An Open-Label, Two-Arm, Phase II Clinical Trial of Neoadjuvant mFOLFOX6 Combined with Citrus Flavonoid Tablets (Alvenor) for Locally Advanced Rectal Cancer with High YWHAB Expression

Informed consent

NCT number:

Main research unit:	**The Sixth Affiliated Hospital of Sun Yat-sen University**
Version of the study protocol:	**Version 2.1, April 23,2025**
Version of informed consent:	**Version 2.1, April 23,2025**

The Sixth Affiliated Hospital of Sun Yat-sen University

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 this clinical study. Please read it carefully. If you have any questions, feel free to ask the researcher in charge of the study, who will provide detailed answers. You can make a decision based on your own circumstances, and you will have ample time to consider it.

1. research background

Compared to colon cancer, rectal cancer patients have a higher risk of pelvic recurrence, and local recurrence is significantly associated with a poorer prognosis. Determining the optimal treatment plan for locally advanced rectal cancer patients is a complex process. Besides deciding whether the surgery is curative or palliative, it is essential to consider potential post-treatment outcomes, including maintaining or restoring normal bowel function and anal control, as well as preserving urogenital function. For patients with locally advanced low rectal cancer, achieving both a cure and minimizing the impact on quality of life is particularly challenging. A common strategy to promote tumor regression in locally advanced rectal cancer patients is to enhance neoadjuvant therapy by adding systemic chemotherapy before radiotherapy and chemotherapy. Previous research by the applicant's team has found that the YWHAB/β-TrCP/β-catenin signaling axis may serve as a potential biomarker and therapeutic target for precise chemotherapy in YWHAB high-expressing colorectal cancer patients. Both in vitro and in vivo experiments have shown that FOLFOX combined with hesperidin, doxorubicin, or citrus flavonoid tablets (Aimilan, primarily composed of hesperidin and doxorubicin) can be potential treatment options for YWHAB high-expressing colorectal cancer patients. Therefore, citrus flavonoid tablets (Aimilan) have good application prospects for improving the neoadjuvant chemotherapy effect in YWHAB high-expressing locally advanced rectal cancer patients. mFOLFOX6 is one of the chemotherapy regimens recommended by guidelines for treating advanced colorectal cancer. A prospective, multicenter, randomized controlled trial (FOWARC) conducted earlier in our center found that the mFOLFOX6 regimen offers better local response rates for patients with

locally advanced rectal cancer compared to neoadjuvant radiochemotherapy. Additionally, it has lower rates of adverse reactions and postoperative complications and is safer. Based on these findings, this study aims to conduct a prospective, open-label, double-arm, Phase II clinical trial. The trial will evaluate the effectiveness and safety of the mFOLFOX6 regimen combined or not combined with citrus flavonoid tablets (Aimalang) as neoadjuvant therapy for YWHAB high-expressing locally advanced rectal cancer patients. The evaluation will include the proportion of patients achieving tumor downstaging (ypTNM 0-I stage), the proportion of patients achieving pathological complete remission, the three-year disease-free survival rate, overall survival time, and tumor regression grade (TRG). The study also aims to explore further ways to enhance the effectiveness, safety, and tolerability of neoadjuvant chemotherapy regimens for YWHAB high-expressing locally advanced rectal cancer patients, providing evidence-based medical evidence for the application of the mFOLFOX6 combined citrus flavonoid tablets (Aimalang) neoadjuvant chemotherapy regimen in this patient population.

