1) Efficacy evaluation of chemoradiotherapy

- CR: Pelvic MR: complete regression of primary tumor or only fibrotic scar, MR no mesangial lymph node enlargement; ultrasound colonoscopy: complete regression of primary tumor or only erythematous tiny ulcer or scar, no cancer remaining on biopsy; digital rectal tumor disappeared and no stiffness or nodules of intestinal wall.
- PR: tumor volume reduced by more than 30%, no new lesions;
- PD: tumor volume increased more than 20%, or new lesions.
- SD: The tumor volume did not change significantly, the reduction degree did not reach PR, and the increase degree did not reach PD;

2) Evaluation of the degree of radical operation

- R0 microscopic pathology examination cut margin has no residual tumor cells;
- The R1 microscopic pathological examination of the resection margin showed residual tumor cells;
- Residual tumor cells were visible at the macroscopic lower margins of R2.

3) Tumor response assessment

It is recommended to evaluate postoperative pathological specimens according to the tumor pathological withdrawal grade (tumor regression grading, TRG) criteria (see Annex 2); if not, a complete pathological response must be reported.

4) Evaluation of local recurrence or metastasis

When clinical symptoms occur (anal pain, hematochezia, lower limb edema, etc.), progressive elevation of CEA, or suspicious signs in chest or abdominal imaging, further examination is needed to find local recurrence or disease metastasis progression. Regional recurrence mainly refers to tumor recurrence in the local area or near the adjacent organs; distant metastasis refers to tumor recurrence outside the above areas. Disease-free survival is the absence of tumor recurrence or the occurrence of new colorectal cancer by systematic evaluation.

Clinical diagnosis of recurrence and metastasis must meet at least one of the following:

1 Imaging suggested recurrence (ultrasound, CT, MRI, PET-CT)

2 Positive cytology biopsy (ascites, anastomotic recurrence, suspicious imaging findings)

The reported date of recurrence is the date when recurrence was detected using the diagnostic method described above. In case of recurrence, the investigator should specify the site of recurrence and the diagnostic method used. When definitive imaging evidence cannot be obtained, a positive result of cytology or biopsy should be obtained. Elevated CEA alone could not be used as evidence of local recurrence or metastasis of rectal cancer.

5) Calculation of the survival period

Local-regional recurrence-free survival was defined as the time interval from the onset of randomization to the appearance of a local recurrence event. Tumor evaluation (CT / MRI of the abdomen and pelvic cavity or ultrasound and chest CT) and CEA testing must be performed every 6 or 12 months after randomization, or when the patient shows signs of progression (i. e., clinically indicated).

Disease-free survival (DFS) is defined as the time interval from the start of randomization and the occurrence of the event in the next segment. Tumor evaluation (CT / MRI of the abdomen and pelvic cavity or ultrasound and chest CT) and CEA testing must be performed every 6 or 12 months after randomization, or when the patient shows signs of progression (i. e., clinically indicated). The suspected lesion detected by ultrasound must be confirmed by CT / MRI. All re-operations or further anticancer therapy should also be documented.

Based on the purpose of this study, events that identified patients were no longer in the disease-free condition were defined as follows:

- The patient showed signs of the original tumor recurrence;
- The patient showed signs of a new colorectal cancer,
- Death from any cause.

Note: recurrence of any original tumor or occurrence of new colorectal cancer should be determined by cytological or histological methods

Confirm. No supporting evidence of other specific test findings (such as radiography, histology / cytology) cannot be based on isolated events such as increased CEA or unexplained clinical deterioration of the disease. The date of relapse was defined as the date of final confirmation of the targeted findings. Patients will thereafter be followed up for survival as planned.

If a recurrence of a confirmed colorectal cancer or the occurrence of a new colorectal cancer occurs during the study treatment period, patients will be withdrawn from the study treatment for survival follow-up. If the recurrence of colorectal cancer or the occurrence of a new colorectal cancer occurs during the study treatment period, the patient may be treated further according to the guidance of the investigator.

All tested patients will be followed for at least 2 years. For a biopsy, a biopsy report should be provided. Overall survival was the time from randomization to death. When the patient survived, the time to the last follow-up was taken as the overall survival period.

6) Evaluation of the toxic and side effects of adjuvant therapy

Toxicity evaluation according to the CTC criteria (version 5.0)

Follow-up of patient safety should include during treatment and 30 days after the end of the last cycle. The reason for the delay or interruption should be recorded in the CRF table.

7) ECOG (Appendix)

## 4.8 Ethical and informed consent aspects

### 4.8.1 Ethical requirements

The investigator ensured that the study was conducted in accordance with the Declaration of Helsinki principles for maximum protection of the individual. This study was reviewed and approved by the ethics committee of Yunnan Provincial Cancer Hospital.

### 4.8.2 informed consent

The investigator or a person assigned by the investigator is responsible (as permitted by local regulations) to obtain written informed consent for the purpose, methods, prospective benefits, and potential hazards of the study. Subjects who fail or fail to sign a legal consent must sign an informed consent by their legal representative. If the subject and his legal representative will not read, a notary should be present during the informed consent discussion. After the subject and his representative verbally agree to participate in the trial,

the witness should sign the informed consent form to prove that the contents of the agreement are accurately interpreted and understood. The Investigator or designee should also state that the subject may refuse to participate in the study or withdraw from the study at any time for any reason. The CRF of this study includes the section documenting the subject's informed consent, which should be completed accurately. If new safety information leads to significant changes in the hazard / benefit evaluation, the informed consent should be re-reviewed or updated as needed. All subjects (including those who have started treatment) should be informed of the new information, given an updated informed consent form, and obtained their consent to continue the study.

#### 4.8.3 confidentiality

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 principal investigator of this project will publish the final research results in a journal after the end of the project for academic communication and promoting medical progress, but will not disclose any of your personal information.

If you decide to withdraw from the study, the study doctor will stop collecting data, but previously collected data and samples will be saved and used to ensure the validity of the study and managed in accordance with regulatory requirements.

