Clinical Trial Protocol

A Single-Arm, Multicentre, Phase II Clinical Trial of Anlotinib Maintenance Treatment after First-line Anthracycline-based Chemotherapy in Advanced Soft Tissue Sarcoma

Protocol Number: ALTER-S006

Current Version Number: March 16, 2020, Version 3.0

Study Phase: II

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Protocol Synopsis

Protocol Title		A single-arm, multicentre, phase II clinical trial of anlotinib maintenance treatment after first-line anthracycline-based chemotherapy in advanced soft tissue sarcoma
Protocol Number		ALTER-S006
Version Number and Date		3.0 and March 16, 2020
Sponsor		Sun Yat-sen University Cancer Centre
Co-sponsor		Chia-tai Tianqing Pharmaceutical Co., Ltd.
Study Nature		An exploratory study
Study Population		Patients with recurrent/metastatic/inoperable soft tissue sarcoma who achieved stable disease/partial response after first-line anthracycline-based chemotherapy (≥ 4 cycles)
Objective	Primary objective	To evaluate the progression-free survival (PFS) of anlotinib maintenance treatment in patients with recurrent/metastatic/inoperable soft tissue sarcoma who achieved stable disease (SD)/partial response (PR) after first-line anthracycline-based chemotherapy (≥ 4 cycles)
	Secondary objectives	• To observe and evaluate the objective response rate (ORR), disease control rate (DCR) and overall survival (OS) of anlotinib maintenance therapy in patients with soft tissue sarcoma; • To evaluate the safety/quality of life (QoL) of first-line maintenance therapy with anlotinib in patients with soft tissue sarcoma.
Endpoints		Primary Endpoints: PFS Secondary Endpoints: ORR, DCR, OS and safety/QoL
Study Design		This is an open-label, single-arm, multicentre, phase II study of anlotinib

	maintenance treatment after first-line anthracycline-based chemotherapy in advanced soft tissue sarcoma
Planned Sample Size	48 patients
Principal Investigator	Professor Xing Zhang
Clinical Study Unit	Sun Yat-sen University Cancer Centre
Screening Criteria	Inclusion criteria: 1. Subjects who are willing to participate in the study and able to provide signed informed consent, and comply with all aspects of the protocol; 2. Age 18-70 years; Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-2; predicted life expectancy of ≥ 3 months; 3. Subjects with pathologically confirmed advanced synovial sarcoma, leiomyosarcoma, liposarcoma, angiosarcoma, etc. (except malignant peripheral nerve sheath tumor, undifferentiated sarcoma, rhabdomyosarcoma, chondrosarcoma, osteosarcoma, dermato-fibrosarcoma protuberans, gastrointestinal stromal tumor, ewing's sarcoma/primitive neuroectodermal tumor, inflammatory myofibroblastic tumor, and malignant mesothelioma); 4. Subjects who have at least one measurable lesion within the previous 3 months according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) criteria and can be accurately measured by magnetic resonance imaging (MRI) or computed tomography (CT) in at least 1 direction (maximum diameter needs to be documented), with ≥ 20 mm on conventional CT or ≥ 10 mm on spiral CT; 5. Subjects who achieved stable disease/partial response after 4 or more cycles of anthracycline-based therapy; 6. Adequate organs function within 7 days before treatment as evidenced by the following criteria:

	1) Hemanalysis (no blood transfusion within 14 days): hemoglobin (Hb) ≥ 90 g/L; absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L; platelets (PLT) ≥ 80 × 10^9/L; 2) Biochemistry: total bilirubin (TBil) ≤ 1.5 × upper limits of normal (ULN); alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN; ALT and AST ≤ 5 × ULN in patients with liver metastases; blood creatinine (Cr) ≤ 1.5 × ULN or creatinine clearance rate (CCr) ≥ 60 mL/min; 3) Doppler ultrasound assessment: left ventricular ejection fraction (LVEF) ≥ 50% ULN. 7. Male or female subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 8 weeks after the last dose of study; a negative serum and urine pregnancy test are received within 7 days before the enrollment. Exclusion criteria: 1. Subjects who have previously received anlotinib or other anti-angiogenic targeted drugs; 2. Other malignancies currently or within the past 5 years, except cured carcinoma in situ of the cervix, non-melanoma skin cancer, and superficial bladder tumors (Ta [non-invasive tumor], Tis [carcinoma in situ], and T1 [tumor infiltrating basement membrane]); 3. Subjects who have received cytotoxic therapy, signal transduction inhibitors, and immunotherapy (or mitomycin C within 6 weeks prior to first dose) within 4 weeks before enrollment or are planning to receive these therapies during maintenance therapy with anlotinib. Subjects receive extended-field radiotherapy (EF-RT) within 4 weeks or limited-field radiation therapy within 2 weeks before enrollment; 4. Previous unrelieved treatment-related toxicity (> Grade 1, excluding alopecia) per the Common Terminology Criteria for Adverse Event

	(CTCAE v4.03); 5. Subjects who have multiple factors affecting oral medication (such as inability to swallow, chronic diarrhea, and intestinal obstruction), which are not controllable by symptomatic treatment; 6. Subjects with uncontrolled pleural effusion or ascites, causing respiratory syndrome (≥ CTCAE Grade 2 dyspnea [defined as shortness of breath with moderate exertion; limiting instrumental activities of daily living]); 7. Brain metastases with symptoms or symptoms controlled for less than 2 months; 8. Subjects with abnormal thyroid function after optimal drug therapy; 9. Any severe and/or uncontrolled disease: (1) Poor blood pressure control (systolic blood pressure ≥ 150 mmHg or diastolic blood pressure ≥ 100 mmHg); (2) Class I or more of myocardial ischemia or myocardial infarction, arrhythmia (including subjects with corrected QT interval [QTc] ≥ 480 ms and congestive heart failure in New York Heart Association [NYHA] functional class II-IV); (3) Active or uncontrolled severe infection (≥ Grade 2) per the CTCAE; (4) Liver cirrhosis, decompensated liver disease, active hepatitis, or chronic hepatitis that needs to receive antiviral therapy; (5) Kidney failure needs haemodialysis and peritoneal dialysis; (6) History of immune deficiency disorders including human immunodeficiency virus (HIV)-positive or other acquired or congenital immunodeficiency diseases or a history of organ transplantation; (7) Poor blood glucose control (fasting blood glucose [FBG] > 10

	mmol/L); (8) Urinary protein ≥ 2+, and confirmed 24-hour urinary protein > 1.0 g; (9) Subjects who have seizures and need treatment; (10) Abnormal coagulation function (international normalized ratio [INR] > 1.5 or prothrombin time [PT] > ULN + 4 s or activated partial thromboplastin time [APTT]) > 1.5 ULN) with a bleeding tendency, or are receiving thrombolytic/anticoagulant therapy; note, on the premise that the INR of prothrombin time is ≤ 1.5, the use of low-dose heparin (daily dosage of 6,000-12,000 U for adults) or low-dose aspirin (daily dosage of ≤ 100 mg) is allowed for prophylactic purposes; 10. The major surgical operation, biopsy, or obvious traumatic injury within 28 days before enrollment; 11. Invasion between tumors and great vessels by imaging or subjects whose tumors are judged by the investigators to be at high risk of invading vital blood vessels and causing fatal hemorrhage during the study; 12. Regardless of the severity, patients with any bleeding constitution or medical history; patients with any bleeding or ≥ Grade 3 bleeding per the CTCAE within 4 weeks before enrollment; patients with unhealed wounds, ulcers, or fractures; 13. Subjects with excessive arterial/venous thrombosis events within 6 months before enrollment, such as cerebrovascular accidents (including transient ischemic attacks), deep vein thrombosis, and pulmonary embolism; 14. Subjects with a history of psychotropic substance abuse with the inability to quit, or dysphonia; 15. Participation in other clinical trials of antitumor drugs within 4 weeks

	prior to the study; 16. Concomitant diseases seriously endanger patients' safety or interfere with the completion of the study in the opinion of investigators.
Dropout/Removal Criteria	1. Participants who failed to meet the inclusion criteria or meet the exclusion criteria; 2. Participants who are unable to evaluate for efficacy or unable to evaluate safety without receiving 1 dose of the drug; 3. Participants who are treated with chemotherapy, surgical or experimental drugs other than this protocol during the trial; 4. Participant's concurrent use of National Medical Products Administration (NMPA)-approved modern herbal agents and immunomodulatory agents for the treatment of tumors; 5. Violation of the clinical study protocol, not following the prescribed dose, method, and course of drug administration;
Withdrawal Criteria	1. Withdrawal of informed consent voluntarily at any given moment; 2. Radiographic evidence of disease progression; 3. Subjects cannot tolerate treatment after twice dose reduction of anlotinib; 4. Pregnancy events occurred during the study; 5. Subjects developed disease progression and cannot benefit from further treatment determined by the investigators; 6. Decisions to withdraw from study by the investigators.
Termination Criteria	Subject must termination the study if the following cases occur (including but certainly not limited to): 1. The unintended, meaningful, or unacceptable risk occurs in the subjects;

	2. Serious mistakes are found in the protocol during trial implementation; 3. The investigational drug/treatment is not effective or the continuation of the trial is not meaningful; 4. Completion of the trial was extremely difficult due to severe delays in subject enrollment or major deviations from protocol.
Sample Size calculation	The study is designed according to the endpoint of PFS. The primary objective is to evaluate the efficacy and safety of anlotinib maintenance treatment in patients with recurrent/metastatic/inoperable soft tissue sarcoma after first-line anthracycline-based chemotherapy (≥ 4 cycles). The primary endpoint of this study is investigator-assessed PFS of anlotinib maintenance treatment in patients with soft tissue sarcomas after first-line anthracycline-based chemotherapy. Based on the historical data and results of comparable drugs, the median PFS of the placebo was 3.3 months. Meanwhile, on the basis of the ALTER-0203 study and current clinical practice requirements, the expected median PFS of anlotinib as maintenance therapy after first-line chemotherapy is 5 months. Assuming that α=0.05 one-sided), β=0.2, 12-month enrollment period, 12-month follow-up period, and 10% drop-out rate, a total of 48 subjects is required. NCSS&PASS 15.0 software with the Log-Rank test for a single sample and sample correction is used for the sample size calculation.
Statistical Analysis	Analysis set/population This study will involve the following analysis sets or analysis populations: 1. Full analysis set (FAS) is defined as all subjects have been screened for eligibility and have received the study drug. FAS is the primary analysis set for efficacy analysis; 2. Per-protocol set (PPS) is defined as subjects from the full analysis set (FAS) who had no major protocol violations. PPS is the subset of FAS

	and is the secondary analysis set for efficacy analysis; 3. Safety set (SS) is defined as subjects who have received the study drug and have post-drug safety evaluation data. SS is the primary analysis set for safety analysis. Universal analysis Descriptive statistics are used to summarize data unless otherwise specified. For quantitative variables, summary statistics will include the number of subjects, mean, standard deviation (SD), median, minimum, and maximum. For categorical variables, frequency counts and percentage of patients will be presented. Kaplan-Meier method is used for time-to-event analysis to estimate the median survival time and its 95% confidence interval (CI). Efficacy analysis PFS of anlotinib maintenance therapy in patients with soft tissue sarcoma after first-line anthracycline-based chemotherapy is used as the primary efficacy endpoint and is evaluated by investigators. Kaplan-Meier method is used to estimate its median time and two-sided 95% CI. The secondary endpoints are ORR, DCR and OS. The Kaplan-Meier method is used to estimate their median time and two-sided 95% CI. DCR (complete remission [CR] plus PR plus SD) and ORR (CR plus PR) will be compared between subgroups using Fisher's Exact Test, and two-sided 95% CI are presented. *P* values less than 0.05 will be considered statistically significant for the differences tested (except as otherwise noted). Safety analysis Safety analyses are based on descriptive statistical analysis to describe the treatment emergent adverse events (TEAEs), serious AEs (SAEs), laboratory data, vital signs, etc. A statistical summary of study drug exposures (including treatment cycles, total dose, and dose intensity) will

	also be performed. All of the above data will be analyzed and summarized using current standard clinical reporting guidelines. This standard includes but is not limited to the following: 1. Summary of AEs (all-cause and treatment-related AEs); 2. Incidence and severity of AEs (all-cause and treatment-related AEs); 3. The relationship between AEs and study drugs; 4. The outcome of AEs; 5. SAEs; 6. Descriptive statistics of laboratory, vital signs, and electrocardiograms (ECG) data (absolute values of post-baseline and changes from baseline to post-baseline); 7. Summary of post-baseline vital sign data and ECG classification.
Study Procedures	Anlotinib (12 mg, p.o., qd) is administered orally on an empty stomach in a 21-day cycle with 2 weeks on and 1 week off until disease progression.