2. purpose of research

2.1. Main research objectives:

To evaluate the proportion of patients achieving tumor downstaging (ypTNM 0-I stage) in the neoadjuvant treatment of YWHAB high-expressing locally advanced rectal cancer patients using the mFOLFOX6 regimen combined with Citrus Flavonoid Tablets (Aimalang), providing evidence-based medical evidence for the enhanced efficacy of the mFOLFOX6 regimen in YWHAB high-expressing locally advanced rectal cancer patients

2.2. Secondary research objectives:

- Efficacy evaluation: The proportion of pathological complete remission, 3-year disease-free survival (DFS), overall survival time (OS) and tumor regression grade TRG were evaluated in patients with YWHAB high expression locally advanced rectal cancer treated with mFOLFOX6 combined with citrus flavonoid tablets (Aimalang) as neoadjuvant therapy.
- Safety evaluation: The treatment-related adverse reaction rate (grade 3 or above) of mFOLFOX6 combined with citrus flavonoid tablets (Aimalang) regimen for neoadjuvant treatment of YWHAB high expression local advanced rectal cancer patients was evaluated.

3. Selection and withdrawal of subjects

3.1 Inclusion criteria:

(1) Histopathology was diagnosed as rectal adenocarcinoma, all other histological types were excluded, and the colonoscopy report or clinical physical examination suggested the presence of hemorrhoids;

(2) Clinical pathological staging of the tumor is T3-4 or N+ and M0; 9th edition AJCC TNM staging, Appendix 1)

(3) Immunohistochemical staining of tissue samples showed that YWHAB was highly expressed in rectal cancer patients;

(4) The age of obtaining informed consent is 18-75 years old;

(5) Eastern United States Cooperative Group Physical Status Score (ECOG) was 0-1 points (refer to Appendix 3);

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

(7) Based on the following laboratory test values obtained during the screening period, appropriate organ function is present: white blood cell count ≥ 3 x 109/L, neutrophil count ≥ 1.5 x 109/L, platelet count ≥ 75 x 109/L, serum total bilirubin ≤ 1.5 x upper limit of normal (UNL), aspartate aminotransferase or alanine aminotransferase ≤ 2.5 x UNL, serum creatinine ≤ 1.5 x UNL;

(8) Women of childbearing age must have a negative serum pregnancy test within 3 days prior to the start of study medication and be willing to use a medically recognized effective contraceptive method (e.g., IUD, pill or condom) during the study and for 3 months after the last dose of study medication;

(9) For male subjects whose partner is a woman of reproductive age, effective contraception was used during the study and within 3 months after the last study dose;

(10) The subject has given his/her own consent and signed an informed consent form, and the subject is willing and able to comply with planned visits, research treatments, laboratory tests and other trial procedures.

3.2 Exclusion criteria:

(1) Whole body CT, MR or PET-CT (at least including chest, whole abdomen and pelvis) confirmed distant metastasis;

(2) Whole genome testing for DPD enzyme deficiency or 7/7 homozygotes for UGT1A1*28 locus in patients;

(3) The patient has complete intestinal obstruction, active bleeding or perforation and requires emergency surgery;

(4) Previous or concurrent presence of other active malignancies (excluding malignancies that have been treated curatively and have not recurred for more than 5 years or carcinoma in situ that can be cured by adequate treatment);

(5) Having had a thrombotic or embolic event, such as a cerebrovascular accident (including transient ischemic attack), pulmonary embolism, or deep vein thrombosis, within 12 months prior to enrollment;

(6) In the 12 months prior to enrollment, the following conditions occurred: myocardial infarction, severe/unstable angina, NYHA class II or higher heart failure, clinically significant supraventricular or ventricular arrhythmias, and symptomatic congestive heart failure;

(7) Systemic use of antibiotics for more than 7 days within 4 weeks prior to enrollment, or unexplained fever>38.5°C during screening/ prior to first dose (fever due to tumor can be enrolled by investigator);

(8) Received major surgery or severe trauma, such as cesarean section, thoracotomy, or organ resection through laparoscopic surgery, within 2 months prior to enrollment (surgical incisions should be completely healed before enrollment in this clinical trial);

(9) Known to have human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS)-related diseases;

(10) The presence of interstitial lung disease, non-infectious pneumonia or uncontrolled systemic diseases (e.g., diabetes, hypertension, pulmonary fibrosis and acute pneumonia);

(11) Untreated active hepatitis (Hepatitis B, defined as HBV-DNA ≥ 500 IU/mL; Hepatitis C, defined as HCV-RNA above the detection limit of the assay) or co-infection with hepatitis B and C;

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

(13) Patients who the researchers thought were not suitable for the study.

