Informed Consent Form

Gossypol acetate Combined with Bevacizumab and FOLFIRI as Second-Line Therapy for Metastatic Colorectal Cancer with TP53 Mutation and LRPPRC Positivity: A Single-Center, Single-Arm Clinical Study

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We are initiating a ('Gossypol acetate Combined with Bevacizumab and FOLFIRI as Second-Line Therapy for Metastatic Colorectal Cancer with TP53 Mutation and LRPPRC Positivity: A Single-Center, Single-Arm Clinical Study'). You meet the inclusion criteria for this study, and we would like to invite you to participate. This informed consent form explains the study purpose, procedures, potential benefits, risks, and possible inconveniences or discomforts. Please read it carefully before making your decision regarding participation. During the explanation and discussion of the informed consent form by the researchers, you may ask questions at any time and request clarification on any aspects you do not understand. You may discuss with family members, friends, and your attending physician before making a decision.

The principal investigator of this study is (Guiying Wang, The Second Hospital of Hebei Medical University). The research is funded by (Hebei Provincial Major Science and Technology Support Program Project, Special Category: Biomedical Innovation Initiative, Project Title: Research and Clinical Translation of Chemosensitizing Drugs for P53-Mutated Colorectal Cancer).

1. Why was this study conducted?

This study aims to explore a novel therapeutic combination to enhance chemotherapy efficacy in patients with advanced colorectal cancer harboring specific genetic characteristics. Colorectal cancer represents a prevalent malignant tumor, and many patients develop chemoresistance during treatment, leading to diminished therapeutic outcomes. Among these factors, TP53 gene mutation constitutes a major contributor to drug resistance, yet effective targeted therapies for this mutation remain unavailable.

Recent research has revealed that a protein called LRPPRC plays a pivotal role in the chemoresistance mechanism induced by TP53 mutations. The clinically approved drug Gossypol acetate (GAA) specifically reduces LRPPRC protein levels. Preclinical studies demonstrate its combination with chemotherapeutic agents can reverse drug resistance mediated by TP53 mutations.

Therefore, this study aims to evaluate the efficacy and safety of Gossypol acetate tablets combined with Bevacizumab and FOLFIRI chemotherapy regimen for patients with TP53-mutated, LRPPRC-positive metastatic colorectal cancer who have experienced first-line treatment failure, seeking to provide new therapeutic options for this population.

2. Which individuals will be invited to participate in this study?

(1) TP53 mutation and LRPPRC-positive status; (2) Patients with metastatic colorectal cancer who have failed prior first-line therapy; (3) Patients with metastatic colorectal cancer meeting all inclusion criteria and no exclusion criteria.

Inclusion Criteria:

1. Female patients aged ≥18 years;
2. Histopathologically or cytologically confirmed colon or rectal adenocarcinoma;
3. Imaging studies confirming unresectable metastatic disease;
4. At least one measurable lesion (per RECIST v1.1);
5. Received first-line oxaliplatin-based therapy received;
6. ECOG performance status of 0-2;
7. Expected survival time ≥3 months;
8. Bone marrow function: neutrophil count (ANC) ≥1.5×10⁹/L, platelets (PLT) ≥100×10⁹/L, hemoglobin (Hb) ≥90g/L, white blood cell count (WBC) ≥3.0×10⁹/L;
9. Liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) ≤2.5×ULN (upper limit of normal), or ≤5×ULN in cases with

liver metastases; total bilirubin ≤1.5×ULN;

10. Renal function: Serum creatinine (Cr) ≤1.5×ULN or creatinine clearance ≥60 ml/min (calculated by Cockroft-Gault formula), with urine protein < 2+.

11. Coagulation profile: Normal coagulation function (International Normalized Ratio INR ≤1.5).

12. Capable of fully comprehending the study details; patients and/or legal representatives voluntarily agree to participate in this trial and sign the informed consent form.

Exclusion Criteria:

1. Patients diagnosed with other malignant tumors within 5 years prior (excluding cured carcinoma in situ and basal cell carcinoma of the skin).

