mFOLFOX6 Combined with Citrus Flavonoid Tablets (Aimailang) as Neoadjuvant Therapy for Locally Advanced Rectal Cancer with High YWHAB Expression: A Prospective, Multi-center, Open-Label, Randomized Controlled Phase II Clinical Trial

Informed Consent Form

NCT Number:	**NCT07176182**
Primary Research Institution:	**The Sixth Affiliated Hospital of Sun Yat-sen University**
Research Protocol Version:	**Version 5.1, March 27, 2026**
Informed Consent Form Version:	**Version 5.1, March 27, 2026**

Please read the following carefully

You will be invited to participate in a clinical study. This informed consent form provides you with information to help you decide whether to participate in a clinical study. Please read the informed consent form carefully. If you have any questions, please feel free to submit them to the investigator in charge of the study, who will give you detailed answers. You can make your decision according to your own situation, and you will have sufficient time to consider it.

1. Research Background

Patients with Rectal cancer have a higher risk of pelvic recurrence than those with Colon cancer, and locally recurrent rectal cancer is significantly associated with poor prognosis. Determining the best treatment for a patient with locally advanced rectal cancer is a complex process. In addition to deciding the purpose of rectal cancer surgery (i.e., curative or palliative), it is also necessary to consider the possible functional outcomes after treatment, including the possibility of maintaining or restoring normal bowel function/anal continence and preserving urogenital function. Especially for patients with locally advanced low rectal cancer, simultaneously achieving the goal of cure with minimal impact on quality of life can be challenging. A common strategy to promote tumor regression in patients with locally advanced rectal cancer is to intensify neoadjuvant therapy by adding systemic chemotherapy before radiotherapy. Our previous study found that YWHAB/β-TrCP/β-catenin signaling axis is a potential biomarker and therapeutic target for precise chemotherapy in patients with YWHAB-high colorectal cancer. Both Hesperidin and diosimine can effectively target YWHAB/β-TrCP signaling axis. Both in vitro and in vivo experiments have shown that FOLFOX combined with Hesperidin, diosmin or citrus flavone tablets (ElM, the main ingredients are hesperidin and diosmin) can be used as a potential treatment option for colorectal cancer patients with YWHAB high expression. Therefore, citrus flavone tablets (Elam) has a good application

prospect for improving the effect of neoadjuvant chemotherapy in patients with locally advanced rectal cancer with high YWHAB expression. mFOLFOX6 is one of the guideline-recommended chemotherapy regimens for advanced colorectal cancer. Our previous prospective, multicenter, randomized controlled trial (FOWARC) found that for patients with locally advanced rectal cancer, mFOLFOX6 regimen had a better local response rate, lower incidence of adverse reactions and postoperative complications, and better safety than neoadjuvant chemoradiotherapy. Based on this, this study intends to conduct a prospective, multicenter, open, randomized controlled, phase II clinical trial. To evaluate the efficacy of mFOLFOX6 combined with or without citrus flavone tablet (Aimeilan) regimen as neoadjuvant therapy in patients with locally advanced rectal cancer with high YWHAB expression (achieving tumor downstaging (ypTNM) in each treatment group Stage 0-I), proportion of patients with pathological complete response, 3-year disease-free survival rate, overall survival time and tumor regression grade TRG, etc.) and safety (drug-related adverse events, etc.). To evaluate the efficacy, safety and feasibility of mFOLFOX6 combined with or without citrus flavanone (ElM) as neoadjuvant therapy in patients with locally advanced rectal cancer (LARC) with YWHAB overexpression. To explore a regimen that can further improve the efficacy, safety and tolerance of neoadjuvant chemotherapy in patients with locally advanced rectal cancer with high YWHAB expression, and to provide evidence-based medical evidence for the application of mFOLFOX6 combined with citrus flavone tablets (Elam) neoadjuvant therapy in patients with locally advanced rectal cancer with high YWHAB expression.