3.3 Exit criteria:

Participants may withdraw from the trial at any time, or be asked to withdraw by the investigator or sponsor for safety or behavioral reasons or for failing to comply with the required study visit time or steps. Withdrawal criteria include:

(1) The subject withdrew the informed consent to participate in the study and refused further follow-up;

(2) Clinical adverse events, laboratory abnormalities or concurrent diseases occur, and the subject considers that continuing to participate in the study is not in the best interest of the subject;

(3) A general deterioration of health status, making it impossible to continue participation in the trial;

(4) Pregnancy events in subjects during the study;

(5) Significant deviations from the protocol, such as unqualified or non-compliance of subjects, were found after enrollment;

(6) Disappearance;

(7) Subject death;

(8) The researchers identified other situations in which withdrawal from the study was necessary, such as significant protocol violations.

4. Number of planned enrollees

This study primarily focuses on the rate of tumor downstaging (ypTNM 0-I stage) in each treatment group. Based on current data, after neoadjuvant chemotherapy with mFOLFOX6, approximately 35% of locally advanced rectal

cancer patients achieve tumor downstaging (ypTNM 0-I stage). Among these patients, about one-third (n=90) with high YWHAB expression receive a tumor downstaging rate of around 25%, while about two-thirds (n=90) with low YWHAB expression receive a tumor downstaging rate of around 43%. It is estimated that the tumor downstaging rate for patients with high YWHAB expression receiving the mFOLFOX6 combined with citrus flavonoid tablets (Aimalang) neoadjuvant chemotherapy is 40%. The significance level is set at 0.05, with a power of 0.8 and a dropout rate of 10%. The sample size was estimated to be 236 using PASS V15 software.

5. therapeutic regimen

5.1. Subject screening period

All patients with locally advanced rectal cancer (cT3-4 or N+ and M0) who agreed to participate in this clinical trial underwent YWHAB immunohistochemical testing on their colonoscopy biopsy specimens. Patients with high YWHAB expression were selected and included in the study. They were then randomly assigned to either the mFOLFOX6 group or the mFOLFOX6 combined with citrus flavonoid tablets (Aimalang) group for neoadjuvant therapy.

The following related examinations and other work should be completed within 28 days before the start of drug therapy:

- Obtain informed consent signed by the subject;
- Collect demographic data: name, sex, date of birth, height, weight, etc.;
- Collect adverse events: record adverse events from the time of signing informed consent;
- Tumor diagnosis: date of pathological confirmation, pathological grading, clinical imaging staging (TNM), clinical staging, etc.;
- History of cancer treatment;
- Imaging examination: enhanced CT of chest, abdomen and pelvis or enhanced CT of chest, abdomen and pelvis + enhanced MRI of pelvic cavity;
- The YWHAB immunohistochemical detection was performed on the endoscopic biopsy specimens.
- (Non-essential) Specify the KRAS exon 2 codons 12 and 13, exon 3 codons 59 and 61, exon 4 codons 117 and 146, NRAS exon 2 codons 12 and 13, exon 3 codons 59 and 61, exon 4 codons 117 and 146, and BRAF V600E gene status;

