Clinical Study of Irinotecan Liposome Combined With Temozolomide and Bevacizumab in the Treatment of Relapsed Refractory Soft Tissue Sarcoma

Scheme

Version: 1.1

Date of version: 25 April 2025

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Lead Clinical Trial Institution: The Second Affiliated Hospital of Zhejiang University School of Medicine

Sponsoring Institution: The Second Affiliated Hospital of Zhejiang University School of Medicine

Scenario Summary

Research topic	Clinical study of irinotecan liposome combined with temozolomide and bevacizumab in the treatment of relapsed refractory soft tissue sarcoma
Version number	V1.1
Version date	April 25,2025
Principal Investigator	Dong Ying
Nature of the study	Prospective, single-arm, phase II study
Purpose of research	Primary research objectives: ● To evaluate the efficacy and safety of liposomal irinotecan combined with temozolomide and bevacizumab in the treatment of relapsed or refractory soft tissue sarcoma by assessing progression-free survival (PFS) and safety. Secondary research objectives: ● To evaluate the objective response rate (ORR), 12-week progression-free survival (PFS), overall survival (OS), disease control rate (DCR), and duration of response (DoR) of liposomal irinotecan combined with temozolomide and bevacizumab in the treatment of relapsed/refractory soft tissue sarcoma. ● To explore the molecular predictive markers associated with the efficacy of irinotecan combined with temozolomide and bevacizumab in the treatment of relapsed/refractory soft tissue sarcoma.
Study end point	Primary research end point: ● progression @-@ free survival (PFS) ● Safety end points: Adverse events (AE)/serious adverse events (SAE) (judged according to NCI-CTCAE 5.0). ~~Secondary end points~~ ● objective response rate (ORR)

	● 12-week PFS rate; ● overall survival (OS); ● Disease Control Rate (DCR); ● Duration of relief (DoR); ● Exploratory end points: efficacy-related molecular predictive markers, etc.
Subject investiga-ted	Patients with metastatic or unresectable recurrent refractory soft tissue sarcoma confirmed by histological evidence
Research design	This study is a prospective, single-arm, phase II design aimed at evaluating the efficacy and safety of liposomal irinotecan combined with temozolomide and bevacizumab in the treatment of relapsed or refractory soft tissue sarcoma. The study investigates patients with metastatic or unresectable recurrent refractory soft tissue sarcoma confirmed by histological evidence. After signing informed consent and passing screening, subjects receive treatment. The primary endpoints are progression-free survival (PFS) and safety. Irinotecan liposome (II) + temozolomide + bevacizumab, with a 21-day cycle, until disease progression or intolerable toxicity. Safety visits: After enrollment, subjects will undergo safety visits on Day 1 of each treatment cycle and at the end of treatment. Subjects will receive survival follow-up every 3 months after treatment completion. Imaging assessment: All lesions were recorded and evaluated according to RECIST v1.1. Unless otherwise specified, the allowable window for imaging examinations was ±7 days. During the study period, unplanned imaging examinations could be performed when tumor recurrence or metastasis was suspected. Screening period: Imaging examinations of the chest, abdomen, and pelvis are required. Enhanced MRI/CT scans (with a slice thickness ≤5 mm) are needed for the abdomen and pelvis, while chest CT scans (with a slice thickness ≤5 mm) are required for the chest. For suspected brain metastases, enhanced MRI/CT of the cranium is also required to exclude brain metastases. Bone scans are necessary to confirm or clinically suspect bone metastases. Baseline tumor assessment should be completed within 2 weeks before randomization. If the investigator determines that

	the imaging findings represent the subject's baseline status, baseline imaging examinations...