2. Objectives of the study

2.1. Main research objectives:

To evaluate the proportion of patients with tumor downstaging (ypTNM stage 0-I) in patients with locally advanced rectal cancer with high YWHAB expression treated with mFOLFOX6 combined with citrus flavone (Aimeilan) regimen as neoadjuvant therapy. To provide evidence-based medical evidence for the efficacy of citrus flavone tablets (Elam) enhanced mFOLFOX6 regimen as neoadjuvant therapy in patients with locally advanced rectal cancer with high YWHAB expression

2.2. Secondary research objectives:

- Efficacy evaluation: The proportion of pathological complete response (PCR), 3-year disease free survival (DFS), overall survival (OS) and tumor regression grade TRG were evaluated in the neoadjuvant treatment of mFOLFOX6 combined with citrus flavone (Elam) regimen in patients with locally advanced rectal cancer with YWHAB high expression.
- Safety evaluation: Treatment-related adverse events (above grade 3) were evaluated in patients with YWHAB-high locally advanced rectal cancer treated with mFOLFOX6 combined with citrus flavone (Elam) regimen as neoadjuvant therapy.

3. Selection and withdrawal of subjects

3.1 Inclusion Criteria:

(1) Rectal adenocarcinoma was diagnosed by histopathology, all other histological types were excluded, and the colonoscopy report or clinical physical examination suggested combined hemorrhoids.

(2) Patients with radiographic measurable or clinically evaluable rectal tumor, and the clinicopathological stage of the tumor was T2N+ or T3-4aNany, M0; Clinical staging was based on the surgeon's physical examination, chest and abdominal/pelvic enhanced CT, pelvic MRI, or pelvic enhanced CT combined with transrectal ultrasonography if MRI was contraindicated (AJCC TNM staging, ninth edition, Appendix 1).

(3) Pelvic MRI showed that the tumor was not adjacent (defined as < 2 mm) to the mesorectal fascia (MRF negative).

(4) Immunohistochemical staining of tissue specimens showed high expression of YWHAB in rectal cancer patients;

(5) The age of obtaining informed consent was 18-75 years old.

(6) An Eastern Cooperative Oncology Group performance-status (ECOG) score of 0-1 (see Appendix 3);

(7) No previous systemic anti-tumor therapy for rectal cancer, including cytotoxic drugs, immune checkpoint inhibitors, molecular targeted therapy, endocrine therapy, etc.

(8) Adequate organ function based on the following laboratory values obtained during the

screening period: White blood cell count ≥3×10^9/L, neutrophil count ≥1.5×10/L, platelet count ≥75×10^9/L, serum total bilirubin ≤ 1.5× upper limit of normal value (UNL), aspartate aminotransferase or alanine aminotransferase ≤2.5×UNL, serum creatinine ≤ 1.5×UNL;

(9) Women of childbearing age had to have a serum pregnancy test with a negative result within 3 days before starting study medication and be willing to use a highly effective, medically approved contraceptive method (e.g., intrauterine device, contraceptive pill, or condom) during the study and for 3 months after the last dose of study medication;

(10) For male subjects whose partner is a woman of childbearing age, use an effective method of contraception during the study period and for 3 months after the last study dose;

(11) Subject is willing and able to follow the planned visits, study treatments, laboratory tests, and other trial procedures if he/she has signed an informed consent form.

3.2 Exclusion Criteria:

(1) Distant metastasis confirmed by whole body CT, MR Or PET-CT(at least chest, whole abdomen and pelvis);

(2) Patients with mismatch repair protein deficiency (dMMR) confirmed by immunohistochemical testing or microsatellite instability high (MSI-H) confirmed by molecular testing.

(3) Patients with complete intestinal obstruction, active bleeding or perforation required emergency surgery.

(4) Previous or concurrent presence of other active malignancies (except for malignancies that had been treated curably and had not recurred for more than 5 years or carcinoma in situ that was curable with adequate treatment);

(5) Thrombotic or embolic events, such as cerebrovascular accident (including transient ischemic attack), pulmonary embolism, deep vein thrombosis, occurred within 12 months before study entry;

(6) Myocardial infarction, severe or unstable angina, cardiac dysfunction of NYHA class 2 or higher, clinically significant supraventricular or ventricular arrhythmias, or symptomatic congestive heart failure within 12 months before study entry;

(7) Systemic antibiotic use for ≥ 7 days within 4 weeks before enrollment or unexplained fever >38.5°C during screening or before the first dose of study medication (fever due to cancer, as judged by the investigator, was eligible);