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

## 5. Project implementation years and annual plan

| | |
|---|---|
| The total length of the project implementation | In 2 years.5 |
| General schedule: March 2023-September 2025 | |
| Phase time schedule | Main contents and results of the stage objectives |
| March 2023-June 2023<br>(3 Months) | Study enrollment stage: 15 patients were enrolled to evaluate safety and side effects of neoadjuvant therapy |
| June 2023-September 2023<br>(3 Months) | 35 patients were enrolled, and the follow-up stage was: evaluation of safety, feasibility, toxicity and side effects of neoadjuvant therapy, tumor withdrawal, incidence of surgical complications, RO resection rate, etc |
| September 2023-March 2024<br>(6 Months) | All cases were followed up for 6 months after the end of enrollment to evaluate the safety, toxicity and side effects of neoadjuvant therapy, local recurrence rate, distant metastasis rate, and incidence of surgical complications |
| March 2024-September 2024<br>(6 Months) | All cases were followed for 1 year after enrollment, and local recurrence and distant metastasis were analyzed |
| September 2024-September 2025<br>(12 Months) | All cases were followed up for 2 years after enrollment, and analyzed the local recurrence rate, distant metastasis rate, 2-year DFS and 2-year OS. Conclusion and report to evaluate the effect of envafolimab combined with chemoradiotherapy for the whole neoadjuvant treatment of pMMR / MSS rectal cancer. |

# 6. appendix

## 6.1 Attachment 1: Tumor pathological withdrawal grade (tumor regression grading, TRG) criteria

| classify | Pathological tumor withdrawal profile |
|---|---|
| 0 (Complete Response) | The tumor had completely subsided, and the cancer cells could not be found at all |
| 1 (almost complete remission) | Only single cancer cells or several cancer cell groups were visible |
| 2 (Partial Response) | The tumor shrank significantly but showed residual cancer cells, and the number was not limited to a single cancer cell or several cancer cell groups |
| 3 (poor or no remission) | No significant shrinkage of the tumors was observed, and a large number of residual cancer cells were visible |

## 6.2 Attachment 2: ECOG PS Scoring criteria

| classify | Behavioral state |
|---|---|
| 0 | Ability to perform all daily activities without restriction |
| 1 | Severe physical activity is limited, but he can walk and can perform light physical work. |
| 2 | Can walk, live can take care of themselves, but can not engage in any work, awake, more than half of the time can get out of bed and walk |
| 3 | Can only have limited self-care, more than half of the waking time to bed or chair. |
| 4 | Unable to move; unable to take care of themselves; bed or chair. |

## 6.3 Attachment 3: Efficacy Evaluation Criteria for Solid Tumor Version 1.1 (Response Evaluation Criteriain Solid Tumors RECIST Version1.1)

### 1 Measureability of tumors at baseline levels

#### 1.1 Definition

At baseline, tumor lesions / nodes will be measurable and not measurable as defined below:

#### 1.1.1 Measureable lesions

Tumor lesion: at least one diameter (which can be recorded as maximum) with the following minimum length:

- CT scan 10mm (CT scan layer thickness not greater than 5mm)
- Clinical routine examination instrument 10mm (tumor lesion cannot be accurately measured with diameter instrument should be recorded as unmeasurable)
- Chest X-ray at 20mm
- Malignant lymph nodes: Pathologically enlarged and measurable, short CT scan diameter 15mm (CT scan thickness recommended not more than 5mm). At baseline and follow-up, only short paths were measured and followed up.

#### 1.1.2 Non-measurable lesions

All other lesions, including small lesions (<10mm or 10mm to <15mm) and unmeasurable lesions. Unmeasured lesions include meningeal disease, ascites, pleural or pericardial effusion, inflammatory breast cancer, cancerous lymphangitis of the skin / lung, imaging of unconfirmed and follow-up abdominal mass, and cystic lesions.

#### 1.1.3 Special considerations regarding lesion measurement

Bone lesions, cystic lesions, and previously locally treated lesions should be specifically noted:

Bone lesions:

- Bone scan, PET scan or plain film are not suitable for measuring bone lesions, but can be used to confirm the presence or disappearance of bone lesions;
- If an osteolytic lesion or a mixed osteogenic lesion has a defined soft tissue component that meets the above measurable definition, these lesions can be considered as measurable lesions if they can be evaluated by tomographic imaging techniques such as CT or MRI;
- Osteogenic lesions are non-measurable lesions.

Cystic lesions:

- Lesions that meet the criteria of the definition of pure cyst by radioimaging should not be considered malignant because they are a simple cyst by definition, neither measurable lesions nor unmeasurable lesions;
- If it is a cystic metastatic lesion and meets the above measurable definition, it may be a measurable lesion. However, if non-cystic lesions exist in the same patient, non-cystic lesions should be preferred as the target lesion.

Topically treated lesions:

- Lesions located at sites previously irradiated or treated with other regional areas are generally considered as non-measurable lesions, unless the lesion has clearly progressed. The study protocol should describe in detail the conditions under which these lesions are measurable lesions.

**1.2 Description of the measurement method**

**1.2.1 Lesion measurement**

For clinical evaluation, all tumor measurements were recorded in the metric rice system. All baseline assessments of tumor lesion size should be completed as close as possible prior to treatment initiation and must be completed within 28 days (4 weeks) before treatment initiation.

**1.2.2 Evaluation method**

The same technique and methods should be used for the baseline assessment and subsequent measurements of the lesions. All lesions must be evaluated using imaging, except for those that cannot be evaluated by imaging but only by clinical examination.

Clinical lesions: Clinical lesions can only be considered as measurable lesions (such as skin nodules) when they are superficial and measured at 10mm in diameter. For patients with skin lesions, color photographs containing a scale to measure the size of the lesion, are recommended for archiving. When the lesions are evaluated using both imaging and clinical examination, imaging evaluation should be used as far as possible because the imaging is more objective and reproducible at the end of the study.

Chest X X: When tumor progression is an important study endpoint, chest CT should be preferred because CT is more sensitive than X-ray, especially for new lesions. Chest X-ray detection is applicable only if the measured lesions are well defined and the lungs are well ventilated.

CT, MRI: CT is currently the best available and reproducible method for efficacy evaluation. The definition of measurable ability is based on the 5mm thickness of the CT scan

layer. If the CT layer thickness is greater than 5mm, the minimum measurable lesion should be 2 times the layer thickness. MRI is also acceptable in some cases (e. g. whole body scan).