2. Previous receipt of Irinotecan or Irinotecan liposome-based chemotherapy;

3. Massive pleural effusion or ascites requiring therapeutic intervention;

4. Active, uncontrolled bacterial, viral, or fungal infection requiring systemic therapy, defined as persistent signs/symptoms related to the infection without improvement despite appropriate antibiotics, antiviral agents, and/or other treatments;

5. Known active HIV infection (i.e., HIV1/2 antibody positive); Untreated active HBV infection (defined as HBsAg/HBcAg positivity with HBV-DNA copies exceeding the upper limit of normal at the local laboratory of the investigational site) and HCV infection (HCV antibody positive with HCV-RNA levels above the upper limit of normal);

6. Uncontrolled systemic diseases, including cardiovascular conditions such as unstable angina, myocardial infarction, congestive heart failure, severe unstable ventricular arrhythmias, or history of severe pericardial disease; Uncontrolled hypertension (defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg after standardized antihypertensive therapy), or history of hypertensive crisis/hypertensive encephalopathy; uncontrolled diabetes mellitus;

7. Presence of severe gastrointestinal diseases (including active bleeding, obstruction greater than grade 1, diarrhea greater than grade 1, or gastrointestinal perforation);

8. History of laparotomy, thoracotomy, or bowel resection within 28 days prior to enrollment;

9. Presence of interstitial pneumonia or pulmonary fibrosis;

10. Known allergy or intolerance to the investigational drugs or their excipients;

11. History of pulmonary hemorrhage/hemoptysis ≥ grade 2 (defined as bright red blood ≥ 2.5 mL) within one month prior to enrollment;

12. History of arterial thrombosis, severe hemorrhage (except surgery-related bleeding), or predisposition to thrombosis/severe hemorrhage within 6 months prior to enrollment;

13. Presence of central nervous system metastases;

14. Serum albumin ≤3 g/dL;

15. Concomitant use of strong inhibitors or inducers of CYP3A4, CYP2C8, or UGT1A1;

16. Pregnant or lactating women, or patients of childbearing potential who refuse to adopt appropriate contraceptive measures during the trial;

17. Participation in other investigational studies within 30 days before the first dose of study drug;

18. Patients allergic to Bevacizumab, irinotecan, fluorouracil, calcium folinate, or compound gossypol acetate tablets;

19. Patients deemed by the investigator to be unsuitable for participation in this study.

3. How many participants will be enrolled in this study?

This study plans to enroll (20) subjects.

4. What does this study involve?

This single-center, single-arm clinical study plans to enroll 20 patients with advanced colorectal cancer who have received first-line therapy. The treatment regimen consists of

gossypol acetate tablets + Bevacizumab + FOLFIRI.

The primary endpoint is objective response rate (ORR), with secondary endpoints comprising disease control rate (DCR), duration of response (DoR), overall survival (OS), progression-free survival (PFS), and safety.

If you decide to participate in this study, your physician will first have you sign this informed consent form (ICF), and subsequently determine your eligibility for participation before treatment initiation. Your participation in this study is expected to require 16 months (4 months for treatment and 12 months for follow-up duration).

Prior to study enrollment, you will undergo eligibility determination: your physician may conduct the following inquiries and examinations:

• Obtain your past medical history, present medical history, date of birth, and ethnicity;

• Measure your height, weight, and vital signs, and perform a physical examination;

• Require you to undergo the following tests: complete blood count, blood biochemistry, urinalysis, coagulation profile, biomarkers (including CEA and CA199), electrocardiogram, pregnancy test, HIV/HBV/HCV screening, and imaging studies (CT or MRI);

• Require UGT1A1 genetic testing (a gene associated with irinotecan adverse reactions) and colorectal cancer histopathological or cytological testing. If previous test results exist, you must provide them for confirmation by your physician.

• For women of childbearing potential, physicians will additionally require a pregnancy test.

• If you meet the inclusion criteria, during the treatment phase you will receive therapy with gossypol acetate tablets + bevacizumab + FOLFIRI regimen:

Irinotecan 70 mg/m², administered as a 90-minute intravenous infusion;

5-Fluorouracil 2400 mg/m², delivered as a 46-hour continuous intravenous infusion;

Calcium folinate 400 mg/m², administered as a 30-minute intravenous infusion;

Bevacizumab 5 mg/kg, administered as a 30-90 minute intravenous infusion.

Gossypol acetate tablets, 20mg orally once daily

Administration occurs on day 1 of each cycle, repeated every two weeks, continuing until disease progression or intolerable toxicity occurs.

During treatment, your physician will adjust the dosage based on your individual circumstances and tolerance to chemotherapy.

Before each treatment cycle, medical staff will measure your height, weight, and vital signs; perform a physical examination and ECOG performance status assessment; you will undergo complete blood count, blood biochemistry, and urinalysis; imaging studies (CT or MRI) will be conducted every 8 weeks; coagulation profile and biomarker testing will be performed every 4 weeks.

The study doctor will inquire about any discomfort experienced during the research period and any new treatments received. Concurrently, your study physician will further evaluate whether your condition remains suitable for continued participation in the trial.

