Title: A multicenter, randomized, open-label phase II clinical study of anti-PD-1 antibody SHR-1210 combined with apatinib mesylate vs. doxorubicin combined with ifosfamide in treatment of soft tissue sarcoma

NCT number: NCT03711279

Date: 25 Feb., 2019

A MULTICENTER, RANDOMIZED, OPEN-LABEL PHASE II CLINICAL STUDY OF ANTI-PD-1 ANTIBODY SHR-1210 COMBINED WITH APATINIB MESYLATE

VS. DOXORUBICIN COMBINED WITH IFOSFAMIDE IN TREATMENT OF SOFT TISSUE SARCOMA

Protocol No.:	SHR-1210-II-212
Study Phase:	II
Compound:	Camrelizumab for injection (SHR-1210), Apatinib Mesylate Tablets
Medical Director:	[redacted]
Leading Center of Clinical Study:	Shanghai Sixth People's Hospital
Principal Investigator:	Prof. Yang Yao
Version No.:	3.0
Version Date:	25 Feb., 2019
Sponsor:	Jiangsu Hengrui Pharmaceuticals Co., Ltd. No. 7 Kunlunshan Road, Lianyungang Economic and Technological Development Zone, Jiangsu 222047, China

VERSION HISTORY/REVISION HISTORY

Document	Version Date	Amendment Rationale and Summary of Changes
Initial version	25 Jul., 2018	Not applicable
Version 2.0	5 Sep., 2018	Page 40, revised adverse events based on the latest CDE dossier submission
Version 3.0	25 Feb., 2019	Added imaging assessments for tumor lesions of other sites; added exploratory endpoints: investigator-assessed PFS (as per iRECIST) and corresponding evaluation criteria; modified the dose of apatinib; SHR-1210 administration may be delayed for up to 7 days after the specified time point.

Sponsor's Signature Page

I have read and confirmed this clinical study protocol (protocol No.: SHR-1210-II-212, version No.: 3.0, version date: 25 Feb., 2019). I agree to fulfill my duties in accordance with Chinese laws, the Declaration of Helsinki, the Chinese GCP, and this study protocol.

Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Study Director (print)	Study Director (signature)	Signature Date (DD/MM/YYYY)

Principal Investigator's Signature Page (Leading Center)

I will carefully execute the duties as an investigator in accordance with the Chinese GCP, and personally participate in or directly lead this clinical study. I have received the Investigator's Brochure for the study drugs; I have read the materials of preclinical studies of the study drugs and the protocol for this clinical study. I agree to fulfill my duties in accordance with Chinese laws, the Declaration of Helsinki, the Chinese GCP, and this study protocol. I agree that any modifications to the protocol must be reviewed and approved by the sponsor, and can only be implemented upon approval by the ethics committee, unless measures must be taken to protect the safety, rights, and interests of the subjects. It is my responsibility to make clinically relevant medical decisions to ensure appropriate and timely treatments in subjects experiencing adverse events during the study period, and to document and report such adverse events in accordance with relevant state regulations. I will document all data in a truthful, accurate, complete and timely manner. I agree to be monitored and audited by the clinical research associate or auditor assigned by the sponsor, and to be inspected by the drug regulatory authorities, to ensure the quality of the clinical study. I will keep the personal information of and matters related to the subjects confidential. I agree to disclose my full name and occupation to the sponsor, and the expenses related to the clinical study upon request. I agree not to engage in any commercial and economic activities related to this study. I agree for the study results to be used for drug registration and publication. I will provide a resume before the start of the study, submit it to the ethics committee, and to the drug regulatory authority for filing purposes.

Study Center: Shanghai Sixth People's Hospital

Yang Yao		
Principal Investigator (print)	Principal Investigator (signature)	Signature Date (DD/MM/YYYY)

Principal Investigator's Signature Page (Participating Center)

I will carefully execute the duties as an investigator in accordance with the Chinese GCP, and personally participate in or directly lead this clinical study. I have received the Investigator's Brochure for the study drugs; I have read the materials of preclinical studies of the study drugs and the protocol for this clinical study. I agree to fulfill my duties in accordance with Chinese laws, the Declaration of Helsinki, the Chinese GCP, and this study protocol. I agree that any modifications to the protocol must be reviewed and approved by the sponsor, and can only be implemented upon approval by the ethics committee, unless measures must be taken to protect the safety, rights, and interests of the subjects. It is my responsibility to make clinically relevant medical decisions to ensure appropriate and timely treatments in subjects experiencing adverse events during the study period, and to document and report such adverse events in accordance with relevant state regulations. I will document all data in a truthful, accurate, complete and timely manner. I agree to be monitored and audited by the clinical research associate or auditor assigned by the sponsor, and to be inspected by the drug regulatory authorities, to ensure the quality of the clinical study. I will keep the personal information of and matters related to the subjects confidential. I agree to disclose my full name and occupation to the sponsor, and the expenses related to the clinical study upon request. I agree not to engage in any commercial and economic activities related to this study. I agree for the study results to be used for drug registration and publication. I will provide a resume before the start of the study, submit it to the ethics committee, and to the drug regulatory authority for filing purposes.

Study Center: _____

Principal Investigator (print)	Principal Investigator (signature)	Signature Date (DD/MM/YYYY)

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PROTOCOL SYNOPSIS

Study Title	A multicenter, randomized, open-label phase II clinical study of anti-PD-1 antibody SHR-1210 combined with apatinib mesylate vs. doxorubicin combined with ifosfamide in treatment of soft tissue sarcoma
Protocol No.	SHR-1210-II-212
Version No.	3.0
Sponsor	Jiangsu Hengrui Pharmaceuticals Co., Ltd.
Principal Investigators	Professor Yang Yao
Participating Study Centers	Approximately 30 sites
Study Objectives	**Primary objective** • To evaluate whether SHR-1210 combined with apatinib is better than doxorubicin combined with ifosfamide in the treatment of soft tissue sarcoma based on the progression free survival (PFS). **Secondary objectives** • To evaluate and compare the overall survival (OS), objective response rate (ORR), duration of response (DoR), and disease control rate (DCR) in subjects with soft tissue sarcoma after treatment with SHR-1210 combined with apatinib vs. doxorubicin combined with ifosfamide; • To evaluate and compare the safety of SHR-1210 combined with apatinib vs. doxorubicin combined with ifosfamide in the treatment of soft tissue sarcoma; • To evaluate and compare the quality of life scores in subjects with soft tissue sarcoma after treatment with SHR-1210 combined with apatinib vs. doxorubicin combined with ifosfamide. **Exploratory objectives:** • To explore the correlation between the immunogenicity and the efficacy/safety of SHR-1210; • To explore the correlation between the concentrations of SHR-1210 and apatinib and the efficacy/safety; • To evaluate the investigator-assessed PFS, ORR, DoR and DCR (as per iRECIST) in the SHR-1210 plus apatinib group; • To evaluate the PFS (as per RECIST v1.1 and iRECIST) of subjects in the doxorubicin plus ifosfamide group after crossover treatment; • To evaluate the ORR, DoR, and DCR (as per RECIST v1.1 and iRECIST), OS, safety, and quality of life scores of subjects in the doxorubicin plus ifosfamide group after crossover treatment.

Study Endpoints	**Primary endpoints** • PFS assessed by the independent review committee (as per RECIST v1.1) **Secondary endpoints** • PFS assessed by the investigator (as per RECIST v1.1) • OS • ORR assessed by the investigator and independent review committee (as per RECIST v1.1) • DoR assessed by the investigator and independent review committee (as per RECIST v1.1) • DCR assessed by the investigator and independent review committee (as per RECIST v1.1) • Incidence and severity of adverse events (AEs) and serious adverse events (SAEs), abnormalities in vital signs, ECG, and laboratory tests • Quality of life score (EORTC QLQ-C30) **Exploratory endpoints:** • Anti-drug antibody and neutralizing antibody levels of SHR-1210 • Serum concentration of SHR-1210 and plasma concentration of apatinib • Investigator-assessed PFS, ORR, DoR, and DCR (as per iRECIST) of the investigational treatment group • PFS of subjects in the doxorubicin plus ifosfamide group after crossover treatment (as per RECIST v1.1 and iRECIST); • ORR, DoR, and DCR (as per RECIST v1.1 and iRECIST), OS, safety, and quality of life scores of subjects in the doxorubicin plus ifosfamide group after crossover treatment
Study Population	Subjects with soft tissue sarcoma who have not received any prior systemic therapy or have sensitive relapse after chemotherapy (sensitive relapse refers to recurrence more than 6 months after the last chemotherapy).
Study Design	This study is a multicenter, randomized, open-label phase II clinical study, with a total of 292 subjects planned to be enrolled. Qualified subjects with soft tissue sarcoma will be randomized in a 1:1 ratio into the SHR-1210 plus apatinib group (investigational treatment group) and the doxorubicin plus ifosfamide/ifosfamide monotherapy group (control group). Stratification factors include: 1) ECOG PS, > 0 or not; 2) Whether the pathological type of the tumor has poor sensitivity to chemotherapy (see Appendix 2. Common Soft Tissue Sarcomas with Poor Chemotherapy Sensitivity); 3) Whether subjects have previously undergone chemotherapy. The administration regimens for investigational treatment group and control group are as follows: • Investigational treatment group: SHR-1210 200 mg q3w (up to 2 years of treatment) + apatinib 500 mg qd.

	• Control group: doxorubicin 60 mg/m^2 on D1 + ifosfamide 2 g/m^2/d on D1-D4, in 3-week cycles (i.e., the total dose per cycle shall be 8 g/m^2); 6 cycles are recommended. If the investigator judges that the subject benefits from doxorubicin + ifosfamide chemotherapy, additional chemotherapy cycles may be administered. When the subject's anthracyclines have reached the recommended maximum cumulative dose of doxorubicin (see Appendix 3. Dose Conversion of Anthracyclines), the chemotherapy regimen should be adjusted to ifosfamide monotherapy, 2 g/m^2/d on D1-D5, in 3-week cycles (i.e., the total dose per cycle shall be 10 g/m^2). Similarly, when the investigator judges that the subject can benefit from ifosfamide monotherapy, the number of chemotherapy cycle can be increased. In this study, the screening period should be no more than 28 days. After completing screening examinations and assessments, eligible subjects will enter the treatment period and receive the study treatment and study visits according to the protocol. Among them, tumor imaging assessment will be performed once in every 2 cycles during the first 16 cycles and once every 4 cycles thereafter. The independent review adjudication committee (IRaC) will review the imaging evaluation results of each study center. The safety follow-up period of subjects in the investigational treatment group starts after the last dose, and the subjects will be followed up once every 30 days until 90 days after the last dose. Among them, the first safety follow-up will be carried out at the study center; the second and the third follow-up visits will be made via phone calls. For subjects in the control group, if they do not receive SHR-1210 + apatinib treatment, their safety follow-up period will be 21 days after the last dose; otherwise, the same arrangement as that in the investigational treatment group will be used. The survival follow-up period will start after the end of the safety follow-up period. The survival follow-up period will end upon the subject's death, lost to follow-up, withdrawal of informed consent, or study termination by the sponsor. During this period, a follow-up shall be conducted every 2 months via phone calls or other effective methods to collect information on subject survival and subsequent anti-tumor treatment.
Study Drugs and Method of Administration	**Investigational treatment group: SHR-1210 + Apatinib** • SHR-1210 for injection, 200 mg, will be administered via intravenous drip infusion (total time of drip infusion including tube flushing shall be no less than 20 min and no more than 60 min) once every 3 weeks; the longest duration of treatment shall not exceed 2 years. • Apatinib mesylate tablets, 500 mg, will be administered orally once daily. Administered with warm water approximately half an hour after meals (administration time should be the same in each day whenever possible). **Control group: doxorubicin + ifosfamide or ifosfamide monotherapy** • Doxorubicin 60 mg/m^2 on D1, ≤ 2 h of intravenous drip infusion; once every 3 weeks. • Ifosfamide 2 g/m^2/d on D1-D4, 4-6 h of intravenous drip infusion, in 3-week cycles (i.e., the total dose per cycle is 8 g/m^2). Or • Ifosfamide monotherapy: 2 g/m^2/d on D1-D5, once every 3 weeks (i.e., the total dose per cycle is 10 g/m^2).

Inclusion Criteria

Patients must meet all of the following criteria to be eligible.