Study Procedures Table

Study visits	Screening [1]		During the treatment period			Dropout	End-of-treatment	Before progression [2]	Follow-up of survival after progression	Follow-up of survival after DCO [3]
	V_1	V_2	V_3	V_4	V_{5+} [4]	NA	NA	NA	NA	NA
Visit windows (days)	-28-(0)	-7-0	Examination period ±3 Medication period ±3			0	±3	±7		
Treatment cycles	NA	NA	C_1D_7	C_1D_{21}	C_3D_{21}	NA	Anlotinib discontinued For 21 days	Per 8 weeks		
Subject baseline characteristics										
Informed consent	×									
Demographics	×									
Inclusion/ exclusion criteria	×									
Physical examination [5]		×	×	×	×	×				
Vital signs [6]		×	×	×	×	×				
History of tumors and	×									

Other medical [7]										
Laboratory evaluations										
Hemanalysis [8]		×	×	×	×	×	×			
Urinalysis [9]		×	×	×	×	×	×			
Stool tests [10]		×	×	×	×	×				
Blood biochemistry [11]		×	×	×	×	×	×			
Thyroid function [12]		×	×	×	×	×				
Coagulation function [12]		×	×	×	×	×				
12 lead-electrocardiogram (ECG) [13]		×	×	×	×	×				
Myocardial enzyme profile [14]		×								
Echocardiography [15]		×				×				
Hepatitis B virus (HBV), Hepatitis C virus (HCV), HIV [16]	×									
Pregnancy test [17]		×				×				

Radiology (completion of initial post-treatment imaging evaluation at C1D21 and performed every 6 weeks±7 days subsequently)										
Radiology [18]	×			×	×	×		×		
Other clinical assessments										
QoL [19]		×		×	×	×				
ECOG scores		×		×	×	×	×			
Blood pressure [20]	×	×	×	×	×	×				
AEs [21]			×	×	×	×	×			
Study drug										
Anlotinib			3 weeks of a cycle with 2 weeks on and 1 week off							
Concomitant treatment [22]	×	×	×	×	×	×	×	×	×	×
Drug compliance [23]			×	×	×	×				
Follow-up of survival [24]										
Time to disease progression [25]						Imaging evaluation is performed every 8 weeks (±3 days) until disease progression or the initiation of other oncologic treatment (non-imaging PD patients)				
Time to death									×	×
Antitumor treatment [26]							×	×	×	×

Note: The examinations and procedures are performed according to the study schedule and are

not affected by the length of drug discontinuation, but occasional changes in the window period of each examination item due to holidays, vacations, or other administrative reasons are allowed. The window period of 3 days for screening indicators and examination must be completed before the initiation of the treatment cycle, for example, screening should not be repeated if performed within 3 days before the initiation of the first cycle of treatment. NA: not applicable.

[1]. Subjects must complete the screening visit within 28 days after imaging progression;

[2]. Subjects who withdraw from the study without objective progress will continue to be followed up until the date of objective progress occurred or data cut-off;

[3]. DCO: Data cut-off;

[4]. Subjects are visited every 6 weeks from V5;

[5]. Physical examination: whole body system examination (facial features, integumentary system, lymph nodes, eyes, ears, nose, throat, abdomen, spine, extremities, and nervous system) are performed within 7 days before enrollment, on C1D7, C1D21, Day 21 of every two cycles (odd numbered cycles) subsequently, and at dropout visit;

[6]. Vital signs: temperature, pulse rate, and respiratory rate are performed on C1D7, C1D21, and Day 21 of odd numbered cycles, and at the post-treatment visit. Blood pressure monitoring is described in [22];

[7]. Medical history: pathological results, EGFR T790M mutation test report; history of tumor surgery, chemotherapy, radiotherapy, and other disease treatment;

[8]. Hemanalysis: hemoglobin, red blood cells, white blood cells, neutrophil count, lymphocyte count, and platelets count are performed within 7 days before enrollment, on C1D7, C1D21, Day 21 of each subsequent odd numbered cycles, at the outgroup visit, and on Day 21 after treatment. If the neutrophil count $\leq 1 \times 10^9$/L or platelets (PLT) $\leq 50 \times 10^9$/L, additional examination (once per 2-3 days) is required; weekly hemanalysis is required if there is a delay in dosing or dose adjustment due to hematological toxicity;

[9]. Urinalysis: urine protein, glucose, occult blood (red blood cell and white blood cell), pH, and ketone bodies are performed within 7 days before enrollment, on C1D7, C1D21, Day 21 of each subsequent odd numbered cycles, at the outgroup visit, and Day 21 after

treatment; If the semi-quantitative method shows the levels of protein ≥ 2+ (e.g., urine test strip), 24-hour urine protein quantification should be performed;

[10]. Stool tests: occult blood test is performed on C1D7, C1D21, Day 21 of each subsequent odd numbered cycle, and at the outgroup visit;

[11]. Blood biochemistry: liver function (TP, A, G, ALT, AST, LDH, ALP, TBil, DBil, and IBil), renal function (BUN, Cr, and UA), blood lipid tetrachoric (TC, TG, HDL, and LDL), electrolytes (K^+, Na^+, CL^-, Ca^{2+}, Mg^{2+}, and P), lipase, amylase, fasting glucose, etc. are performed on C1D7, C1D21, Day 21 of each subsequent odd numbered cycles, at the outgroup visit, and Day 21 after treatment; during the drug administration, patients who develop early symptoms of liver injury (e.g., appetite loss, vomiting, right upper abdominal discomfort, malaise, etc.) before blood biochemical abnormalities should undergo blood biochemistry immediately. If ALT or AST is up to 3 times ULN or baseline value and total bilirubin up to 2 times the ULN or baseline value, the frequency of tests should be increased (recommended 1-2 times/week);

[12]. Thyroid function (T3, T4, FT3, FT4, and TSH) and coagulation function (PT, APTT, TT, Fbg, and INR) are performed within 7 days before enrollment, on C1D7, C1D21, and on Day 21 of each subsequent odd numbered cycles;

[13]. 12 lead-ECG performed within 7 days before enrollment, on C1D7, C1D21, and Day 21 of each subsequent odd numbered cycles. If an abnormal ECG is identified, two additional confirmations must be performed (each 5 minutes apart and the QTc interval should be indicated);

[14]. One examination is done within 7 days before enrollment. This examination is supplemented only when symptoms such as precordial pain, palpitations, and ECG abnormalities are present;

[15]. Echocardiography is performed within 7 days before enrollment, followed by additional tests only if clinically meaningful ECG abnormalities occur during treatment;

[16]. HBV and HCV examination: HBV examination (HBsAg, HBsAb, HBeAg, HBeAb, and HBcAb) is performed and if the test result is abnormal, viral replication (HBA DNA) and anti-HCV antibody test should be conducted;

[17]. Pregnancy testing is limited to women of childbearing age, who are required to

undergo a pregnancy test within 7 days before enrollment;

[18]. Radiology: including CT or MRI of the chest, abdomen, pelvis, and head. Baseline assessment of screening period tumors can be extended to within 3 weeks before treatment, and CT/MRI scans obtained before signing informed consent can be used for screening period tumor assessment if they meet the criteria; bone scans are required if suspected bone metastasis; no symptoms of cerebral hemorrhage need to be confirmed within 28 days before treatment in patients with stable brain metastases.

The imaging examination should be performed on chest and abdominal lesions under the same conditions as the baseline (layer thickness of the scan, use of contrast agents, etc.) on C1D7 and Day 21 of every odd numbered cycle; Other lesions identified at baseline or new lesions suspected subsequently should also be examined at the appropriate time. Subjects should be promptly imaged when outgroup for any reason;

The window of the imaging schedule is ±7 days. An unplanned imaging examination may be performed when disease progression (e.g., worsening of symptoms) is suspected. Subjects who end-of-treatment for reasons other than imaging-confirmed disease progression should perform an image evaluation at the date of end-of-treatment, meanwhile, tumor efficacy evaluations are performed every 8-week follow-up after the end of the trial until documented disease progression or new tumor treatment is initiated.

[19]. QoL: the questionnaire should be completed by the subjects themselves. However, if the subject is unable to read or write on his or her own, it may be performed by an authorized staff member or guardian. QoL scores were performed within 7 days before enrollment, on C1D7, C1D21, on Day 21 of each subsequent odd numbered cycles, at the end of the study, and on 21 days after treatment.

[20]. Blood pressure is measured by the subject himself/herself and recorded in the patient diary card. Blood pressure is tested at least 3 times per week for the first 2 cycles and followed up each day if the blood pressure is abnormal. In addition, blood pressure is measured again by the investigator at each follow-up visit, coffee, and tobacco intake are prohibited within 30 minutes before each blood pressure is measured. The measurement of blood pressure is taken in the sitting position with the arm at heart level after at least 10 minutes of quiet sitting, and each blood pressure measurement is taken on the same side;

[21]. AEs are recorded from the first dose of the study drug until at least 21 days after the last dose and follow-up until the AEs resolved or stabilized;

[22]. Concomitant medications and therapy during the trial should be recorded, and the concomitant medication and therapy are recorded only in the case of novel or unresolved AEs associated with treatment if the subject discontinues treatment;

[23]. Study drug compliance: drug doses, counts, and compliance for the previous cycle are calculated and recorded in case report form (CRF) at the first day of each treatment cycle;

[24]. Survival follow-up: after discontinuation of trial treatment, survival status and subsequent antitumor therapy can be collected every 8 weeks by clinical or telephone follow-up until death;

[25]. Time to disease progression: for patients with non-imaging evidence of progression (intolerable and other conditions), imaging evaluation should continue every 8 weeks until disease progression, initiation of other oncologic therapy, death, or end of the study;

[26]. Documentation of anti-tumor treatment should be performed during the follow-up period.