Ultrasound: Ultrasound should not be used as a measurement method to measure the lesion size. Because of its operation dependence, the ultrasound examination is not reproducible after the end of the measurement, which cannot guarantee the identity of the technology and measurement between different measurements. If new lesions are identified using ultrasound during testing, they should be confirmed using CT or MRI. If radiation exposure to CT is considered, MRI can be used instead.

Endoscopy, laparoscopy: These techniques are not recommended for objective tumor evaluation, but they can be used to confirm CR in biopsy specimens obtained or in trials of recurrence after the study endpoint of CR or surgical resection.

Tumor markers: Tumor markers cannot be used alone to evaluate objective tumor response. However, if the marker level exceeds the upper normal limit at baseline, it must return to normal when used to evaluate complete remission. Because tumor markers vary by disease, this factor needs to be taken into account when writing the measurement criteria into the protocol. Specific criteria for CA-125 remission (recurrent ovarian cancer) and PSA (recurrent prostate cancer) remission have been published. In addition, the International Gynecological Cancer Organization has formulated the CA-125 progression criteria, which will be added to the tumor objective evaluation criteria for the first-line treatment of ovarian cancer.

Cytology / histology techniques: in the specific circumstances specified in the protocol, these techniques can be used to identify PR and CR (such as residual benign tumor tissue often present in lesions of germ cell tumors). When exudation may be a potential side reaction of a therapy (e. g., treatment with taxane compounds or angiogenesis inhibitors), and a measurable tumor meets the criteria for remission or disease stabilization, tumor-related exudation occurrence or aggravation during treatment can be confirmed by cytology to distinguish between remission (or disease stabilization) and disease progression.

**2 It was used for tumor remission assessment**

**2.1 Evaluation of all tumors and measurable lesions**

To evaluate the objective response or possible future progression, a baseline assessment of the total tumor burden in all tumor lesions is necessary for the subsequent measurements. In a clinical regimen with objective remission as the primary treatment endpoint, only patients with measurable lesions at baseline will be enrolled. A measurable lesion was defined as the presence of at least one measurable lesion. For trials with disease progression (time to

progression or degree of fixed date progression) as the primary treatment endpoint, the protocol inclusion criteria must be limited to patients with measurable lesions or no measurable lesions can be included.

**2.2 Baseline recordings of target lesions and non-target lesions**

When there are more than one measurable lesions during the baseline assessment, all lesions should be recorded and measured, a total of not more than 5 (no more than 2 each organ), as the target lesions represent all involved organs (that is, patients with only one or two cumulative organs up to choose two or four target lesions as the baseline measurement lesions).

The target lesion must be selected based on size (longest diameter), representative of all organs involved, and the measurements must be well reproducible. Sometimes when the largest lesion cannot be repeatedly measured, the largest lesion can be reselected.

Lymph nodes need special attention because they are normal tissue and can be detected by imaging even in the absence of tumor metastasis. Pathological lymph nodes defined as measurable nodules or even target lesions must meet the following criteria: CT measurement of a short diameter of 15mm. Baseline only detects the short diameter. Radiologists usually use the short diameter of the nodule to determine whether the nodule has a metastatic tumor. The cle size is generally expressed by two-dimensional data from imaging detection (CT axial plane and MRI selects a plane from the axial, sagittal or coronal plane). The minimum value is the short diameter. For example, a 20mm 30mm abdominal nodule with a short diameter of 20mm can be regarded as a malignant, measurable nodule. In this example, 20mm is the measurement of the nodule. Nodules with 10mm diameter but <15mm should not be considered as target lesions. However, nodules <10mm do not belong to the category of pathological nodules and do not need to be recorded and further observed.

The sum of the total diameter calculated together (including the longest diameter of the non-nodular lesion and the short diameter of the nodular lesion) will be reported as the sum of the baseline diameters. If containing the lymph node diameter, as mentioned above, only the short diameter is included. The sum of the baseline diameters will serve as the reference value for the disease baseline level.

All remaining lesions including pathological lymph nodes may be considered non-target lesions, but should be recorded at baseline assessment. If recorded as "present", "missing" or in rare cases "clear progress". Widespread target lesions can be recorded with target organs (e. g., massive expanded pelvic lymph nodes or large liver metastases).

**2.3 Mitigation criteria**

**2.3.1 Evaluation of the target lesions**

Complete response (CR): All target lesions disappear, and the short diameter of all pathological lymph nodes (including target nodules and non-target nodules) must be reduced to <10mm.

Partial response (PR): The sum of target lesion diameter decreased by at least 30% from baseline.

Disease progression (PD): Using the minimum value of the sum of all measured target lesions throughout the experimental study, the diameter and relative increase is at least 20% (baseline value if the minimum); otherwise, the absolute increase of at least 5mm must be met (occurrence of one or more new lesions is also considered as disease progression).

Disease stability (SD): the degree of target lesion reduction does not reach the PR, the degree of increase does not reach the PD level, in between the two, the minimum value of the sum of the diameter can be used as a reference.

**2.3.2 Precautions for target lesion evaluation**

Lymph node: Even if the lymph nodes identified to be the target lesion decrease to less than 10mm, the actual short diameter value corresponding to the baseline should be recorded at each measurement (consistent with the anatomical plane at the baseline measurement). This means that if the lymph node belongs to the target lesion, even if the criteria for complete remission are achieved, it cannot be said that the lesion has all disappeared, because the short diameter of the normal lymph node is defined as <10mm. The target lymph short lesion needs to be recorded at a specific location in the CRF table or other recording methods: for CR, all lymph short diameters must be <10mm; for PR, SD, and PD, the actual measurements of the target lymph short diameter will be included in the sum of the target lesion diameter.