1. Aged 16-70 years, male or female.
2. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1; the criterion can be relaxed to 2 points for amputation subjects.
3. Life expectancy of ≥ 3 months.
4. Patients with distant metastasis or locally advanced soft tissue sarcoma that render the patient not suitable for surgical treatment as per the investigator's judgment (pathologically or cytologically diagnosed, except gastrointestinal stromal tumors, osteochondroma, embryonic/acinar rhabdomyosarcoma, Ewing's sarcoma, and intermediate soft tissue tumors without extensive metastasis, such as dermatofibrosarcoma protuberans and inflammatory myofibroblastic sarcoma, see Appendix 1. The WHO Soft Tissue Tumor Classification (2013 Edition) for details).
5. Patients who have not received previous chemotherapy for soft tissue sarcoma, or have benefited from chemotherapy but have recurrence or metastasis more than 6 months after drug discontinuation.
6. With measurable lesion as per RECIST v1.1.
7. All acute toxicities due to previous anti-tumor treatments must have resolved to Grade 0-1 (as per NCI CTCAE 4.03) or to the level specified in the inclusion/exclusion criteria before C1D1 (except for toxicities such as alopecia that are deemed by the investigator as not posing safety risks to the patient).
8. With adequate organs and bone marrow functions, as defined below:

   Hematology (without blood transfusion, G-CSF, or medication correction within 14 days prior to screening)

   - Absolute neutrophil count (ANC) ≥ 1500/mm^3 (1.5 × 10^9/L);
   - Blood platelet count (PLT) ≥ 100,000/mm^3 (100 × 10^9/L);
   - Hemoglobin (Hb) ≥ 9 g/dL (90 g/L);

   Blood Biochemistry

   - Serum creatinine (Cr) ≤ 1.5 × upper limit of normal (ULN), or creatinine clearance (Cockroft-Gault formula) ≥ 60 mL/min;
   - Total bilirubin (TBIL) ≤ 1.5 × ULN;
   - Aspartate transaminase (AST) or alanine transaminase (ALT) ≤ 2.5 × ULN; for patients with liver metastasis, ALT and AST should be ≤ 5 × ULN;

   Coagulation Function

   - International normalized ratio (INR) ≤ 1.5, prothrombin time (PT) and activated partial thromboplastin time (APTT) ≤ 1.5 × ULN;

   Urinalysis

   - Urine protein < 2+; If urine protein is ≥ 2+, then the 24-hour urine protein must be ≤ 1 g;

	Thyroid Function • Thyroid-stimulating hormone (TSH) ≤ ULN; if abnormal, FT3 (T3) and FT4 (T4) levels should be examined, and the subject can be enrolled if FT3 (T3) and FT4 (T4) levels are normal. 9. Female subjects of childbearing potential must have a negative serum pregnancy test within 7 days prior to C1D1, and be willing to use a recognized effective contraceptive measure (such as: intra-uterine contraceptive devices, contraceptive pills, or condoms) during the study and within 3 months after the last dose of the study drug; male subjects with partners of childbearing potential must either be surgically sterilized or agree to take effective contraceptive measures during the study and within 3 months after the last dose of the study drug. 10. Subjects must agree and have signed the informed consent form, be willing and able to follow the scheduled visits, study treatment, laboratory tests, and other study procedures.
Exclusion Criteria	Patients meeting any one of the followings are not eligible to participate in this study: 1. Those who have received the following treatments within 4 weeks prior to C1D1: • Previously received radiotherapy, surgery, chemotherapy, immune or molecular targeted therapy for tumors; • Received other investigational drug of clinical studies; • Inoculated with a live attenuated vaccine. 2. Subjects who previously received anti-PD-1/PD-L1/CTLA4 antibodies, or VEGFR single target/multiple target inhibitors. 3. Those who plan to receive surgical treatment and/or radiation therapy for soft tissue sarcoma during the study period. 4. Presence of tumor lesions in the central nervous system confirmed by imaging diagnosis. 5. Having been treated by immunosuppressive drugs within 14 days prior to C1D1, excluding intranasal and inhaled corticosteroids or systemic steroids of physiological doses (i.e., no more than 10 mg/d of prednisolone or equivalent physiological doses of other corticosteroids). 6. Any active autoimmune disease, history of autoimmune disease (the subject with vitiligo or asthma that has completely resolved during childhood and currently does not require medical intervention can be included), or known history of allogeneic organ transplantation or allogeneic hematopoietic stem cell transplantation. 7. Complicated with severe infection (such as one requiring intravenous drip infusion of antibiotics, antifungals, or antivirals) within 4 weeks prior to C1D1, or any unexplained fever of > 38.5 ℃ during screening/prior to the first dose. 8. Hypertension uncontrolled by antihypertensives (systolic pressure > 140 mmHg or diastolic pressure > 90 mmHg).

	9. Patients with clinically significant bleeding symptoms or a clear bleeding tendency within 3 months prior to C1D1, such as hemorrhage of digestive tract, stomach ulcer with hemorrhage, fecal occult blood ++ and above, or vasculitis; or arterial/venous thrombus events, such as cerebrovascular accidents (including transient ischemic attack, cerebral hemorrhage, and cerebral infarction), deep vein thrombus, pulmonary embolism, etc. within 6 months before C1D1; or requiring long-term anticoagulation therapy with warfarin or heparin, or requiring long-term antiplatelet therapy (aspirin of ≥ 300 mg/d or clopidogrel of ≥ 75 mg/d). 10. Active heart diseases within 6 months before C1D1, including myocardial infarction, severe/unstable angina, etc. Left ventricular ejection fraction < 50% as revealed by echocardiography and poorly controlled arrhythmia (including QTcF interval > 450 ms in males and > 470 ms in females). 11. Having been diagnosed with any other malignancies within 3 years before C1D1, excluding adequately treated basal cell carcinoma and squamous cell skin cancer, and cervical carcinoma in situ. 12. Known allergies to the study drug or their excipients; severe allergic reactions to other monoclonal antibodies. 13. With human immunodeficiency virus (HIV) infection, or active hepatitis B (positive hepatitis B surface antigen and HBV DNA ≥ 500 IU/mL) or hepatitis C (positive for hepatitis C antibody, and HCV-RNA higher than the lower limit of detection of the analytical method). 14. Presence of accompanying diseases (such as poorly controlled hypertension, severe diabetes, neurological or mental illness, etc.) or any other situation that may pose serious risks to the safety of the subjects, confuse the research results, or affect the ability of the subjects to complete the study as judged by the investigator.
Pharmacokinetic/ Immunogenicity Studies	Subjects receiving the combination therapy of SHR-1210 and apatinib shall undergo blood sampling for the pharmacokinetics and immunogenicity study of SHR-1210, as well as the pharmacokinetics study of apatinib. Blood sampling time points for pharmacokinetics and immunogenicity study of SHR-1210: within 0.5 h pre-administration on C1D1, C2D1, C4D1, C6D1, C9D1 and once every 4 cycles thereafter, with 4-6 mL of peripheral venous blood collected at each time point; 4-6 mL of peripheral venous blood shall be collected once at 30 days after the last dose. Blood sampling time points for pharmacokinetics study of apatinib: within 0.5 h pre-administration and 4 h (± 10 min) post-administration on C1D1, C2D1, C4D1, and C6D1, with 2-4 mL of peripheral venous blood collected at each time point. The time interval between the administration of apatinib on the day of blood sampling and the previous administration should be no less than 20 h.
Study Withdrawal Criteria	Reasons for withdrawal may include: 1. Withdrawal of informed consent and refusal of further follow-ups by subjects; 2. Other investigator-assessed reasons requiring withdrawal, such as the inability to provide voluntary consent due to imprisonment or quarantine; 3. Lost to follow-up; 4. Death; 5. Study termination by the sponsor.

Criteria for Treatment Discontinuation	Criteria for treatment discontinuation are as follows: 1. Treatment discontinuation requested by subjects; 2. Radiographic or clinical features indicate progression, except for the following two situations: 1) The subject in the investigational treatment group meet the criteria for treatment beyond progression (see 8.3.3 for details); 2) The subject in the control group who had radiographic progression and meet the inclusion/exclusion criteria may be cross over to receive the SHR-1210 + apatinib treatment (see 8.3.4 for details);; 3. Occurrence of subject pregnancy during the study; 4. Any clinical AEs, laboratory abnormalities, or other medical conditions indicating that the subject can no longer benefit from the treatment; 5. General deterioration of health status and inability to continue study participation; 6. Major protocol deviations such as ineligibility found after enrollment; 7. Lost to follow-up; 8. Study termination by the sponsor; 9. Death; 10. Other reasons as determined by the investigator.
Determination of Sample Size	In this study, IRC-assessed PFS (as per RECIST v1.1) will be used as the primary endpoint for superiority test with the control group. An interim analysis will be performed to determine the efficacy of the drugs and to determine whether to terminate or continue the study. The parameters for sample size calculation are as follows: Enrollment rate = 13 subjects/month (156 subjects/year), enrollment time = 20 months (the overall time will be 26 months) Randomization in a 1:1 ratio; one-sided $\alpha = 0.025$; the power of the test is 90%; Hazard ratio (investigational treatment group/control group [HR]) = 0.64 (estimated median PFS is 4.5 months in the control group and 7.0 months in the investigational treatment group) An interim analysis will be performed when 67% of PFS events are collected to determine the safety and efficacy of the drug by IDMC. Based on the above parameters, at least 214 PFS events shall be collected according to the log-rank test for PFS comparison in the two groups and the O'Brien & Fleming spending function (EAST 6.4.1) in the α spending function method proposed by Lan-DeMets, i.e., approximately 262 subjects are needed. Considering a 10% dropout rate, 292 subjects are finally required for enrollment.
Data Analysis/ Statistical Methods	This study plans to conduct an interim analysis for efficacy and a final analysis. The interim analysis will be carried out when 67% of PFS events (approximately 143 subjects) are collected to determine whether the drug is effective and whether to terminate or continue the study. The final analysis will be performed when the number of PFS events reaches 214. ■ General analysis For this study, efficacy data will be summarized in accordance with the following general principles using descriptive statistics, unless otherwise stated.

	Two-category and multi-category data will be summarized using frequency and percentage. Measurement data will be summarized using mean, standard deviation, median, maximum, and minimum. Time-event data will be analyzed using the Kaplan-Meier method, so as to estimate the survival function of both groups and plot the survival curves. All statistical analyses will be performed using SAS version 9.4 or later. ■ Efficacy analysis In addition to the general principles of efficacy analysis described above, the analysis of primary and secondary efficacy indicators also includes: ORR and DCR: The Clopper-Pearson method will be used to calculate the 95% confidence interval of the ORR. PFS and OS: The Kaplan-Meier method will be used to plot the survival curve, and the Brookmeyer Crowley method will be used to calculate the 95% confidence interval of the median survival. In addition, the Cox regression model will be used to estimate the hazard ratio between the two groups and its 95% confidence interval (95% CI). The general analysis principle also applies to DoR analysis, but whenever necessary, the 95% confidence interval of the median survival will be calculated to estimate and plot the survival curve. ■ Safety analysis The AEs, SAEs, and adverse drug reactions will be analyzed mainly using descriptive statistics. Laboratory tests that are normal before the study but become abnormal after starting treatment will be described.
Interim Analysis	In this study, one interim analysis will be carried out for the primary efficacy endpoint PFS. In order to control the overall type I error, the O'Brien-Fleming spending function in the α spending function method will be used to evaluate the efficacy of the drugs and to determine whether the study shall end early when 67% of PFS events (143 subjects) are collected. When the z-score of PFS based on the log-rank test result exceeding the unbound effective boundary is -2.506 (P-value [one-sided] < 0.006), the study will end early because it is effective. If the efficacy is not established, the study will continue. If, in the interim analysis, the actual number of observed events does not reach or exceed 143, the boundary should be timely monitored and adjusted using EAST (e.g., using IM tool for monitoring). The final analysis will be performed when 214 PFS events are collected. The results of interim analysis will be reviewed by the IDMC, which will recommend whether to continue the study.
Study Period	Anticipated enrollment of the first subject: Sep. 2018 Anticipated enrollment of the last subject: Dec. 2020 Anticipated study completion: Sep. 2022

1 FLOW DIAGRAM OF EXPERIMENT — INVESTIGATIONAL TREATMENT GROUP (SHR-1210 COMBINED WITH APATINIB)

STUDY PROCEDURES	Screening Period		Cycle 1	Cycle 2	Cycle 3 and Beyond	Safety Follow-Up[24]		Survival Follow-Up[25]
	D-28 to D-1	D-7 to D-1	D1	D1	D1 (once per cycle)	30 days after the last dose	60 and 90 days after the last dose	Once every 2 months
Time Window				±3	±3	±5	±5	±5
Signing of Informed Consent Form[1]	×							
Demographics, Medical History, and Treatment History[2]	×							
Inclusion/ Exclusion Criteria and Randomization		×	(Eligibility for randomization)					
ECOG PS[3]		×		×	×	×		
Vital Signs[4]		×		×	×	×		
Physical Examination[5]		×		×	×	×		
Virology [[6]	×							
Hematology[7]		×		×	×	×		
Urinalysis[8]		×			×(once every 2 cycles)	×		
Fecal Occult Blood[9]		×		×	×	×		
Blood Biochemistry[10]		×		×	×	×		
Coagulation Function[11]		×			×(once every 2 cycles)	×		
Thyroid Function[12]		×			×(once every 2 cycles)	×		
Myocardial Zymogram[13]		×						
12-Lead ECG[14]		×		×	×	×		
Echocardiography[15]	×							
Pregnancy Test [16]		×			×(once every 2 cycles)			
Tumor Imaging	×				×(once every	×		

STUDY PROCEDURES	**Screening Period**		**Cycle 1**	**Cycle 2**	**Cycle 3 and Beyond**	**Safety Follow-Up**[24]		**Survival Follow-Up**[25]
	D-28 to D-1	**D-7 to D-1**	**D1**	**D1**	**D1 (once per cycle)**	**30 days after the last dose**	**60 and 90 days after the last dose**	**Once every 2 months**
Examination[17]					2 cycles or once every 4 cycles)			
Dispensation/Retrieval of Drugs and Study Treatment[18]			×	×(D -3 to D+7)	×(D -3 to D+7)			
Adverse Events[19]	×	×	×	×	×	×	×	
Concomitant Medications/ Treatments[20]	×	×	×	×	×	×	×	
PK and Immunogenicity Blood Sampling[21]			×	×[21]	×[21]	×		
Quality of Life Questionnaires [[22]		×			×(once every 2 cycles or once every 4 cycles)	×		
Subject Diary Card Dispensing, Retrieval, and Filling[23]			×[23]	×[23]	×[23]			
Subsequent Anti-Tumor Treatment and Survival Status						×	×	×

Note: In addition to the examinations and time points listed in the table, the investigator may add visits and other examinations if needed.