List of Abbreviations

Abbreviations	Full term
ACEI	Angiotensin-converting enzyme inhibitors
AE	Adverse event
AKP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
ARB	Angiotensin II receptor blockers
AST	Aspartate aminotransferase
bFGF	Basic fibroblast growth factor
BSC	Best supportive care
BUN	Blood urea nitrogen
B-scan	B-scan ultrasonography
Ca	Calcium
CI	Chlorine
Cr	Creatinine
CR	Complete remission
eCRF	Electronic case report form
CT	Computed tomography
DCR	Disease control rate
DLT	Dose-limiting dose

Abbreviations	Full term
DRQ	Data rating questionnaire
ECOG PS	Eastern cooperative oncology group performance status
EGFR	Epidermal growth factor receptor
FGFR	Fibroblast growth factor receptor
FAS	Fall analysis set
GCP	Good Clinical Practice
Glu	Glucose
Hb	Hemoglobin
HFS	Hand-foot syndrome
ITT	Intention-to-treat
K	Kalium
LD_{50}	Median lethal dose
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
MRI	Magnetic resonance imaging
Na	Natrium
NCCN	National comprehensive cancer network
NCI-CTC	National cancer institute common toxicity criteria
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival

Abbreviations	Full term
PFR	Progression-free rate
PFS	Progression-free survival
PD	Progressive disease
PDGFR	Platelet-derived growth factor
PI	Principal investigator
PLT	Platelet
PR	Partial response
PRO	Protein
PPS	Per protocol set
PT	Prothrombin time
Qd	Once a day
QoL	Quality of life
RBC	Red blood count
RECIST	Response evaluation criteria in solid tumors
γ-GT	Gamma glutamyl transpeptidase
SAE	Serious adverse event
SAS	Safety analysis set
SD	Stable disease
STS	Soft tissue sarcoma
TT	Thrombin time
TTP	To tumor progression

Abbreviations	Full term
UNL	Upper normal limit
UA	Uric acid
VEGFR	Vascular endothelial growth factor receptor
WBC	White blood cell count
WT	Wild type

1. Study objective

1.1 Primary objective

To evaluate the progression-free survival (PFS) of anlotinib maintenance therapy in patients with recurrent/metastatic/inoperable soft tissue sarcoma who achieved stable disease (SD)/partial response (PR) after first-line anthracycline-based chemotherapy (≥ 4 cycles).

1.2 Secondary objective

To evaluate the overall survival (OS), objective response rate (ORR), disease control rate (DCR) and safety of anlotinib maintenance treatment after first-line anthracycline-based chemotherapy in patients with soft tissue sarcoma.

2. Study design

2.1 Study design

This is an open-label, single-arm, multicentre exploratory study of anlotinib maintenance treatment after anthracycline-based chemotherapy in advanced soft tissue sarcoma.

2.2 Sample size calculation

The study is designed according to the endpoint of PFS. The primary objective is to evaluate the efficacy and safety of anlotinib maintenance treatment in patients with recurrent/metastatic/inoperable soft tissue sarcoma after first-line anthracycline-based chemotherapy (≥ 4 cycles). The primary endpoint of this study is investigator-assessed PFS of anlotinib maintenance treatment in patients with soft tissue sarcomas after first-line anthracycline-based chemotherapy. Based on the historical data and results of comparable drugs, the median PFS of the placebo was 3.3 months. Meanwhile, on the basis of the ALTER-0203 study and current clinical practice requirements, the expected median PFS of anlotinib as maintenance therapy after first-line chemotherapy is 5 months. Assuming that α=0.05 one-sided), β=0.2, 12-month enrollment period, 12-month follow-up period, and 10% drop-out rate, a total of 48 subjects is required. NCSS&PASS 15.0 software with the Log-Rank test for a single sample and sample correction is used for the sample size calculation.

2.3 Treatment regimen

Initial dose: anlotinib is given once daily under fasting conditions for 2 weeks followed by 1-week rest (every 3 weeks in one cycle). If there are missed medications and the interval from

the next medication is < 12 hours, no medication is supplemented.

Subjects with complete response (CR), PR, and SD who are tolerable to treatment are allowed to continue the treatment.

Treatment will be discontinued when the subjects is unsuitable for treatment according to the investigator's judgment, or the disease progressed as per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) criteria.

2.4 Efficacy assessment

Primary endpoint: PFS of anlotinib maintenance treatment;

Secondary endpoints: OS; ORR; DCR; Safety;

PFS is defined as the time from treatment initiation to the first time of disease progression or death from any cause, whichever occurs first.

OS is defined as the time from treatment initiation to the date of death due to any cause.

Object response is assessed by the investigator as per RECIST v1.1.

DCR is defined as the percentage of subjects with PR, CR, or SD lasting for ≥ 4 weeks in evaluable subjects.

Safety endpoints: vital signs; laboratory data; AEs and SAEs as per National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Event version 4.03 (CTCAE v4.03).

2.4.1 Efficacy assessment and analysis

Efficacy assessment is performed at the first cycle and thereafter every two cycles. All imaging data have to be retained for the patient with CR, PR, SD, and progressive disease (PD).

For the subject who discontinued the study before disease progression and receive no other anti-tumor therapies, an imaging assessment is required every 8 weeks to observe the progression of the disease.

2.4.2 Follow-up of survival

For the subject who withdrew from the study but has no disease progression, the tumor response assessment will be collected during the follow-up period and recorded in the case report form (CRF), until disease progression. Any other anti-tumor therapies have to be recorded in the CRF. For the analysis of OS, data for patients who are alive will be censored at

the last date they were known to be alive. Subjects (including withdrawn subjects) will receive long-term follow-up (by telephone). Subjects will be followed up for OS every 8 weeks after the end of the study. During the follow-up period, information on anti-tumor therapies and survival status will be collected.

2.4.3 Follow-up of AEs

Any unresolved AEs after treatment discontinuance have to be followed up and assessed. Safety assessment should be continued 21 days after the end of the last dose to observe any new AEs.

3. Subjects

3.1 Inclusion criteria

(1) Subjects who are willing to participate in the study and able to provide signed informed consent, and comply with all aspects of the protocol

(2) Age 18-70 years; Eastern cooperative oncology group performance status (ECOG PS) of 0-2; predicted life expectancy of ≥ 3 months;

(3) Subjects with pathologically confirmed advanced synovial sarcoma, leiomyosarcoma, liposarcoma, angiosarcoma, etc. (except malignant peripheral nerve sheath tumor, undifferentiated sarcoma, rhabdomyosarcoma, chondrosarcoma, osteosarcoma, dermato-fibrosarcoma protuberans, gastrointestinal stromal tumor, ewing's sarcoma/primitive neuroectodermal tumor, inflammatory myofibroblastic tumor, and malignant mesothelioma);

(4) Subjects who have at least one measurable lesion within the previous 3 months according to RECIST v1.1 criteria and can be accurately measured by magnetic resonance imaging (MRI) or computed tomography (CT) in at least 1 direction (maximum diameter needs to be documented), with ≥ 20 mm on conventional CT or ≥ 10 mm on spiral CT;

(5) Subjects who achieved stable disease/partial response after 4 or more cycles of anthracycline-based therapy;

Note: The cumulative dose of anthracyclines can be calculated as an intolerable dose when reaching a specific dose. The most widely used maximum lifetime cumulative dose of anthracyclines are as follows:

The most widely used maximum lifetime cumulative dose of anthracyclines	
Doxorubicin (ADM)	550 mg/m^2, radiotherapy or combined medication < 350-400 mg/m^2
Epirubicin (EPI)	900-1000 mg/m^2, if doxorubicin has been applied, < 800 mg/m^2
Pirarubicin (THP)	950 mg/m^2

The maximum cumulative dose of doxorubicin liposome (PLD) is not limited. Cited from: Chinese Society of Clinical Oncology, Chinese Society of Hematology, Guidelines for cardiotoxicity control of anthracyclines (2013 Edition), Journal of Clinical Oncology, 2013,18(10):925-934.

(6) Adequate organs function within 7 days before treatment as evidenced by the following criteria:

1) Hemanalysis (no blood transfusion within 14 days): hemoglobin (Hb) ≥ 90 g/L; absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L; platelets (PLT) ≥ 80 × 10^9/L;

2) Biochemistry: total bilirubin (TBil) ≤ 1.5 × upper limits of normal (ULN); alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN; ALT and AST ≤ 5 × ULN in patients with liver metastases; blood creatinine (Cr) ≤ 1.5 × ULN or creatinine clearance rate (CCr) ≥ 60 mL/min;

3) Doppler ultrasound assessment: left ventricular ejection fraction (LVEF) ≥ 50% ULN.

(7) Male or female subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 8 weeks after the last dose of study; a negative serum and urine pregnancy test are received within 7 days before the enrollment.

3.2 Exclusion criteria

Subjects who meet any of the following criteria are not eligible to enter the study:

(1) Subjects who have previously received anlotinib or other anti-angiogenic targeted drugs;

(2) Other malignancies currently or within the past 5 years, except cured carcinoma in situ of the cervix, non-melanoma skin cancer, and superficial bladder tumors (Ta [non-invasive tumor], Tis [carcinoma in situ] and T1 [tumor infiltrating basement membrane]);

(3) Subjects who have received cytotoxic therapy, signal transduction inhibitors, and

immunotherapy (or mitomycin C within 6 weeks prior to first dose) within 4 weeks before enrollment or are planning to receive these therapies during maintenance therapy with anlotinib. Subjects receive extended-field radiotherapy (EF-RT) within 4 weeks before enrollment or limited-field radiation therapy within 2 weeks before enrollment;

(4) Previous unrelieved treatment-related toxicity (> Grade 1, excluding alopecia) per the Common Terminology Criteria for Adverse Event (CTCAE v4.03);

(5) Subjects who have multiple factors affecting oral medication (such as inability to swallow, chronic diarrhea, and intestinal obstruction), which are not controllable by symptomatic treatment;

(6) Subjects with uncontrolled pleural effusion or ascites, causing respiratory syndrome (≥ CTCAE Grade 2 dyspnea [defined as shortness of breath with moderate exertion; limiting instrumental activities of daily living]);

(7) Brain metastases with symptoms or symptoms controlled for less than 2 months;

(8) Subjects with abnormal thyroid function after optimal drug therapy;

(9) Any severe and/or uncontrolled disease:

1) Poor blood pressure control (systolic blood pressure ≥ 150 mmHg or diastolic blood pressure ≥ 100 mmHg);

2) Class I or more of myocardial ischemia or myocardial infarction, arrhythmia (including subjects with corrected QT interval [QTc] ≥ 480 ms and congestive heart failure in New York Heart Association [NYHA] functional class II-IV);

3) Active or uncontrolled severe infection (≥ Grade 2) per the CTCAE;

4) Liver cirrhosis, decompensated liver disease, active hepatitis, or chronic hepatitis that need to receive antiviral therapy;

5) Kidney failure needs haemodialysis and peritoneal dialysis;