Small to unmeasurable target lesions: In clinical studies, all baseline recorded lesions (nodules or non-nodules) should be recorded again in the later evaluation, even if the lesions are very small (e. g. 2mm). But sometimes it may be too small to cause the CT scan to be blurred, and the radiologist is struggle to define the exact value, potentially it as "too small to measure."In this case, it is important to record a value on the CRF table. If the radiologist believes that the lesion may have disappeared, it should also be recorded as 0mm. If the lesion is indeed present but is vague and a precise measurement cannot be given, the default can be 5mm.(Note: lymph nodes are unlikely to do this because they normally have a measurable size or are often enclosed by adipose tissue as in the retroperitoneal cavity; but if this measurement cannot be given, the default is 5mm). The default value of 5mm stems from

the cut thickness of the CT scan (this value is not changed by the different cut thickness values of the CT scan). Since the same measurement is not repeated, providing this default will reduce the risk of misassessment. But it should be reiterated that if the radiologist can give the exact value of the lesion size, the actual value must be recorded even if the lesion is less than 5mm in diameter.

Isolated or combined lesion: When the non-nodular lesion divides into fragments, the longest diameter of the separated part together calculates the total diameter of the lesion. Similarly, for the binding lesions, they can be distinguished by the plane between the bound parts, and then the respective maximum diameter is calculated. However, if the combination is inseparable, the longest diameter should be taken as the longest of the fusion lesion.

**2.3.3 Assessment of non-target lesions**

This section defines the remission criteria for non-target lesion tumors. Although some non-target lesions are actually measurable, no measurement requires only qualitative assessment at the time points specified in the protocol.

Complete response (CR): All non-target lesions disappeared and tumor markers returned to normal levels. All lymph nodes were of non-pathological dimensions (short diameter <10mm).

Non-complete response / non-disease progression: presence of one or more non-target lesions and / or persistence of tumor markers at levels greater than normal.

Disease progression: a definite progression of preexisting non-target lesions. Note: The presence of one or more new lesions is also considered as disease progression.

**2.3.4 Special considerations for the progression assessment of non-target lesions**

The supplementary explanation of the definition of non-target lesion progression is as follows: When a patient has a measurable non-target focus, even if the target lesion is assessed as stable or partial remission, to make a clear definition of progression based on the non-target focus, the overall deterioration of the non-target lesion has reached the point that the treatment must be terminated. However, the general increase in the size of one or more non-target lesions is often not enough to meet the progression criteria. Therefore, the overall tumor progression is almost rare in the target lesion when the target lesion is stable or partially relieved.

This occurs when none of the non-target lesions are measurable: in some phase trials, when measurable lesions are not specified in the inclusion criteria. The overall assessment was based on the above criteria, but because there was no measurable data for the lesion in this case. The deterioration of the target lesions is not easy to assess (according to the

definition: must all non-target lesions are not measured), so when the target lesions change to increase the overall disease burden is the target of the disease progression, according to the definition of the target focus progress, need to establish an effective detection method to evaluate. As described, an increase in tumor burden is equivalent to an additional 73% increase in volume (equivalent to a 20% increase in measurable lesion diameter). Or peritoneal exudation from "trace" to "massive"; lymphangiopathy from "local" to "widespread spread"; or described in the protocol as "sufficient to change treatment". Examples include pleural exudate from trace to mass, spread of lymphatic involvement from the primary site to the distance, or may be described as "necessary therapeutic changes" in the protocol. If definite progression is found, the patient should be treated as disease progression at that time point. It is best to have objective criteria that can be applied to the assessment of unmeasurable lesions, noting that the increased criteria must be reliable.

**2.3.5 New lesions**

The appearance of new malignant lesions indicates the progression of the disease; therefore some evaluation of new lesions is very important. There are no specific criteria for imaging detection of lesions, however the discovery of a new lesion should be clear. For example, progression cannot be attributed to differences in imaging techniques, changes in imaging morphology, or other lesions other than tumors (for example, some so-called new bone lesions are merely the cure of the original lesion, or the recurrence of the original lesion). This is important when a patient's baseline lesion is partially or completely reactive, for example, a necrosis of a liver lesion may be identified as a new cystic lesion on the CT report, but not.

Lesions detected at follow-up but not detected at baseline will be considered as new and estive of disease progression. For example, if a patient with a visceral lesion on baseline examination has metastases on CT or MRI, his intracranial metastases will be considered as the basis for disease progression, even if he did not have a cranial examination at baseline examination.

If a new lesion is unclear, for as due to its small morphology, further treatment and follow-up evaluation are needed to confirm whether it is a new lesion. If repeated examinations confirms it is a new lesion, the time of disease progression should be counted from the time of its initial discovery.

FDG-PET assessment of lesions generally requires additional testing for complementary confirmation, and the combination of FDG-PET and supplementary CT test

results is reasonable to evaluate progression (especially for new suspected diseases). New lesions may be identified by FDG-PET according to the following procedures:

Baseline FDG-PET was negative and the following up FDG-PET was positive, indicating progression of the disease.

No baseline FDG-PET test was performed, and the subsequent FDG-PET test result was positive:

If the follow-up FDG-PET positive test results matched the CT test results, the disease progression was proved.

If the new lesion found by the positive test result of the follow-up FDG-PET is not confirmed by the CT test result, the CT test should be confirmed again (if confirmed, the time of disease progression starts from the previous FDG-PET abnormality).

If the follow-up FDG-PET results with a preexisting lesion by CT and the lesion does not progressive on imaging tests, no disease progression.

**2.4 Best of the overall efficacy evaluation**

The best overall efficacy evaluation is the best efficacy record from the beginning of the trial to the end of the trial, with any necessary conditions taken into consideration for confirmation. Sometimes the efficacy response occurs after the end of treatment, so the regimen should specify whether the efficacy evaluation after the end of treatment should be considered in the best overall efficacy evaluation. The protocol must clarify how any new treatment affects optimal efficacy response. The best response response depends on the outcome of the target and non-target lesions and the performance of the new lesions. In addition, it relies on the nature of the trial, protocol requirements, and outcome measures. Specifically, the efficacy response profile is the primary goal in non-randomized trials, and the confirmation of efficacy by PR or CR is mandatory to confirm which is the best overall efficacy response.

**2.4.1 Time-point reaction**

It is assumed that an efficacy response will occur at the specific time point of each regimen. Table 6 will provide a summary of the overall efficacy response of a patient population with disease measurable at baseline level at each time point.

If the patient has no measured lesions (no target lesion), the evaluation is presented in Table 7.