[1] Subjects who have failed screening may be screened again in this study, but the informed consent form must be re-signed and a new subject number should be given for re-screening. If the re-screening fails, no further screening will be performed. Data from virology, echocardiography, and imaging assessment (tested at this study center only) performed prior to the signing of informed consent for clinical needs may be used if they are within the specified window period.

[2] Demographics, medical history, and treatment history: including date of birth, gender, ethnicity, tumor history (tumor diagnosis, surgery, radiotherapy, chemotherapy history, etc.), other concurrent diseases and corresponding treatments. Among them, the tumor history should include: the time of initial diagnosis, pathological diagnosis, clinical staging, etc.

[3] ECOG PS scoring: Performed within 7 days before the first dose, on day 1 of each cycle from cycle 2 onwards, and at 30 days after the last dose.

[4] Vital signs: pulse, respiratory rate, temperature, and blood pressure. Performed within 7 days before the first dose, on day 1 of each cycle from cycle 2 onwards, and at 30 days after the last dose.

[5] Physical examination: Performed within 7 days before the first dose, on day 1 of each cycle from cycle 2 onwards, and at 30 days after the last dose; comprehensive examinations (height, weight, general condition, head and face, neck, chest, abdomen, perineum, extremities, etc.) will be performed; height will be measured only once within 7 days before the first dose and weight will be measured at each visit point (except for C1D1); a targeted physical examination will be performed when clinically indicated.

[6] Virology: HBsAg (quantitative HBV DNA test if positive); HCV-Ab (quantitative HCV-RNA test if positive) and HIV-Ab: within 28 days before the first dose.

[7] Hematology: red blood cell count (RBC), hemoglobin (Hb), blood platelet count (PLT), white blood cell count (WBC), absolute neutrophil count (ANC), and lymphocyte count (LYM); tested within 7 days before the first dose, on day 1 of each cycle from cycle 2 onwards, and at 30 days after the last dose.

[8] Urinalysis: WBC, RBC, and urine protein; tested within 7 days before the first dose, on day 1 of every 2 cycles from cycle 3 onwards, and at 30 days after the last dose. If urine protein is ≥ 2+, then a quantitative 24-h urine protein test should be added.

[9] Fecal occult blood: performed within 7 days before the first dose, on day 1 of each cycle from cycle 2 onwards, and at 30 days after the last dose.

[10] Blood biochemistry: Alanine transaminase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (γ-GT), total bilirubin (TBIL), direct bilirubin (DBIL), alkaline phosphatase (AKP), blood urea nitrogen (BUN) or urea, total protein (TP), albumin (ALB), creatinine (Cr), blood glucose (GLU), serum potassium (K^+), serum natrium (Na^+), serum calcium (Ca^{2+}), serum magnesium (Mg^{2+}), and blood chloride (Cl^-); tested within 7 days before the first dose, on day 1 of each cycle from cycle 2 onwards, and at 30 days after the last dose.

[11] Coagulation function: Activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), fibrinogen (FIB), and international normalized ratio (INR); tested within 7 days before the first dose, on day 1 of every 2 cycles from cycle 3 onwards, and at 30 days after the last dose.

[12] Thyroid function: serum thyroid stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4); if FT3 and FT4 are not available, T3 and T4 are allowed for substitution; tested within 7 days before the first dose, on day 1 of each cycle from cycle 2, and at 30 days after the last dose.

[13] Myocardial zymogram: lactate dehydrogenase (LDH), creatine kinase (CK), and hybrid creatine kinase (CK-MB); tested within 7 days before the first dose.

[14] 12-Lead ECG: Attentions should be paid to QT, QTcF, and P-R intervals. Performed within 7 days before the first dose, on day 1 of each cycle from cycle 2 onwards, and at 30 days after the last dose. QTcF can be calculated as: $QTcF = QT/(60/\text{heart rate})^{0.33}$.

[15] Echocardiography: within 28 days before the first dose.

[16] Pregnancy test: Serum pregnancy test will be performed for women of childbearing potential. Performed within 7 days before the first dose and on day 1 of every 2 cycles from cycle 3 onwards.

[17] Tumor imaging evaluation: CT or MRI of lesions in the head, chest, abdomen, pelvis, and other sites. Sites with bone metastasis as shown by bone scans, PET-CT, or clinical indications must also be reexamined by CT or MRI at baseline but no longer undergo bone scan or PET-CT for efficacy follow-up. CT or MRI follow-ups of lesions in the head, chest, abdomen, pelvis, and other sites will be performed at each response evaluation. The CT/MRI examination methods and techniques for a subject shall remain the same throughout the study period.

- ✓ At screening, tumor evaluations (at this study center only) up to 4 weeks before the first dose and before signing the informed consent may be used as long as they meet the requirements.
- ✓ Study treatment period: The imaging examination cycles will start from C1D1. In the first 16 treatment cycles, imaging examinations will be performed once every 2 cycles (the first assessment will be on C3D1), and once every 4 cycles thereafter. If radiographic progression is noted and pseudoprogression has been ruled out, imaging examinations will no longer be performed; subjects who discontinue the study treatment for reasons other than radiographic progression will still be followed up according to the established cycle. If the previous imaging examination does not show progression and no imaging examination is performed within 4 weeks before the 30-day visit after the last dose, an imaging examination must be performed at the 30-day visit after the last dose. The time window for tumor evaluation is ± 7 days. Additional tumor evaluations may be performed if PD is suspected (for example, worsening of symptoms).

[18] Dispensation/retrieval of drugs and study treatment: SHR-1210 200 mg, intravenous drip infusion, once every 3 weeks starting from C1D1; if SHR-1210 administration of the current cycle cannot be performed due to adverse events, it can be delayed for up to 7 days from the scheduled administration point. SHR-1210 will not be administered in this cycle if the scheduled administration is delayed for more than 7 days. Apatinib 500 mg, continuous oral administration, once daily. Each treatment cycle lasts for 21 days. The first dose of apatinib will be dispensed on C1D1 or one day in advance; subsequent apatinib tablets are allowed to be dispensed at the scheduled time point within ± 3 days; remaining apatinib must be retrieved before each dispensation. For dose interruption due to AEs or other reasons, unscheduled drug dispensation and retrieval are permitted.

[19] Adverse events: Recorded from the date of signing the informed consent form to the end of the safety follow-up period or the start of a new anti-tumor treatment. See Table 11.Principles of AE/SAE collection and follow-up for details.

[20] Concomitant medication/treatment: Recorded from 28 days before the first dose of study treatment to the end of the safety follow-up period; If a new anti-tumor treatment is started during this period, only concomitant medications for treatment-related adverse events will be recorded thereafter. After the safety follow-up period, only concomitant medications/treatments for adverse events are required to be recorded.

[21] Pharmacokinetics/immunogenicity test: Blood sampling time points for pharmacokinetics and immunogenicity study of SHR-1210: within 0.5 h pre-administration on C1D1, C2D1, C4D1, C6D1, C9D1, and every 4 cycles thereafter, with 4-6 mL of peripheral venous blood collected at each time point; 4-6 mL of peripheral venous blood will be collected once at 30 days after the last dose. Blood sampling time points for pharmacokinetics study of apatinib: within 0.5 h pre-administration and 4 h (± 10 min) post-administration on C1D1, C2D1, C4D1, and C6D1, with 2-4 mL of peripheral venous blood collected at each time point. The time interval between the administration of apatinib on the day of blood sampling and the previous administration should be no less than 20 h.

[22] Quality of life scoring: Performed within 7 days before the first dose, on day 1 of every 2 cycles from cycle 3 onwards, on day 1 of every 4 cycles from cycle 17 onwards, and at 30 days after the last dose.

[23] Diary card dispensing, retrieval, and filling: The subjects will measure blood pressure by themselves or others during the treatment period, and shall fill out the diary card every day to record blood pressure and other discomforts.

[24] Safety follow-up: performed on days 30, 60, and 90 after the last dose. The first safety follow-up visit (day 30) will be carried out at the study center, where the evaluations specified in the protocol will be completed. The second (day 60) and the third (day 90) follow-ups will be performed via phone calls. Information on new anti-tumor treatment, survival, concomitant medications/treatments, and adverse events will be collected.

[25] Survival follow-up: At the end of the safety follow-up period, the subjects will enter the survival follow-up period until death, lost to follow-up, withdrawal of informed consent or termination of the clinical study by the sponsor. During this period, follow-up will be conducted via phone calls or other effective methods once every 2 months to collect information on subject survival and subsequent treatments (if the subjects start a new anti-tumor treatment, the therapeutic regimen and the start and end time should be recorded).

2 FLOW DIAGRAM OF EXPERIMENT — CONTROL GROUP (DOXORUBICIN + IFOSFAMIDE OR IFOSFAMIDE MONOTHERAPY)

STUDY PROCEDURES	Screening Period		Cycle 1	Cycles 2-6	Cycles 7-16	Cycle 17 and beyond	Safety Visit[22]	Survival Follow-Up[23]
	D-28 to D-1	D-7 to D-1	D1	D1 (once every 1 cycle)	D1 (once every 2 cycles)	D1 (once every 4 cycles)	21 days after the last dose	Once every 2 months
Time Window				±3	±7	±7	±5	±5
Signing of Informed Consent Form[1]	×							
Demographics, Medical History, and Treatment History[2]	×							
Inclusion/Exclusion Criteria and Randomization		×	(Eligibility for randomization)					
ECOG PS[3]		×		×			×	
Vital Signs[4]		×		×			×	
Physical Examination[5]		×		×			×	
Virology[6]	×							
Hematology[7]		×		×			×	
Urinalysis[8]		×		×			×	
Fecal Occult Blood Test[9]		×		×			×	
Blood Biochemistry[10]		×		×			×	
Coagulation Function[11]		×		×			×	
Thyroid Function[12]		×					×	
Myocardial Zymogram[13]		×		×			×	
12-Lead ECG[14]		×		×			×	
Echocardiography[15]	×			×			×	
Pregnancy Test [16]		×		× (once every 2 cycles from cycle 3 onwards)			×	

STUDY PROCEDURES	Screening Period		Cycle 1	Cycles 2-6	Cycles 7-16	Cycle 17 and beyond	Safety Visit[22]	Survival Follow-Up[23]
	D-28 to D-1	D-7 to D-1	D1	D1 (once every 1 cycle)	D1 (once every 2 cycles)	D1 (once every 4 cycles)	21 days after the last dose	Once every 2 months
Tumor Imaging Examination[17]	×			× (once every 2 cycles from cycle 3 onwards)	×	×	×	
Study Treatment[18]			×	×				
Adverse Events[19]	×	×	×	×	×	×	×	
Concomitant Medications/ Treatments[20]	×	×	×	×	×	×	×	
Quality of Life Score[21]		×		× (once every 2 cycles from cycle 3 onwards)	×	×	×	
Subsequent Anti-Tumor Treatment and Survival Status							×	×

Note: In addition to the examinations and time points listed in the table, the investigator may add visits and other examinations if needed. Subjects crossed over for SHR-1210 combined with apatinib will be followed up according to the crossover treatment flow chart.

[1] Subjects who have failed previous screening may be screened again in this study. The informed consent form must be re-signed and a new subject number should be given for re-screening. If the re-screening fails, no further screening will be performed. Data from virology, echocardiography, and imaging assessment (tested at this study center only) performed prior to the signing of informed consent for clinical needs may be used if they are within the specified window period.

[2] Demographics, medical history, and treatment history: including date of birth, gender, ethnicity, tumor history (tumor diagnosis, surgery, radiotherapy, chemotherapy history, etc.), other concurrent diseases and corresponding treatments. Among them, the tumor history should include: the time of initial diagnosis, pathological diagnosis, clinical staging, etc.

[3] ECOG PS scoring: Performed within 7 days before the first dose, on day 1 of each cycle in cycles 2-6, and at 21 days after the last dose.

