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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Study Duration: February 1, 2026 - February 1, 2028

Protocol Version Number: V1.0

Protocol Version Date: January 4, 2026

I. **Study Background**

Globally, colorectal cancer (CRC) ranks third in incidence and fourth in mortality among malignant tumors. Approximately 900,000 individuals die from colorectal cancer annually, accounting for about 10% of all cancer-related deaths, posing a severe threat to human health [1]. Chemotherapy resistance in colorectal cancer is a complex multifactorial biological process. Recent studies indicate that mutations in tumor suppressor genes are also key contributors to chemotherapy resistance, with tumor protein p53 (TP53) gene being the most representative example [2]. Whole-genome analyses reveal that 60% of colorectal cancer patients harbor TP53 gene mutations [2], rising to 80% among Stage IV colorectal cancer patients with distant metastases. TP53 mutations not only abolish the protein's transcriptional activation of tumor suppressor genes but also confer novel pro-oncogenic and chemotherapy-resistant functions. Multiple previous studies have reported that TP53 gene mutations promote chemotherapy resistance in colorectal cancer by facilitating tumor cell DNA damage repair, chemotherapeutic drug efflux and inactivation, and apoptosis resistance [3]. Over recent decades, restoring TP53 protein function has become a highly attractive strategy for developing novel antitumor drugs [4]. However, as a nuclear transcription factor, the TP53 protein lacks typical druggable characteristics. Regrettably, few TP53-targeted drug development programs have advanced to late-stage clinical

trials [5]. Therefore, identifying novel therapeutic targets and corresponding agents to reverse TP53-induced chemotherapy resistance holds significant importance for improving the prognosis of patients with TP53-mutant colorectal cancer.

In our recent study, we first reported that Leucine-Rich Pentatricopeptide Repeat Containing protein (LRPPRC) serves as a critical functional downstream effector and therapeutic target in TP53 mutation-induced chemotherapy resistance in colorectal cancer. Wild-type TP53 and mutant TP53 oppositely regulate LRPPRC expression. In wild-type TP53 cells, the TP53-miR-34a-LRPPRC-MDR1 signaling pathway is activated, leading to reduced LRPPRC and MDR1 protein levels. Conversely, in mutant P53 cells, this pathway is activated in reverse, resulting in accumulation of LRPPRC and MDR1 proteins that mediate chemotherapy resistance in colorectal cancer. Silencing LRPPRC demonstrates substantial potential for reversing TP53 mutation-driven chemotherapy resistance [6]. In previous research, Professor Fang Xiaohong from the Institute of Chemistry, Chinese Academy of Sciences and Professor Song Yongmei from the Cancer Hospital of the Chinese Academy of Medical Sciences discovered that Gossypol Acetate (GAA), a clinically approved established gynecological drug, can specifically target and degrade LRPPRC [7]. This finding provides a potential approach to reverse TP53-mediated chemotherapy resistance by targeting LRPPRC. Our further

experiments demonstrate that combining GAA with chemotherapeutic agents can reverse chemotherapy resistance caused by TP53 mutations.

In second-line treatment for advanced unresectable metastatic colorectal cancer, FOLFIRI (irinotecan + 5-FU/LV) or FOLFOX (oxaliplatin + 5-FU/LV) with or without targeted therapy drugs constitute standard regimens. For patients who received first-line oxaliplatin-based chemotherapy, second-line irinotecan-based chemotherapy is recommended [8].

Based on our preliminary basic research findings and previous studies, gossypol acetate (GAA) demonstrates synergistic effects with conventional chemotherapy in TP53-mutated colorectal cancer cells. It is worthwhile to clinically investigate whether this combination strategy can yield superior therapeutic outcomes in metastatic colorectal cancer patients with both TP53 mutation and LRPPRC positivity. Therefore, this study aims to evaluate the efficacy and safety of Gossypol Acetate Tablets combined with Bevacizumab and FOLFIRI as second-line treatment for metastatic colorectal cancer with TP53 mutation and LRPPRC positivity.