- (Mandatory) MMR/MSI detection of tumor tissue;
- The following screening should be completed within 7 days prior to the start of study drug therapy:
- Weight and ECOG score;
- Life signs: pulse, respiratory rate, body temperature and blood pressure;
- Comprehensive physical examination: general condition, head and face, skin, lymph nodes, eyes, ear, nose and throat, oral cavity, respiratory system, cardiovascular system, abdomen, reproductive and urinary system, musculoskeletal, nervous system and mental state;
- Complete blood count: red blood cell count, hemoglobin, platelet count, white blood cell count, neutrophil count and lymphocyte classification count;
- Routine urine: white blood cells, red blood cells, protein in urine; if protein in urine is greater than or equal to 2+,24-hour urine protein quantification should be added;
- Blood biochemical: ALT, AST, γ-GT, TBIL, DBIL, AKP, BUN or urea (preferably BUN), TP, ALB, Cr, GLU, K+, Na+, Ca2+, Mg2+, Cl−;
- Tumor markers;
- Coagulation function: activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), fibrinogen (FIB), international normalized ratio (INR);
- 12. Lead electrocardiogram: attention should be paid to QT, QTc and P-R intervals. If there are abnormalities, other relevant tests should be done according to the investigator's judgment;
- Echocardiography: at least the assessment of left ventricular ejection fraction (LVEF) should be included;
- Pregnancy test: suitable for women of childbearing age, using serum pregnancy test.

5.2. mFOLFOX6 combined or not combined with citrus flavonoid tablets (Aimalang) for neoadjuvant chemotherapy and adjuvant chemotherapy

The mFOLFOX6 regimen, in combination with Citrus Flavonoid Tablets (Aimalang), is administered for 6 preoperative and 6 postoperative cycles, with each cycle lasting 14 days. On day 1, 85 mg/m² of oxaliplatin is administered intravenously over 180 minutes; 400 mg/m² of leucovorin is administered intravenously over 120 minutes on day 1; and 2400 mg/m² of 5-fluorouracil is administered intravenously for 46 hours. Citrus Flavonoid Tablets

(Aimalang) 500mg are given orally three times daily, from day 1 to day 14 of each 14-day cycle, either in combination or alone.

This trial allows for dose adjustments. Patients who experience disease progression during neoadjuvant therapy may stop the study treatment and directly undergo surgery or treatment according to local guidelines. If a patient cannot tolerate the planned 6 cycles of neoadjuvant therapy, early surgery can be considered. Any patient who received another non-scheduled anticancer treatment before surgery will stop the study treatment and be managed according to local guidelines. The postoperative treatment for both groups is determined by the investigator, which may include continuing the mFOLFOX6 regimen combined with Citrus Flavonoid Tablets (Aimalang). It is important to note that all patients in the control group are not allowed to take Citrus Flavonoid Tablets (Aimalang) without authorization during the trial. If a patient needs to take this medication for any reason, they should consult their primary physician, who will decide whether to use an alternative drug or discontinue the patient's participation in the trial.

The following assessments should be completed prior to each treatment administration:

- Weight and ECOG score;
- vital sign ；
- check-up ；
- Complete blood count: red blood cell count, hemoglobin, platelet count, white blood cell count, neutrophil count and lymphocyte classification count;
- Blood biochemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (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), glucose (GLU), K+, Na+, Ca2+, Mg2+, Cl-.
- Routine urine: white blood cells, red blood cells, protein in urine; if protein in urine is greater than or equal to 2+,24-hour urine protein quantification should be added;
- Coagulation function: activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), fibrinogen (FIB), international normalized ratio (INR);

- Tumor markers;
- 12. Lead electrocardiogram: attention should be paid to QT, QTc and P-R intervals. If there are abnormalities, other relevant tests should be done according to the investigator's judgment;
- Document adverse events;
- Imaging Evaluation: Before surgery, after completing six cycles of the mFOLFOX6 regimen combined with Citrus Flavonoid Tablets (Aimalang), imaging evaluations were conducted, including chest, abdomen, and pelvic enhanced CT scans and pelvic enhanced MRI. If any participant suspected disease progression (such as symptom worsening) during treatment, an additional imaging examination could be performed. After completing six cycles of the mFOLFOX6 regimen, either with or without Citrus Flavonoid Tablets (Aimalang), postoperative imaging evaluations were conducted, including chest, abdomen, and pelvic enhanced CT scans and pelvic enhanced MRI. If any participant suspected disease progression (such as symptom worsening) during treatment, an additional imaging examination could be performed.