[4] Vital signs: pulse, respiratory rate, temperature, and blood pressure. Performed within 7 days before the first dose, on day 1 of each cycle in cycles 2-6, and at 21 days after the last dose.

[5] Physical examination: Performed within 7 days before the first dose, on day 1 of each cycle in cycles 2-6, and at 21 days after the last dose; comprehensive examinations (height, weight, general condition, head and face, neck, chest, abdomen, perineum, extremities, etc.) will be performed; height will be measured only once within 7 days before the first dose and weight will be measured at each visit point; a targeted physical examination will be performed when clinically indicated.

[6] Virology: HBsAg (quantitative HBV DNA test if positive); HCV-Ab (quantitative HCV-RNA test if positive) and HIV-Ab.

[7] Hematology: red blood cell count (RBC), hemoglobin (Hb), blood platelet count (PLT), white blood cell count (WBC), absolute neutrophil count (ANC), and lymphocyte count (LYM); tested within 7 days before the first dose, on day 1 of each cycle in cycles 2-6, and at 21 days after the last dose.

[8] Urinalysis: WBC, RBC, and urine protein. If urine protein is ≥ 2+, then a quantitative 24 h urine protein test should be added; performed within 7 days before the first dose, on day 1 of each cycle in cycles 2-6, and at 21 days after the last dose.

[9] Fecal occult blood: performed within 7 days before the first dose, on day 1 of each cycle in cycles 2-6, and at 21 days after the last dose.

[10] Blood biochemistry: Alanine transaminase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (γ-GT), total bilirubin (TBIL), direct bilirubin (DBIL), alkaline phosphatase (AKP), blood urea nitrogen (BUN) or urea, total protein (TP), albumin (ALB), creatinine (Cr), blood glucose (GLU), serum potassium (K^+), serum natrium (Na^+), serum calcium (Ca^{2+}), serum magnesium (Mg^{2+}), and blood chloride (Cl^-); tested within 7 days before the first dose, on day 1 of each cycle in cycles 2-6, and at 21 days after the last dose.

[11] Coagulation function: Activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), fibrinogen (FIB), and international normalized ratio (INR); tested within 7 days before the first dose, on day 1 of each cycle in cycles 2-6, and at 21 days after the last dose.

[12] Thyroid function: serum thyroid stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4); if FT3 and FT4 are not available, T3 and T4 are allowed for substitution; tested within 7 days before the first dose, and at 21 days after the last dose.

[13] Myocardial zymogram: lactate dehydrogenase (LDH), creatine kinase (CK), and hybrid creatine kinase (CK-MB); tested within 7 days before the first dose, on day 1 of each cycle in cycles 2-6, and at 21 days after the last dose.

[14] 12-Lead ECG: Attentions should be paid to QT, QTcF, and P-R intervals. Performed within 7 days before the first dose, on day 1 of each cycle in cycles 2-6, and at 21 days after the last dose. Investigators may decide whether to perform additional ECGs and/or myocardial zymographic tests if the subject complains of symptoms such as chest pain or palpitations. QTcF can be calculated as: $QTcF = QT/(60/\text{heart rate})^{0.33}$.

[15] Echocardiography: performed within 28 days before the first dose, on day 1 of each cycle in cycles 2-6, and at 21 days after the last dose. Additional echocardiography may be performed if the subject complains of symptoms such as chest pain or palpitations.

[16] Pregnancy test: Serum pregnancy test will be performed for women of childbearing potential. Performed within 7 days before the first dose, on day 1 of every 2 cycles in cycles 3-6, and at 21 days after the last dose.

[17] Tumor imaging evaluation: CT or MRI of lesions in the head, chest, abdomen, pelvis, and other sites. Sites with bone metastasis as shown by bone scans, PET-CT, or clinical indications must also be reexamined by CT or MRI at baseline but no longer undergo bone scan or PET-CT for efficacy follow-up. CT or MRI follow-ups of lesions in the head, chest, abdomen, pelvis, and other sites will be performed at each response evaluation. The CT/MRI examination methods and techniques for a subject shall remain the same throughout the study period.

- ✓ At screening, tumor evaluations (at this study center only) up to 4 weeks before the first dose and before signing the informed consent may be used as long as they meet the requirements.

- ✓ Study treatment period: The imaging examination cycles will start from C1D1. In the first 16 treatment cycles, imaging examinations will be performed once every 2 cycles (the first assessment will be on C3D1), and once every 4 cycles thereafter. Imaging examinations will no longer be performed in case of radiographic progression; subjects who discontinue the study treatment for reasons other than radiographic progression will still be followed up according to the established cycle. If the previous imaging examination does not show progression and no imaging examination is performed within 4 weeks before the 21-day visit after the last dose, an imaging examination must be performed at the 21-day visit after the last dose. The time window for tumor evaluation is ± 7 days. Additional tumor evaluations may be performed if PD is suspected (for example, worsening of symptoms).

[18] Study treatment: (doxorubicin + ifosfamide/ifosfamide monotherapy): doxorubicin 60 mg/m^2, on D1, ifosfamide 2 g/m^2/d, on D1-D4, q3w, and 6 cycles are recommended; if the investigator considers that the subject benefits from the chemotherapy, additional chemotherapy cycles may be administered; the content of visits in subsequent treatment cycles will be the same as those in cycles 2-6. If intolerability is noted, the investigator may delay the administration of this cycle or the chemotherapy drug, and adjust the administration time of the next cycle to 21 days after the administration of the previous cycle. If the maximum cumulative dose of doxorubicin is reached, the treatment will be switched to ifosfamide monotherapy 2 g/m^2/d on D1-D5 q3w.

[19] Adverse events: Recorded from the date of signing the informed consent form to the end of the safety follow-up period or the start of a new anti-tumor treatment. See Table 11.Principles of AE/SAE collection and follow-up for details.

[20] Concomitant medication/treatment: Recorded from 28 days before the first dose of study treatment to the end of the safety follow-up period; If a new anti-tumor treatment is started, only concomitant medications for treatment-related adverse events will be recorded thereafter. After the safety follow-up period, only concomitant medications/treatments for adverse events are required to be recorded. Subjects crossed over for SHR-1210 + apatinib treatment will be followed up according to the procedures after crossover.

[21] Quality of life scoring: Performed within 7 days before the first dose, on day 1 of every 2 cycles in cycles 3-6, on day 1 of every 2 cycles in cycles 7-16, on day 1 of every 4 cycles from cycle 17 onwards, and at 21 days after the last dose.

[22] Safety visit: Subjects shall go to the study center for safety visit at 21 days after the last dose in accordance with protocol requirements.

[23] Survival follow-up: At the end of the safety follow-up period, the subjects will enter the survival follow-up period until death, lost to follow-up, withdrawal of informed consent or termination of the clinical study by the sponsor. During this period, follow-up will be conducted via phone calls or other effective methods once every 2 months to collect information on subject survival and subsequent treatments (if the subject starts a new anti-tumor treatment, the therapeutic regimen and the start and end time should be recorded).

3 SCHEDULE OF ACTIVITIES — CROSSOVER TREATMENT (SHR-1210 + APATINIB AFTER PROGRESSION FOLLOWING DOXORUBICIN + IFOSFAMIDE OR IFOSFAMIDE MONOTHERAPY)

STUDY PROCEDURES	Screening Period	Cycle 1	Cycle 2	Cycle 3 and Beyond	Safety Follow-Up[22]		Survival Follow-Up[23]
	D-7 to D-1	D1	D1	D1 (once per cycle)	30 days after the last dose	60 and 90 days after the last dose	Once every 2 months
Time Window				±3	±5	±5	±5
Signing of Informed Consent and Verification of Eligibility[1]	×						
ECOG PS[2]	×		×	×	×		
Vital Sign[3]	×		×	×	×		
Physical Examination[4]	×		×	×	×		
Virology[5]	×						
Hematology[6]	×		×	×	×		
Urinalysis[7]	×			×(once every 2 cycles)	×		
Fecal Occult Blood[8]	×		×	×	×		
Blood Biochemistry[9]	×		×	×	×		
Coagulation Function[10]	×			×(once every 2 cycles)	×		
Thyroid Function[11]	×			×(once every 2 cycles)	×		
12-Lead ECG[12]	×		×	×	×		
Echocardiography[13]	×						
Pregnancy Test[14]	×			×(once every 2 cycles)			
Tumor Imaging Examination[15]	×(within 28 days)			×(once every 2 cycles or once every 4 cycles)	×		
Dispensation/Retrieval of Drugs and Study Treatment[16]		×	×(D -3 to D+7)	×(D -3 to D+7)			

STUDY PROCEDURES	Screening Period	Cycle 1	Cycle 2	Cycle 3 and Beyond	Safety Follow-Up[22]		Survival Follow-Up[23]
	D-7 to D-1	D1	D1	D1 (once per cycle)	30 days after the last dose	60 and 90 days after the last dose	Once every 2 months
Adverse Events[17]	×	×	×	×	×	×	
Concomitant Medications/ Treatments[18]	×	×	×	×	×	×	
Pharmacokinetics/Immunogenicity Blood Sampling[19]		×	×[19]	×[19]	×		
Quality of Life Score[20]	×			×(once every 2 cycles or once every 4 cycles)	×		
Diary Card Dispensing, Retrieval, and Filling[21]		×[21]	×[21]	×[21]			
Subsequent Anti-Tumor Treatment and Survival Status					×	×	×

Note: In addition to the examinations and time points listed in the table, the investigator may add visits and other examinations if needed.

[1] Subjects in the control group who develop radiographically confirmed progressive disease may be crossed over to receive SHR-1210 + apatinib. There should be at least a 3-week interval between the first dose of SHR-1210 + apatinib and the last dose of the previous standard chemotherapy. The first dose and subsequent visits will be carried out according to the schedule of activities of crossover treatment. Subjects should sign an informed consent form for the crossover treatment. Examination results within 7 days before the first dose of the subject may be used to evaluate whether the inclusion and exclusion criteria of crossover treatment are met (see 8.3.4). If the criteria are met, the subject will receive crossover treatment, i.e., SHR-1210 + apatinib. If the inclusion and exclusion criteria are not met, the subject may receive supportive treatment for adjustment. But during this period, anti-tumor treatment must not be performed. If, at the reexamination 2 months after progressive disease, the inclusion and exclusion criteria for crossover treatment are still not met, crossover to receive SHR-1210 + apatinib will not be permitted.

[2] ECOG PS scoring: Performed within 7 days before the first dose (*), on day 1 of each cycle from cycle 2 onwards, and at 30 days after the last dose.

[3] Vital signs: pulse, respiratory rate, temperature, and blood pressure. Performed within 7 days before the first dose (*), on day 1 of each cycle from cycle 2 onwards, and at 30 days after the last dose.

[4] Physical examination: Performed within 7 days before the first dose (*), on day 1 of each cycle from cycle 2 onwards, and at 30 days after the last dose; comprehensive examinations (height, weight, general condition, head and face, neck, chest, abdomen, perineum, extremities, etc.) will be performed; height will be measured only once within 7 days before the first dose and weight will be measured at each visit point (except C1D1); a targeted physical examination will be performed when clinically indicated.

[5] Virology: HBsAg (quantitative HBV DNA test if positive); HCV-Ab (quantitative HCV-RNA test if positive) and HIV-Ab.

[6] Hematology: red blood cell count (RBC), hemoglobin (Hb), blood platelet count (PLT), white blood cell count (WBC), absolute neutrophil count (ANC), and lymphocyte count (LYM); tested within 7 days before the first dose (*), on day 1 of each cycle from cycle 2 onwards, and at 30 days after the last dose.

[7] Urinalysis: WBC, RBC, and urine protein. If urine protein is ≥ 2+, then a quantitative 24-h urine protein test should be added; performed within 7 days before the first dose (*), on day 1 of every 2 cycles from cycle 3 onwards, and at 30 days after the last dose.

[8] Fecal occult blood: performed within 7 days before the first dose (*), on day 1 of each cycle from cycle 2 onwards, and at 30 days after the last dose.

[9] Blood biochemistry: Alanine transaminase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (γ-GT), total bilirubin (TBIL), direct bilirubin (DBIL), alkaline phosphatase (AKP), blood urea nitrogen (BUN) or urea, total protein (TP), albumin (ALB), creatinine (Cr), blood glucose (GLU), serum potassium (K^+), serum natrium (Na^+), serum calcium (Ca^{2+}), serum magnesium (Mg^{2+}), and blood chloride (Cl^-); tested within 7 days before the first dose, on day 1 of each cycle from cycle 2 onwards, and at 30 days after the last dose.

[10] Coagulation function: Activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), fibrinogen (FIB), and international normalized ratio (INR); tested within 7 days before the first dose (*), on day 1 of every 2 cycles from cycle 3 onwards, and at 30 days after the last dose.

[11] Thyroid function: serum thyroid stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4); if FT3 and FT4 are not available, T3 and T4 are allowed for substitution; tested within 7 days before the first dose (*), on day 1 of every 2 cycles from cycle 3 onwards, and at 30 days after the last dose.