5. How long will this study last?

If you decide to participate in this study, your physician will first have you sign this informed consent form (ICF), and subsequently determine your eligibility for participation before treatment initiation. Your participation in this study is expected to require 16 months (4 months for treatment and 12 months for follow-up, with assessments every 2 months).

6. What are the risks associated with participating in this study?

(1) The most common serious adverse reactions (occurring in ≥2% of patients) during Irinotecan treatment are:

Diarrhea, vomiting, febrile neutropenia, nausea, fever, sepsis, dehydration, septic shock, pneumonia, acute renal failure, and thrombocytopenia.

(2) Potential adverse events associated with 5-fluorouracil include:

1) Nausea, anorexia, or vomiting. These symptoms are generally mild at standard doses. May occasionally cause stomatitis, oral ulcers, abdominal discomfort, or diarrhea. Peripheral leukopenia is common (typically reaching nadir at 2-3 weeks after treatment initiation and resolving by 3-4 weeks), while thrombocytopenia is rare. Rare occurrences include cough, dyspnea, or cerebellar ataxia.

2) Long-term administration may induce neurotoxicity.

3) Myocardial ischemia has been occasionally observed following administration, potentially manifesting as angina pectoris and electrocardiogram changes. Discontinue therapy if cardiovascular adverse reactions (arrhythmias, angina, ST-segment changes) are confirmed.

(3) Potential adverse events associated with Bevacizumab include:

1) The most frequently reported drug adverse reactions in patients receiving Bevacizumab across clinical trials were hypertension, fatigue or asthenia, diarrhea, and abdominal pain.

2) Analysis of clinical safety data suggests that the occurrence of hypertension and proteinuria during Bevacizumab treatment may be dose-dependent.

3) Hemorrhagic events, including pulmonary hemorrhage/hemoptysis observed more frequently in non-small cell lung cancer patients. Across clinical trials for all indications, the overall incidence of Grade 3-5 bleeding events in Bevacizumab-treated patients ranged from 0.4% to 6.9%.

4) Arterial thromboembolism. Across clinical trials, the overall incidence of arterial thromboembolism in the bevacizumab group was 5.9%, compared to 1.7% in the chemotherapy control group.

(4) Potential Risks of Gossypol

Gossypol exerts inhibitory effects on hormone synthase enzymes and endometrial cell DNA synthesis, while also demonstrating regulatory actions on ovarian hormones and exhibiting inhibitory effects on tumor cell growth. It is used to treat gynecological diseases, including menorrhagia or irregular menstruation, uterine fibroids, endometriosis, among others. The initial daily dose ranges from 20mg to 30mg, typically requiring 60-80 days to accumulate the total effective dose of 1-2g. Subsequently, the regimen transitions to a maintenance phase of 15-40mg administered twice weekly. Studies indicate that Gossypol monotherapy (30-50 mg) demonstrates efficacy in refractory breast cancer after multiple lines (3-4 lines) of treatment. The maximum tolerated dose (MTD) was established at 40mg/day, with dose-limiting toxicity (DLT) occurring at 50mg/day. The disease stabilization rate reached 60% in the 30mg cohort, while one patient in the 40mg group achieved minimal response (MR), with overall acceptable patient tolerability. Common treatment-related adverse events in the 30mg-40mg dose group included nausea (30%, Grade I-II), fatigue (15%, Grade I-II), vomiting (15%, Grade I-II), dysgeusia (15%, Grade I-II), and diarrhea (10%, Grade I-II). Dose-limiting dermatological toxicity was observed in the 50mg/day treatment group (60%, Grade III).

5. Risks of CT

During the CT scan, you will be exposed to minimal radiation. This exposure level falls within safe limits and poses very low health risk.

6. Risks of Blood Sampling

Risks associated with blood draws from the arm include transient discomfort and/or bruising. Although unlikely, infection, excessive bleeding, clotting, or fainting may occur.

Further details are elaborated in the package insert. All anti-tumor therapies carry inherent risks. While the drugs used in this study are domestically approved, unforeseen adverse reactions may arise during research due to the disease itself, pre-existing comorbidities, or drug combinations. Prior to each treatment, the Investigator will conduct

examinations/assessments of the Subjects. Treatment continuation is permitted only if eligibility criteria are met; otherwise, treatment should be delayed or study therapy discontinued.

Investigators will monitor adverse events occurring during the study. It is critically important that you promptly inform the Investigator of any discomfort experienced during the trial or if you are hospitalized. The Investigator may administer additional medications to manage adverse events. Should either you or the Investigator determine that you are unable to tolerate these adverse events, the investigational drug dosage may be reduced, temporarily held, or permanently discontinued.