**2.4.2 Misof missing and unevaluassessment**

If lesion imaging or measurement cannot be performed at a particular point in time, the patient will not be evaluated at that time point. If only some of the lesions can be evaluated in

an evaluation, it is usually considered impossible to evaluate at that time point, unless there is evidence that the missing lesion does not affect the efficacy response evaluation at the specified time point. This situation is very likely to occur in the case of disease progression. For example, a patient with three lesions with a total of 50mm at baseline, but then only two lesions, with a total of 80mm, will be evaluated as disease progression, regardless of the impact of the missing lesion.

**2.4.3 Best total response: all time points**

Once all the patient data are available, the best total response can be determined.

Assessment of best total response when the study does not require confirmation of a complete or partial efficacy response: best efficacy response in the trial was best response at all time points (e. g., a patient was evaluated as SD in the first cycle, PR in the second cycle, PD in the last cycle, but the best total response as PR. When the best total response is evaluated as an SD, it must meet the minimum time from the baseline level specified in the protocol. If the standard of the shortest time is not met, even if the best overall response evaluation as SD is not approved, the best overall response of this patient will depend on the subsequent evaluation. For example, a patient was evaluated as SD in the first cycle and the second cycle as PD, but it did not meet the shortest time requirement of SD, and its best overall response was evaluated as PD. The same patient lost to follow-up after the first cycle evaluation of SD will be considered as nonevaluable.

Assessment of the best total response when the study requires confirmation of complete or partial response: a complete or partial response is confirmed only if each subject meets the partial or complete response criteria specified in the trial and is specifically mentioned in the protocol at subsequent time points (usually four weeks later). In this case, the best total response is as described in Table 7.

**2.4.4 Special tips for efficacy assessment**

When nodular lesions are included in the total target lesion assessment and the nodule size decreases to a "normal" size (<10mm), they will still have a lesion size scan report. To avoid excessive assessment based on the increased nodule size, the measurements will be recorded even if the nodule is normal. As already mentioned, this means that subjects with complete response will not be recorded as 0 on the CRF table.

During the trial. The analytical plan of the trial must state that these missing data / assessments can be explained when determining efficacy. For example, in most trials, the response of a subject PR-NE-PR can be confirmed as the efficacy.

It should be reported as symptomatic progression when the subject experienced an overall deterioration of his or her health, but with no objective evidence. Objective progression should be assessed even after treatment termination. Symptomatic deterioration is not an objective assessment of assessment: it is the reason for discontinuing treatment. The objective response of such subjects will be assessed by the target and non-target lesion conditions shown in Table 6 to 8.

Defined as early progression, early death and nonevaluable conditions are study exceptions and should be clearly described in each protocol (depending on the treatment interval and treatment cycle).

In some cases, it is difficult to identify local lesions from normal tissue. When evaluation of complete response is based on such a definition, we recommend biopsy before efficacy evaluation of local focal complete response. When some subjects with abnormal local lesion imaging findings are considered to represent lesion fibrosis or scar formation, FDG-PET is used as a similar assessment criterion to biopsy to confirm the efficacy of complete response. In such cases, the application of FDG-PET should be prospectively described in the protocol, while supported by reports of the specialist medical literature for this situation. However, it must be realized that the limitation of FDG-PET and biopsy itself (including their resolution and sensitivity) will lead to false positive results in complete remission evaluation.

**Table 6 Time point response: Subjects with target lesions (including or excluding non-target lesions)**

| Target focus | Non-target lesions | New lesions | Total relief |
|---|---|---|---|
| CR | CR | mistake | CR |
| CR | Non-CR / non-PD | mistake | PR |
| CR | Can't evaluate | mistake | PR |
| PR | Non-progressive or could not be fully assessed | mistake | PR |
| SD | Non-progressive or could not be fully assessed | mistake | SD |
| Not fully evaluated | Non-progression | mistake | NE |
| PD | Any situation | Yes or no | PD |

| | | | |
|---|---|---|---|
| Any situation | PD | Yes or no | PD |
| Any situation | Any situation | yes | PD |
| CR= complete remission | PR= partial remission | SD= disease | PD= PD<br>NE =, which could not be assessed |

**Table 7 Time point responses-Only subjects with non-target lesions**

| Non-target lesions | New lesions | Total relief |
|---|---|---|
| CR | mistake | CR |
| Non-CR or non-PD | mistake | Non-CR or non-PD |
| Not fully evaluated | mistake | Can't evaluate |
| Can not be clearly defined for the PD | Yes or no | PD |
| Any situation | yes | PD |

Note: For non-target lesions, "non-CR / non-PD" means superior efficacy over SD. As SD is increasingly used as an endpoint indicator for evaluating efficacy, non-CR / non-PD efficacy is developed to address no measurable lesions.

Treatment with ambiguous progressive findings (e. g. very small uncertain new lesions; preexisting cystic or necrotic lesions) can be continued until the next evaluation. If disease progression is confirmed in the next assessment, the date of progression should be the date of prior suspected progression.

**Table 78 Optimal overall response for CR and PR efficacy**

| Total remission at the first time point | Total remission at the subsequent time point | Best total relief |
|---|---|---|
| CR | CR | CR |
| CR | PR | SD,PD perhaps PR[a] |
| CR | SD | SD if SD lasts sufficient duration, otherwise PD |
| CR | PD | SD if SD lasts sufficient duration, otherwise PD |
| CR | NE | SD if SD is sufficient, otherwise NE |
| PR | CR | PR |
| PR | PR | PR |

| | | |
|---|---|---|
| PR | SD | SD |
| PR | PD | SD if SD lasts sufficient duration, otherwise PD |
| PR | NE | SD if SD is sufficient, otherwise NE |
| NE | NE | NE |

Note: CR is complete remission, PR is partial remission, SD is stable disease, PD is disease progression, and NE is not evaluable. Superscript "a": If any disease occurs at the first CR point and at a next CR point, the efficacy evaluation will remain PD at the time point at the next time point (as the disease will reappear after CR). Optimal response depends on having SD within the shortest treatment interval. However, sometimes the first evaluation is CR, but the subsequent time point scan indicates that small lesions seem to appear, so the subject efficacy should be PR rather than CR at the first time point. In this case, the first CR judgment should be modified to PR, while the best reaction is PR.