	It can be extended to the first 4 weeks before randomization; Tumor recurrence follow-up: Imaging examinations were performed every 12 weeks after treatment initiation, including contrast-enhanced MRI/CT scans. Additional imaging of the suspected metastatic site was required if metastasis was suspected. The imaging evaluation continued until imaging progression or recurrence, initiation of alternative antitumor therapy, withdrawal of informed consent, loss to follow-up, or death.
Research on drug	Iritinib Liposome (II) 56.5 mg/m ^{2} D 1 Temozolomide 100 mg/m ^{2}/day × 5 days Bevacizumab 7.5 mg/kg iv D1
Administrat-ion method	● Iliotinib liposome: 56.5 mg/m ^{2}, intravenous infusion for 90 minutes (+30 minutes), with 1 study cycle defined as days 1 and 3. ● temozolomide: 100 mg/m ^{2}/day for 5 days, with 3 weeks as one study cycle; ● bevacizumab: 7.5 mg / kg, intravenous infusion, D 1,3 week as one study period.
Enrollment Criteria	Participants must meet all the following inclusion criteria to be eligible for this study. 1. Age ≥14 years, gender not restricted; 2. For metastatic or unresectable recurrent refractory soft tissue sarcoma confirmed by histological evidence, the combination therapy regimen may be considered based on the investigator's assessment. 3. Disease progression or intolerable toxicity after at least one line of systemic therapy (with or without targeted therapy). 4. at least one measurable lesion (RECIST v1.1); 5. ECOG：0 ~ 2; 6. expected survival ≥3 months; 7. The primary organ functions are adequate, meaning the following criteria are met (no blood components or cell growth factors were administered within 14 days prior to randomization): （1）Neutrophils ≥1.5×10 ^{9}/L; platelets ≥80×10 ^{9}/L; hemoglobin ≥9g/dl; serum albumin ≥3g/dl; （2）Total bilirubin ≤ 1.5 times the upper limit of normal

	(biliary obstruction allows biliary drainage); ALT and AST ≤ 3 times the upper limit of normal (for patients with liver metastases, the limit may be relaxed to ≤ 5 times the upper limit of normal).

（3） Serum creatinine ≤1.5 times the upper limit of normal, and creatinine clearance ≥ 60 ml/min;

（4） INR ≤ 1.5 times the upper limit of normal and APTT ≤ 1.5 times the upper limit of normal (eligible for screening if stable-dose anticoagulation therapy such as low molecular weight heparin or warfarin is being used and the INR is within the expected therapeutic range of the anticoagulant);

（5） ECG: QTcF ≤450ms (male), ≤470ms (female);

（6） Cardiac ultrasound: LVEF (left ventricular ejection fraction) ≥ 50%;

8. Women of childbearing age must have a negative blood pregnancy test within 3 days prior to randomization and be willing to use appropriate contraceptive methods during the trial and for 6 months after treatment. For men, consent must be obtained to use appropriate contraceptive methods during the study and for 3 months after treatment.

9. All participants voluntarily enrolled in this study and signed the informed consent form.

Exclusion Criteria Subjects who meet any of the following criteria will not be eligible for this study:

1. patients with known central nervous system metastases;

2. severe gastrointestinal dysfunction (with bleeding, obstruction; inflammation greater than grade 2; diarrhea greater than grade 1);

3. patients with a prior history of treatment with irinotecan, temozolomide, bevacizumab, or similar agents;

4. Presence of third space effusion (e.g., massive pleural effusion) that cannot achieve a stable state (no intervention required after drainage tube removal) within the first two weeks prior to randomization, excluding ascites.

5. Patients with clinical symptoms of ascites requiring puncture and drainage, or those who have undergone ascites drainage within the past 3 months (excluding cases where imaging only shows minimal ascites that is controllable but without clinical symptoms);

6. Currently diagnosed with interstitial pneumonia or interstitial lung disease, or with a history of interstitial pneumonia or interstitial lung disease requiring corticosteroid therapy, or other conditions that may interfere with the assessment and management of immune-related pulmonary toxicity, such as pulmonary fibrosis, organizing pneumonia (e.g., obstructive bronchiolitis), pneumoconiosis, drug-induced pneumonia, idiopathic pneumonia, or subjects with active pneumonia or severe impaired lung function on chest CT during the screening period; active tuberculosis;

7. active autoimmune disease or a history of autoimmune disease with potential for recurrence

Inclusion criteria include but are not limited to autoimmune hepatitis, interstitial pneumonia, uveitis, enteritis, pituitaryitis, vasculitis, nephritis, hyperthyroidism, and hypothyroidism (participants whose conditions can be controlled solely through hormone replacement therapy may be enrolled); those with non-systemic dermatoses such as vitiligo, psoriasis, or alopecia, well-controlled type 1 diabetes mellitus treated with insulin, or childhood asthma that has been completely remitted without subsequent intervention in adulthood may also be enrolled.