6) History of immune deficiency disorders including human immunodeficiency virus (HIV)-positive or other acquired or congenital immunodeficiency diseases or a history of organ transplantation;

7) Poor blood glucose control (fasting blood glucose [FBG] > 10 mmol/L);

8) Urinary protein ≥ 2+, and confirmed 24-hour urinary protein > 1.0 g;

9) Subjects who have seizures and need treatment;

10) Abnormal coagulation function (international normalized ratio [INR] > 1.5 or prothrombin time [PT] > ULN + 4 s or activated partial thromboplastin time [APTT] > 1.5 ULN) with a bleeding tendency, or are receiving thrombolytic/anticoagulant therapy; note, on the premise that the INR of prothrombin time is ≤ 1.5, the use of low-dose heparin (daily dosage of 6,000-12,000 U for adults) or low-dose aspirin (daily dosage of ≤ 100 mg) is allowed for prophylactic purposes;

(10) The major surgical operation, biopsy, or obvious traumatic injury within 28 days before enrollment;

(11) Invasion between tumors and great vessels by imaging or subjects whose tumors are judged by the investigators to be at high risk of invading vital blood vessels and causing fatal hemorrhage during the study;

(12) Regardless of the severity, patients with any bleeding constitution or medical history; patients with any bleeding or ≥ Grade 3 bleeding per the CTCAE within 4 weeks before enrollment; patients with unhealed wounds, ulcers, or fractures;

(13) Subjects with excessive arterial/venous thrombosis events before enrollment or within 6 months, such as cerebrovascular accidents (including transient ischemic attacks), deep vein thrombosis, and pulmonary embolism;

(14) Subjects with a history of psychotropic substance abuse with the inability to quit, or dysphonia;

(15) Participation in other clinical trials of antitumor drugs within 4 weeks prior to the study;

(16) Concomitant diseases seriously endanger patients' safety or interfere with the completion of the study in the opinion of investigators.

3.3 Drug discontinuation criteria

(1) Identification of PD based on efficacy evaluation criteria or clinically recognized disease progression;

(2) Treatment should be discontinued in the opinion of the study physician in terms of optimal patient benefit;

(3) Confirmed the occurrence of intolerable AEs or SAEs by the investigator;

(4) Patients with poor compliance and those who receive over 80% to 120% of their medication dosage;

(5) Withdrawal of informed consent;

(6) Treatment with other anti-tumor drugs that affect efficacy (such as chemotherapy, targeted therapy, or biotherapy therapy);

(7) Unplanned pregnancy;

(8) Death.

3.4 Dropout/removal criteria

(1) Participants who failed to meet the inclusion criteria or meet the exclusion criteria;

(2) Participants who are unable to evaluate for efficacy or unable to evaluate safety without receiving 1 dose of the drug;

(3) Participants who are treated with chemotherapy, surgical or experimental drugs other than this protocol during the trial;

(4) Participant's concurrent use of National Medical Products Administration (NMPA)-approved modern herbal agents and immunomodulatory agents for the treatment of tumors;

(5) Violation of the clinical study protocol, not following the prescribed dose, method, and course of drug administration;

3.5 Processing of subjects who dropped out

The investigator must complete the efficacy and safety assessment at the time of patients who drop out from the trial, complete the safety follow-up, and fully document of AEs and its outcome. The investigator may suggest or offer subjects new or alternative treatments based on the patient's condition. Patients with the non-progressive disease will continue to be followed for imaging evaluation until the patient begins novel treatment or disease progression.

4. Study drugs

4.1 Drug overview

Study drugs: Anlotinib is provided by Chia Tai Tianqing Pharmaceutical Group Co., Ltd.

Specification: 12 mg/tablet; 10 mg/tablet; 8 mg/tablet.

Drug storage: Store in a sealed and dark place below 25°C; expiration date: 18 months.

According to the requirements of Good clinical practice (GCP), hospital custody is responsible for drug storage, distribution, and recovery. The drug distribution and recovery are required to be recorded completely. Recovered drugs will be handed over to the sponsor after study completion. Clinical research associates (CRA) are responsible for the check of drug use, record, and recall regularly.

4.2 Dose and administration regimens

Anlotinib administration:

12 mg/tablet, 1 tablet, qd, administered under fasting conditions. Anlotinib is given for 2 weeks followed by 1-week rest (every 3 weeks in one cycle). Subjects with CR, PR, and SD are allowed to be treated until disease progression, intolerable toxicity, and withdrawal of consent. Subjects with PD are required to discontinue treatment.

4.3 Dose adjustment

The doses of anlotinib include (1) initial dose:12 mg, qd; (2) dose reduction: 10 mg, qd; (3) dose reduction: 8mg, qd. The dose levels and adjustments were listed in the following:

Dose	**Anlotinib**
Initial dose	12 mg/day, qd
First dose reduction	10 mg/day, qd
Second dose reduction	8 mg/day, qd

4.3.1 Criteria of dose suspension and reduction

Drug administration should be suspended for reasons of no recovery of drug toxicity. The duration of dose suspension should not exceed 2 weeks per cycle; the dose suspension should not exceed 2 times per cycle to ensure that the subject receives an adequate strength of drugs (the trial should be terminated if the above criteria are exceeded, including for patients whose next cycle of treatment is delayed by more than 2 weeks). However, when recovery from proteinuria is prolonged resulting in the duration of dose suspension for more than 2 weeks, if the investigator determines that the subject may benefit from continuing the drug, a decision to continue the trial drug may be discussed with the group leader after the subject has recovered

to ≤ 2 g/24h of proteinuria.

The subjects cannot return to the previous dosing pattern after dosage reduction and a maximum of two dose reductions are allowed in anlotinib treatment.

When patients experienced Grade 3 hematological toxicities and Grade 2 non-hematological toxicities, dose suspension and reduction are considered. Non-hematological toxicities, including controllable nausea, vomiting, and fever with a definite cause (below 38°C), can be managed and treated aggressively without dose suspension or dose downregulation.

To ensure consistency of dose adjustment, dose suspension is performed at the time of dose adjustments for each cycle. The criteria of dose suspension and reduction are as follows (once the criteria of dosage reduction are met which is considered poorly tolerated, a reduction should be performed).

Criteria of dose suspension and reduction

Grades of AEs (NCI-CTCAE v4.03)	**Time of administration**	**Dose adjustment**
Grade 0-2	Administering drugs on time	Maintain original dose
Grade 3	Dose delay until recovery to Grade 2[#]	Continue administration after a reduced dose level
Grade 4	Dose delay until recovery to < Grade 2[#]	Continue administration after a reduced dose level; the investigator can stop the treatment permanently judging by the treatment.

[#] If the toxicity is not recovered after 2 weeks of dose suspension, treatment should be terminated permanently

4.3.2 Dose reduction due to hematological toxicities

If subjects in each group experience hematological toxicities meeting the following criteria, dose reductions will be performed.

Criteria of dose reduction due to hematological toxicities

Worst toxicity	Minimum value	Dose adjustment
ANC	ANC < 1.5×10^9/L with infection or fever or ANC < 0.5×10^9/L for more than 5 days	Continue administration after a reduced dose level [a, b]
Platelet	Platelet < 25×10^9/L	Continue administration after a reduced dose level [a]

[a] If toxicity occurs again, continue administration after another reduced dose level until discontinuation;

[b] Support therapy with colony-stimulating factors may be required.

4.3.3 Dose reduction due to non-hematological toxicities

If subjects in each group experience non-hematological toxicities meeting the following criteria, dose reductions will be performed.

Criteria of dose reduction due to non-hematological toxicities

Grades of toxicities	Non-hematological toxicities
Grade 1	Maintain the original dose (appropriate symptomatic treatment should be provided).
Grade 2	Symptomatic treatment and continue drug treatment should be provided. If AE resolves to Grade ≤ 1 within 2 weeks, continue drug treatment; If AE does not improve or aggravate, drug interruption until AE resolves to Grade ≤ 1 and continue drug treatment with original dose level.
Grade 3	Drug interruption and symptomatic treatment should be provided. If AE resolves to Grade ≤ 1 within 2 weeks, continue drug treatment with the original dose level or at a dose reduced by one level by investigator's discretion; Discontinuing treatment and withdrawing from the clinical study is recommended if a Grade 3 or above adverse reaction occurs.

Grade 4	Drug interruption and symptomatic treatment should be provided, and the dose is reduced by one level if AE resolves to Grade ≤ 1; Discontinue treatment and withdrawal from the clinical study is recommended if a Grade 4 AE occurs (such as Grade 4 kidney injury, neurotoxicity, cardiotoxicity, hepatotoxicity and other life-threatening).

Note: For subjects with nausea and vomiting, the full anti-emetic regimen, including 5-HT3 receptor antagonists, dexamethasone, or others, was administered prior to dose adjustment.

AEs of special interest: In case of fatal AEs such as hypertensive crisis, intracerebral hemorrhage, pulmonary hemorrhage (≥ Grade 2), other hemorrhages (≥ Grade 3), arterial thrombosis, venous thrombosis (Grade 4), leukoencephalopathy syndrome, gastrointestinal perforation, and cardiotoxicity (such as prolonged QT interval), discontinue treatment and withdraw from the clinical study is recommended and aggressive symptomatic treatment should be provided.

4.4 Management of common AEs

Management of anlotinib-related AEs will be performed by the investigator based on the actual clinical situation (reference the following management).

1) Abnormal liver function

Recommended management for dose suspension and/or dose reduction in the presence of abnormal liver function (elevated ALT, elevated AST, or elevated TBil) are listed below.

Grades of AEs	Dose adjustment	Recommended treatment
Grade 1	Maintain original dose	Follow up as scheduled
Grade 2 (normal baseline)	Drug interruption should be provided. If AE resolves to ≤ Grade 2 within 2 weeks, continue drug treatment at a dose reduced by one level	Active hepatoprotective treatment and close monitoring of liver function, once a week

Grade 2 (abnormal baseline)	Maintain original dose	Active hepatoprotective treatment and close monitoring of liver function, once a week
Grade 3	Drug interruption should be provided. If AE resolves to ≤ Grade 2 within 2 weeks, continue drug treatment at a dose reduced by one level	Active hepatoprotective treatment and close monitoring of liver function twice weekly until toxicity recovers to < Grade 2 or there is an explanation
Grade 4	Discontinuing treatment permanently	Active hepatoprotective treatment and close monitoring of liver function 1-2 times a week until toxicity recovers to < Grade 2 or there is an explanation

2) Hand-foot syndrome (HFS)

HFS, also called palmar-plantar erythrodysesthesia or acral erythema, is a skin toxicity that may be pronounced in the areas under mechanical stress/pressure. It can occur in patients with tumors who are undergoing chemotherapy or molecular-targeted therapy. HFS is characterized by numbness, dullness of sensation, abnormal sensation, tingling, absence of pain, swelling of the skin, erythema, flaking, cracking, hard nodular blisters, and severe pain.

Grades of HFS:

Grade 1: Numbness/dullness/abnormal sensation of the hands and/or feet, painless swelling or erythema, and/or discomfort that does not interfere with normal activities.

Grade 2: Painful erythema and swelling of the hands and/or feet and/or discomfort that interfere with normal activities.