II. Study Objectives

To investigate the efficacy and safety of Gossypol Acetate Tablets combined with Bevacizumab and FOLFIRI as second-line treatment for metastatic colorectal cancer with TP53 mutation and LRPPRC positivity in the Chinese population.

III. Study Design

(I) Study Population

Patients meeting all criteria: TP53 mutation and LRPPRC positivity; metastatic colorectal cancer patients with failure of first-line treatment. Patients with metastatic colorectal cancer who meet the inclusion criteria without meeting any exclusion criteria.

Inclusion Criteria:

1. Female patients aged ≥18 years;

2. Histopathologically or cytologically confirmed colon or rectal adenocarcinoma;

3. Imaging-confirmed unresectable metastatic disease;

4. At least one measurable lesion (per RECIST v1.1);

5. Previously received first-line oxaliplatin-based therapy;

6. ECOG score 0-2;

7. Expected survival time ≥3 months;

8. Bone marrow function: Neutrophils (ANC) ≥1.5×10^9/L, Platelets (PLT) ≥100×10^9/L, Hemoglobin (Hb) ≥90 g/L, White blood cells (WBC) ≥3.0×10^9/L;

9. Liver function: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) ≤2.5×ULN (upper limit of normal); ≤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); urine protein <2+;

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

12. Capable of comprehending the study details. Patients and/or their legal guardians voluntarily agree to participate in this trial and sign the Informed Consent Form.

Exclusion criteria:

1. Patients diagnosed with other malignancies within the past 5 years (except cured carcinoma in situ and basal cell carcinoma of the skin);

2. Previous chemotherapy based on irinotecan/liposomal irinotecan;

3. Massive pleural effusion or ascites requiring interventional treatment;

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

5. Known active HIV infection (i.e., positive for HIV-1/2 antibodies); Untreated active HBV infection (defined as positive for HBsAg/HBcAg with HBV-DNA copies exceeding the upper limit of normal at the central laboratory) and active HCV infection (positive for HCV antibodies 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 disorders (including active bleeding, obstruction of Grade >1, diarrhea of Grade >1, or gastrointestinal perforation);

8. History of laparotomy, thoracotomy, or intestinal 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 ≥2.5 mL of bright red blood) within one month prior to enrollment;

12. History of arterial thromboembolism, severe hemorrhage (excluding surgical bleeding), or existing predisposition to thromboembolism/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, and UGT1A1;

16. Women who are pregnant or breastfeeding, as well as patients of childbearing potential who refuse to use adequate contraception during the trial;

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

18. Patients with allergies to Bevacizumab, irinotecan, fluorouracil, calcium folinate, or Compound Gossypol Acetate Tablets;

19. Patients deemed unsuitable for participation by the Investigator's judgment.

(II) Patient Grouping

This single-arm, single-center clinical study does not involve patient grouping.

（三）Study Content

3.1 Study Content

3.2 Follow-up Plan (Schedule and Components)

Visit / Visit Point	Screening Period [1]	Treatment Period [2]	End of Treatment [3]	Follow-up [4]
Informed Consent Form	×			
Inclusion/Exclusion Criteria	×			
Medical History Collection [5]	×			
Demographic Data [6]	×			
Height and Weight	×	×		
Vital Signs [7]	×	×	×	
Physical Examination [8]	×	×	×	
ECOG score	×	×	×	
Complete Blood Count [9]	×	×	×	
Blood Biochemistry [10]	×	×	×	
Urinalysis [11]	×	×	×	
Coagulation Function [12]	×	×	×	
Biomarker [13]	×	×	×	
Electrocardiogram	×		×	
Pregnancy Test [14]	×			
HIV/HBV/HCV Testing	×			
UGT1A1*28 Testing	×			
RAS and TP53 Status Testing, and LRPPRC Immunohistochemical Testing [15]	×			
Histopathological or Cytological Testing	×			
Tumor Assessment [16]	×	×	×	×
Chemotherapy/Targeted Therapy Drugs [17]		×		
Concomitant Medication/Treatment [18]	×	×	×	
Adverse Event [19]		×	×	