5.3. Follow-up period:

Survival follow-up period: This period ends when the subject dies, is lost to follow-up, withdraws from the study, or refuses to continue providing information, or when the sponsor terminates the study. During this period, a visit is conducted every three months through telephone or other effective methods to collect survival and subsequent anti-tumor treatment information (if the subject starts new anti-tumor treatment, the treatment plan and its duration should be recorded). For subjects without evidence of disease progression on imaging, imaging assessments should continue according to the frequency specified in clinical guidelines (the follow-up examination includes regular chest, abdomen, and pelvis enhanced CT scans or chest, abdomen, and pelvis enhanced CT scans + pelvic enhanced MRI as required by the oncology department) until disease progression, death, loss to follow-up, withdrawal from the study, refusal to continue providing information, initiation of other anti-tumor treatment, or termination of the study. Every effort should be made to obtain imaging evidence of disease progression for these subjects.

During the follow-up period, the attending physician should suggest whether the patient should go to the local hospital or return to our hospital for further examination to clarify the

disease progress according to the actual situation of the patient, which should include the following contents:

- Medical history and physical examination (e.g. digital rectal examination)
- Routine blood tests (including red blood cell count, hemoglobin, platelet count, white blood cell count, neutrophil count, and lymphocyte differential count), biochemical tests (such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transferase (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), potassium (K+), sodium (Na+), calcium (Ca2+), magnesium (Mg2+), chloride (Cl-)), coagulation function tests (such as activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), fibrinogen (FIB), international normalized ratio (INR)), and tumor-related markers such as CEA and CA19-9, will be monitored postoperatively: once every 3 months for 2 years, then once every 6 months for 5 years, and annually after 5 years;
- Imaging evaluation: enhanced CT of chest, abdomen and pelvis or enhanced CT of chest, abdomen and pelvis + enhanced MRI of pelvic cavity every six months for the first two years after surgery, then once a year for five years;
- A colonoscopy should be performed within one year after surgery. If any abnormalities are found, a follow-up examination should be conducted within one year; if no polyps are detected, a follow-up examination should be conducted within three years; then once every five years. All colorectal adenomas identified during follow-up examinations are recommended for excision. If the preoperative colonoscopy did not complete a full colon examination, it is recommended to perform a colonoscopy 3 to 6 months postoperatively;
- (Not mandatory) PET-CT is not a routine recommended examination item. For patients with existing or suspected recurrence and distant metastasis, PET-CT examination can be considered to exclude recurrence and metastasis;
- (Not required) 12-lead electrocardiogram, routine urine, echocardiogram and pregnancy test.

6. matters need attention

You should know the following:

1) In most cases, treatment and examination will be carried out in accordance with the above regulations. However, if your doctor considers it necessary, other examinations will be carried out at any time.
2) Please follow your doctor's instructions for treatment. If you have any discomfort or adverse reactions, please inform your doctor immediately. If it is necessary to discontinue the study treatment, he/she will discuss the next treatment plan with you.
3) After your treatment, your research doctor will stay in touch with you.
4) Be sure to tell your doctor: What other medications are you taking, have you seen another doctor, have you received a new treatment, have you participated in another clinical study, or how has your feeling changed since your last follow-up.
5) If other doctors invite you to participate in other clinical programs, please tell him or her that you are participating in this program.

7. Pregnancy and contraception

You should not take part in this study if you think you are pregnant or if you might become pregnant during treatment. Therefore, your doctor will check that you are using a reliable method of contraception before starting drug treatment.

For women:

Women of childbearing age must have a pregnancy test within 7 days of randomization. If there is any suspicion that contraception may have failed or if menstrual cycles change, the pregnancy test must be repeated. If you become pregnant during the study, you must immediately inform your study doctor.

For men:

Because the effects of the drugs used in this study on germ cells are unknown, you and your partner must use contraception during this period. If your partner becomes pregnant during or within 6 months after you stop taking the drug, you must inform your doctor.