Grade 3: Wet flaking of the hands and/or feet, ulcers, blisters or severe pain and/or severe discomfort that prevents the patient from working or carrying out daily activities. Intense pain and loss of skin function are less common.

Symptomatic treatment and management of HFS: Symptomatic supportive treatment as necessary, including reinforced skin care to keep the skin clean and avoid secondary infection; avoiding pressure or friction; using emollient creams or lubricants, topical lotions or lubricants containing urea and corticosteroid ingredients; and topical antifungal or antibiotic treatment if necessary.

Note: If there are 3 consecutive Grade 2 or higher HFS with a tendency to worsen, discontinuing treatment and withdrawing from the clinical study is recommended.

3) Hypertension

Before patients are enrolled, the blood pressure (BP) requirements in the inclusion and exclusion criteria should strictly adhere. BP control can be accomplished by adjusting the dose of antihypertensive drugs or adding new antihypertensive drugs before the trial drug is administered to patients with hypertension, and BP must be controlled to 140/90 mmHg or less (average value of 2 BP at intervals of 24 hours or more) before randomization. Monitoring and management of this type of hypertension: BP monitoring should be performed at least 3 times a week for the first 2 cycles of targeted drug therapy.

BP should be monitored daily for the first 6 weeks of initiation of treatment in this study. Any increase in BP should be actively discussed with your doctor and can usually be controlled with conventional anti-hypertensive therapy. For uncontrollable BP increase, it can usually be relieved by dose reduction or discontinuation of the targeted drug.

As anti-VEGF/VEGFR targeted therapies cause a decrease in NO synthesis and ultimately activate the renin-angiotensin-aldosterone system causing hypertension. Therefore, antihypertensive therapy is best administered with angiotensin-converting enzyme (ACE) inhibitors (ACEIs, such as captopril, enalapril, benazepril, and cilazapril). Some patients who are allergic or intolerant to ACEIs can be treated with angiotensin II receptor blockers (ARBs, such as losartan, valsartan, irbesartan, and telmisartan). ARBs are beneficial in relieving proteinuria in addition to decreasing BP. ACE inhibitors are used in patients with chronic kidney disease, proteinuria, and metabolic syndrome; dihydropyridine calcium antagonists are recommended for elderly patients.

Patients who develop hypertension or worsening of hypertension during treatment should 1) adjust the study drug according to the protocol; 2) administered anti-hypertensive drugs or adjust the dose of the targeted drug.

The principle of dose adjustment for hypertension

Hypertension	Dose adjustment
(A) SBP 120-139 mmHg, or DBP 80-89 mmHg	Monitor BP closely; maintain the original dose
(B) Grade 2 hypertension without a symptomatic presentation: persistent (≥ 24 h) or recurrent SBP to 140-159 mmHg or DBP to 90-99 mmHg; DBP ≥ 20 mmHg higher than before	1) Maintain original dose; 2) Administering antihypertensive drugs, or adjust the dose of existing antihypertensive drugs; 3) If blood pressure is effectively controlled by a two-week titration of antihypertensive medication [a], continue to administer the drug at the original dose level; if it is not effectively controlled, refer to (C).
(C) Grade 2 or 3 hypertension with symptomatic presentation: SBP ≥ 160 mmHg or DBP ≥ 100 mmHg; or Grade 2 hypertension that cannot be effectively controlled within two weeks	1) Suspension of anlotinib; 2) Administering antihypertensive drugs, or adjusting the dose of existing antihypertensive drugs; 3) If blood pressure is effectively controlled by a two-week titration of antihypertensive medication, continue to administer the drug at the original dose level or at a dose reduced by one level (according to the researcher's judgment)
(D) Multiple (two or more) hypertensive symptoms or hypertensive crises occurred despite management with antihypertensive drugs and dose adjustment of anlotinib	Discontinue treatment and withdraw from the clinical study

[a] blood pressure is effectively controlled, SBP < 140 mmHg and DBP < 90 mmHg.

The drugs recommended in the trial for the treatment of hypertension include: 1) ACEIs; 2) ARBs; 3) dihydropyridine calcium channel antagonists; and 4) beta-blockers.

Antihypertensive drugs such as nicardipine, diltiazem, and verapamil, which inhibit CYP3A4, are forbidden during the administration of anlotinib.

Note: Discontinuing anlotinib treatment and withdrawing from the clinical study is

recommended for subjects who develop hypertensive crisis.

4) Bleeding

The presence of gastrointestinal bleeding, including fecal occult blood (2+) and above, vomiting blood, or fresh blood in the stool, should be treated actively and symptomatically. For upper gastrointestinal bleeding, fasting should be performed and treatment consisting of anti-acid, gastric mucosa protection, anti-bleeding (hemostatic cyclic acid, reptilase, etc.) and, if necessary, octreotide should be administered; for lower gastrointestinal bleeding, anti-bleeding, blood transfusion and supportive treatment should be given; for uncontrolled bleeding, assistance from a surgeon is required immediately.

Patients with hemoptysis should be given anti-bleeding, blood transfusion, and supportive treatment; for uncontrolled bleeding, assistance from a surgeon is required immediately.

Note: For patients with confirmed cerebral hemorrhage, Grade 2 and above pulmonary hemorrhage, and Grade 3 and above bleeding, the drug must be discontinued immediately, treated symptomatically, and withdrawn from the clinical study.

In the presence of bleeding and coagulation abnormalities (except cerebral hemorrhage, Grade 2 or higher pulmonary hemorrhage), the dose adjustment principles are listed as follows:

The principle of dose adjustment for bleeding and coagulation abnormalities

Grades of AEs	Dose adjustment
Grade 1	Anlotinib is maintained at the original dose level and closely monitored.
Grade 2	Suspension of anlotinib and close monitoring until toxicity recovers to ≤ Grade 1, and continue drug treatment at a dose reduced by one level
≥ Grade 3 or ≥ Grade 2 recurrence (after discontinuation/dose adjustment)	Withdraw from the clinical study

5) Proteinuria

The proteinuria should be monitored closely for all subjects during the treatment period,

particularly for subjects with a history of hypertension. For subjects with 2 consecutive results of urine protein (2+), 24-hour urinary protein measurement should be performed.

Subjects who occur nephrotic syndrome are required to discontinue treatment and withdraw from the study.

Dose adjustment for proteinuria is listed as follows:

Dose adjustment for proteinuria

Definition	Grades of AEs	**Dose adjustment**
Urine protein (+) or 24-hour urine protein < 1.0 g	Grade 1	Initial anlotinib dose
Urine protein (2+) or 1.0 g ≤ 24-hour urine protein < 2.0 g	Grade 2	Initial anlotinib dose
Urine protein (2+) or more; 2.0 g ≤ 24-hour urine protein < 3.5 g	Grade 2	Dose delay. Toxicity returned to Grade ≤ 2 within 2 weeks, reduce the dose by 1 level; If the toxicity occurs three times, the dose discontinues.
24-hour urine protein ≥ 3.5 g	Grade 3	Dose delay. Toxicity returned to Grade ≤ 2 within 2 weeks, reduce the dose by 1 level; If the toxicity occurs three times, the dose discontinues.

6) Thrombus

If any arterial thrombosis (e.g., cerebral ischemia, stroke, angina, myocardial infarction) or symptomatic Grade 4 venous thrombosis occurs, subjects are required to discontinue treatment immediately and withdraw from the study.

For subjects with thrombotic symptoms, symptomatic treatment, surgery, or anticoagulant drugs should be scheduled immediately.

For subjects with venous thrombosis, the criteria for dose adjustment are as follows:

Grades of AEs	Dose adjustment
Grade 2	Anlotinib is maintained at the original dose level and closely monitored.
Grade 3 or asymptomatic Grade 4	(1) Anlotinib is discontinued. (2) Symptomatic treatment with anticoagulants (small-molecular-weight heparin). (3) Patients with thrombosis could continue treatment with one level dose reduction if they have improved after at least 1-week of treatment with anticoagulants and no severe (Grade 3, 4) bleeding, according to the investigator's judgment.

7) Diarrhea

Grade 1 to 2 diarrhea could be treated with supportive care, such as loperamide at the onset (e.g., 4mg orally followed by 2 mg every 2 hours until diarrhea is resolved).

8) Fatigue and weakness

Fatigue and weakness are common clinical symptoms associated with tumors. Electrolyte disorders, abnormal liver function, and abnormal heart function may all contribute to fatigue and weakness. Meanwhile, fatigue and weakness are also common adverse effects of anti-angiogenic drugs such as sunitinib, pazopanib, and sorafenib. It has been reported that anti-angiogenic drugs may increase the incidence of fatigue and weakness by causing hypothyroidism.

In previous clinical trials of anlotinib, the incidence of fatigue and weakness was higher in the anlotinib group than those in the control group, and the exact mechanism that triggered the increased incidence of fatigue and weakness is unclear.

Therefore, patients who experience or report Grade 2 or higher fatigue or weakness should be treated seriously. When Grade 3 or higher fatigue or weakness occurs, patients should be admitted to the hospital immediately to check and rule out possible causes such as electrolyte disorders, abnormal liver function, cardiac function disorders (ECG, cardiac ultrasound),

abnormal hormone levels (adrenal hormones, thyroid hormones), and the dose of anlotinib should be suspended or adjusted according to the principles of dose adjustment.

9) Pneumothorax

Pneumothorax is an abnormal accumulation of gas in the pleural space, resulting in compression of the lungs. The typical symptoms are sudden onset of chest pain, followed by chest tightness or breathlessness and an irritating dry cough. In some cases, the onset of the disease is slow and there may be no conscious symptoms.

Clinical signs depend on the amount of gas accumulation, and a small amount of pneumothorax may have no obvious signs. When there is a high volume of gas, the patient's chest is full, breathing is reduced, palpatory fibrillation is reduced or absent, percussion sounds are drummed and auscultatory breath sounds are reduced or absent. In patients with emphysema complicated by pneumothorax, although the breath sounds are diminished on both sides, the diminution is more pronounced on the pneumothorax side, even if the amount of pneumothorax is small, so attention should be paid to left-right contrast and up-down contrast during percussion and auscultation. In massive pneumothorax, the mediastinum is shifted to the healthy side. In a right-sided massive pneumothorax, the hepatic nasal boundary is shifted downwards, and in a left-sided pneumothorax or mediastinal emphysema, a click or high-pitched metallic sound (Ham-man sign) is heard at the left sternal border in line with the heartbeat. Tension pneumothorax should be considered when the patient presents with cyanosis, profuse sweating, severe shortness of breath, tachycardia, and hypotension.