Subsequent Anti-tumor Therapy [20]				×
Survival Follow-up				×

Note:

1. Screening Period: Data requiring documentation includes: Medical History, Demographic Data, Height and Weight, Vital Signs, Physical Examination, ECOG Score, Complete Blood Count, Blood Biochemistry, Urinalysis, Coagulation Function, Biomarker, Electrocardiogram, Pregnancy Test, HIV/HBV/HCV Testing, UGT1A1 Testing, RAS and BRAF Gene Testing, Histopathological or Cytological Testing, and Tumor Assessment. Imaging examinations conducted within 28 days prior to subject enrollment are acceptable; Historical histopathological/cytological examination results and genetic testing results (including but not limited to sequencing, microarray, or qPCR) are acceptable, provided they are confirmed by the Investigator; other examination items must have been performed within 14 days prior to enrollment.

2. Treatment period: Data requiring documentation includes: height/weight, vital signs, physical examination, ECOG score, Complete Blood Count, Blood Biochemistry, Urinalysis, Coagulation function, Biomarker testing, Tumor Assessment, and chemotherapy/targeted therapy drugs. If screening assessments were completed within 7 days prior to Cycle 1 Day 1 (C1D1), they need not be repeated on C1D1. Imaging examinations will be conducted every 8 weeks (±7 days; approximately every 4 treatment cycles); Coagulation function and Biomarker testing will be performed every 4 weeks (±7 days; approximately every 2 treatment cycles); other examination items will be conducted within 5 days prior to each cycle administration.

3. End of Treatment: Data to be recorded includes vital signs, physical examination, ECOG score, complete blood count, blood biochemistry, urinalysis, coagulation function, biomarkers, electrocardiogram, and tumor assessment. Examinations shall be conducted within 28 days after treatment cessation. If imaging results within 28 days are available, additional imaging examination will not be required.

4. Follow-up: Data to be recorded includes tumor assessment, subsequent anti-tumor therapy, and survival follow-up. After entering the follow-up period, examinations shall be performed every 12 weeks (±10 days); Until death, loss to follow-up, informed withdrawal, or completion of 1-year follow-up (whichever occurs first).

5. Medical history collection: Past medical history (colorectal adenoma, inflammatory bowel disease, and other colorectal cancer-related conditions without time window restriction; myocardial infarction and other bevacizumab-related histories without time window; other past medical histories recorded within 28 days) and present illness history. Colorectal cancer-related history (including date of diagnosis, histological type, tumor assessment scan results, disease stage, multidisciplinary team consultation outcomes, prior antitumor therapy, primary tumor site, and metastatic sites) will be documented.

6. Demographic data: Date of birth, gender, and ethnicity will be recorded.

7. Vital signs: including blood pressure, pulse, respiration, and temperature (axillary/forehead).

8. Physical examination: encompassing skin and mucous membranes, lymph nodes, head and neck, chest, abdomen, spine and limbs, nervous system, general condition, and others.

9. Complete Blood Count: including white blood cell count, red blood cell count, hemoglobin, platelet count, neutrophil count, and lymphocytes.

10. Blood Biochemistry: including Alanine Aminotransferase, Aspartate Aminotransferase, Alkaline Phosphatase, Total bilirubin, Direct bilirubin, Indirect bilirubin, Total protein, Albumin, Lactate Dehydrogenase, Urea or Blood Urea Nitrogen, Serum Creatinine, Uric acid, Phosphorus, Magnesium, Potassium, Sodium, Chloride, and Calcium.