(8) Had undergone major surgery or major trauma (e.g., laparotomy, thoracotomy, or laparoscopic resection of organs) within 2 months before enrollment (surgical incisions were expected to be fully healed before enrollment);

(9) Patients with known human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS) related diseases;

(10) With interstitial lung disease, non-infectious pneumonia or uncontrolled systemic diseases (such as diabetes mellitus, hypertension, pulmonary fibrosis and acute pneumonia);

(11) Untreated active hepatitis (hepatitis B, defined as HBV-DNA ≥ 500 IU per milliliter; hepatitis C, defined as HCV-RNA higher than the lower limit of detection of the assay) or coinfection with hepatitis B and C;

(12) A known or suspected history of allergy to any of the relevant drugs used in the study;

(13) Other ineligibility conditions as judged by the investigator (as described in the informed consent form).

3.3 Withdrawal Criteria:

A participant may withdraw from the trial at any time or be asked to do so by the investigator or sponsor for safety or behavioral reasons or for an inability to adhere to protocol-required study visit times or procedures. Criteria for withdrawal include:

(1) The subject withdrew informed consent to participate in the study and was unwilling to return to the original study center for all study assessments (including refusal of surgical treatment after neoadjuvant therapy);

(2) After neoadjuvant therapy, patients with local disease progression or evidence of distant metastasis evaluated by imaging examination are recommended to receive the standard treatment recommended by the current clinical guidelines after multidisciplinary consultation (oncology, radiotherapy, imaging, colorectal surgery, hepatobiliary surgery, intervention, ultrasound, etc.).

(3) Patients who experienced clinical adverse events, laboratory abnormalities or

complications and were considered by the investigators to be not in the best interest of the subjects to continue to participate in the study;

(4) General deterioration of health such that participation in the trial is not possible;

(5) Pregnancy during the study;

(6) Significant protocol deviations such as unqualified and non-compliance were found after enrollment.

(7) Loss of follow-up;

(8) Death of the subject;

(9) Other circumstances deemed by the investigator to warrant withdrawal from the study, such as significant protocol violations.

4. Planned enrollment

The primary end point was the rate of downstaging (ypTNM stage 0-I) in each treatment group. Based on previous data from our center, about 35% of patients with locally advanced rectal cancer received mFOLFOX6 neoadjuvant chemotherapy had tumor downstaging (ypTNM 0-I). Among them, about 25% of patients with YWHAB high expression rectal cancer received mFOLFOX6 neoadjuvant chemotherapy, about 1/3 (n=86) had tumor downstaging. In patients with YWHAB low expression (approximately 2/3, n=86), the tumor downstaging rate after mFOLFOX6 neoadjuvant chemotherapy was about 43%. Our previous single-center, prospective, open-label, small cohort exploratory trial found that the tumor downstaging rate of YWHAB high expression rectal cancer patients was about 25%. The tumor downstaging rate of patients with YWHAB high expression rectal cancer who received mFOLFOX6 neoadjuvant chemotherapy was about 25.0% (total number of 20 cases, including 5 cases of ypTNM 0-I stage). The tumor downstaging rate of YWHAB high expression rectal cancer patients treated with mFOLFOX6 combined with Amelanin neoadjuvant therapy was about 42.9% (total number of 28 cases, including 12 cases of ypTNM 0-I stage). We estimated that the tumor downstaging rate of YWHAB high expression rectal cancer patients treated with mFOLFOX6 combined with Iceronone tablets was 40%, the significance level was 0.05, the test power was 0.8, and the loss to follow-up rate was 10%. The sample

size was 236 patients estimated by PASS V15 software.

5. Treatment Options

5.1. Subject screening period

All patients with locally advanced rectal cancer (cT2N+ or cT3-4aNany, M0, and MRF negative) who agreed to participate in this clinical trial were enrolled in this study. YWHAB immunohistochemistry was performed on colonoscopy pathological biopsy specimens, and patients with locally advanced rectal cancer with high YWHAB expression were screened for inclusion in this study. Patients with locally advanced rectal cancer were randomly assigned to mFOLFOX6 group or mFOLFOX6 combined with citrus flavone tablets (Aimeilang) group for neoadjuvant therapy.