X-rays are an important method for the diagnosis of pneumothorax. If there is a high clinical suspicion of pneumothorax and the posteroanterior chest radiograph is normal, a lateral chest radiograph or lateral recumbent chest radiograph should be performed. Most chest radiographs of pneumothorax have a clear pneumothorax line, which is a junction line between atrophied lung tissue and the gas in the pleural cavity, with an outwardly convex line shadow, a translucent area without lung texture outside the pneumothorax line, and compressed lung tissue inside the line. In massive pneumothorax, the mediastinum and heart are shifted to the healthy side. In combination with pleural effusion, an air-fluid surface can be seen. A restricted pneumothorax is easily missed on posteroanterior x-ray. a lateral chest radiograph can assist in the diagnosis, as can a rotation of the body under x-ray fluoroscopy. The diagnosis of restricted pneumothorax is easily missed on posteroanterior x-ray, and lateral chest radiographs and rotation of the body under X-ray fluoroscopy can assist in the diagnosis. Mediastinal

emphysema should be considered if there is a translucent band around the cardiac border. CT is more sensitive and accurate than X-ray chest radiographs in identifying small amounts of pneumothorax, restricted pneumothorax, and bullae pulmonary. The basic CT presentation of a pneumothorax is a very low-density gas shadow in the pleural cavity with varying degrees of compression and atrophy of the lung tissue. It is important to distinguish pneumothorax from bullae pulmonary, acute myocardial infarction, pulmonary embolism, chronic obstructive pulmonary disease, and bronchial asthma.

In previous clinical trials of anlotinib, the incidence of pneumothorax among patients in the anlotinib group was lower, but higher than that in the placebo group, with no statistical difference.

For subjects with pneumothorax, the criteria for dose adjustment are as follows:

Dose adjustment for pneumothorax

Grades of AEs	Dose adjustment	Recommended treatment
Grade 1	Maintain original dose	Monitoring closely; performing chest radiographs as necessary; maintaining weekly telephone follow-up
Grade 2	If AE resolves to ≤ Grade 2 within 2 weeks, continue drug treatment at a dose reduced by one level	Monitoring signs and symptoms closely after closed drainage and maintaining weekly telephone follow-up
≥ Grade 3	Discontinuing treatment permanently	Performing closed drainage or emergency medical intervention

Treatment methods include conservative treatment, exhaustion therapy, recurrence prevention measures, surgical treatment, and prevention and control of complications.

10) Hyperlipidemia

The management of hyperlipidemia should consider the patient's pre-treatment state and dietary habits. In addition to dietary control, hypercholesterolemia of Grade 2 or higher (≥ 7.75 mmol/L) or hypertriglyceridemia of Grade 2 or higher (≥ 2.5 × UNL) should be treated with HMG-CoA reductase inhibitors (atorvastatin, etc.) or appropriate lipid-lowering agents.

11) Thyroid hypofunction

The thyroid function should be monitored closely for all subjects. Alternative treatment with Euthyrox is required when TSH ≥ 20 mU/L or any value of T3, T4, FT3, and FT4 is lower than the normal value.

4.5 Strategy after disease progression

(1) Subjects who are diagnosed with progressive disease as per RECIST v1.1 are allowed to continue treatment until the investigator-assessed clinical progression of the disease if they meet one of the following conditions:

1) Central necrosis or decreased density of the tumor and/or 2) slow or local progression; meanwhile, investigator(s) assess that subjects may benefit from the study drugs and subjects apply for continued medication. With the signature of the principal investigator of each participating centre, at least one other physician with a senior title, and the consent of the sponsor, they could continue treatment.

(2) Subjects with an outbreak progression have to withdraw from the study.

(3) Notes:

Local progression: isolated extracranial or intracranial progression; symptom score ≤ 1.

Slow progression: a slight increase in tumor burden compared to previous assessments (≤ 2); symptom score ≤ 1.

Outbreak progression: a rapid increase in tumor burden compared to previous assessments (> 2); symptom score = 2.

Symptom score: No symptom = 0; No change in symptom = 1; Aggravating symptom = 2.

The tumor burden score is represented by the non-target lesion score. lesion progression = 1, new intrathoracic lesion = 1, new extrathoracic lesion = 1, malignant pleural effusion = 1. The total score is 4.

4.6 Drug compliance

Investigator(s) is required to fill in the drug distribution form provided by the sponsor, including the following information:

(1) Identification Information of subjects who received drugs.

(2) Date and number of distributive drugs.

(3) Date and number of returned drugs by subjects. The inventory must be prepared for CRA's examination.

Subjects are required to return all unused empty boxes of anlotinib to investigator(s) at the next visit and return to the sponsor at the end of the study. The supply of anlotinib (empty boxes, partially used and unused drugs) should be checked at each visit. Investigator(s) is required to check the returned drugs (if any), calculate the compliance, and encourage subjects to use appropriate doses of anlotinib according to the treatment protocol. Thus, investigator(s) is required to encourage subjects to return all unused drugs (including all distributive boxed, and unused empty boxes), to count the number of drugs.

4.7 Drug distribution, use, and recovery

4.7.1 Drug distribution

Drug distribution should be managed strictly. Specially-assigned person in each participating centre is responsible for drug distribution and storage. Investigator(s) is required to record detailed information of drug distribution and storage.

According to the requirements of GCP, the participating centre is responsible for drug storage, distribution, and recovery.

Investigator(s) is required to record the following information from the date of first-day treatment to the day before each cycle.

(1) The number of different doses of anlotinib in the next treatment cycle.

(2) The information should be recorded in the CRF and the drug distribution form.

(3) Investigator(s) is responsible for guiding patients to follow treatment protocols. All unused drugs and packing boxes (empty boxes and those with capsules) should be returned.

4.7.2 Drug use

Investigator(s) is required to check the compliance at each visit and the following information at the last day of each cycle.

(1) Inquiry the number of anlotinib hydrochloride capsules used daily during this cycle.

(2) The information should be recorded in the CRF

(3) Calculate the number of anlotinib hydrochloride capsules returned by the patient,

(4) Record the number of the distributive and returned capsules in the CRF.

(5) Check whether subject received the study drugs according to the protocol in the previous cycle. At each visit, the number of returned capsules (including differences and reasons) and whether the dose adjustment is required should be recorded in the CRF.

4.7.3 Drug recovery

The total quantity of study drugs shall be 120% of the design quantity, and the remaining drugs shall be returned to t Chia Tai Tianqing Pharmaceutical Group Co., Ltd. after the end of the study, which shall be recovered by the inspectors.

The investigator may destroy the used study drugs (non-state-controlled chemicals) and empty boxes/bottles after written notification to the co-organizer without endangering the health of the population. The investigator should keep all study drug-handling records.

These records must document the evidence and quantity of each batch of destroyed drugs, disposal methods (as required by local law), and the person who handled the study drugs.

4.8 Concomitant medications

4.8.1 Drugs prohibited or used with caution during the study

4.8.1.1 Medications that interfere with hepatic cytochrome P450 enzymes

Anlotinib has strong inhibition effects on CYP3A4, YP2C9, and CYP2C19 (IC_{50} <0.5 μM). Thus, CYP3A inducers (dexamethasone, carbamazepine, rifampin, and phenobarbital), its inhibitors (ketoconazole, itraconazole, erythromycin, and clarithromycin), CYP3A4 substrate (simvastatin, cyclosporine, and piperidine), other medications metabolized by CYP3A4 (benzodiazepines, dihydropyridine calcium antagonist, calcium antagonists, and HMG-CoA reductase inhibitors), as well as the substrate for CYP2C9 and CYP2C19 will be used cautiously (Details listed in the table).

P450 enzyme	Substrate
CYP2C9	Diclofenac, phenytoin, diclofenac, tolbutamide, and s-warfarin
CYP2C19	Diazepam, promethazine, lansoprazole, and s-mephenytoin

4.8.1.2 Medications that prolong the cardiac QTc

Medications that prolong the cardiac QT will be used cautiously due to the toxicity of anlotinib will prolong the QT interval in clinical practice, and medications including but not limited to:

(1) Antimicrobials (clarithromycin, azithromycin, erythromycin, roxithromycin, metronidazole, and moxifloxacin);

(2) Antiarrhythmic drugs (quinidine, sotalol, amiodarone, disopyramide, and procaine amide);

(3) Antipsychotics (risperidone, fluphenazine, haloperidol, haloperidol, thioridazine, pimozide, olanzapine, and clozapine);

(4) Antifungal drugs (fluconazole and ketoconazole);

(5) Antimalarial drugs (mefloquine and chloroquine);

(6) Antidepressants (amitriptyline, imipramine, clomipramine, dosulepin, and doxepin).

4.8.1.3 Traditional Chinese medicine and immunomodulators with anti-cancer activity.

This protocol prohibits the use of traditional Chinese medicine and immunomodulators that is approved by Chinese Food and Drug Administration (CFDA, e.g., thymosin, interferon, interleukin-2, zilongjinpian, and fungal polysaccharides).

4.8.2 Permitted concomitant medications/treatments

During the study drug treatment period, subjects are allowed to receive other symptomatic supportive treatments. Unconventional therapies (e.g., herbal or acupuncture) and vitamin/mineral supplements are allowed if these have no effects on study endpoints as assessed by investigator (s). Bisphosphonates are allowed for subjects with bone metastases during the trial. Palliative radiation therapy in a small area (< 5% bone marrow region) will be permitted for subjects with uncontrolled pain of bone metastases after systemic therapy or topical analgesia. Antiviral medication should be administered during enrollment for patients with positive hepatitis B surface antigens during the screening period. Clinical comorbidities and the emergence of AEs should be treated aggressively. Any concomitant medications should be recorded in the electronic CRFs in accordance with GCP regulations.

5. Study procedures

All patients must read and sign an informed consent approved by the ethics committee before the initiation of the study. All study procedures are required to be performed according to the time window in the schematic flow diagram, which is independent of the duration of drug

discontinuance. However, the study procedures are allowed for modification within the time window due to holidays or other reasons.

5.1 Screening

The following procedures must be completed before study initiation:

(1) Collection of medical history and baseline characteristics, including subjects' ID, gender, age, mailing address, and telephone;

(2) Collection of medical history, previous anti-tumor therapies, QoL;

(3) Systematic physical examination: ECOG PS, height, weight, vital signs, and physical examination;

(4) 12-lead electrocardiogram (ECG; particularly QTc), echocardiography, myocardial enzymonram;

(5) Hemanalysis, urinalysis, and stool analysis (including occult blood);

(6) Liver function (TP, A, G, ALT, AST, LDH, ALP, TBil, DBil, IBil), renal function (BUN or UREA, Cr, UA), blood lipid profile (TC, TG, HDL, LDL), electrolyte (K^+, Na^+, CL^-, Ca^{2+}, Mg^{2+}, P), blood lipase, blood amylase, fasting blood glucose, etc.

(7) Serum pregnancy test: HCG testing (applicable to women of childbearing age);

(8) Coagulation function (PT, APTT, TT, Fbg, INR); thyroid function (T3, T4, FT3, FT4, TSH); serum carcinoembryonic antigen (CEA) and squamous cell carcinoma antigen (SCC); screening for infection, including HIV test, hepatitis B virus (HBV) test, and hepatitis C virus (HCV) antibody test.

(9) Imaging examination (CT or MRI) will be conducted within 28 days before treatment. PET will not be used as a routine method in the imaging assessment. Enhanced CT or MRI of the chest, abdomen, and pelvis is required for all subjects before administration. All suspected lesions will be evaluated by imaging. MRI are allowed for subjects with anaphylactic reactions to contrast agents to replace the CT scan. For subjects with suspect brain metastases or clinical symptoms, a cranial MRI is required.