8. known peripheral neuropathy (CTCAE grade ≥3);
9. known dihydropyrimidine dehydrogenase (low activity) or deficiency;
10. Serious infection (CTCAE> grade 2) occurring within the first 4 weeks of randomization, such as severe pneumonia, bacteremia, or infection-related complications requiring hospitalization; presence of symptoms and signs of infection within the first 2 weeks of randomization necessitating intravenous antibiotic therapy (excluding prophylactic antibiotic use).
11. received any of the following treatments:
    - Concomitant medications within the first 2 weeks of randomization contained strong inhibitors/strong inducers of CYP3A4 or CYP2C8, or strong inhibitors of UGT1A1.
    - Administration of immunosuppressants or systemic corticosteroids for immunosuppression during the first 2 weeks (dose>10 mg/day of prednisone or other equivalent therapeutic corticosteroids);
    - received radiotherapy within the first 2 weeks of randomization;
    - Surgery (e.g. thoracotomy, laparotomy) in the first 4 weeks of randomization;
    - Received any other investigational drug in the previous 4 weeks, except for observational (non-interventional) clinical studies or follow-up in intervention studies.
12. Impaired coagulation function, bleeding tendency, or ongoing thrombolytic or anticoagulant therapy. Prophylactic use of low-

dose aspirin (≤100 mg/day) and low-molecular-weight heparin (enoxaparin 40 mg/day or other low-molecular-weight heparins at equivalent doses) is permitted;

13. Patients with poorly controlled cardiac clinical symptoms or diseases, such as: (1) NYHA class 2 or higher heart failure; (2) unstable angina; (3) myocardial infarction (MI) within the past 6 months; (4) clinically significant supraventricular or ventricular arrhythmias requiring treatment or intervention.

14. Malignant tumors other than recurrent or refractory soft tissue sarcoma occurring within the preceding 3 years, excluding well-treated carcinoma in situ, basal cell carcinoma of the skin, or squamous cell carcinoma, etc.

15. Known hypersensitivity to irinotecan liposomes, other liposomal products, temozolomide, bevacizumab, or any component of the aforementioned products;

16. known to have acquired immunodeficiency syndrome (AIDS) or HIV testing positive, active syphilis infection;

17. A clear history of neurological or psychiatric disorders, including epilepsy or dementia;

18. According to the investigator's assessment, the subject may have other factors that could lead to forced discontinuation of the study, such as non-compliance with the protocol, having other serious illnesses (including psychiatric disorders) requiring concomitant treatment, clinically significant laboratory test values with severe abnormalities, or family/social factors that may affect the subject's safety or the collection of trial data.

Criteria for discontinuation of study therapy	Discontinuation of study therapy does not mean withdrawal from the study. 1. The subject requested to discontinue the trial drug therapy; 2. pregnancy occurred during the study; 3. The occurrence of any clinical adverse event, abnormal laboratory findings, or other medical conditions that may render continued medication unbeneficial to the subject; 4. The overall deterioration of health status makes it impossible to continue participating in the trial. 5. loss to follow-up; 6. Subject death; 7. Other reasons for discontinuation of treatment were considered by the investigators.
Exit study criteria	Reasons for subject withdrawal from the study may include: 1. The subject withdrew informed consent and declined further follow-up; 2. loss to follow-up; 3. Subject death; 4. the sponsor discontinued the study.

Study termination criteria	The study termination criteria include but are not limited to: 1. identifying an unexpected, significant or unacceptable risk to the patient; 2. During the execution of the trial, significant errors were identified in the protocol. 3. The study drug/trial treatment is ineffective, or continuing the trial is meaningless; 4. The sponsor decided to terminate the study due to reasons such as significant delays in patient enrollment or frequent protocol deviations.
Sample capacity	The progression-free survival (PFS, Recist v1.1) of irinotecan liposome (II) combined with temozolomide and bevacizumab in the treatment of relapsed/refractory soft tissue sarcoma was expected to increase from the previous study result of 3.8 months to 7.5 months. With an alpha=0.05 and power=0.80, a sample size of 21 cases was required, considering a 10% loss to follow-up, with a planned enrollment of 24 cases. This study aims to preliminarily evaluate the progression-free survival (PFS, Recist v1.1) of irinotecan liposome (II) combined with temozolomide and bevacizumab in the treatment of relapsed/ refractory soft tissue sarcoma.
Statistical method	**General analysis** For continuous data, the statistical measures of frequency, mean, standard deviation, median, minimum, and maximum were used for summarization; for categorical data, the statistical measures of frequency and percentage were employed for summarization; for time-event data, the Kaplan-Meier method was utilized to estimate the survival function and the median time to event, and survival curves were plotted. **Efficiency analysis** The analysis of the primary end points will be based on the per @-@ protocol set. For the primary endpoint of PFS, the median was estimated using the Kaplan-Meier method, with the 95% confidence interval calculated by the Brookmeyer-Crowley method, and survival curves were plotted. The analysis of primary endpoint safety will be conducted in the SS