8. potential risk

The primary components of this study (mFOLFOX6) are all recommended standard first-line treatment regimens for colorectal cancer, as outlined in the 'China Colorectal Cancer Diagnosis and Treatment Guidelines (2024 Edition)' by the National Health Commission and

other domestic and international guidelines. Previous data indicate that the toxic side effects are within a safe and controllable range. During blood draws, there may be slight pain or bruising, which can be temporarily caused by peripheral intravenous infusion and injection site congestion. The study medication may also cause side effects.

The potential side effects of the drugs used in the treatment regimen that may be used in this clinical trial are as follows:

(1) Common adverse reactions of 5-FU include decreased white blood cell and platelet count, diarrhea, decreased appetite, stomatitis, nausea, vomiting, and skin reactions.

(2) The common adverse reactions of oxaliplatin include neurotoxicity, nausea, vomiting, diarrhea, decreased white blood cells and platelets, abdominal pain, and liver and kidney function impairment.

(3) The relatively common adverse reactions of citrus flavonoid tablets (Aimalang) are gastrointestinal reactions: diarrhea, indigestion, nausea, vomiting, etc. (the incidence of gastrointestinal adverse reactions is less than 1/100 <1/10).

In previous studies, patients have experienced these side effects, but you may also experience other side effects that are unpredictable at this point.

These side effects may cause minor inconvenience or be serious, but if any occur, your doctor will keep a close eye on you.

Although the treatment is effective for your condition, these side effects are still possible.

The doctor will regularly assess the effectiveness of the treatment. If no effectiveness is observed, the treatment will be discontinued.

If any new information related to the study drug that may affect your decision to continue participating in the study arises during the course of the study, the doctor will inform you in a timely manner.

The trial subjects received neoadjuvant chemotherapy for 4-6 cycles and adjuvant chemotherapy for 6-8 cycles, using the mFOLFOX6 regimen combined with Citrus Flavonoid Tablets (Aimalang). Compared to the current NCCN guidelines for the mFOLFOX6 regimen, some trial subjects received an additional dose of Citrus Flavonoid Tablets (Aimalang). The overall adverse reaction rate with Aimalang may be slightly higher than that of the current standard regimen.

Risk management:

During the study treatment, the subjects will be continuously monitored for drug-related adverse reactions. If a low-level toxicity reaction occurs, the investigator may, after consultation with the medical monitor or sponsor, decide that dose adjustment or delayed administration is beneficial to the subject's safety and may adjust the dose or delay the administration. If any interruption in medication occurs, the resumption of treatment can be delayed by up to 14 days to allow the subject to recover from the toxicity. In cases of severe hematological and liver adverse events (excluding liver function impairment due to disease progression), the doses of oxaliplatin and 5-FU should be reduced simultaneously. If severe diarrhea and mucosal toxicity (excluding vomiting and hair loss) occur, the dose of 5-FU should be reduced.

alternative scheme ：

Participants in this study had the option of CAPEOX with or without citrus flavonoid tablets (Aimalang), or FOLFIRI with or without citrus flavonoid tablets (Aimalang).

9. Potential benefits

Based on our center's existing clinical data, patients with locally advanced rectal cancer who received mFOLFOX6 neoadjuvant chemotherapy had a tumor downstaging rate of about 35% (ypTNM 0-I stage). Among these patients, those with high YWHAB expression (about one-third, n=90) had a tumor downstaging rate of about 25%, while those with low YWHAB expression (about two-thirds, n=90) had a tumor downstaging rate of about 43%. Our team's earlier research on the underlying mechanisms also found that hesperidin (the main component of citrus flavonoids tablets) combined with FOLFOX for treating YWHAB/β-catenin axis may serve as a potential biomarker and therapeutic target for precise chemotherapy in patients with high YWHAB expression colorectal cancer. Therefore, patients receiving the mFOLFOX6 regimen combined with citrus flavonoids tablets (Aimalang) for 4-6 cycles of neoadjuvant chemotherapy before surgery and 6-8 cycles of adjuvant chemotherapy after surgery may see further improvements in tumor downstaging rate, complete pathological response rate, tumor shrinkage grade TRG, 3-year disease-free

survival rate, and overall survival time.