5.1.1 Baseline tumor lesions

At baseline assessment, subjects are required to have a least one measurable lesion as per

RECIST v1.1. All measurable lesions should be measured but the total number of target lesions should be no more than 5 (≤ 2 in each organ). For example, at most 2 or 4 target lesions could be considered measurable target lesions at baseline measurement for subjects with only one or two cumulative organs.

The selection of target lesions has to be based on their size (maximum diameter), which could represent all the involved organs. Meanwhile, the measurement must have good repeatability. When the maximum lesions cannot be measured repeatedly, another measurable maximum lesion could be selected.

Measurable lymph nodule has to meet the following criteria: short diameter (CT scan) ≥ 15 mm. Only a short diameter will be measured at baseline. The diagnosis of tumor metastasis is generally according to the short diameter of the lymph nodule. The size of the lymph nodule is expressed with the two-dimensional data in imaging examination (axial plane for CT, either axial, sagittal, or coronal plane for MRI) and the minimum value is set as a short diameter. For example, the short diameter of an abdominal nodule (20 mm × 30 mm) was 20 mm, thus, it could be considered a malignant, measurable nodule and 20 mm is the measured value. A nodule with a size of ≥ 10 mm and < 15 mm will not be determined as a target lesion; and a nodule with a size of < 10 mm is not a pathological nodule and could not be recorded and measured.

The sum of diameters of all target lesions (including the maximum diameter of the nonnodular lesion and short diameter of nodule) is recorded as the sum of diameters at baseline. As mentioned above, if lymph nodule diameter is included, only the short diameter will be counted. The sum of baseline diameters will be used as a reference value for baseline disease levels.

All other lesions (including pathological lymph nodule) will be considered non-target lesions, which are not required to be measured but required to be recorded at baseline assessment, as presence, absence, and definite progression (on rare occasions). Extensive target lesions may be recorded with target organs (e.g., extensive liver metastases).

5.2 Visits during the treatment period

(1) Blood pressure monitoring: during the administration period, blood pressure is measured by the subjects themselves and recorded in the patient diary card. Blood pressure is measured at least 3 times every week in the first two cycles. For subjects with abnormal blood pressure, blood pressure is measured every day after 2 cycles, but for subjects with

normal blood pressure, blood pressure is measured at least 3 times every week. Blood pressure is measured by the investigator at each visit. Coffee and tobacco intake are prohibited within 30 minutes before blood pressure measurement. The measurement is taken in the sitting position with the arm at heart level after at least 10 minutes of quiet sitting, and each measurement is taken on the same side;

(2) Physical examination at every visit: height, weight, vital signs, and physical examination;

(3) Hemanalysis: hemoglobin, red blood cells, white blood cells, absolute neutrophil count, lymphocyte count, and platelet count. Hemanalysis will be performed on days 1 and 21 for the first cycle and on the end of the following odd-numbered cycle. The time window for visiting is ± 3 days.

(4) Urinalysis: urine protein, glucose, occult blood (red blood cell and white blood cell), pH, and ketone bodies; If the semi-quantitative method shows the levels of protein ≥ 2+ (e.g., urine test strip), 24-hour urine analysis is performed. Urinalysis will be performed on days 1 and 21 for the first cycle and on the end of the following odd-numbered cycle. The time window for visiting is ± 3 days.

(5) Blood biochemistry: liver function (TP, A, G, ALT, AST, LDH, ALP, TBil, DBil, IBil), renal function (BUN or UREA, Cr, UA), blood lipid profile (TC, TG, HDL, LDL), electrolyte (K^+, Na^+, CL^-, Ca^{2+}, Mg^{2+}, P), blood lipase, blood amylase, fasting blood glucose, etc. Blood biochemistry will be detected on days 1 and 21 for the first cycle and at the end of the following odd-numbered cycle. The time window for visiting is ± 3 days.

(6) Stool tests: occult blood. Stool tests will be performed at on days 1 and 21 for the first cycle and at the end of the following odd-numbered cycle. The time window for visiting is ± 3 days. If there is any abnormality, subjects should seek medical attention promptly

(7) Coagulation function (PT, APTT, TT, Fbg, INR) and thyroid function (T3, T4, FT3, FT4, TSH). These tests will be performed at on days 1 and 21 for the first cycle and at the end of the following odd-numbered cycle. The time window for visiting is ± 3 days.

(8) 12-lead ECG (particularly QTc) will be detected at each visit. Measurement of echocardiography, myocardial enzyme (CK, CK-MB), and troponin is required for patients with chest pain and palpitations.

(9) Imaging examination: the target lesion identified at baseline should be examined under the same conditions as the baseline examination (layer thickness of the scan, use of contrast

agent, etc.).

- ✓ The first post-treatment imaging examination is scheduled at the end of the first cycle, which is then confirmed after 6 weeks. For imaging examination, a CT scan and MRI of the chest, abdomen, and pelvis, as well as other lesions observed at baseline will be performed at the end of every subsequent 2 cycles. The time window for imaging examination is ± 7 days. Suspected new lesions should also be detected as appropriate.
- ✓ Unscheduled imaging may be performed when disease progression is suspected (e.g., worsening of symptoms)

(10) QoL: Conducting by the investigator asking questions and the subject answering

(11) ECOG PS

(12) AEs: AEs will be recorded from the date of the first dose of the study drug to at least 21 days after the last dose and follow up until the AEs resolved or stabilized.

(13) Concomitant medications: concomitant medications and therapy during the trial should be recorded. If the subject discontinues treatment, the concomitant medication and therapy are recorded only in the case of novel or unresolved AEs associated with treatment.

5.3 End-of-treatment and withdrawal study

At the end-of-treatment and withdrawal study, if the patient is not examined within 7 days before the end of treatment, the following tests should be performed.

(1) ECOG PS

(2) Vital signs: heart rate, respiratory rate, temperature, and blood pressure;

(3) Physical examination: facial features, integumentary system, lymph nodes, eyes, ears, nose, throat, oral, respiratory system, cardiovascular system, abdomen, urinary tract system, musculoskeletal system, nervous system, and spiritual status;

(4) Blood pressure monitoring: blood pressure is measured by the investigator. Coffee and tobacco intake are prohibited within 30 minutes before blood pressure measurement. The measurement is taken in the sitting position with the arm at heart level after at least 10 minutes of quiet sitting, and each measurement is taken on the same side;

(5) Hemanalysis: hemoglobin, red blood cell, white blood cells, absolute neutrophil count, lymphocyte count, and platelet count;

(6) Urinalysis: Urine protein, glucose, occult blood (red blood cell and white blood cell), pH, and ketone bodies; If the semi-quantitative method shows the levels of protein ≥ 2+ (e.g., urine test strip), 24-hour urine analysis is performed;

(7) Blood biochemistry: liver function (TP, A, G, ALT, AST, LDH, ALP, TBil, DBil, IBil), renal function (BUN or UREA, Cr, UA), blood lipid profile (TC, TG, HDL, LDL), electrolyte (K^+, Na^+, CL^-, Ca^{2+}, Mg^{2+}, P), blood lipase, blood amylase, fasting blood glucose, etc.

(8) Stool tests: Occult blood;

(9) Coagulation function: PT, APTT, TT, Fbg, and INR;

(10) 12-lead ECG;

(11) Echocardiography;

(12) Serum pregnancy test;

(13) QoL;

(14) AEs assessment;

(15) Medication recall;

(16) Patient compliance assessment;

(17) Imaging examination: If imaging is not performed within 3 weeks before the end of treatment, an imaging examination is required at the end of study treatment or withdrawal study. For subjects with non-imaging progression (intolerable, other conditions), tumor evaluation performs every 8 weeks until disease progression, death, or the initiation of other anti-tumor therapies.

5.4 21-day post-withdrawal follow-up

Safety assessment should be continued 21 days after the end of the last dose. Concomitant medications should be also recorded. The following tests should be performed.

(1) ECOG PS

(2) Hemanalysis: hemoglobin, red blood cell, white blood cells, absolute neutrophil count, lymphocyte count, and platelet count;

(3) Urinalysis: urine protein, glucose, occult blood (red blood cell and white blood cell), pH,

and ketone bodies; If the semi-quantitative method shows the levels of protein ≥ 2+ (e.g., urine test strip), 24-hour urine analysis is performed;

(4) Blood biochemistry: TBil, DBil, ALT, AST, AKP, r-GT, TP, A, G, LDH, BUN or UREA, Cr, UA, TC, TG, HDL, LDL, K^+, Na^+, CL^-, Ca^{2+}, Mg^{2+}, P, etc.

(5) AEs assessment;

(6) Concomitant medications.

5.5 Follow-up requirements

For subjects who discontinued the study due to disease progression, a withdrawal follow-up is required within ± 7 days after study discontinuation. Data from systematic examination and medical history should be collected. An end-of-study follow-up is required at 21 ± 3 days after study discontinuation, followed by the survival follow-up every 8 weeks.

For subjects who discontinued the study due to other reasons, a withdrawal follow-up is required at the day of study discontinuation. Data of systematic examination and medical history should be collected. An end-of-study follow-up is required at 21 ± 3 days after study discontinuation, followed by the efficacy assessment every 8 weeks until disease progression. After disease progression, the subject will be followed every 8 weeks for survival analysis.

For the subject who has no disease progression after treatment completion, an end-of-treatment follow-up is required at 21 ± 3 days after treatment completion. Data from systematic examination and medical history should be collected. Then, the efficacy assessment will be performed every 8 weeks until disease progression. The withdrawal follow-up is required on the day of confirmed disease progression, and data from systematic examination and medical history should be collected. After disease progression, the subject will be followed every 8 weeks for survival analysis.

The following data should be recorded during the follow-up period. For subjects without disease progression, the time to disease progression or death should be recorded. Other anti-tumor therapies (treatment regimens, cycles, and outcomes), drug-related SAE, and survival (followed by telephone).

5.6 Follow-up of survival

Survival follow-up will start at the end of 21 days post-withdrawal follow-up. Subjects will be followed at least every 8 weeks by telephone (asking the subjects and their relatives or a local

physician) until death, loss of follow-up, or termination of the study by the sponsor. The survival status (date and reasons of death) and post-treatment information (including subsequent therapies) will be collected. Outcomes in each survival follow-up visit will be is recorded in the follow-up form.

5.7 Dropout

All subjects who have signed the informed consent and are eligible for enrollment have the right to withdraw from the study. Subjects will be considered as dropout cases when they cannot complete one cycle of treatment and are unevaluable for efficacy and safety analysis, regardless of the time and reasons. Enrolled subjects who withdraw due to disease progression with definite medical evidence (Imaging data is required) or due to intolerance toxicity will not be considered dropout cases. Investigator(s) is required to record the dropout reasons in the CRF and complete all assessments that can be completed. The data from the last visit should be recorded in detail. Screened subjects who withdraw before treatment will not be considered as dropout cases.

6. Efficacy assessments

6.1 Primary endpoint

- **PFS**

PFS is defined as the time from treatment initiation to the first time of disease progression or death from any cause, whichever occurs first.