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

By participating in this clinical research, your disease may potentially be alleviated; however, it is also possible that the expected outcomes may not be achieved, or disease progression may occur. While the treatment in this study may not provide direct benefit to you, your participation will assist physicians in advancing research and understanding of this disease category, thereby improving future diagnosis and treatment standards. We hereby express our sincere appreciation for your participation in scientific research and your contribution to the advancement of medical science.

8. Am I obligated to participate in and complete this study?

Your participation in this study is entirely voluntary.

You may decline participation if unwilling, and this decision will not have any negative impact on your current or future medical care. Even after providing consent, you retain the right to withdraw from the study at any time by notifying the Investigator. Your withdrawal will not affect your access to normal medical services. As a general principle, after your withdrawal, the Investigator will securely maintain your relevant information until its final destruction and will neither continue using nor disclosing such information during this period. However, in the following very rare circumstances, the Investigator will continue using or disclosing your relevant information even after your withdrawal or study completion. These circumstances include:

- Removing your information may compromise the scientific validity of the research outcomes or the assessment of data security;
- To provide limited information for research, teaching, or other activities (such information will not include your name, ID number, or other personally identifiable details);

Should any information emerge that might affect your decision to continue participating in this study, we will promptly notify you.

9. Regarding Research Costs and Compensation

All medications used in this study are commercially available in China, and the related examinations constitute routine clinical procedures. During the study treatment period, the investigational drug Gossypol acetate tablets and chemotherapeutic agents for the FOLFIRI regimen (Irinotecan + Calcium folinate + Fluorouracil) will be provided by the Investigator. You will be required to bear the costs of other medications and all research-related medical examinations, diagnostic and treatment expenses out of pocket.

This study does not provide financial compensation for transportation, meals, lost wages, or other incidental expenses.

10. Will subjects receive remuneration for participating in this study?

This study does not provide remuneration

11. Procedures for handling study-related injuries?

In the event of accidental injury resulting from study procedures performed to achieve research objectives, we will provide necessary medical care. Pursuant to relevant Chinese laws and regulations, we shall bear corresponding medical expenses and provide appropriate financial compensation for such injuries.

12. Will my information be kept confidential?

If you decide to participate in this study, both your participation and personal data will remain confidential. Your blood/urine specimens will be labeled with study codes rather than your name. No identifiable information about you will be disclosed to anyone outside the research team without your prior permission. All research personnel and relevant parties are required to maintain the confidentiality of your identity. Your records will be securely stored and accessible only to authorized researchers. To ensure compliance with regulations, members of government regulatory authorities, school authorities, or ethics committees may review your personal information at the research institution when necessary. No personally identifiable information about you will be disclosed when the research results are published.

13. If I have any questions or difficulties, whom should I contact?

If you have any questions regarding this study, please contact Haisong Xin Doctor, Telephone: 16630159968 。

For questions concerning subjects' rights and interests, you may contact the Scientific Research Ethics Committee of the Second Hospital of Hebei Medical University at Telephone: 0311-66002811, Email: scitech_2h@188.com.

Investigator Statement

"I have informed the subject about the background, objectives, procedures, risks, and benefits of the single-center, single-arm clinical research investigating Gossypol acetate tablets combined with Bevacizumab and FOLFIRI as second-line therapy for TP53-mutated, LRPPRC-positive metastatic colorectal cancer. Sufficient time was provided to read the informed consent form, discuss with others, and all study-related questions were answered; I have informed the subject that they may contact Dr. Wang Guiying regarding any study-related questions at any time, and may contact the Peking University Biomedical Ethics Committee regarding matters concerning their rights/interests at any time, and have provided accurate contact information; I have informed the subject that they may withdraw from this study; I have informed the subject that they will receive a copy of this informed consent form containing both my signature and their signature.

Signature of Investigator Obtaining Informed Consent Date

Subject Statement

"I have been informed about the background, purpose, procedures, risks, and benefits of Gossypol acetate Combined with Bevacizumab and FOLFIRI as Second-Line Therapy for Metastatic Colorectal Cancer with TP53 Mutation and LRPPRC Positivity: A Single-Center, Single-Arm Clinical Study."I have been given sufficient time and opportunity to ask questions, and I am satisfied with the answers provided. I have also been informed whom to contact when I have questions, wish to report difficulties or concerns, have suggestions regarding the study, or need further information or assistance. I have read this informed consent form and agree to participate in this study. I understand that I may withdraw from this study at any time during the research period without giving any reason. I have been informed that I will receive a copy of this informed consent form bearing both my signature and the Investigator's

signature.

Subject Signature Date

(When the subject lacks or has insufficient capacity to provide informed consent, add or substitute the following method:)

Signature of Legal Representative Date

Relationship to the Subject