	(Safety Analysis Set) population. The safety endpoint analysis will be performed in the overall population. For TEAEs and SAEs, the percentage of occurrences (defined as the proportion of patients who experienced at least one event) and the incidence rate (number of risk events per 100 patient-years) will be reported. The 95% confidence interval for the percentage of occurrences will be calculated using the exact method of the binomial distribution.

	Time.
	For the secondary efficacy endpoints, including objective response rate (ORR), 12-week progression-free survival (PFS), overall survival (OS), disease control rate (DCR), and duration of response (DoR), the number and percentage of subjects with events and censored data were collected, and summary statistics were provided for event types and causes of censored data. The median values were estimated using the Kaplan-Meier method, and the 95% confidence intervals for median ORR/PFS/OS/ DCR/DoR were estimated using the Brookmeyer-Crowley method, with survival curves plotted.
Study timeline	Estimated first participant enrollment time after ethics approval The estimated time of enrollment for the last subject is 1 year after initiation. Estimated 2 years after the study ends

Clinical Trial Flowchart

All tests/inspections are recommended items, and specific tests/inspections are subject to clinical practice 1.Screening steps

Project	Filter period Baseline[1], -14 days	Explanatory note
Enrollment assessment		
Sign the informed consent form	√	**Informed consent for enrollment in this study must be obtained during the screening phase. The designated screening procedures for this study shall not commence until written informed consent is secured. Special provisions apply to baseline tumor imaging examinations, with specific details to be consulted in the "Tumor Imaging Assessment" section of this flowchart during the screening period. Participants who fail pre-treatment screening are permitted one additional screening opportunity[2]. For this re-screening phase, participants must obtain renewed informed consent and complete re-registration to receive a new participant number.**
Verify admission criteria	√	**Assessment during the screening period (including re-enrollment screening)**
Demographic data	√	
Medical history	√	**Including medical history and tumor history (initial diagnosis, treatment course, etc.).**
Safety evaluation		
ECOG **score**	√	**Administer within** 14 **days before the first dose**
Check-up	√	**Administer within** 14 **days before the first dose**
Vital sign	√	**Including blood pressure, pulse, body temperature, and respiratory rate. Screening visits are performed during and within** 72h **before the first dose. If screening is completed within** 72h **before the first dose, no further testing is required before the first dose.**
Collect and consolidate medication/treatment	√	**Including information on combination therapy within** 1 **month prior to signing the informed consent form**
Collect adverse events	√	**Including symptoms and signs**