11. Urinalysis: including urine protein, red blood cells, and white blood cells.

12. Coagulation function: prothrombin time, International Normalized Ratio, activated partial thromboplastin time, thrombin time, fibrinogen.

13. Biomarkers: CEA, CA199.

14. Pregnancy test: Women of childbearing potential must undergo blood/urine human chorionic gonadotropin (hCG) testing during the screening period.

15. RAS and TP53 status testing, LRPPRC immunohistochemical testing: Genetic testing and immunohistochemical testing.

16. Tumor Assessment: CT or MRI is recommended for evaluation, with consistent imaging modality maintained for each patient throughout the study.

17. Chemotherapy/Targeted Therapy Drugs: Record the generic drug name, administration date, dosage, and reasons for any chemotherapy delays or regimen modifications.

18. Concomitant Medication/Treatment: Document all concomitant therapies from the signing of the Informed Consent Form through the end-of-treatment visit, including medications used for preventive and therapeutic management of adverse events, treatment of comorbid conditions, or enhancement of immune function.

19. Adverse Events: Record from the first dose administration until 28 days after the last dose. Record the adverse event name, cycle of occurrence, severity (according to NCI-CTCAE v5.0), relationship to study treatment, relationship to investigational product, action taken with investigational product, outcome, start and end dates, whether symptomatic treatment was administered, and whether it was a Serious Adverse Event (SAE).

20. Subsequent anti-tumor therapy: Record any antitumor therapy received by subjects after the end-of-treatment visit, including generic drug names, dosage and administration, start date, and end date.

3.3 Selection and Confirmation of Primary Measures or Outcome Indicators

3.3.1 Primary Endpoint

Objective Response Rate (ORR), defined as the percentage of patients

achieving Complete Response (CR) and Partial Response (PR) among the Intent-to-Treat (ITT) analysis set population.

3.3.2 Secondary Endpoints

Secondary Endpoint 1: Progression-Free Survival (PFS), defined as the time from the date of first dose of Study Treatment to the first documented disease progression (PD) or death from any cause, whichever occurs first.

Secondary Endpoint 2: Clinical Benefit Rate (CBR), calculated as the percentage of patients in the ITT analysis set who achieve complete response (CR), partial response (PR), or stable disease (SD) for at least 24 weeks.

Secondary Endpoint 3: Duration of Response (DoR), defined as the time from the first documented CR or PR to disease progression or death from any cause.

Secondary Endpoint 4: Time to Response (TTR), defined as the time from the date of first dose of Study Treatment to the first documented objective tumor response of CR or PR.

Secondary Endpoint 5: Overall Survival (OS), defined as the time from the first administration of Study Treatment until death from any cause.

Secondary Endpoint 6: Adverse Events (AE), assessed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

IV. Data Management

4.1 Data Entry (selection of paper/electronic record forms, whether double data entry will be performed, whether electronic data capture system will be used, etc.)

The Investigator will be responsible for data management in this study. All case report forms (CRF) will be completed by designated, trained trial site personnel, with the Investigator reviewing CRFs and signing with name and date.

To ensure data accuracy, completeness, and consistency, Investigators shall maintain source documents including but not limited to: hospitalization records, clinical and outpatient charts, laboratory records, memoranda, patient-reported outcomes, assessment inventories, pharmacy dispensing logs, automated instrument data records, verified accurate and complete transcript copies, patient files, and records maintained by pharmacies, laboratories, or medical technical departments participating in the clinical trial.

4.2 Scope and Methods of Data Verification and Management

After all case report forms undergo double-entry and verification, the data manager will generate a database audit report. This report shall include: study completion status (with a list of discontinued subjects), eligibility/exclusion criteria verification, completeness verification,

logical consistency verification, outlier data verification, time window verification, concomitant medication verification, and adverse event verification.

4.3 Statistical Analysis

4.3.1 Analysis Populations

Full Analysis Set (FAS): Includes all subjects who pass screening and are enrolled, with at least one treatment record. FAS serves as the primary analysis set.