[12] 12-Lead ECG: Attentions should be paid to QT, QTcF, and P-R intervals. Performed within 7 days before the first dose (*), on day 1 of each cycle from cycle 2 onwards, and at 30 days after the last dose. Investigators may decide whether to perform additional ECGs, echocardiography, or myocardial zymographic tests if the subject complains of symptoms such as chest pain or palpitations. QTcF can be calculated as: QTcF = QT/(60/heart rate)$^{0.33}$.

[13] Echocardiography: within 7 days before the first dose (*).

[14] Pregnancy test: Serum pregnancy test will be performed for women of childbearing potential. Performed within 7 days before the first dose (*) and on day 1 of every 2 cycles from cycle 3 onwards.

[15] Tumor imaging evaluation: CT or MRI of lesions in the chest, abdomen, pelvis, and other sites. Brain MRI or CT should be performed for suspected or confirmed brain metastases. MRI or CT confirmation should be performed for bone metastases radiographically or clinically indicated. CT or MRI follow-ups of lesions in the head, chest, abdomen, pelvis, and other sites will be performed at each response evaluation. The CT/MRI examination methods and techniques for a subject shall remain the same throughout the study period.

- ✓ Screening period: tumor evaluations within up to 4 weeks before the first dose and before signing the informed consent may be used as long as they meet the requirements.
  - ✓ Study treatment period: Treatment period starting from C1D1 of crossover treatment: The imaging examination cycles will start from C1D1. In the first 16 treatment cycles, imaging examinations will be performed once every 2 cycles (the first assessment will be on C3D1), and once every 4 cycles thereafter. If radiographic progression is noted and pseudoprogression has been ruled out, imaging examinations will no longer be performed; subjects who discontinue the study treatment for reasons other than radiographic progression will still be followed up according to the established cycle. If the previous imaging examination does not show progression and no imaging examination is performed within 4 weeks before the 30-day visit after the last dose, an imaging examination must be performed at the 30-day visit after the last dose. The time window for tumor evaluation is ± 7 days. Additional tumor evaluations may be performed if PD is suspected (for example, worsening of symptoms).

[16] Dispensation/retrieval of drugs and study treatment: SHR-1210 200 mg, intravenous drip infusion, once every 3 weeks starting from C1D1; if SHR-1210 administration of the current cycle cannot be performed due to adverse events, it can be delayed for up to 7 days from the scheduled administration point. SHR-1210 will not be administered in this cycle if the scheduled administration is delayed for more than 7 days. Apatinib 500 mg, continuous oral administration, once daily. Each treatment cycle lasts for 21 days. The first dose of apatinib is dispensed on C1D1 or one day in advance; subsequent apatinib tablets are allowed to be dispensed at the scheduled time point ± 3 days; remaining apatinib must be retrieved before each dispensation. For dose interruption due to AEs or other reasons, unscheduled drug dispensation and retrieval are permitted.

[17] Adverse events: Recorded from the date of signing the informed consent form to the end of the safety follow-up period or the start of a new anti-tumor treatment. See Table 11.Principles of AE/SAE collection and follow-up for details.

[18] Concomitant medication/treatment: Recorded from 28 days before the first dose of study treatment to the end of the safety follow-up period; If a new anti-tumor treatment is started, only concomitant medications for treatment-related adverse events will be recorded thereafter. After the safety follow-up period, only concomitant medications/treatments for adverse events are required to be recorded.

[19] Pharmacokinetics/immunogenicity test: Blood sampling time points for pharmacokinetics and immunogenicity study of SHR-1210: within 0.5 h pre-administration on C1D1, C2D1, C4D1, C6D1, C9D1, and every 4 cycles thereafter, with 4-6 mL of peripheral venous blood collected at each time point; 4-6 mL of peripheral venous blood will be collected once 30 days after the last dose. Blood sampling time points for pharmacokinetics study of apatinib: within 0.5 h pre-administration and 4 h (± 10 min) post-administration on C1D1, C2D1, C4D1, and C6D1, with 2-4 mL of peripheral venous blood collected at each time point. The time interval between the administration of apatinib on the day of blood sampling and the previous administration should be no less than 20 h.

[20] Quality of life scoring: Performed within 7 days before the first dose (*), on day 1 of every 2 cycles from cycle 3 onwards, on day 1 of every 4 cycles from cycle 17 onwards, and at 30 days after the last dose.

[21] Diary card dispensing, retrieval, and filling: The subjects will measure blood pressure by themselves or others during the treatment period, and shall fill out the diary card every day to record blood pressure and other discomforts.

[22] Safety follow-up: performed on days 30, 60, and 90 after the last dose. The first safety follow-up visit (day 30) will be carried out at the study center, where the evaluations specified in the protocol will be completed. The second (day 60) and the third (day 90) follow-ups will be performed via phone calls. Information on new anti-tumor treatment, survival, concomitant medications/treatments, and adverse events will be collected.

[23] Survival follow-up: At the end of the safety follow-up period, the subjects will enter the survival follow-up period until death, lost to follow-up, withdrawal of informed consent or termination of the clinical study by the sponsor. During this period, follow-up will be conducted via phone calls or other effective methods once every 2 months to collect information on subject survival and subsequent treatments (if the subjects start a new anti-tumor treatment, the therapeutic regimen and the start and end time should be recorded).

(*) For the control group, if the examinations of the visit at 21 days after the last dose of chemotherapy are qualified, the results may be used for the visit within 7 days before the first dose of crossover treatment.

4 ABBREVIATIONS

Abbreviations	Full Name
12-Lead ECG	12-Lead electrocardiogram
ADA	Anti-drug antibody
AE	Adverse event
AKP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
Cl^-	Blood chlorine
Cr	Creatinine
CR	Complete response
CRF	Case report form
CRO	Contract research organization
CTLA-4	Cytotoxic T lymphocyte antigen 4
D	Day
DC	Dendritic cell
DCR	Disease control rate
DoR	Duration of response
EC	Ethics Committee
ER	Estrogen receptor
FAS	Full analysis set
GCP	Good Clinical Practice
h	Hour
Hb	Hemoglobin
HR	Hazard ratio
HUVEC	human vascular endothelial cells
IB	Investigator's brochure
IC_{50}	Half maximal inhibitory concentration
irAE	Immune-related adverse event
IU	International unit
K+	Serum potassium
kg	Kilogram

Abbreviations	Full Name
LDH	Lactate dehydrogenase
mg	Milligram
mL	Milliliter
mm	Millimeter
MTD	Maximum tolerated dose
Na+	Plasma sodium
NEUT	Neutrophil
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed death-1
PD-L1	Programmed death-ligand 1
PDGFR	Platelet-derived growth factor receptors
PFS	Progression free survival
PPS	Per-protocol set
PR	Partial response
PLT	Blood platelet
RBC	Red blood cell count
RECIST	Response Evaluation Criteria in Solid Tumors
sec	Second
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SS	Safety set
TBIL	Total bilirubin
TEAE	Treatment emergent adverse event
UA	Uric acid
URBC	Urine red blood cell
VEGF	Vascular endothelial growth factor
WBC	White blood cell count

5 INTRODUCTION: BACKGROUND AND SCIENTIFIC RATIONALE

5.1 Background

5.1.1 Introduction to soft tissue sarcoma

Soft tissue sarcoma is a group of malignant tumors originating from connective tissues such as mucus, fiber, fat, smooth muscle, synovium, striated muscle, mesothelium, blood vessels, and lymphatic vessels, including nerve tissue tumors originating in neuroectoderm, but does not include those originate from bone, cartilage, and lymphoid hematopoietic tissue. The incidence of soft tissue sarcoma is approximately 1.28-1.72/100,000 (approximately 17,600-23,700), accounting for 0.73-0.81% of malignant tumors in adults and 6.5% of malignant tumors in children under 15 years old. The incidence is higher in men than women[1-2]. Soft tissue sarcoma is classified into several pathological types. The World Health Organization (WHO) classifies the disease into more than 50 subtypes. Common subtypes include liposarcoma, leiomyosarcoma, angiosarcoma, synovial sarcoma, fibrosarcoma, pleomorphic undifferentiated sarcoma, and malignant schwannoma[3]. Soft tissue sarcoma can occur in almost any part of the body, 50-60% of which occurs in the limbs; at least 80% are potentially malignant, of which 50% are prone to distant metastasis, and 50% are prone to local recurrence[4]. The most common metastatic site of limb sarcoma is the lungs, while retroperitoneal and gastrointestinal sarcomas most often metastasize to the liver. If metastasis occurs, the 5-year survival period is still less than 10% despite active treatment [5]. At present, the systemic treatment of non-specific soft tissue sarcoma is mainly based on anthracycline and ifosfamide chemotherapy. The median progression free survival period is approximately 4.5 months. Alveolar soft tissue sarcoma, well-differentiated liposarcoma/atypical lipomatous tumor, clear cell sarcoma, and other subtypes are generally considered poorly sensitive to chemotherapy[6].

In recent years, with the continuous deepening of research, targeted therapy and immunotherapy have exhibited impressive efficacy in the treatment of many types of malignant tumors. In soft tissue sarcoma, targeted therapy has also shown satisfactory efficacy and has been included in the diagnosis and treatment guidelines. For example, the NCCN guidelines recommend pazopanib for the treatment of non-specific soft tissue sarcoma after the failure of previous chemotherapy, as well as imatinib, sunitinib, and regorafenib for the alternative treatment of gastrointestinal stromal tumors. However, there is still a lack of high-grade evidence-based clinical drugs for some soft tissue sarcomas (such as alveolar soft tissue sarcoma). Therefore, it is of great clinical significance to explore effective therapeutic drugs.

This study is a clinical study on the inhibitor targeting the VEGF-VEGFR pathway combined with anti-PD-1 monoclonal antibody for the treatment of advanced soft tissue sarcoma. The goal is to lay a solid foundation for new combination therapies urgently needed in clinical practice. The present study has important clinical and academic significance.

5.1.2 Introduction to SHR-1210

PD-1 is a protein receptor expressed on the surface of T cells and is involved in the apoptosis process. PD-1 is a member of the CD28 family and has a 23% consistency in amino acid sequence with cytotoxic T lymphocyte antigen 4 (CTLA-4). However, different from CTLA-4, it is primarily expressed on activated T cells, B cells, and myeloid cells. PD-1 has two ligands, PD-L1 and PD-L2. PD-L1 is primarily expressed on T cells, B cells, macrophages, and dendritic cells (DCs), and is up-regulated on activated cells. In contrast, the expression of PD-L2 is mainly restricted to antigen presenting cells, such as activated macrophages and DCs. Humanized anti-PD-1 mAb can specifically bind to PD-1, blocking the interaction between PD-1 and its ligands, and restore T cell immune response against tumor cells.

This study involves recombinant humanized anti-programmed death-l (anti-PD-1) monoclonal antibody injection (SHR-1210), a new class 1 therapeutic biological product developed by Jiangsu Hengrui Pharmaceuticals Co., Ltd. that has not been marketed either in China or abroad. Preclinical studies have shown that SHR-1210 has comparable *in vivo* pharmacological and safety profiles to those of drugs of the same class abroad, and may have a better clinical potential for anti-tumor treatment.

Studies on the binding affinity of SHR-1210 antibody to human, monkey and rat antigens (Table 1) showed that the affinities of SHR-1210 to human and monkey PD1 antigens were quite close, being 6.9 nM and 4.1 nM, respectively, but no binding was detected with rat PD-1 antigens. In another study, the affinity of SHR-1210 for the antigen (human PD-1) was 3.0 nM, which was comparable to those of control antibodies nivolumab and pembrolizumab (Table 2).