Project	Filter period Baseline[1], -14 days	Explanatory note
12 **lead ECG**	√	**Administer within** 14 **days before the first dose**
Echocardiogram	√	**Including** LVEF **assessment, performed within** 14 **days prior to the first dose**
Routine blood test	√	**Include complete blood count and differential (white blood cells, red blood cells, lymphocytes, neutrophils, hemoglobin, etc.), and platelet count. Test within** 14 **days before the first dose. If the screening period is completed within** 72h **before the first dose, no additional testing is required before the first dose.**
Routine urine test	√	**The tests include white blood cells, red blood cells, urine protein, urine occult blood, and urine glucose. These tests should be performed within** 14 **days before the first medication. If urine protein levels are** ≥2+ **during the screening phase, a** 24-hour **urine protein quantification test must be added. If the screening phase is completed within** 72 hours **before the first medication, no additional testing is required prior to the initial administration.**
Fecal occult blood	√	**Test within** 14 **days before first medication.**
Blood biochemistry	√	**Including liver function (**ALT,AST, **total bilirubin, conjugated bilirubin,**AKP,γ GT**), kidney function (**BUN **or serum urea level, creatinine, uric acid), total protein, albumin, fasting blood glucose, triglycerides, cholesterol, amylase (if abnormal and clinically significant, lipase must be measured), blood glucose,**LDH**. Testing should be performed within** 14 **days before the first dose. If screening tests are completed within** 72 hours **before the first dose, no additional testing is required before the first dose.**
Blood electrolytes	√	**Including potassium, sodium, calcium, chloride, magnesium, and phosphorus ions. Test within** 14 **days before the first dose. If the screening period is completed within** 72h **before the first dose, no further testing is required before the first dose.**
Coagulation function	√	**International Normalized Ratio (**INR**), if** INR **is not available, prothrombin time (**PT**) is used instead. Test within** 14 **days before the first dose.**
Myocardial enzyme profile and troponin	√	**The myocardial enzyme spectrum includes creatine kinase (**CK**), creatine kinase isoenzyme (**CK-MB**), lactate dehydrogenase (**LDH**); and troponin (**CTn1**) detection.Test within** 14 **days before first medication.**
Tumor markers	√	**Test within** 14 **days before first medication.**
Thyroid function	√	**Including** TSH, FT3, and FT4.

Pituitary-adrenal axis function	√	**This includes the measurement of** 8 **point** ACTH **and cortisol, as well as the measurement of follicle-stimulating hormone, which is performed during the screening period and only later if there are any suspicious symptoms.**

Project	Filter period Baseline[1], -14 days	Explanatory note
Virological testing	√	**Including** HIV-Ab,HBV, **and** HCV **infection testing. For** HBV **testing: During the screening phase, test** HBsAg **to determine if** HBV **infection is present. If positive, test** HBsAg**(quantitative),**HBsAb**(qualitative),**HBcAb**(qualitative),**HBeAg**(qualitative),**HBeAb**(qualitative), and** HBV-DNA**(qualitative; if positive, also test quantitative). For** HCV **testing: During the screening phase, test** HCV-Ab **to determine if** HCV **infection is present. If positive, test** HCV-RNA**(qualitative; if positive, also test quantitative).**
Blood HCG **test**	√	**For women of childbearing age only (**WOCBP**). Testing must be performed within** 72h **before the first dose.**
Effectiveness evaluation		
Tumor Imaging Assessment	√	**Baseline imaging assessment must be performed according to the** RECIST1.1 **criteria, including enhanced** CT **scans of the chest, abdomen, pelvis, and affected areas. If there is an allergy to enhanced** CT **contrast agents, a chest** CT **plain scan plus abdominal and pelvic** MRI **scans may be performed. Bone scans are only performed when clinically indicated. If routine tumor imaging assessment has been completed before the informed consent form is signed, as long as these** CT **or** MRI **scans were completed within** 28 **days before the initiation of the study drug (bone scans may be completed within** 42 **days before the first dose), there is no need to repeat** CT **or** MRI **during the screening period. Brain** MRI **or enhanced** CT **scans are performed during the screening period.**
Other		
Biomarker collection	√	**If applicable, including blood sample collection and tumor histopathology section collection.**

2. Treatment Phase Steps

Project	Treatment period [3] (21 days as a cycle)		Explanatory note
	Treat	Maintenance treatment	
Safety evaluation			
ECOG score	√	√	Perform within 72 hours before each administration
Check-up	√	√	A physical examination of the target site should be performed within 72h before each dose, including at least the heart, lungs, abdomen, and skin.
Vital sign	√	√	Including blood pressure, pulse, body temperature, and respiratory rate. Conducted within 72 hours before each medication administration.
Collect and consolidate medication/treatment	√	√	
Collect adverse events	√	√	Including symptoms and signs
12 lead ECG[4]	√		Starting from the 2 cycle, each cycle is D 1 detected.
Echocardiogram			During the study period, examinations were conducted according to local standards when clinically indicated.
Routine blood test	√	√	Including complete blood count and differential (leukocytes, red blood cells, lymphocytes, neutrophils, hemoglobin, etc.) and platelet count. Testing should be performed within 72 hours before each medication administration.
			Including white blood cells, red blood cells, urinary protein, urinary occult blood, urine Sugar 2 hours before each Test within 7 days of medication. Urine protein ≥ If 2+ , Xu