The following tests should be completed within 28 days before starting study medication:

- Signed informed consent form was obtained from the subjects;
- Demographic data including name, gender, date of birth, height and weight were collected.
- Adverse events were collected: adverse events were recorded from the date of signing the informed consent.
- Tumor diagnosis: date of pathological diagnosis, pathological grade, clinical imaging stage (TNM), clinical stage, etc.
- History of tumor treatment;
- Imaging examination: chest, abdomen and pelvis enhanced CT+ transrectal ultrasound or chest, abdomen and pelvis enhanced CT+ pelvic enhanced MRI.
- YWHAB immunohistochemical staining was performed on biopsy specimens.
- KRAS codons 12 and 13 in exon 2, codons 59 and 61 in exon 3, codons 117 and 146 in exon 4, NRAS codons 12 and 13 in exon 2, and codons 59 and 61 in exon 3 were determined in tumor tissue (not required). Codons 117-146 of exon 4 and BRAF V600E gene status;
- MMR/MSI of tumor tissues were detected.
- The following screening should be completed within 7 days before starting study drug treatment:

- Body weight and ECOG score;
- Vital signs: pulse, respiratory rate, temperature and blood pressure;
- Comprehensive physical examination: general status, head and face, skin, lymph nodes, eyes, ear, nose and throat, mouth, respiratory system, cardiovascular system, abdomen, genitourinary system, musculoskeletal system, nervous system and mental status, etc.
- Blood routine: red blood cell count, hemoglobin, platelet count, white blood cell count, neutrophil count and lymphocyte differential count;
- Urine routine: white blood cell count, red blood cell count, urine protein; If urine protein ≥2+, 24-hour urine protein quantification should be performed.
- Blood biochemistry: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), glutamyl transpeptidase (γ-GT), total bilirubin (TBIL), direct bilirubin (DBIL), alkaline phosphatase (AKP), blood urea nitrogen (BUN) or urea (preferably blood urea nitrogen), total protein (TP), albumin (ALB), creatinine (Cr), blood glucose (GLU)), K^+, Na^+, $Ca2^+$, Mg^{2+}, Cl^-;
- Tumor related markers;
- Coagulation function: activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), fibrinogen (FIB), international normalized ratio (INR);
- 12-lead ECG: attention should be paid to QT, QTc and P-R interval. If there is any abnormality, other relevant examinations should be performed according to the investigator's judgment.
- Echocardiography, which should include, at a minimum, left ventricular ejection fraction (LVEF) assessment;
- Pregnancy test: for women of childbearing age, serum pregnancy test should be used.

5.2. mFOLFOX6 with or without citrus flavone tablets (Ai Mai Lang) neoadjuvant chemotherapy and adjuvant chemotherapy treatment period

mFOLFOX6 regimen combined with citrus flavone tablets (Aimailang)× preoperative 4-6 cycles, every 14 days as a treatment cycle. Oxaliplatin 85 mg/m² intravenous infusion 180 min, day 1; Leucovorin 400 mg/m² IV infusion 120 min, day 1; 5-fluorouracil 2400 mg/m², continuous IV infusion for 46 hours; With or without citrus flavone tablets (Ai Mai

Lang)500mg administered orally twice daily on days 1 to 14 of each 14-day cycle.

Dose modification was permitted, and patients who had disease progression while receiving neoadjuvant therapy discontinued the study treatment and either proceeded directly to surgery or were treated according to clinical guidelines. Early surgery could also be performed if the planned six cycles of neoadjuvant therapy were not tolerated. Any patient who received an alternative regimen of anticancer therapy prior to surgery was discontinued from the study treatment and managed in accordance with clinical guidelines. Postoperative treatment the two groups on the basis of routine clinical diagnosis and treatment norms "Chinese colorectal cancer diagnosis and treatment norms (2025 edition) and the Chinese society of clinical oncology (notes) for colorectal cancer diagnosis and treatment of guidelines (2025 edition). It should be noted that all the patients in the control group were not allowed to take citrus flavone tablets (Elam) without permission during the trial. If they needed oral medication for various reasons, they should communicate with the attending physician and decide whether to use other drugs instead or stop the trial for the patient.