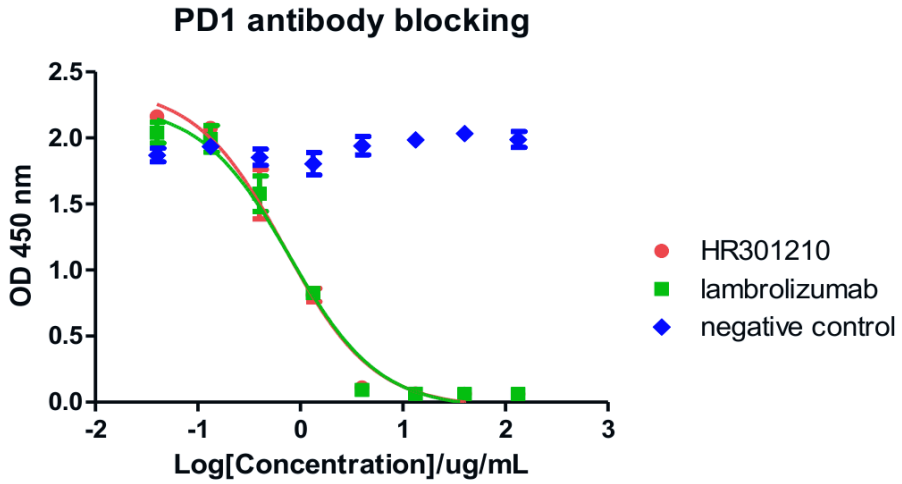
Table 1. Binding affinity of SHR-1210 to human, monkey, and rat PD-1 antigens

Stationary Phase	Mobile Phase	Affinity (nM)
SHR-1210	Human PD-1 antigen	6.9
SHR-1210	Murine PD-1 antigen	Extremely weak signals, no binding detected
Monkey PD-1 antigen (-hFc)	SHR-1210	4.1

Table 2. Inhibition of PD-1/PD-L1 binding by SHR-1210

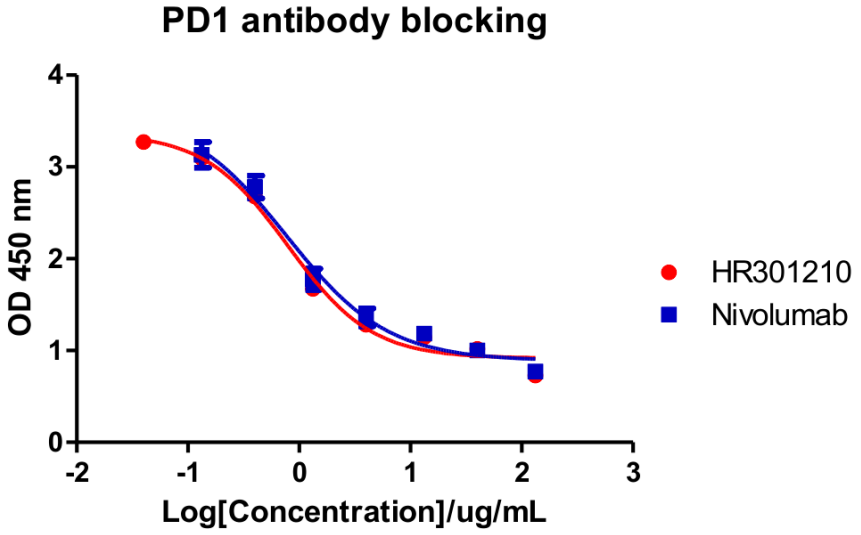
Antibody	Antigen	Affinity (nM)
SHR-1210	Human PD-1 antigen	3.0
Nivolumab	Human PD-1 antigen	4.0
Pembrolizumab	Human PD-1 antigen	3.2

Experimental results from inhibition of PD-1/PD-L1 binding by SHR-1210 showed that (Figure 1 and Figure 2) *in vitro* binding inhibition activity of SHR-1210 was similar to those of nivolumab and pembrolizumab, with IC_{50} being 0.70 nM/0.79 nM and 0.79 nM/0.77 nM, respectively.



	HR301210	lambrolizumab
IC50	0.7007	0.7864

Figure 1. Inhibition of PD-1/PD-L1 binding by SHR-1210 and pembrolizumab



	HR301210	Nivolumab
IC50	0.7913	0.7745

Figure 2. Inhibition of PD-1/PD-L1 binding by SHR-1210 and nivolumab

Since 2015, Jiangsu Hengrui Pharmaceuticals Co., Ltd. has initiated 15 clinical studies of SHR-1210 at multiple centers in Australia and China, which preliminarily validated the safety, tolerability, and efficacy of SHR-1210 in patients with advanced solid tumors. As of 25 Aug., 2017, 624 subjects had received SHR-1210 treatment.

Four phase I clinical studies showed that different doses of SHR-1210 (1 mg/kg, 3 mg/kg, 6 mg/kg, 10 mg/kg and fixed doses of 60 mg, 200 mg, and 600 mg) were well tolerated. No DLT was observed in any of the dose groups during the tolerability observation period, i.e., the maximum tolerated dose (MTD) was greater than 10 mg/kg or 600 mg (refer to the IB for the pharmacokinetics data).

5.1.3 Introduction to apatinib

Apatinib is a highly effective and selective inhibitor of VEGFR-2. The activity assay showed that its inhibitory effect against VEGFR-2 is stronger than that of drugs of same class (sorafenib, sunitinib, pazopanib, etc.); its selectivity for VEGFR-2 is ≥ 30 times stronger than that of other targets (VEGFR-1/PDGFR, SRC, etc.). Apatinib can effectively inhibit the *in vitro* lumen formation of Human Umbilical Vein Endothelial Cells (HUVEC) and the formation of arterial ring capillaries in rats, and has a strong inhibitory effect against neovascularization.

The efficacy and safety of apatinib in the treatment of advanced gastric cancer were evaluated in a multicenter, randomized, double-blind, placebo-controlled phase III clinical study. A total of 267 subjects with advanced gastric cancer, including gastroesophageal junction adenocarcinoma, who had failed second-line therapy (definition of treatment failure: intolerable toxic and side effects, progressive disease during treatment, or recurrence after the end of treatment) were enrolled in the study. The median age of subjects treated with apatinib was 58 years old, and 75% were male; 27% had an ECOG PS of 0 and 73% had an ECOG PS of 1; about 60% of the subjects had once received radical surgery, including about 22% with total gastrectomy and 35% with gastrectomy; 68% of the primary lesions were GC, and 22% were GEJ adenocarcinoma; 21% of the subjects had more than 2 organs affected by metastases cumulatively, and 56% of the subjects had liver metastases; 92% of the subjects were clinically classified as stage IV; 66% of the subjects had once received at least 2 types of systemic chemotherapy; the basic drugs used in first-line chemotherapy included fluorouracil, platinum, paclitaxel, and doxorubicin; the second-line chemotherapy is primarily based on irinotecan. The investigational treatment group and the placebo group were comparable in baseline features and demographics of subjects. The subjects were randomized in a 2:1 ratio to receive either apatinib tablet 850 mg once daily (n = 176) or placebo once daily (n = 91) in 28-day cycles. The mean chemotherapy cycles were 2.9 in the investigational treatment group, with 72% of the subjects receiving 2 or more cycles of treatment.

The primary efficacy endpoint was overall survival (OS). The secondary efficacy endpoints included progression free survival (PFS), disease control rate (DCR), and objective response rate (ORR). The median overall survival in the investigational treatment group was prolonged compared with the placebo group, while the death risk was reduced by about 30%. The secondary endpoints PFS and DCR were also higher in the treatment group than those in the placebo group. Generally, no symptoms specific to advanced GC or deterioration of health-related life quality were caused. In the investigational treatment group and the placebo group, the incidences of adverse drug reactions were 92.05% and 71.43%, respectively; the incidences of Grade 3/4 adverse drug reactions were 51.70% and 24.18%, respectively. Among the common adverse drug reactions (incidence ≥ 5%), the ones that were statistically different between the two groups in incidence included hematologic toxicities (WBC decreased, granulocytopenia, and platelets decreased) and non-hematologic toxicities (proteinuria, hypertension, hand-and-foot syndrome, asthenia, and hoarse voice). The incidences of serious adverse drug reactions in the investigational treatment group and the control group were 6.25% and 6.59%, respectively. The common serious adverse drug reaction was upper gastrointestinal hemorrhage in both groups.

Based on the phase III study, in Oct. 2014, apatinib was approved for treating patients with refractory or recurrent advanced gastric adenocarcinoma or gastroesophageal junction adenocarcinoma who had been treated with at least 2 systemic chemotherapies, with the requirement that patients undergoing the treatment must be in good general conditions.

5.1.4 Progress in the clinical studies of SHR-1210 plus apatinib

As of Jun. 2018, 7 clinical studies on SHR-1210 combined with apatinib are in progress, involving three dose groups of SHR-1210 combined with apatinib, i.e., 250 mg, 375 mg, and 500 mg. More than 200 subjects in the 7 studies received SHR-1210 combined with apatinib.

5.2 Scientific Rationale

Tumor immune escape is a great challenge in cancer immunotherapy. Cancer cells' suppressive effect on the immune system promotes uncontrolled tumor growth. There is an extremely complex relationship between the immune escape mechanism of tumors and the body's immune response. Specific killer T cells have certain biological activities in the early stage of the cancer development, but they lose their cytotoxicity in the late stage of tumor growth. Cancer immunotherapy aims to maximize a patient's own immune response against the tumor. It not only activates the original immune response in the body, but also maintains the duration and intensity of the immune responses, which is the key to the cancer immunotherapy.

Although the anti-PD-1 antibody monotherapy has achieved obvious efficacy in some tumor types, it is one of the main study directions at this moment as how to further enhance the anti-tumor efficacy of anti-PD-1 antibody monotherapy by using other drugs in combination. Related study results showed that the VEGF-VEGFR pathway may have a huge impact on the immune response of tumor patients. VEGFA expressed by tumor cells can inhibit DC cell maturation, induce PD-L1 expression, up-regulate T_{reg} cells, inhibit the differentiation of hematopoietic precursor cells, and cause immunosuppression. While, in a mouse model of intestinal carcinoma, apatinib significantly regulated the environment of tumor immune response (such as by down-regulating T_{reg} cells), thereby up-regulating the immune response and further enhancing the anti-tumor efficacy of SHR-1210 (Table 3).

Table 3. Anti-tumor and immunomodulatory effects of SHR-1210 and apatinib in a mouse model of intestinal carcinoma

Group	Administration	Average Tumor Volume (mm^3) D21	Tumor Growth Inhibition (%) D21	$CD8^+$ in $CD3^+$ (%)	$CD4^+$ in $CD3^+$ (%)	Treg in $CD4^+$ (%)	$CD8^+$: Treg
Vehicle	Q2D × 8/QD × 21	1467.7 ± 218.2	----	38.7	39.3	5.5	22.1
Apatinib 100 mg/kg	QD × 21	539.1 ± 126.4	63.3*	40.8	43.5	0.5	189.5
SHR-1210 3 mg/kg	Q2D × 8	917.0 ± 204.0	37.5	37.2	33.9	0.4	409.9
SHR-1210 3 mg/kg + Apatinib 100 mg/kg	Q2D × 8/QD × 21	186.2 ± 90.5	87.3	41.4	35.4	0.4	565.1

In fact, VEGFR inhibitors combined with PD-1/PD-L1 antibodies have also achieved many successes in clinical studies. "Avelumab (anti-PD-L1 antibody) + axitinib (axitinib) in the first-line treatment of advanced renal cell carcinoma" and "pembrolizumab (anti-PD-1 antibody) + lenvatinib in the first-line treatment of advanced renal cell carcinoma" obtained FDA designation of breakthrough therapy in Dec. 2017 and Jan. 2018, respectively. In addition, "pembrolizumab (anti-PD-1 antibody) + axitinib (axitinib) vs. sunitinib in the first-line treatment of advanced renal cell carcinoma (KEYNOTE-426 study)", "atezolizumab (PD-L1 card antibody) + PC (paclitaxel + carboplatin) ±Bev (bevacizumab) vs. PC (paclitaxel + carboplatin) + Bev (bevacizumab) in the first-line treatment of NSCLC (IMPOWER150 study)" also proved the advantages of combination therapy.

Based on the above evidence and the current treatment status of soft tissue sarcoma, VEGFR inhibitor SHR-1210 combined with apatinib may also exert considerable synergistic effect in the treatment of soft tissue sarcoma, providing a novel and effective non-chemotherapy treatment for patients with soft tissue sarcoma.

5.3 Potential Risks and Benefits

Any investigational drug or treatment may have unpredictable or even serious side effects.

Among the 258 subjects, 256 subjects (99.2%) experienced at least one treatment-related adverse event. Treatment-related AEs with an incidence ≥ 10% mainly included: skin and subcutaneous tissue disorders: cutaneous capillary endothelial proliferation (81.8%), pruritus (22.1%), rash (16.3%); systemic symptoms: asthenia (37.6%), fever (20.9%); investigations: aspartate aminotransferase increased (21.7%), alanine aminotransferase increased (18.6%), conjugated bilirubin increased (16.7%), white blood cell count decreased (14.7%), serum natrium decreased (14.3%), blood bilirubin increased (12.0%); gastrointestinal disorders: diarrhea (11.2%), nausea (10.5%); respiratory, thoracic, and mediastinal disorders: cough (19.0%); metabolism and nutrition disorders: hypoproteinemia (19.4%); blood and lymphatic system disorders: anemia (27.5%); kidney and urinary tract disorders: proteinuria (22.1%); infection and infestations: upper respiratory tract infection (10.1%); endocrine disorders: hypothyroidism (19.8%).

Investigator-assessed immune-mediated AEs were predominantly skin toxicities (such as rash and capillary proliferation). Most immune-mediated AEs were grade 1-2 in severity. The above data was compared with adverse drug reactions reported for other approved anti-PD-1 antibodies - nivolumab from BMS and pembrolizumab from Merck. The incidence and severity were both low. Overall, the adverse drug reactions of this product are expected to be similar to those of nivolumab and pembrolizumab. Recommended management of common side effects and protocol-specified dose modifications have been established for this study, so that, in the presence of clinical benefit, subjects may continue the SHR-1210 treatment.