Routine urine test	✓	✓	**Quantitative determination of** 24h **urine protein in Gacha.**
Fecal occult blood	✓	✓	**Test within** 14 **days before first medication.**
Blood biochemistry	✓	✓	**Including liver function (**ALT**,**AST**, total bilirubin, conjugated bilirubin,**AKP**,**γ-GT**), renal function (**BUN **or serum urea level, creatinine, uric acid), total protein, albumin, fasting blood glucose, triglycerides, cholesterol, amylase (if abnormal and clinically significant, lipase should be measured additionally), blood glucose,**LDH**. Testing should be performed within** 72 hours **before each medication administration.**
Blood electrolytes	✓	✓	**Including potassium, sodium, calcium, chloride, magnesium, and phosphorus ions. Testing should be performed within** 72 hours **before each medication administration.**
Coagulation function[[4]	✓	✓	**International Normalized Ratio (**INR**), if** INR **is not available, prothrombin time (**PT**) is used instead. From cycle** 2**, every cycle** D 1 **is tested.**
Myocardial enzyme spectrum and troponin[4]	✓	✓	**Starting from the** 2 **cycle, each cycle is** D 1 **detected.**
Effectiveness evaluation			
			Tumor imaging assessment must be performed according to the RECIST1.1 **criteria.**

			Assessments should be performed every 2 **cycles after the initiation of treatment, regardless of whether the drug is**

Tumor Imaging Assessment	√	√	**No delay. For subjects who have started treatment, i.e., more than** 12 **months after the first study dose, if continued tumor assessment is still required, it should be performed every** 12 **weeks (±7 days). If a new lesion is suspected, it should be examined as appropriate. The first** PR/CR **must be confirmed after** 4~6 **weeks; the first** PD **must be confirmed after** 4~6 **weeks (except for significant changes in symptoms or rapid tumor progression). Enhanced** CT **scans should be performed for the chest, abdomen, pelvis, and sites of lesions. If there is an allergy to enhanced** CT **contrast agents, chest** CT **plain scans plus abdominal and pelvic** MRI **scans may be performed. Bone scans should only be performed when clinically indicated. If disease progression (e.g., symptom worsening) is suspected, unplanned imaging studies may be performed.**
Research and treatment			
Iritinib Liposome (II**)**	√	√	
Temozolomide	√	√	
Bevacizumab	√	√	

3. Treatment Completion and Follow-up Phase Steps

Project	Treatment ended [5]	Follow-up period		Explanatory note
		Safety follow @-@ up[6]	Survival follow-up[7]	
Safety evaluation				
ECOG **score**	√	√		
Check-up	√	√		
Vital sign	√	√		**Including blood pressure, heart rate, body temperature, and respiratory rate.**
Collect and consolidate medication/treatment	√	√		
Collect adverse events	√	√		**Including symptoms and signs**
12 **lead ECG**	√			
Echocardiography	√			**During the study period, examinations were conducted according to local standards when clinically indicated.**
Routine blood test	√	√		**The complete blood count (CBC) and platelet count were performed.**
Routine urine test	√	√		**If the proteinuria is ≥2+, the** 24h **urine protein quantification must be added.**
Blood biochemistry	√	√		**Including liver function (**ALT,AST**, total bilirubin, conjugated bilirubin,** AKP,γ-GT**), renal function (**BUN **or serum urea level, creatinine, uric acid), total protein, albumin, fasting blood glucose, triglycerides, cholesterol, amylase (if abnormal and clinically significant, lipase should be measured), blood glucose,**LDH**.**
Blood electrolytes	√	√		**Including potassium, sodium, calcium, chloride, magnesium, and phosphorus ions.**

Coagulation function	√			**International standardization ratio (**INR**), if** INR **is not available, prothrombin time (**PT**) is used instead.**
Myocardial enzyme profile and troponin	√			