### 2.5. Frequency of tumor reevaluation

The frequency of tumor reevaluation during treatment is determined by the treatment regimen and should be consistent with the type and schedule of treatment. However, in phase trials where the benefit of treatment is unclear, follow-up every 6 to 8 weeks (designed at the end point of a cycle) is reasonable, and the length of the interval can be adjusted under special protocol or circumstances. The protocol should specify which tissue sites require baseline evaluation (usually those most likely to be closely associated to the metastatic lesion of the tumor type studied) and the frequency of evaluation repeats. Normally, target lesions and non-target lesions should be evaluated at each evaluation. In some optional cases, some non-target lesions can be evaluated less frequently. For example, the bone scan should be repeated when the efficacy evaluation of the target disease is confirmed as CR or bone lesion progression is suspected.

After completion of treatment, the tumor re-evaluation depends on taking the response rate or the time to an event (progression / death) as the clinical trial endpoint. Time for an event (e. g. TTP / DFS / PFS) requires the routine repeat evaluation specified in the protocol. In particular, in randomized comparative trials, scheduled evaluations should be included in the schedule (e. g., 6 to 8 weeks during treatment, or 3 to 4 months after treatment) and should not be affected by other factors, such as treatment delay, dosing interval, and any other events that may lead to unbalanced treatment arm in the choice of disease evaluation time.

### 2.6. Efficacy assessment / confirmation of remission period

#### 2.6.1. Confirmation

For non-randomized clinical studies with efficacy as the primary study endpoint, the efficacy of PR and CR must be confirmed to ensure that efficacy is not the result of misevaluation. This also allows for a reasonable interpretation of the results where historical

data are available, but the efficacy in the historical data of these trials should also have been confirmed. However, in all other cases, such as randomized trials (or periods) or studies with disease stability or disease progression as the primary endpoint, efficacy confirmation is no longer required because this is of no value in the interpretation of trial results. Removing the requirement for efficacy confirmation, however, makes the central review even more important, especially in unblinded experimental studies.

In the case of SD, at least one measurement during the shortest time interval after the start of the trial (generally not less than 6 to 8 weeks) will meet the SD criteria specified in the protocol.

**2.6.2 Overall remission period**

The total remission period was from the time of measuring the first CR or PR (which was measured first) to the time of the first true record of disease recurrence or progression (using the minimum measurement recorded in the trial as a reference for disease progression). The time to total complete response was from time to first meeting CR criteria to time of first true recording of disease relapse or progression.

**2.6.3. Stable disease period**

Is the time from the start of treatment to disease progression (in the randomized trial, from the time of randomization), with the smallest sum in the trial as a reference (if the sum of baseline is the minimum, as the reference for PD calculation). The clinical relevance of disease stabilization varies between studies and different diseases. If the proportion of the patients maintaining the shortest time stability period is used as the study endpoint, the protocol should specifically state the shortest time interval between the two measurements in the SD definition.

Note: Response, stabilization, and PFS were affected by the frequency of follow-up after baseline evaluation. Defining standard follow-up frequency is not within this guideline. The frequency of follow-up should consider many factors, such as disease type and stage, treatment cycle and standard norms. However, if inter-trial comparisons are required, the endpoint accuracy limitations of these measurements should be considered.

**2.7.PFS/TTP**

**2.7.1. Phase of the clinical trial**

This guideline focuses on the use of objective remission as a research endpoint in phase clinical trials. In some cases, remission rates may not be optimal for evaluating the potential anticancer activity of new drugs / novel regimens. In these cases, PFS / PPF at the demarcation time points can be considered a suitable surrogate indicator for the original

signal that provides the biological activity of new drugs. But it is clear that in a noncontrolled trial, these evaluations will be questioned, because seemingly valuable observations may be related to biological factors such as patient screening, rather than the role of pharmacological interventions. Therefore, phase clinical trials with these as study endpoints are best designed as randomized controls. But the clinical manifestations of some tumors is consistent (usually always poor) and non-randomized trials are reasonable. However, in these cases, the evidence of efficacy should be carefully documented when assessing the expected PFS or PPF due to the lack of positive controls.

## 6.4 Attachment 4: The EORTC QLQ-C30 scale and the EORTC-QLQ-CR29 scale

### 1) EORTC Quality of Life Measurement Scale QLQ-C30 (V3.0)

We would like to know something about you and your health, please answer all the questions for yourself. There is no "right" or "wrong" here, but only to draw circles on the number that best reflects your situation. The information you provide will be kept strictly confidential.

| | | not have | some | match | extraordinary |
|---|---|---|---|---|---|
| 1 | Do you have difficulty engaging in some laborious activities, Like carrying a very heavy shopping bag or a suitcase? | 1 | 2 | 3 | 4 |
| 2 | Is long-distance walking so difficult for you? | 1 | 2 | 3 | 4 |
| 3 | Is it difficult for you to walk over a short distance outdoors? | 1 | 2 | 3 | 4 |
| 4 | Do you need to stay in bed or in a chair during the day? | 1 | 2 | 3 | 4 |
| 5 | Do you need help while eating, dressing, bathing, or going to the bathroom? | 1 | 2 | 3 | 4 |

| | In the past one week: | not have | some | match | extraordinary |
|---|---|---|---|---|---|
| 6 | Are you restricted in your work and daily activities? | 1 | 2 | 3 | 4 |
| 7 | Are you restricted in engaging in your hobbies or leisure activities? | 1 | 2 | 3 | 4 |