The following assessments should be completed before each dose of treatment:

- Body weight and ECOG score;
- Vital signs;
- Physical examination;
- Blood routine: red blood cell count, hemoglobin, platelet count, white blood cell count, neutrophil count and lymphocyte differential count;
- Blood biochemistry: Alanine aminotransferase (ALT), aspertate aminotransferase (AST), GGTP (gamma glutamyl transpeptidase) (gamma GT), total bilirubin (TBIL), direct bilirubin (DBIL), alkaline phosphatase (AKP), blood urea nitrogen (BUN) and urea (optimal blood urea nitrogen), total protein (TP), albumin (propagated), creatinine (Cr), glucose (GLU), K^+, Na^+, $Ca2^+$, Mg^{2+}, Cl^-;
- Urine routine: white blood cell, red blood cell, urine protein; If urine protein ≥2+, 24-hour urine protein quantification should be performed.
- Coagulation function: activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), fibrinogen (FIB), international normalized ratio (INR);

- Tumor-related markers;
- 12-lead ECG: QT, QTc, and P-R intervals should be noted. If there is any abnormality, other relevant examinations should be performed according to the investigator's judgment.
- Adverse events were recorded;
- Radiographic evaluation: preoperative after 6 cycles of mFOLFOX6 joint citrus flavonoids (love vein lang) scheme after neoadjuvant chemotherapy, imaging evaluation respectively, check the content for the enhanced CT chest basin, pelvic cavity enhanced magnetic resonance imaging (MRI), or by transrectal ultrasound. Any subjects during treatment doubt appeared disease progression (e.g., deterioration of symptoms), can be an unplanned imaging examination; Imaging evaluation was performed after 6 cycles of postoperative adjuvant chemotherapy with or without mFOLFOX6 regimen. The examination included chest, abdomen and pelvis enhanced CT and pelvic enhanced MRI. Any subjects during treatment doubt appeared disease progression (e.g., deterioration of symptoms), unplanned imaging examination can be performed.

5.3. Follow-up Period:

Survival was followed up until death, loss to follow-up, withdrawal of informed consent, refusal to provide further information, or termination of the study by the sponsor. During this period, follow-up visits were conducted every 3 months by effective means such as telephone follow-up to collect information on survival and subsequent antineoplastic therapy (if the subject started a new antineoplastic therapy, the treatment plan and the start and end time should be recorded). For those without radiographic evidence of disease progression, radiographic evaluation should continue at the frequency specified in clinical guidelines (follow-up examination included regular chest, abdomen and pelvis enhanced CT or chest, abdomen and pelvis enhanced CT+ pelvic enhanced MRI as required by oncology department). Imaging evidence of disease progression should be obtained until disease progression, death, loss of follow-up, withdrawal of informed consent and refusal to provide further information, initiation of other antineoplastic therapy, or termination of the study by the sponsor.

The attending physician during the follow-up period should be based on the actual

situation of patients advice whether patients go to a local hospital or return to our further checks clear the progress of the disease, should include the following contents:

- Medical history and physical examination (e.g., digital rectal examination)
- Blood routine (such as red blood cell count, hemoglobin, platelet count, white blood cell count, neutrophil count and lymphocyte differential count), biochemical (such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (γ-GT), total bilirubin (TBIL), direct bilirubin (DBIL), alkaline phosphatase (AKP), blood Blood urea nitrogen (BUN) or urea (preferably blood urea nitrogen), total protein (TP), albumin (ALB), creatinine (Cr), blood glucose (GLU), K^+, Na^+, $Ca2^+$, Mg^{2+}, Cl^-), coagulation function (such as activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), fibrinogen (FI) B), international normalized ratio (INR), CEA, CA19-9 and other tumor related markers were monitored every 3 months for 2 years, then every 6 months for 5 years, and once a year after 5 years;
- Imaging evaluation: chest, abdomen and pelvis enhanced CT or chest, abdomen and pelvis enhanced CT+ pelvic enhanced MRI was performed once every 6 months in the first 2 years after surgery, and then once a year for 5 years.
- Colonoscopy was performed within 1 year after surgery, and reexamination was performed within 1 year if abnormal results were found. If no polyps were found, the patients were reexamined within 3 years. Then every 5 years, and resection of colorectal adenoma is recommended. If the whole colon is not examined by colonoscopy before operation, colonoscopy is recommended at 3-6 months after operation.
- PET-CT is not routinely recommended. For patients with or suspected recurrence or distant metastasis, PET-CT can be considered to rule out recurrence and metastasis.
- (Non-essential) 12-lead electrocardiogram, urine routine, ultrasound electrocardiogram, pregnancy test, etc.