All monotherapies using anti-PD-1 antibodies outperformed conventional chemotherapy and targeted therapy in terms of adverse drug reactions on the whole. However, immune-related adverse drug reactions still require special attention, mainly including immune-related interstitial pneumonia, rash, thyroiditis, as well as those with lower incidence (≤ 1%), such as vitiligo, colitis, nephritis, hepatitis, uveitis, adrenal insufficiency, and nerve paralysis. These immune-related adverse drug reactions are mostly mild and manageable. Very few are SAEs or potentially life-threatening. Thanks to established procedures for toxicity management, the majority of immune-mediated AEs can be adequately controlled.

Subjects receiving macromolecular protein monoclonal antibody drugs may also encounter other risks including infusion reactions, which prominently manifest as chilliness, shivers, facial and peripheral cyanosis, followed by fever and probably accompanied by nausea, vomiting, headache, dizziness, dysphoria, delirium, etc. In severe cases, there may be coma, fall in blood pressure, and symptoms such as shock and respiratory failure, etc. These risks may arise due to various factors during intravenous infusion, such as pyrogens, drugs, impurities, low temperature of drug formulation, high concentration of drug, and high rate of infusion, etc. SHR-1210 is a fully humanized monoclonal antibody. Its reported infusion reactions were low in incidence and mild in severity.

Refer to the latest version of the investigator's brochure for the updates of new adverse events of SHR-1210.

Doxorubicin and ifosfamide are common cytotoxic chemotherapy drugs. Apatinib is a marketed anti-angiogenic drug. Their adverse events have been well understood. Refer to the package insert for details.

As mentioned earlier, soft tissue sarcoma is a common malignant tumor, seriously threatening human health and lives. Many patients with soft tissue sarcoma have already missed the optimal surgical timing at the time of diagnosis. They usually have poor life quality and heavy disease burden. Despite an active combination chemotherapy, the median survival of patients with these soft tissue sarcomas is only about 1 year. It is expected that subjects with soft tissue sarcoma may benefit from the combination therapy of PD-1 inhibitor and apatinib, may gain prolonged survival, but they also may not benefit.

6 OBJECTIVES AND ENDPOINTS

6.1 Study Objectives

6.1.1 Primary objective

- To evaluate whether SHR-1210 combined with apatinib is better than doxorubicin combined with ifosfamide in the treatment of soft tissue sarcoma based on the progression free survival (PFS).

6.1.2 Secondary objectives

- To evaluate and compare the overall survival (OS), objective response rate (ORR), duration of response (DoR), and disease control rate (DCR) in subjects with soft tissue sarcoma after treatment with SHR-1210 combined with apatinib vs. doxorubicin combined with ifosfamide;
- To evaluate and compare the safety of SHR-1210 combined with apatinib vs. doxorubicin combined with ifosfamide in the treatment of soft tissue sarcoma;
- To evaluate and compare the quality of life scores in subjects with soft tissue sarcoma after treatment with SHR-1210 combined with apatinib vs. doxorubicin combined with ifosfamide.

6.1.3 Exploratory objectives

- To explore the correlation between the immunogenicity and the efficacy/safety of SHR-1210;
- To explore the correlation between the concentrations of SHR-1210 and apatinib and the efficacy/safety;
- To evaluate the investigator-assessed PFS, ORR, DoR and DCR (as per iRECIST) in the SHR-1210 plus apatinib group;
- PFS after crossover treatment of subjects in the doxorubicin plus ifosfamide group (as per RECIST v1.1 and iRECIST);
- To evaluate the ORR, DoR, and DCR (as per RECIST v1.1 and iRECIST), OS, safety, and quality of life scores of subjects in the doxorubicin plus ifosfamide group after crossover treatment.

6.2 Study Endpoints

6.2.1 Primary endpoints

- PFS assessed by the independent review committee (as per RECIST v1.1)

6.2.2 Secondary endpoints

- PFS assessed by the investigator (as per RECIST v1.1)
- OS
- ORR assessed by the investigator and independent review committee (as per RECIST v1.1)
- DoR assessed by the investigator and independent review committee (as per RECIST v1.1)
- DCR assessed by the investigator and independent review committee (as per RECIST v1.1)
- Incidence and severity of AEs and SAEs, vital signs, ECG, and laboratory abnormalities.
- Quality of life score (EORTC QLQ-C30)

6.2.3 Exploratory endpoints

- Anti-drug antibody and neutralizing antibody levels of SHR-1210
- Serum concentration of SHR-1210 and plasma concentration of apatinib
- Investigator-assessed PFS, ORR, DoR, and DCR (as per iRECIST) of the investigational treatment group;
- PFS of subjects in the doxorubicin plus ifosfamide group after crossover treatment (as per RECIST v1.1 and iRECIST)
- ORR, DoR, DCR (as per RECIST v1.1 and iRECIST), OS, safety, and quality of life scores of subjects in the doxorubicin plus ifosfamide group after crossover treatment

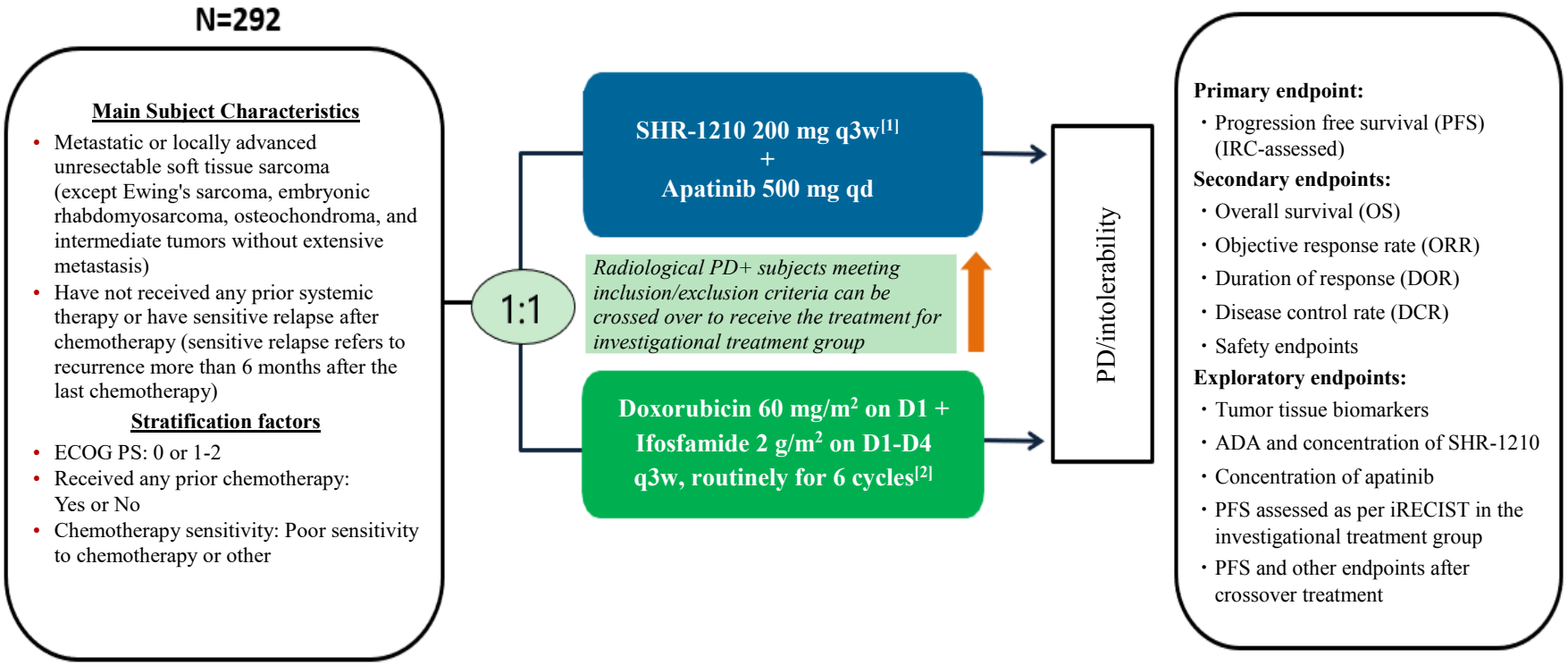
7 STUDY DESIGN

7.1 Overview of Study Design

This study is a multicenter, randomized, open-label phase II clinical study, with a total of 292 subjects planned to be enrolled.

Qualified subjects with soft tissue sarcoma will be randomized in a 1:1 ratio into the SHR-1210 + apatinib group (investigational treatment group) and the doxorubicin + ifosfamide/ifosfamide monotherapy group (control group). Stratification factors include: 1) ECOG PS, 0 vs. 1-2; 2) Whether the pathological type of the tumor had poor sensitivity to chemotherapy (see Appendix 2. Common Types of Soft Tissue Sarcoma with Poor Chemotherapy Sensitivity); 3) Whether subjects have previously undergone chemotherapy. The administration regimens for investigational treatment group and control group are as follows:

- Investigational treatment group: SHR-1210 200 mg q3w (up to 2 years of treatment) + apatinib 500 mg qd.
- Control group: doxorubicin 60 mg/m^2 on D1 + ifosfamide 2 g/m^2/d on D4, in 3-week cycles (i.e., the total dose per cycle shall be 8 g/m^2), 6 cycles are recommended. If the investigator judges that the subject benefits from doxorubicin + ifosfamide chemotherapy, additional chemotherapy cycles may be administered. When the subject's anthracyclines have reached the recommended maximum cumulative dose of doxorubicin (see Appendix 3. Dose Conversion Table for Anthracycline), the chemotherapy regimen should be adjusted to ifosfamide monotherapy, 2 g/m^2/d on D1-D5, in 3-week cycles (i.e., the total dose per cycle shall be 10 g/m^2). Again, if the investigator judges that the subject benefits from ifosfamide chemotherapy, additional chemotherapy cycles may be administered.



1. The treatment duration of SHR-1210 should be no more than 2 years; interruption of one drug does not require the interruption of the other; 2. If anthracycline 450 mg/m^2 is used for the control group, the chemotherapy regimen will be adjusted to ifosfamide monotherapy, 2 g/m^2 on D1-D5, q3w; more than 6 chemotherapy cycles may be administered.

In this study, the screening period should be no more than 28 days. After completing screening examinations and assessments, eligible subjects will enter the treatment period and receive the study treatment and study visits according to the protocol. Among them, tumor imaging assessment will be performed once in every 2 cycles during the first 16 cycles and once every 4 cycles thereafter. The independent review committee (IRC) will review the imaging evaluation results of each study center. The safety follow-up period of subjects in the investigational treatment group starts after the last dose, and the subjects will be followed up once every 30 days until 90 days after the last dose. Among them, the first safety follow-up will be carried out at the study center; the second and the third follow-up visits will be made via phone calls. For subjects in the control group, if they do not receive SHR-1210 + apatinib treatment, their safety follow-up period will be 21 days after the last dose; otherwise, the same arrangement as that in the investigational treatment group will be used. The survival follow-up period will start after the end of the safety follow-up period. The survival follow-up period will end upon the subject's death, lost to follow-up, withdrawal of informed consent, or study termination by the sponsor. During this period, a follow-up shall be conducted every 2 months via phone calls or other effective methods to collect information on subject survival and subsequent anti-tumor treatment.

8 SELECTION AND WITHDRAWAL OF SUBJECTS

The enrollment of eligible subjects is critical to ensure the outcome of the study. Subjects must meet the following criteria to be allowed to participate in this study. Any medical or non-medical conditions of a subject are considered for his/her eligibility.

Before the subject's enrollment in the study, the investigator should review, confirm, and document whether the subject is suitable for participating in the study.

8.1 Inclusion Criteria

Patients must meet all of the following criteria to be eligible.

1. Aged 16-70 years, male or female.
2. With an Eastern Cooperative Oncology Group (ECOG) PS of 0-1. The criterion can be relaxed to 2 points for amputation subjects.
3. Life expectancy of ≥ 3 months.
4. Patients with distant metastasis or locally advanced soft tissue sarcoma that render the patient not suitable for surgical treatment as per the investigator's judgment (pathologically or cytologically diagnosed, except gastrointestinal stromal tumors, osteochondroma, embryonic/acinar rhabdomyosarcoma, Ewing's sarcoma, and intermediate soft tissue tumors without extensive metastasis, such as dermatofibrosarcoma protuberans and inflammatory myofibroblastic sarcoma, see Appendix 1. The WHO Soft Tissue Tumor Classification (2013 Edition) for details).