If the subject did not experience disease progression or death, PFS is defined as the date of the last confirmed progression-free. Subjects who discontinued for reasons other than disease progression (no subsequent tumor imaging assessment) and starting subsequent therapy after the trial were censored at the time of discontinuation or the initiation of subsequent therapy. In cases other than those described above, pre-planned sensitivity analyses will undertake to define PFS based on the date of confirming imaging progression events. New onset of other tumor is not considered indicative of PD and is not censored as data.

6.2 Secondary endpoints

- **OS**

OS is defined as the time from enrollment to the date of death due to any cause. For the analysis of OS, data for patients who are alive will be censored for OS at the time of the last follow-up.

Data for patients who were lost to follow-up will be censored for OS at the last date they were known to be alive. Censored OS is defined as the time from enrollment to censor.

- **DCR**

DCR is defined as the percentage of subjects with PR, CR, or SD lasting for ≥ 6 weeks.

- **ORR**

ORR is defined as the percentage of subjects with confirmed tumor volume reduction to pre-specified values and maintenance of minimum time requirements, including subjects with a PR or CR. Objective responses are assessed per RECIST v1.1. Subjects must have at least one measurable lesion at baseline. The response was classified as CR, PR, SD, and PD according to RECIST v1.1.

7. Safety assessment

7.1 Definitions

- **AEs**

AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. Thus, AEs are any poor or unintended physical signs (including abnormal laboratory data), symptoms, or transient drug-related diseases. The causal relationship of AEs with study drugs should be considered.

As required by AEs management practices, any AEs that occur before and after treatment will be determined as AEs. Thus, safety monitoring will be performed from the patient enrollment to the end of the study. Any AEs that occur from the initiation of the study drug to the end of treatment in this trial will be determined as AEs.

Adverse reactions (ADRs)

ADRs are defined as any toxicities and undesirable consequences to drugs occurring at adequate doses. The response to drugs indicates a reasonable probability of the causal relationship of AEs with study drugs, thus, this relationship cannot be excluded.

- **SAEs**

SAE is defined as any adverse event that results in any one of the following unanticipated

events during the clinical trial period:

- **SAEs include the following events:**

A. Death and life-threatening events

B. Events leading to in-patient hospitalization or prolongation of existing hospitalization;

C. Events causing persistent or severe disability;

D. Events causing incapacity

E. Events causing congenital anomalies/birth defects;

- **Other events that should be classified as SAEs:**

Drug exposure in pregnancy and lactation period. In principle, pregnancy and lactation meet the exclusion criteria for this study. If pregnancy occurs during the study period, subjects should withdraw from the study immediately, and the investigator(s) should be informed. Meanwhile, pregnant subjects will be monitored during the pregnancy period until delivery. The outcomes of maternal and newborn should be recorded even if no AEs reported. Despite the pregnancy will not be reported as SAE, it should be reported to the Ethics Committee, as per the reporting standard of SAEs.

- **Events that should be not classified as SAEs:**

Disease progression under the trial will not be reported as an SAE, but the signs and symptoms of progression that meet the criteria of SAEs will be reported as an SAE.

Death is an outcome of disease, will not be reported as an SAE (The reason for death, that is main AEs leading to death will be recorded and reported as an SAE, and the death will be reported as an outcome; if no specific reason for death recorded, the death events will be reported as an SAE).

Due to the severity of the disease in this study, some SAEs will be excluded from the reports, as follows:

A. Optional hospitalization and surgery

B. Optional hospitalization therapy designed to simplify treatment or interventions

7.2 Recording and assessment of AEs

AEs should be reported using the correctly standardized medical terminology. All AEs should be recorded on the CRF. The report of SAEs (including starting and follow-up reports) should be completed. All included subjects should be included in the summary report. Subject withdrawal or analysis exclusion and the reasons should be recorded. If any deaths or subjects with serious toxicity occur, these cases should be recorded in detail and reasons for deaths, particularly the causality to study drugs, should be assessed. All AEs should be followed up until recovery or stabilization of the disease.

The following information should be recorded in the CRF:

- Time of AE occurrence (starting time) and recovery time (ending Time);
- The severity grade of any AEs will be assessed according to the NCI-CTCAE v4.03.

  Grade 1 (mild): A feeling of discomfort but not limiting activities of daily living;

  Grade 2 (moderate): A feeling of discomfort that decreases or limits activities of daily living;

  Grade 3 (severe): Unable to work or perform daily activities;

  Grade 4: Life-threatening or disabling;

  Grade 5: Death.
- The causality of AEs to study drugs will be assessed according to the five criteria (definitely, probably, possibly, unlikely, and unrelated). Definitely, probably, and possibly are classified as drug-related AEs. The incidence of AEs is calculated using the above three as the numerator and the total number of subjects in the safety assessment set as the denominator.

Criteria for causality assessment of AEs to drugs

Criteria	Definite	Probable	Possible	Unlikely	Unrelated
Reasonable administration time	Yes	Yes	Yes	Yes	No
Typical drug reactions	Yes	Yes	Yes	No	No
AEs disappear or mitigate after drug discontinuation	Yes	Yes	Yes/No	Yes/No	No

Same AEs recurred after repetitive administration of the study drugs.	Yes	? (Unclear)	? (Unclear)	? (Unclear)	No
AEs can be explained by other reasons	No	No	No	Yes	Yes

- The managements of study drug (none, treatment discontinuation, dose reduction, dose delay, reduction of intravenous infusion speed) or other managements (none, concomitant medications, in-patient hospitalization or prolongation of existing hospitalization; surgery, delayed chemotherapy, chemotherapy discontinuation, dose reduction of chemotherapy).
- Outcomes will be assessed according to five criteria: recovery with sequelae, recovery without sequelae, uncured but not require treatment, uncured and require treatment, and death. Whether the changes in grade and severity of toxicity are severe (Yes or No). If one subject reported the same AE repeatedly, the AE must be recorded and re-evaluated every time.

  The criteria for whether abnormal laboratory data is determined as AEs are as follows:

  - Laboratory data is related to the concomitant symptoms (and/or);
  - Laboratory data that is required for other diagnostic examinations or treatment/surgical operation;
  - Laboratory data leading to dose adjustment or study termination, or the use of other concomitant drugs or treatments (and/or);
  - Laboratory data as judged by investigator(s) should be reported as AEs.

The repeated measurement for abnormal laboratory data but not meeting any of the above criteria will not be determined as AEs. Any incorrect abnormal laboratory data will also not be determined as AEs.

7.3 SAEs reporting requirements

SAEs should be reported from the date of treatment initiation until 21 (inclusive) calendar days after the last dose of the study drug. If an SAE occurs, the SAE form should be filled out,

signed, and noted the occurrence time immediately. Investigator(s) are required to report SAE by fax to the Pharmacovigilance Department of Chia Tai Tianqing Pharmaceutical Group Co., Ltd., CRA, the principal investigator, leading centre, the ethics committee of each participating centre, the Guangdong Food and Drug Administration (FDA), the Guangdong Health and Family Planning Commission.

SAEs that occurred beyond 21 days after the last dose of the study drug will not be reported, except for the AEs that are suspected to be drug-related.

The symptoms, severity, causality to study drugs, occurrence time, management time, management methods, follow-up duration, and outcomes of AEs should be recorded faithfully. If the investigator(s) consider that an SAE is unrelated to the study drug but is potentially related to the clinical process (e.g., discontinuation of treatment, or comorbidity during the trial), this relationship should be detailed in the narrative section of the SAEs page in the CRF. If any changes in the grade of SAEs or any changes in the causality to study drugs occurred during the study, the follow-up report of SAEs must be reported to the sponsor. All SAEs should be followed up until recovery or stabilization of the disease.

7.4 SAEs reporting procedures

Any SAE occurring during the clinical period and within 21 days after discontinuation of the drug must be reported immediately to the CRA of the sponsor, the PI of the clinical study site, and the Ethics Committee. The contact information is as follows:

Sites	Contact	Telephone/Fax
Sun Yat-sen University Cancer Centre	Ethics Committee	+8620 87242009
Chia Tai Tianqing Pharmaceutical Group Co., Ltd.	Pharmacovigilance Department	+8610 65053288/+8610 65059826

8. Statistical analysis

This study is a single-arm design. The primary efficacy endpoint is PFS and compared with historical data.

8.1 Analysis datasets

① FAS

FAS included all patients who received at least one dose of the study drug according to the intention to treat (ITT) principle. For the data of subjects without the whole treatment process, the last observation carried forward (LOCF) method will be performed.

② PPS

PPS will be defined as all patients who met the trial protocol, with favorable compliance, and received at least 2 cycles of the study drug (patients who had received one or more cycles of the study drug and had imaging evidence of progressive disease will be included in PPS), did not take any prohibited drugs, and completed CRF. No imputation of missing data. Efficacy analysis will be conducted based on both the FAS and PPS populations.

③ SS

SS included all patients who received at least one dose of the study drug and had a post-administration safety record. Safety analysis will be conducted in the SS population.

8.2 Statistical analysis plans

All statistical analysis will be performed using the IBM SPSS software with a two-sided test. A P value ≤ 0.05 is considered significant, with a 95% confidence interval (CI).

Baseline data will be analyzed in the FAS. All efficacy outcomes will be analyzed in the FAS and PPS. Safety will be analyzed in the SS.

Quantitative data will be described as mean ± standard deviation (SD) or median (minimum, maximum) and be compared with Student's t-test or non-parametric test. The comparison to baseline data will be performed with Paired Sample t-test. Repeated measure analysis of variance will be used for the within-group comparisons of repeated measurement data. Qualitative data will be described by number (frequency) and be compared with the χ^2 test. Survival will be estimated using the Kaplan-Meier method with a 95% CI and presented with the Kaplan-Meier curve. Between-group comparison of survival will be performed using a log-rank test. The hazard ratio (HR) and the corresponding 95% CIs will be provided based on a Cox proportional hazard model.

Analysis of drop-outs will be mainly descriptively summarized. The between-groups comparison of the total drop-out rate and drop-out rate due to AEs will be performed with the χ^2 test, if necessary.

Efficacy analysis: The primary endpoint PFS will be estimated using the Kaplan-Meier method

with a 95% CI. The secondary endpoints include OS, investigator-assessed ORR, and DCR. OS will be estimated using the Kaplan-Meier method with a 95% CI. The HR and the corresponding 95% CIs will be also provided based on a Cox proportional hazard model. DCR (defined as the proportion of patients with CR, PR, and SD) and ORR (defined as the proportion of patients with CR and PR) will be presented with proportion. A P value ≤ 0.05 is considered significant (except for special circumstances).

Safety analysis will be mainly descriptively summarized. The data of AEs, treatment-emergent AEs (TEAEs), SAE, laboratory tests, and vital signs, as well as the study drug exposure (treatment cycles, total doses, and dose intensity), will be summarized. All the above data will be recorded according to the current reporting standard for clinical trials. This standard includes but is not limited to the following analysis:

Summary of AEs (any cause and treatment-related);

Incidence and severity of AEs;

Attribution analysis of AEs to study drugs;

Outcomes of AEs;

Summary of SAEs;

Descriptive summary of laboratory tests, vital signs, and electrocardiograph (the absolute value after baseline, and the change from baseline);

Descriptive summary of post-baseline data of vital signs, and electrocardiograph.