| | | | | | |
|---|---|---|---|---|---|
| 8 | Do you have the gas to promote? | 1 | 2 | 3 | 4 |
| 9 | Do you have any pain? | 1 | 2 | 3 | 4 |
| 10 | Do you need a break? | 1 | 2 | 3 | 4 |
| 11 | Do you have trouble sleeping? | 1 | 2 | 3 | 4 |
| 12 | Do you feel weak? | 1 | 2 | 3 | 4 |
| 13 | Do you lose your appetite (have no appetite)? | 1 | 2 | 3 | 4 |
| 14 | Do you feel sick? | 1 | 2 | 3 | 4 |
| 15 | Do you vomit? | 1 | 2 | 3 | 4 |
| 16 | Do you have constipation? | 1 | 2 | 3 | 4 |
| | In the past one week: | not have | some | match | extraordinary |
| 17 | Do you have any diarrhea? | 1 | 2 | 3 | 4 |
| 18 | Do you feel tired? | 1 | 2 | 3 | 4 |
| 19 | Does the pain affect your daily activities? | 1 | 2 | 3 | 4 |
| 20 | Do you have difficulty concentrating on doing things, such as reading a newspaper or watching TV? | 1 | 2 | 3 | 4 |
| 21 | Do you feel nervous? | 1 | 2 | 3 | 4 |
| 22 | Do you feel worried? | 1 | 2 | 3 | 4 |
| 23 | Do you feel hot-tempered? | 1 | 2 | 3 | 4 |
| 24 | Do you feel depressed (depressed)? | 1 | 2 | 3 | 4 |

| | | | | | |
|---|---|---|---|---|---|
| 25 | Do you feel difficulty remembering? | 1 | 2 | 3 | 4 |
| 26 | Does your physical condition or treatment affect your family life? | 1 | 2 | 3 | 4 |
| 27 | Does your physical condition or treatment affect your social activities? | 1 | 2 | 3 | 4 |
| 28 | Does your physical condition or treatment get you into financial difficulties? | 1 | 2 | 3 | 4 |

For the following questions, select a number best for you between 1 and 7 and circle.

29 How do you evaluate your overall health in the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| very bad | | | | | | beyond compare |

30 How do you evaluate your total quality of your life over the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| very bad | | | | | | beyond compare |

The EORTCQLQ-C30 scale, which the European Organization for Research on Cancer Treatment (EORTC: The European O-rganization for Reasearch and Treatment of Cancer), launched the cross-cultural and cross-national QOL-C30 (Quality of Life Questionnare-Core 30) in 1993, Evaluation QOL from a multidimensional perspective, Can better reflect the QOL connotation, Has been applied to QOL measurements in cancer patients in multiple European countries and regions.

1. Calculation of the entry score

The EORTC QLQ- -C30 (V3.0) is a core scale for all cancer patients with a total of 30 entries. Among them, items 29 and 30 are divided into seven levels, ranging from 1 to 7 points according to their answer options; other items are divided into four levels: from none, one point, more to many, directly rated from 1 to 4 points.

| dimension | Number of indicators | content |
|---|---|---|
| Physical function | 5 | Physical activity: carrying objects, walking, staying in bed for days and basic self-care conditions |
| Role function | 2 | Whether daily activities, work and hobbies are restricted |
| emotional function | 4 | Tension, worry, emotional control ability |
| cognitive function | 2 | Whether it is difficult to remember things, and whether you can concentrate on doing things |
| social function | 2 | Family life and social activities are hindered |
| Overall health status / quality of life | 2 | Self-rated overall health status and overall quality of life |
| physical symptom | 12 | Fatigue, nausea and vomiting, pain, dysphagia, sleep disturbance, and decreased appetite |
| Health-related economic situation | 1 | The impact of the disease and the treatment on the patient's economy |

2. Calculation of the domain (dimension) score (coarse score)

For the convenience of statistical analysis and application, the scales are often divided into certain fields (domain). The domain is an aspect of the quality of life component, also known as dimensionality (dimension), when analyzed as an independent variable.

E0RTC QLQ- -The 30 items of C30 (V3.0) can be divided into 15 areas, with 5 functional domains (body, role, cognitive, emotional, and social function), 3 symptom domains (fatigue, pain, nausea and vomiting), 1 general health / quality of life area, and 6 single items (each as one area). The score of the field is obtained by adding up and dividing it by the number of items included in the field (coarse RS, Raw Score), namely RS= (Q1 + Q2 + Q?） / n。

QLQ-C30 (V3.0) Scoring method for each fields (coarse RS)

| Field (dimension) | property | Number of entries | Score full distance (R) | scoring method |
|---|---|---|---|---|
| somatic function | functional form | 5 | 3 | (Q1+Q2+Q3+Q4+Q5)/5 |
| Role function | functional | 2 | 3 | (Q6+Q7)/2 |

| | | | | |
|---|---|---|---|---|
| | form | | | |
| emotional function | functional form | 4 | 3 | (Q21+Q22+Q23+Q24)/4 |
| cognitive function | functional form | 2 | 3 | (Q20+Q25)/2 |
| social function | functional form | 2 | 3 | (Q26+Q27)/2 |
| Total health status | | 2 | 6 | (Q29+Q30)/2 |
| tired | Symptomatic type | 3 | 3 | (Q10+Q12+Q18)/3 |
| Nausea and vomiting | Symptomatic type | 2 | 3 | (Q14+Q15)/2 |
| pain | Symptomatic type | 2 | 3 | (Q9+Q19)/2 |
| anhelation | Symptomatic type | 1 | 3 | Q8 |
| lose sleep | Symptomatic type | 1 | 3 | Q11 |
| Loss of appetite | Symptomatic type | 1 | 3 | Q13 |
| astriction | Symptomatic type | 1 | 3 | Q16 |
| diarrhoea | Symptomatic type | 1 | 3 | Q17 |
| economic hardship | Symptomatic type | 1 | 3 | Q28 |

3. Calculation of standard and chemical scores

In order to make the scores of each field compare with each other, the extreme differential method is further used for linear transformation to convert the coarse score into a standardized score (standard score, SS) within 0~100. In addition, the purpose is to change the direction of the score. Because QLQ-C30 scale, except item 29,30 are reverse entry (the greater the value, the worse the quality of life), and in the scoring rules: the

functional and overall health field score higher that functional condition and life quality is better, the higher the score for symptom areas indicates that the more symptoms or problems (worse quality of life). Therefore, the calibration time of the computing function field has to change the direction. Specifically, the following formula is calculated respectively (where R is the full score distance of each field or item).