6. Precautions

Here's what you should know:

1) In most cases, treatments and tests are performed as described above. However, additional tests may be performed at any time if your doctor deems them necessary.

2) Please follow your doctor's instructions. If you feel any discomfort or experience any adverse reactions, please tell your doctor in time. If it is necessary to stop the study treatment, he/she will discuss the next treatment plan with you.
3) Your study physician will be in constant contact with you after completing the treatment.
4) Be sure to remember to tell your doctor what other medications you are taking, if you have seen another doctor, received a new treatment, participated in another clinical study, or how you have changed since your last visit.
5) If another doctor invites you to participate in another clinical program, please tell him or her that you are participating in this program.

7. Pregnancy/Contraception

If you believe that you are pregnant, or that there is a possibility that you may become pregnant during treatment, you should not participate in the study. Your doctor will therefore check that you are actually using a reliable method of birth control before starting medication.

For women:

Women of reproductive age must undergo a pregnancy test within 7 days of randomization. If the possibility of contraceptive failure is suspected, or if the menstrual cycle changes, the pregnancy test must be repeated. If you become pregnant during the study period, you must tell your study doctor immediately.

For men:

Because the effects of the drugs used in this study on the germ cells are not known, you and your spouse must use birth control during this period. If your spouse becomes pregnant while you are taking this medication or within 6 months of stopping this medication, you must notify your doctor.

8. Potential risks

As the main protocol component of this study (mFOLFOX6) is the standard first-line treatment regimen for colorectal cancer recommended by the National Health Commission of the People's Republic of China (2025 edition) and domestic and foreign guidelines, previous data showed that the toxic and side effects were safe and controllable. There may be slight pain or

cyanosis when blood is drawn during the study, and the use of peripheral intravenous drip itself may cause temporary irritation and congestion at the injection site, and the study drug may also have side effects.

Potential side effects of the drugs that may be part of the treatment regimens used in this trial are as follows:

(1) The common adverse effects of 5-FU include leukopenia and thrombocytopenia, diarrhea, loss of appetite, stomatitis, nausea, vomiting, skin reactions, etc.

(2) The common adverse reactions of oxaliplatin included neurotoxicity, nausea, vomiting, diarrhea, leukopenia and thrombocytopenia, abdominal pain, liver and kidney dysfunction, etc.

(3) The most common adverse reactions of citrus flavone tablets were gastrointestinal reactions: diarrhea, dyspepsia, nausea, vomiting, etc. ($1/100 \leq$ gastrointestinal adverse reactions $< 1/10$).

Patients have experienced these side effects in previous studies, but you may also experience other side effects that are not predictable at this time.

These side effects may be minor inconvenience or serious, but if any occur, your responsible doctor will be watching you closely.

These side effects may occur despite treatment that is effective for your condition.

Your doctor will regularly evaluate the effects of the treatment. If effectiveness is not observed, treatment will be discontinued.

If any new information related to the study drug emerges during the course of the study that may affect your decision to continue in the study, you will be promptly notified by your physician.

Patients accept mFOLFOX6 scheme combined citrus flavonoids piece of pulse lang (love) preoperative 4 to 6 cycles of neoadjuvant chemotherapy and postoperative 4 to 8 cycles of conventional adjuvant chemotherapy (mFOLFOX6 scheme and postoperative adjuvant therapy specific period set by the medical oncologist patients based on the actual situation), Compared with the current mFOLFOX6 regimen of the new NCCN guidelines, citrus flavone tablets (Elam) were added to some of the trial patients' regimens, and the overall adverse reaction rate (Elam) may be slightly higher than the current standard regimen.