Per Protocol Set (PPS): Comprises datasets from subjects sufficiently compliant with the trial protocol, including adherence to treatment, availability of primary endpoint measurements, and absence of major protocol violations. PPS is used for efficacy analyses.

Safety Set (SS): Consists of actual data from subjects receiving at least one treatment with recorded post-treatment safety indicators. Adverse reaction incidence rates are calculated using the number of cases in the SS as the denominator.

4.3.2 Statistical Methods

(1) General Principles

Generally, continuous data will undergo normality testing. Based on distribution type, we will report mean ± standard deviation or median (minimum value, maximum value). Categorical data will present counts and percentages for each category. For continuous variables, report

maximum/minimum/mean/median/standard deviation with one decimal place. For categorical variables, report subject counts and percentages (to one decimal place). If a percentage becomes 0.0% after rounding to one decimal, retain it as 0.0%. For survival data, report median time to two decimal places unless otherwise specified. Confidence intervals and p-values retain two decimal places.

(2) Case Enrollment Analysis

List the total number of enrolled cases and those completing treatment to determine the analysis datasets (FAS, PPS, SS).

(3) Demographic Data and Baseline Analysis

Demographic data and baseline characteristics were analyzed based on the FAS set by group and for all subjects.

According to data type: categorical and ordinal data were described by case counts and percentages (%); Continuous data were described with case counts, mean, standard deviation, minimum value, and maximum value. Baseline characteristics included: gender, age, ECOG score, CA19-9 level, histological type, disease stage, primary tumor site, metastatic sites, UGT1A1 test result, RAS and BRAF gene test results.

(4) Medication Compliance

Based on the FAS set, analyses will be performed on the number of treatment cycles, average unit dose of liposomal irinotecan, and reasons for treatment discontinuation. Categorical variables will be described using

number and percentage, while continuous data will be presented as number, mean, standard deviation, minimum value, and maximum value.

(5) Efficacy Analysis

For Objective Response Rate (ORR), analyses will be conducted based on the FAS set and PPS set, reporting the number of patients achieving response and calculating the response rate with its 95% confidence interval.

Disease Control Rate (DCR) will be analyzed based on the FAS set, reporting the number of patients achieving disease control and calculating the control rate with its 95% confidence interval.

Overall Survival (OS), Progression-Free Survival (PFS), and Duration of Response (DoR) will be analyzed based on the FAS set using the Kaplan-Meier method to calculate median time with its 95% confidence interval.

(6) Safety Analysis

Statistical analysis of adverse events will be performed based on the Safety Set (SS).

Adverse events during the treatment period, Grade 3 or higher adverse events, and serious adverse events will be summarized by treatment group and for the overall population, with calculation of occurrences, number of cases, and incidence rates. Detailed listings of all adverse events, adverse events related to the investigational product (adverse reactions), serious

adverse events, and adverse events leading to discontinuation will be provided.

(7) Subgroup Analysis

Subgroup analyses will be conducted based on baseline characteristics including gender, age, ECOG score, CA19-9 level, histological type, disease stage, primary tumor site, metastatic sites, and UGT1A1 test results to explore efficacy differences among subgroups.

(8) Statistical Software

Primary statistical analysis and graphing will be performed using SPSS 25.0 and Graphpad Prism 7.0 or later versions.

V. Safety Evaluation

The number of subjects and occurrences of adverse events (graded per NCI CTCAE v5.0) will be calculated separately.

'Number of subjects' refers to the total count of individuals experiencing adverse events. If a single subject experiences more than one adverse event during the study, it is counted only once.

'Number of occurrences' refers to the total count of all adverse event incidents.

Adverse event incidence rates will be calculated using the number of subjects as the numerator and the total number of participants in the safety analysis set as the denominator.