10. Voluntary participation or withdrawal

Whether to participate in this study is entirely up to you. Even if you choose not to participate, you will not be adversely affected, including the medical treatment and care you are entitled to. If you decide to participate, you will receive and sign this informed consent form. You can withdraw from the study at any time if you choose to do so. Withdrawing from the study will not affect the level of care you are entitled to.

In addition, if the physician conducting the study ("the Study Physician") considers that it is no longer in your best interest to continue the study, he/she will decide to withdraw you.

If you decide to discontinue your research treatment, the doctor will still be able to obtain follow-up information from your future medical history.

Before you sign the consent form, if you have any questions or misunderstandings about this document, please consult your doctor. Before deciding whether to participate in the study, read this document carefully and discuss it with your doctor or any other person you consider necessary (such as family members). Only after you have signed the consent form and the date will your doctor be able to provide a comprehensive evaluation to determine if you are suitable for the study.

11. compensation for damages

If you are injured as a result of participating in this study, you will receive timely treatment and free insurance to cover any medical or other expenses incurred as a result of any adverse events during the study. Any additional treatment costs and damages will be compensated in accordance with Chinese law.

12. privacy protection

If you decide to participate in this study, your personal information during the trial will be kept confidential. All samples will be labeled with a research number rather than your name. Information that could identify you will not be disclosed to anyone outside the research team unless you give permission. All members of the research team and the sponsor are required to

keep your identity confidential. Your records will be stored in a locked file cabinet for researchers to access only. To ensure the study is conducted according to regulations, government authorities or members of the ethics review committee may review your personal information at the research facility as needed. When the results of this study are published, no personal information about you will be disclosed.

13. contact information

If you have any questions, please feel free to consult your attending physician. If for some reason you do not understand the instructions given by your attending physician, or if you would like more detailed instructions on what is still unclear, please call the following number.

Name of the research institution: The Sixth Affiliated Hospital of Sun Yat-sen University

Name of researcher: He Xiaosheng, chief physician

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

In this statement, I have read the subject information of the above study "Open, double-arm, phase II clinical trial of mFOLFOX6 combined with citrus flavonoid tablets (Aimalang) regimen as neoadjuvant therapy for locally advanced rectal cancer with high expression of YWHAB".

1) I have understood the purpose of this study, the expected benefits and risks. I have understood that the research doctor has a responsibility to provide me with any other information about the study itself and the damage caused by the study.
2) I understand that I am participating in the study voluntarily and that I can refuse to participate and/or withdraw my consent at any time and stop participating in this study without penalty or loss of any other interests I have.
3) Within the scope of this study, I agree to allow researchers and sponsors to collect and process my health data. I also agree that my data can be processed confidentially by the research center staff, sponsors' representatives, and health regulatory authorities. I agree

that the sponsor or its representative may directly access and review my original medical records to verify the procedures and/or information of the clinical study, and this will be done in a private and confidential manner. I agree that even if I withdraw from the trial, the data collected about me can still be used.

4) My name or any information that could identify me as a participant in the study will not be disclosed except as required by law or authorized by me/my legal representative.

Page of informed consent signed by the subject

I have read this informed consent form.

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

I understand that participation in this study is voluntary.

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

If I need other treatment, or if I do not follow the study plan, or if there is any injury related to the study or for any other reason, the physician may discontinue my participation in this study.

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

Subject's name: _____

Subject signature: _____

Signature of legal agent: _____

The relationship between legal agent and subject: _____

Date: _____ _____ _____

I have accurately informed the subject of this document, he/she has read this informed consent form accurately and has demonstrated that the subject has had the opportunity to ask questions. I have demonstrated that he/she has given his/her voluntary consent.

Name of researcher: _____

Researcher signature: _____

Date: __ year __ month __ day

(Note: if the subject is illiterate, the witness should sign; if the subject is incompetent, the agent should sign)