Management of risk:

Participants were monitored continuously for drug-related adverse effects while they were receiving study treatment, and in the event of less severe toxic effects, dose adjustments or delays could be made if the investigator, in consultation with the medical monitor or sponsor, determined that such adjustments or delays would be beneficial to the safety of the subjects. Like any drug interruption, 14 days start the longest time can be delayed, so that the subjects recovering from its toxicity. The dose of oxaliplatin and 5-FU should be reduced in the event of serious hematologic and hepatic adverse events (excluding liver function impairment due to disease progression). Severe diarrhea associated with mucosal toxicity (except vomiting, hair loss), should be lower 5 - FU to the dose.

Alternatives:

Enrolling in a study is not your only option for treatment. If you choose not to participate in the study, you can also receive other treatment measures and guidance from your doctor, who will develop a treatment plan based on your actual situation and inform you of the possible benefits and risks.

9. Potential Benefits

This, combined with data from previous clinical cohorts at our center, suggests that: After mFOLFOX6 neoadjuvant chemotherapy, about 35% of patients with locally advanced rectal cancer had tumor downstaging (ypTNM 0-I stage). Among them, about one-third (n=86) of patients with YWHAB high expression received mFOLFOX6 neoadjuvant chemotherapy, the tumor downstaging rate was about 25%. About 2/3 (n=86) of patients with YWHAB low expression received mFOLFOX6 neoadjuvant chemotherapy, and the tumor downstaging rate was about 43%. This team early single-center, prospective, open label, small queue experiment found that high YWHAB expression type mFOLFOX6 neoadjuvant chemotherapy of patients with rectal cancer tumor drop period at a rate of around 25% (20 cases, total ypTNM 0 to 5 patients with stage I); YWHAB high expression in patients with colorectal cancer (mFOLFOX6 joint love vein lang neoadjuvant

therapy of tumor drop period at a rate of around 42.9% (28 cases, total ypTNM 0-12 patients with stage I). At the same time, our previous mechanistic study found that YWHAB/β-TrCP/β-catenin axis was a potential biomarker and therapeutic target for precise chemotherapy in patients with YWHAB-high colorectal cancer, which provided theoretical basis for citrus flavone tablets (Elam) combined with mFOLFOX6 in the treatment of patients with YWHAB-high locally advanced rectal cancer. Therefore, the tumor downstaging rate, pathological complete response rate, tumor regression grade TRG, 3-year disease-free survival rate and overall survival time may be further improved after mFOLFOX6 regimen combined with citrus flavone tablets (ElAM) for 4-6 cycles of preoperative neoadjuvant chemotherapy in these patients.

10. Voluntary participation in or out

It is entirely up to you to decide whether to participate in the study. Even if you refused to participate in this study, you will not be any adverse effects, including you should accept the medical treatment and care. If you decide to participate, you will be given and signed this informed consent form. If you decide to participate, you can still withdraw from the study at any time. Withdrawing from the study will not affect the level of care you are expected to receive.

In addition, if the physician conducting the study (the "study physician") determines that it is no longer in your best interest to continue participating in the study, he or she may decide to withdraw you.

If you decide to discontinue the study treatment, your physician will still have access to follow-up information from your future medical history.

Before you sign the consent form, please ask your doctor if there is anything in this document that you do not understand, or if you have any questions. Before you decide whether to participate in the study, read the full text of this document carefully and discuss the consultation with your doctor or anyone you think needs it (such as your family members). Only after you have signed and dated the consent form will your doctor be able to give you a full evaluation of your suitability for the study.

11. Damages

If you are harmed as a result of participating in this study, you will receive prompt treatment, and Clinical trial liability insurance has been purchased for this study to cover medical or other expenses incurred as a result of adverse events related to the study occurring during the study. The increased cost of diagnosis and treatment and the damage caused will be compensated according to Chinese laws and regulations.

Research-related injury refers to any physical injury or illness resulting from participation in a research study. If you are harmed as a result of a treatment or procedure that you would have received even if you had not participated in the study, it is not a research-related injury and you should follow all study instructions to avoid harm. By signing this informed consent form, you are not waiving any legal rights.