5.1 Definition of Adverse Events (AE) and Serious Adverse Events (SAE)

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical trial subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. Thus, an AE may be any unfavorable or unintended sign (including clinically significant abnormal laboratory findings), symptom, or disease temporally associated with the use of an investigational product, regardless of whether it is considered related to the investigational product. Adverse events may include newly emergent conditions and exacerbations of pre-existing conditions. AEs may include adverse medical conditions occurring at any time (including during baseline or washout periods), even when no study treatment has been administered.

Treatment-emergent adverse events (TEAEs) are defined as any new AE commencing after at least one dose of Study Treatment, or any worsening or exacerbation of a pre-existing condition.

Serious adverse events (SAEs) are defined as any untoward medical occurrence that fulfills one of the following criteria at any dose:

(1) Results in death.

(2) Is life-threatening, where the patient was at immediate risk of death during the event occurrence. This does not imply an outcome that might hypothetically cause death if more severe.

(3) Requires inpatient hospitalization or prolongation of existing hospitalization. Any AE prolonging hospitalization shall be considered an SAE. However, planned hospitalizations (e.g., for observation, protocol compliance, elective procedures, social reasons, etc.) are not considered SAEs; the reason for planned hospitalization should be documented in the Medical History.

(4) Resulting in permanent or significant disability/incapacity.

(5) Congenital anomaly or birth defect.

(6) Important medical events that may not be immediately life-threatening or result in death/hospitalization, but may jeopardize the patient or require intervention to prevent one of the outcomes above. Examples include allergic bronchospasm requiring intensive treatment in emergency rooms or at home, blood dyscrasias, convulsions not requiring hospitalization, or development of drug dependency/abuse.

5.2 Reporting of Adverse Events

During the clinical study, regardless of whether adverse events are related to the investigational product, the Investigator must truthfully and comprehensively complete the Adverse Event Record Form. This includes documenting clinical manifestations, time of onset, severity, duration, measures taken, and outcomes of adverse events. Additionally, concomitant medication usage must be meticulously recorded to facilitate

analysis of the relationship between adverse events and the investigational product.

Except for serious adverse events specified in the study protocol or other documents (e.g., Investigator's Brochure) as not requiring immediate reporting, the Investigator shall immediately submit a written report of all serious adverse events to the Sponsor. This must be followed by timely provision of detailed written follow-up reports. The Sponsor and Investigator shall promptly investigate the serious adverse event and take necessary measures to ensure subject safety and rights.

The Investigator must complete the 'Serious Adverse Event Report Form'. The source documents shall record when, in what manner, and to whom the serious adverse event was reported. The Sponsor guarantees that all reporting procedures required by laws and regulations are fulfilled.

VI. Subject Protection

6.1 Informed Consent

In accordance with local regulatory requirements, each subject (or their legal representative) must provide written informed consent after being fully informed of the nature of the study. Subjects must sign the informed consent form before any study-related procedures are performed. The informed consent form used must be approved by the Sponsor, the Independent Ethics Committee, and the Institutional Review Board, and

must be written in a language understandable to the subject.

Prior to subject enrollment, the investigator or authorized research personnel must explain the study purpose, methodology, potential benefits, inherent risks, and possible discomforts associated with participation to potential subjects or their legal representatives. Subjects shall be informed that participation is voluntary and they may withdraw informed consent to discontinue the study at any time without affecting the treatment of their disease. Subjects shall be advised that alternative treatment options remain available if they choose not to participate, and this decision will not impact their future medical care. Finally, subjects shall be informed that investigators will retain their registration information for potential long-term follow-up when necessary. Drug regulatory authorities or authorized sponsor personnel may review relevant subject records as permitted by applicable laws and regulations, without infringing upon their privacy. By signing the Informed Consent Form, the subject or their legal representative authorizes such access, permitting their research physician to: (1) recontact the subject; (2) obtain consent for additional safety assessments and subsequent disease-related treatment information if required; and (3) acquire information regarding survival status.