Project	Treatment ended[5]	Follow-up period		Explanatory note
		Safety follow @-@ up [6]	Survival follow-up[7]	
Tumor markers	√			
Thyroid function	√			**Test** TSH, FT4, FT3.
Virological testing	√			HBV **infected persons are tested** for HBV-DNA; HCV **infected persons are tested** for HCV-RNA.
Blood HCG **test**	√			**For women of childbearing age only (**WOCBP**).**
Effectiveness evaluation				
Tumor Imaging Assessment	√	√	√	**For subjects who discontinued trial treatment for reasons other than imaging-confirmed disease progression, imaging evaluation must be performed at the end of treatment if no imaging was conducted within** 4 **weeks prior to trial termination. Additionally, tumor response should be assessed every** 3 **months post-trial until documented disease progression or initiation of new oncology therapy. This includes contrast-enhanced** CT **scans of the chest, abdomen, pelvis, and affected areas. For patients with contrast** CT **agent allergies, chest** CT **plain scans combined with abdominal/pelvic** MRI **scans may be performed. Bone scans should only be conducted when clinically indicated.**
Other				
Survival information		√	√	
Subsequent anti-tumor therapy		√	√	

pour：

[1] **All baseline assessments were based on the values closest to the time of study initiation.**

[2] **For subjects who failed the initial screening and subsequently underwent re-screening, the visit steps completed during the initial screening may not need to be repeated during the re-screening phase if they meet the time limit requirements for that step prior to initiating study medication and comply with the enrollment criteria.**

[3] **There was a window period of** ±3 **days on day** 1 **of cycle** 1**.**

[4] **Starting from cycle** 2**, testing should be performed** D1±3 **days or at least every** 21 **days per cycle** 1**, and more frequently if clinically indicated.**

[5] **Study completion/exit: If these tests/steps have been completed within** 7 **days of exit, they do not need to be repeated.**

[6] **Safety Follow-up Period:**90 **days after the last dose. During this period, visits are conducted every** 3 **months (±7 days). The first (within** 30 **days after the last dose) and third (within** 90 **days after the last dose) safety visits are recommended to be conducted at the research center, with one (within** 60 **days after the last dose) phone visit during this period, which only requires collection of survival information, concomitant medications/treatments, and adverse events.**

[7] **Survival follow-up period: After the safety follow-up period, the survival follow-up period was entered. During this period, telephone follow-up was conducted every** 30 **days (**±7 **days) to collect survival information and follow-up treatment information.**

[8] **Irinotecan liposome (**II**) administration: Irinotecan liposome** 56.5mg/m2**,**D 1**, every** 3 **weeks (**Q3W**) was recommended in this study, and every** 3 **weeks was a** 1 **cycle.**

[10] **Temozolomide administration: Temozolomide** 100 mg/m2/day for 5 days**,**3 **weeks was recommended as** 1 **study cycle in this study.**

[11 **Bevacizumab administration: Bevacizumab** 7.5 mg/kg**, intravenous infusion,**D 1,3 **weeks was recommended in this study as** 1 **study cycle.**

Abbreviation/Full English Name	Full Chinese name
ADR	**Drug adverse reaction**
AE	**Adverse event**
AKP	**Alkaline phosphatase**
ALT	**Glutamate-alanine aminotransfer-ase**
ANC	**Absolute neutrophil count**
APTT	**Activated partial thromboplastin time**
AST	**Glutamate Aspartate Aminotrans-ferase**
BUN	**Usea nitrogen**
CHO	**Chinese hamster ovary**
CR	**Complete remission**
Cr	**Creatinine**
CRF	**Case Report Form**
CRP	C-**reactive protein**
CT	**Computed Tomography**
D	**Sky**
DCR	**Disease control rate**
D-Dimer，D-D	D-**dimer**
DLT	**Dose-limiting toxicity**
DoR	**Duration of relief**
DRQ	**Question and Answer Sheet**
ECOG	**Eastern Tumor Cooperative Group**
FIB	**Fibrinogen**
FT3	**Free triiodothyronine**
FT4	**Free tetraiodothyronine**
FullAnalysisSet，FAS	**Complete analytic set**
GCP	**Good Clinical Practice (GCP)**
GEM	**Gemcitabine**
GGT	**Glutamyltranspetidase**
G-CSF	**Granulocyte Colony-Stimulating Factor**
HBcAb	**Hepatitis B virus** c **antibody**
HBeAb	**Hepatitis B virus** e **antibody**
HBeAg	**Hepatitis B virus** e **antigen**
HBsAb	**Hepatitis B virus surface antibody**
HBsAg	**Hepatitis B virus surface antigen**
HBV-DNA	**Hepatitis B virus-**DNA