12. Costs and compensation for participating in the study

(1) Expenses related to the study

The examinations you need to complete to participate in this study (examination content and frequency) are exactly the same as those of patients who do not participate in this study; 5-fluorouracil, oxaliplatin and leucovorin (FOLFOX regimen) are the standard regimen of neoadjuvant chemotherapy for patients with locally advanced rectal cancer, and Aimailan is a common drug for patients with hemorrhoids. The enrolled patients were all locally advanced rectal cancer patients with hemorrhoids. Therefore, the drugs and examinations involved in this study are borne by the subjects.

(2) Compensation for participating in the study

The follow-up and review (content and frequency of follow-up review) required for your participation in this study are exactly the same as those for patients who do not participate in this study, so no additional compensation will be provided.

13. Privacy protection

If you decide to participate in this study, your participation in the study and your personal data during the study will be kept confidential. All specimens will be identified by the study number rather than by your name. Information that could identify you will not be disclosed to members

outside the research team unless your permission is obtained. All study members and study sponsors are asked to keep your identity confidential. Your files will be kept in locked filing cabinets for researchers' access only. To ensure that the study is conducted in accordance with the regulations, if necessary, the government administration or members of the ethical review committee are allowed to access your personal data at the research unit according to the regulations. No personal information about you will be disclosed when the results of this study are published.

fourteen Contact information

Feel free to consult your primary physician if you do not understand anything. If for some reason you are unable to understand the instructions made by the attending physician, or if you wish to get a more detailed explanation about something that is still unclear, please call the number below.

Investigator Institution Name: The Sixth Affiliated Hospital of Sun Yat-sen University

Investigator's name: Chief physician He Xiaosheng

If you have questions about the nature of the work or your rights during the study, or if you feel that you have been harmed by participating in the study, you may contact the Ethics Committee of the Sixth Affiliated Hospital of Sun Yat-sen University at 020-38379764 or zslyllb@mail.sysu.edu.cn. If you have any questions about the study, please contact Dr. Hu at 020-38254009.

I hereby declare that I have read the subject information of the aforementioned study "prospective, multicenter, open, randomized controlled, phase II clinical trial of neoadjuvant mFOLFOX6 plus citrus flavone tablet (ElM) in the treatment of locally advanced rectal cancer with YWHAB high expression".

1) I have understood the objectives, anticipated benefits, and risks of the study. I have understood that it is the responsibility of the research physician to provide me with any other information regarding the study itself and the injury resulting from the study.
2) I understand that my participation in the study is voluntary and that I may refuse to participate and/or withdraw my consent and discontinue participation in the study at any

time without any penalty or loss of any other benefits I have.

3) Within the scope of the study, I consent to the collection and processing of study data by the investigators and the sponsor, including information about my health. I agree that the data from my study may be processed in confidence by personnel at the study site, commissioned personnel of the sponsor, and health authorities. I agree that the sponsor or its proxies will have direct access to and access to my original medical records to verify clinical research procedures and/or information, also in a confidential manner. I agree that even if I withdraw from the trial, the data collected about me may still be used.

4) My name or any information identifying me as a study participant will not be disclosed except as required by law or regulations or as authorized by me or my legal representative.

Signature page of subject informed consent form

I have read this informed consent form.

I had the opportunity to ask questions and all questions were answered.

I understand that participation in this study is voluntary.

I can choose not to participate in this study or withdraw at any time after informing the investigators without facing discrimination or retaliation, and my medical treatment and rights and interests will not be affected.

The study physician could terminate my participation in the study if I needed additional treatment, if I did not adhere to the study plan, if I suffered a study-related injury, or for any other reason.

I received a copy of the signed informed consent form.

Subject Name: _____

Subject signature: _____

Signature of legal representative: _____

The relationship between the legal representative and the subject: _____

Date: _____ YEAR _____ Month _____

I have accurately informed the subject of this document and he/she accurately read this informed consent form and attested that the subject had the opportunity to ask questions. I certify that he/she gave his/her consent voluntarily.

Researcher Name: _____

Investigator signature: _____

Date: _____ year _____ Month _____

(*Note: Witness signature is required if the subject is illiterate or proxy signature is required if the subject is incapacitated*)