Subjects or their legal representatives shall be given sufficient time to read the Informed Consent Form and opportunities to ask questions. After explanations are provided and before enrollment, written informed consent

with the signature and date of the subject or legal representative must be documented. Upon obtaining informed consent, a copy of the Informed Consent Form shall be provided to the subject.

If the subject or legal representative is unable to read or write, an impartial witness must be present throughout the entire informed consent process (including the reading and explanation of all written materials). After obtaining oral consent from the subject or legal representative, the witness shall also sign and date the written informed consent form.

6.2 Personal Information

This study will only collect and process subjects' data strictly necessary for investigating drug efficacy, safety, quality, and application.

The confidentiality of such data shall be fully ensured during collection and usage, with strict adherence to relevant laws and regulations protecting subjects' privacy.

The Sponsor shall ensure that:

(1) The data collection process is fair and lawful;

(2) The purposes of data collection are specific, explicit, and legitimate; No further processing incompatible with these purposes shall occur, nor shall data be processed through other methods contrary to these purposes;

(3) The collected data shall be sufficient, relevant and not excessive in relation to the research purpose, with no collection of data unrelated to

the research objectives;

(4) The collected data shall be accurate and kept up-to-date with necessary updates.

The Investigator shall obtain the Subject's consent prior to collecting personal information. This consent shall include explicit notification regarding potential transfer of data to other institutional entities and countries.

Subjects have the right to access their personal information through the Investigator and may request rectification of erroneous or incomplete data. Such requests shall receive an appropriate response, taking into account their content and purpose, the status of the trial, and applicable laws. Consideration shall be given to the nature of requirements, the status of the trial, and relevant laws and regulations.

Appropriate technical procedures and organizational management measures must be implemented to protect subjects' personal information from unauthorized access or disclosure, accidental or unlawful destruction, and accidental loss or alteration. Throughout the study, sponsor personnel authorized to access subjects' personal data shall maintain its confidentiality.

VII. Protocol Amendments

Prior to study initiation, the study protocol and/or other relevant documents must obtain approval from ethics committees and other

authorities in accordance with local legal requirements. Any protocol amendments must be accompanied by detailed modification records, including signatures, version numbers, and dates. The amended protocol must be submitted to the Ethics Committee for approval before implementation.

Section VIII: Early Termination

8.1 Treatment Termination:

Patients reserve the right to voluntarily discontinue treatment at any time for any reason. Permanent discontinuation of all study treatment will occur if any of the following conditions arise:

• Enrollment error, i.e., the patient fails to meet the study's inclusion/exclusion criteria.

• The Investigator and/or Sponsor determines that the patient's medical condition may compromise their safety.

• The Investigator and/or Sponsor determine that continued study treatment is not in the patient's best interest.

• The Investigator and/or Sponsor deem the patient to have poor compliance with the protocol.

• The patient has concurrent medical conditions unrelated to cancer, where continued treatment would pose safety risks or make regular study visits unfeasible.

• Occurrence of intolerable toxicity or serious adverse event (SAE).

• The patient withdraws informed consent.

• Disease progression (PD) assessed per RECIST 1.1 criteria.

• Lost to follow-up.

• Patient death.

• Pregnancy in female patients.

• Termination of the entire study or this study site by the Sponsor or regulatory authorities.

Patients may withdraw informed consent at any time. Following withdrawal, no additional patient data will be collected, though previously collected data will be retained and continue to be utilized.

8.2 Study-Wide Termination or Site-Specific Termination:

The Sponsor reserves the right to terminate this study at any time. Reasons for termination include, but are not limited to, the following circumstances:

• The incidence or severity of Adverse Events (AEs) in this study indicates potential health hazards to patients from the Investigational Product.

• Patient recruitment lags significantly, with overall enrollment progress severely below expectations.

• Study completion (i.e., all patients have concluded participation and relevant obligations have been fulfilled).

IX. References

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