Functional area: SS= [1- (RS-1) / R] 100

Symptom areas and general health status areas: SS= [(RS-1) / R] 100

**2) The EORTC-QLQ-CR29 scale**

We would like to know something about you and your health, please answer all the questions for yourself. There is no "right" or "wrong" here, but only to draw circles on the number that best reflects your situation. The information you provide will be kept strictly confidential.

| | **In the past week** | **not have** | **some** | **match** | **extraordinary** |
|---|---|---|---|---|---|
| 31 | Have you inated frequently during the day in the past week? | 1 | 2 | 3 | 4 |
| 32 | Have you urinate frequently at night in the past week? | 1 | 2 | 3 | 4 |
| 33 | Have you involuntarily urinate or leaked in the past week? | 1 | 2 | 3 | 4 |
| 34 | Have you had any pain in urinating in the past week? | 1 | 2 | 3 | 4 |
| 35 | Have you had any abdominal pain in the past week? | 1 | 2 | 3 | 4 |
| 36 | Have you had pain in the hip, anal area or rectum in the past week? | 1 | 2 | 3 | 4 |
| 37 | Have you filled your abdomen in the past week? | 1 | 2 | 3 | 4 |

| | | | | | |
|---|---|---|---|---|---|
| 38 | Have you had blood stools in the past week? | 1 | 2 | 3 | 4 |
| 39 | Did you have mucus in your stool in the past week? | 1 | 2 | 3 | 4 |
| 40 | What have you done in the past week? | 1 | 2 | 3 | 4 |
| 41 | Have you treated your hair loss in the past week? | 1 | 2 | 3 | 4 |
| 42 | Have you had any problems with your taste patterns in the past week? | 1 | 2 | 3 | 4 |
| 43 | Have you been worried about your future health in the past week? | 1 | 2 | 3 | 4 |
| 44 | Have you been worried about your weight in the past week? | 1 | 2 | 3 | 4 |
| 45 | Have you experienced less illness or treatment in the past week? | 1 | 2 | 3 | 4 |
| 46 | Have you felt that illness or treatment has reduced your feminine / masculine taste in the past week? | 1 | 2 | 3 | 4 |
| 47 | Have you been dissatisfied with your body in the past week? | 1 | 2 | 3 | 4 |
| 48 | **Do you have a stoma pocket (colostomy or ileostomy)?(Select Yes / No)** | **yes** | **deny** | | |
| | **Question 18 for patients with "yes", please answer the following questions:** | **not have** | **some** | **match** | **extraordinary** |
| 49 | In the past week, have you had an involuntary pocket exhaust or flatulence? | 1 | 2 | 3 | 4 |

| | | | | | |
|---|---|---|---|---|---|
| 50 | Have you leaked in your pocket in the past week? | 1 | 2 | 3 | 4 |
| 51 | Have you had pain in the skin around the fistula in the past week? | 1 | 2 | 3 | 4 |
| 52 | Have you changed your pockets frequently during the day in the past week? | 1 | 2 | 3 | 4 |
| 53 | Have you changed your pocket frequently at night in the past week? | 1 | 2 | 3 | 4 |
| 54 | Have you been embarrassed in the past week? | 1 | 2 | 3 | 4 |
| 55 | Have you had difficulty nursing the fistula in the past week? | 1 | 2 | 3 | 4 |

| | **Patients 18 answered "no", please answer the following questions:** | **not have** | **some** | **match** | **extraordinary** |
|---|---|---|---|---|---|
| 49 | Have you had any involuntary anal exhaust or flatulence in the past week? | 1 | 2 | 3 | 4 |
| 50 | Have you leaked a stool from your anus in the past week? | 1 | 2 | 3 | 4 |
| 51 | In the past week, do you have any skin pain around the anus? | 1 | 2 | 3 | 4 |
| 52 | In the past week, have you frequently defecate frequently during the day? | 1 | 2 | 3 | 4 |
| 53 | Have you done your shit out frequently this week at night in the past week? | 1 | 2 | 3 | 4 |
| 54 | In the past week, have you been embarrassed by your ating? | 1 | 2 | 3 | 4 |

| | **In the past 4 weeks, men should answer** | **not** | **some** | **match** | **extraordinary** |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| | **questions 56,57** | **have** | | | |
| 56 | How interested have you been in sex in the last 4 weeks? | 1 | 2 | 3 | 4 |
| 57 | Have you had difficulty achieving or maintaining an erection in the last 4 weeks? | 1 | 2 | 3 | 4 |
| | **In the past 4 weeks, women were asked to answer questions 58,59** | **not have** | **some** | **match** | **extraordinary** |
| 58 | How interested have you been in sex in the last 4 weeks? | 1 | 2 | 3 | 4 |
| 59 | Have you had any pain or discomfort during sexual intercourse in the last 4 weeks? | 1 | 2 | 3 | 4 |

The Colorectal Cancer Quality of Life Questionnaire (QLQ-CR29), a module of the Quality of Life Questionnaire-Core 30 (QLQ-C30), developed by the European Organization for Research and Treatment of Cancer to assess quality of life for specific aspects of colorectal cancer in cancer patients.

## 6.5 Attachment 5: Anal Incontinence Wexner Scale Scale

一， Scale introduction

1. Evaluation method: conducted by doctors or test-experienced personnel.
2. Scale function: The Wexner incontinence scale was prepared by Wexner, Jorge and other researchers to assess the severity of patient defecation.
3. Applicable population: patients with fecal incontinence caused by various reasons.

二， operating guide

1. Content of the scale: The scale mainly includes four aspects of stool morphology, gastrointestinal incontinence, wearing pads and lifestyle, lasting for more than 4 weeks. There are 5 items, and each score is calculated according to Table 1.
2. Results analysis: the total score is the sum of all scores, the score range is 0-20 points, 0 points = normal, 20 points = complete incontinence.

**Table 1 The Wexner scoring scale of anal incontinence**

| variable | never | once in a while | sometimes | often | always | score |
|---|---|---|---|---|---|---|
| exhaust | 0 | 1 | 2 | 3 | 4 | |
| Loose stools | 0 | 1 | 2 | 3 | 4 | |
| formed stool | 0 | 1 | 2 | 3 | 4 | |
| Sanitary belt | 0 | 1 | 2 | 3 | 4 | |
| Lifestyle change | 0 | 1 | 2 | 3 | 4 | |
| total points | () component | | | | | |

三， Results and interpretation

Total score: () score.

Explanation: Wexner score scale introduces the analysis index is the total score, the score range is 0-20 points, 0 points = normal, 20 points = complete incontinence.