5. Patients who have not received previous chemotherapy for soft tissue sarcoma, or have benefited from chemotherapy but have recurrence or metastasis more than 6 months after drug discontinuation.
6. With measurable lesion(s) as per RECIST v1.1.
7. All acute toxicities due to previous anti-tumor treatments or surgeries must have resolved to Grade 0-1 (as per NCI CTCAE 4.03) or to the level specified in the inclusion/exclusion criteria before C1D1 (except for toxicities such as alopecia that are deemed by the investigator as not posing safety risks to the patient).
8. With adequate organs and bone marrow functions, as defined below:

   Hematology (without blood transfusion, G-CSF, or medication correction within 14 days prior to screening)

   - Absolute neutrophil count (ANC) ≥ 1500/mm^3 (1.5 × 10^9/L);
   - Blood platelet count (PLT) ≥ 100,000/mm^3 (100 × 10^9/L);
   - Hemoglobin (Hb) ≥ 9 g/dL (90 g/L);

Blood Biochemistry

- Serum creatinine (Cr) ≤ 1.5 × upper limit of normal (ULN), or creatinine clearance (Cockroft-Gault formula) ≥ 60 mL/min;
- Total bilirubin (TBIL) ≤ 1.5 × ULN;
- Aspartate transaminase (AST) or alanine transaminase (ALT) ≤ 2.5 × ULN; for patients with liver metastasis, ALT and AST should be ≤ 5 × ULN;

Coagulation Function

- International normalized ratio (INR) ≤ 1.5, prothrombin time (PT) and activated partial thromboplastin time (APTT) ≤ 1.5 × ULN;

Urinalysis

- Urine protein < 2+; If urine protein is ≥ 2+, then the 24-hour urine protein must be ≤ 1 g;

Thyroid function

- Thyroid-stimulating hormone (TSH) ≤ ULN; if abnormal, FT3 (T3) and FT4 (T4) levels should be examined, and the subject can be enrolled if FT3 (T3) and FT4 (T4) levels are normal.

9. Female subjects of childbearing potential must have a negative serum pregnancy test within 7 days prior to C1D1, and be willing to use a recognized effective contraceptive measure (such as: intra-uterine contraceptive devices, contraceptive pills, or condoms) during the study and within 3 months after the last dose of the study drug; male subjects with partners of childbearing potential must either be surgically sterilized or agree to take effective contraceptive measures during the study and within 3 months after the last dose of the study drug.
10. Subjects must agree and have signed the informed consent form, be willing and able to follow the scheduled visits, study treatment, laboratory tests, and other study procedures.

8.2 Exclusion Criteria

Patients meeting any one of the followings are not eligible to participate in this study:

1. Those who have received the following treatments within 4 weeks prior to C1D1:
    - Previously received radiotherapy, surgery, chemotherapy, immune or molecular targeted therapy for tumors;
- Received other investigational drug of clinical studies;
    - Inoculated with a live attenuated vaccine.
2. Subjects who previously received anti-PD-1/PD-L1/CTLA4 antibodies, or VEGFR single target/multiple target inhibitors.
3. Those who plan to receive surgical treatment and/or radiation therapy for soft tissue sarcoma during the study period.
4. Presence of tumor lesions in the central nervous system confirmed by imaging diagnosis.
5. Having been treated by immunosuppressive drugs within 14 days prior to C1D1, excluding intranasal and inhaled corticosteroids or systemic steroids of physiological doses (i.e., no more than 10 mg/d of prednisolone or equivalent physiological doses of other corticosteroids).
6. Presence of any active autoimmune diseases or a history of autoimmune diseases (including but not limited to: autoimmune hepatitis, interstitial pneumonia, uveitis, enteritis, hepatitis, hypophysitis, vasculitis, nephritis, hyperthyroidism, hypothyroidism; adult patient with vitiligo or completely relieved childhood asthma may be enrolled if they do not require any intervention), or known history of allogeneic organ transplantation or allogeneic hematopoietic stem cell transplantation.

7. Complicated with severe infection (such as one requiring intravenous drip infusion of antibiotics, antifungals, or antivirals) within 4 weeks prior to C1D1, or any unexplained fever of > 38.5 ℃ during screening/prior to the first dose.
8. Hypertension uncontrolled by antihypertensives (systolic pressure > 140 mmHg or diastolic pressure > 90 mmHg).
9. Patients with clinically significant bleeding symptoms or a clear bleeding tendency within 3 months prior to C1D1, such as hemorrhage of digestive tract, stomach ulcer with hemorrhage, fecal occult blood ++ and above at baseline, or vasculitis; or arterial/venous thrombus events, such as cerebrovascular accidents (including transient ischemic attack, cerebral hemorrhage, and cerebral infarction), deep vein thrombus, pulmonary embolism, etc. within 6 months before C1D1; or requiring long-term anticoagulation therapy with warfarin or heparin, or requiring long-term antiplatelet therapy (aspirin ≥ 300 mg/d or clopidogrel ≥ 75 mg/d).
10. Active heart diseases within 6 months before C1D1, including myocardial infarction, severe/unstable angina, etc. Left ventricular ejection fraction < 50% as revealed by echocardiography and poorly controlled arrhythmia (including QTcF interval > 450 ms in males and > 470 ms in females).
11. Having been diagnosed with any other malignancies within 3 years before C1D1, excluding adequately treated basal cell carcinoma and squamous cell skin cancer, and cervical carcinoma in situ.
12. Known allergies to the study drug or their excipients; severe allergic reactions to other monoclonal antibodies.
13. With human immunodeficiency virus (HIV) infection, or active hepatitis B (positive hepatitis B surface antigen and HBV DNA ≥ 500 IU/mL) or hepatitis C (positive for hepatitis C antibody, and HCV-RNA higher than the lower limit of detection of the analytical method).
14. Presence of accompanying diseases (such as poorly controlled hypertension, severe diabetes, neurological or mental illness, etc.) or any other situation that may pose serious risks to the safety of the subjects, confuse the research results, or affect the ability of the subjects to complete the study as judged by the investigator.

8.3 Withdrawal from Study or Treatment Discontinuation

8.3.1 Study withdrawal criteria

Reasons for withdrawal may include:

- Withdrawal of informed consent and refusal of further follow-ups by subjects;
- Other investigator-assessed reasons requiring withdrawal, such as the inability to provide voluntary consent due to imprisonment or quarantine;
- Lost to follow-up;
- Death;
- Study termination by the sponsor.

8.3.2 Criteria for treatment discontinuation

The study treatment must be discontinued when any of the following occurs:

1. Treatment discontinuation requested by subjects;
2. Radiographic (assessed by the investigator as per RECIST v1.1) or clinical progression, except for the following two situations: 1) The subjects in the investigational treatment group meet the criteria for continuing treatment beyond progression (see 8.3.3 for details); 2) The subject in the control group who had radiographic progression and meet the inclusion/exclusion criteria may be crossed over to receive the SHR-1210 + apatinib treatment (see 8.3.4 for details);
3. Occurrence of subject pregnancy during the study;
4. Any clinical AEs, laboratory abnormalities, or other medical conditions indicating that the subject can no longer benefit from the treatment;
5. General deterioration of health status and inability to continue study participation;
6. Major protocol deviations such as ineligibility found after enrollment;
7. Lost to follow-up;
8. Study termination by the sponsor.
9. Death;
10. Other reasons as determined by the investigator.

8.3.3 Criteria for continuing treatment beyond progression (investigational treatment group)

Some subjects receiving immunotherapy or anti-angiogenesis therapy can still benefit from continuing treatment after radiographic progression. The tumor of some subjects may be enlarged, but remarkable necrosis, denaturation, or infiltration of immune cells may occur inside the tumor, with CT showing decreased internal density of the tumor lesion. It is generally considered to be beneficial to subjects under this circumstance. A subject meeting the following criteria may continue the treatment after progressive disease (PD, as per the investigator's judgment) based on RECIST v1.1:

- The investigator deems that it is in the best interest of the subject to continue treatment, and subject is not required to start other anti-tumor treatment immediately;
- The subject is able to tolerate continued study treatment;
- No obvious deterioration in subject's performance status, and no marked worsening of cancer-related symptoms;
- Subjects must sign the informed consent form prior to continuing study treatment, in which potential risks, discomforts, and other treatment options shall be included;
- Continued study treatment must be reviewed and approved by the principal investigator of the study center.

The assessment of clinical benefit must consider whether the subject has clinical exacerbations and whether the subject can benefit from continuing treatment. It is recommended that the investigator should discuss with the sponsor whether the subject should continue treatment beyond progression.

If it is decided that the subject will continue the study treatment after progression, the subject should continue to be treated and followed up according to the protocol requirements. Investigators at the study center will perform subsequent imaging evaluations as per iRECIST (see Appendix 11) (independent imaging evaluations will still be performed as per RECIST v1.1).

Subjects should withdraw from the study if the subject has iRECIST-confirmed PD (iCPD) in the subsequent tumor evaluation. The initial date of investigator-assessed progression should be used for the statistical analysis of PFS in secondary endpoints, regardless of whether the subject continues the study treatment beyond progression.

If the subject discontinues treatment due to deterioration of the general condition without objective evidence for progressive disease, the progression will be reported as "general deterioration". More objective evidences (e.g., imaging confirmation) of progressive disease of these subjects should be obtained whenever possible after treatment discontinuation.

8.3.4 Criteria for crossover treatment of subjects in control group after radiographic progression

In a subject in the control group is found to have PD during or after chemotherapy, the safety visit will be conducted. After completing relevant examinations, subjects who are willing to and eligible for crossover treatment may be crossed over to receive the treatment of SHR-1210 combined with apatinib.

If the inclusion and exclusion criteria are not met, the subject may receive supportive treatment for adjustment. But during this period, anti-tumor treatment must not be performed. If, at the reexamination 2 months after progressive disease, the inclusion and exclusion criteria are still not met, crossover to receive SHR-1210 combined with apatinib will not be permitted.

For the schedule of activities for the crossover treatment period and subsequent follow-ups of the control group, please refer to "3. Schedule of activities - crossover treatment" for details.

8.3.4.1 Inclusion criteria for crossover treatment

1. With an Eastern Cooperative Oncology Group (ECOG) PS of 0-1. The criterion can be relaxed to 2 points for amputation subjects.
2. Life expectancy of ≥ 3 months.
3. All acute toxicities due to previous anti-tumor treatments or surgeries must have resolved to Grade 0-1 (as per NCI CTCAE 4.03) or to the level specified in the inclusion/exclusion criteria before C1D1 (except for toxicities such as alopecia that are deemed by the investigator as not posing safety risks to the patient).
4. With adequate organs and bone marrow functions, as defined below:

Hematology: (without blood transfusion within 14 days prior to screening, or G-CSF or other medication within 7 days prior to screening)

- Absolute neutrophil count (ANC) ≥ 1500/mm^3 (1.5 × 10^9/L);
- Blood platelet count (PLT) ≥ 100,000/mm^3 (100 × 10^9/L);
- Hemoglobin (Hb) ≥ 9 g/dL (90 g/L);

Blood Biochemistry

- Serum creatinine (Cr) ≤ 1.5 × upper limit of normal (ULN), or creatinine clearance (Cockroft-Gault formula) ≥ 60 mL/min;
- Total bilirubin (TBIL) ≤ 1.5 × ULN;
- Aspartate transaminase (AST) or alanine transaminase (ALT) ≤ 2.5 × ULN; for patients with liver metastasis, ALT and AST should be ≤ 5 × ULN;

Coagulation Function

- International normalized ratio (INR) ≤ 1.5, prothrombin time (PT) and activated partial thromboplastin time (APTT) ≤ 1.5 × ULN;

Urinalysis

- Urine protein < 2+; If urine protein is ≥ 2+, then the 24-hour urine protein must be ≤ 1 g;

Thyroid function

- Thyroid-stimulating hormone (TSH) ≤ ULN; if abnormal, FT3 (T3) and FT4 (T4) levels should be examined, and the subject can be enrolled if FT3 (T3) and FT4 (T4) levels are normal.

5. Female subjects of childbearing potential must have a negative serum pregnancy test within 7 days prior to C1D1, and be willing to use a recognized effective contraceptive measure (such as: intra-uterine contraceptive devices, contraceptive pills, or condoms) during the study and within 3 months after the last dose of the study drug; male subjects with partners of childbearing potential must either be surgically sterilized or agree to take effective contraceptive measures during the study and within 3 months after the last dose of the study drug.
6. Subjects must agree and have signed the informed consent form, be willing and able to follow the scheduled visits, study treatment, laboratory tests, and other study procedures.

8.3.4.2 Exclusion criteria for crossover treatment

1. Those who have received the following treatments within 4 weeks prior to C1D1:
    - Previously received radiotherapy, surgery, immune or molecular targeted therapy for tumors;
- Received other investigational drug of clinical studies;
    - Inoculated with a live attenuated vaccine.
2. Those who have received the following treatments within 3 weeks prior to C1D1:
3. Subjects who previously received anti-PD-1/PD-L1/CTLA4 antibodies, or VEGFR single target/multiple target inhibitors.
4. Those who plan to receive surgical treatment and/or radiation therapy for soft tissue sarcoma during the study period.
5. Presence of tumor lesions in the central nervous system confirmed by imaging diagnosis.

6. Having been treated by immunosuppressive drugs within 14 days prior to C1D1, excluding intranasal and inhaled corticosteroids or systemic steroids of physiological doses (i.e., no more than 10 mg/d of prednisolone or equivalent physiological doses of other corticosteroids).
7. Presence of any active autoimmune diseases or a history of autoimmune diseases (including but not limited to: autoimmune hepatitis, interstitial pneumonia, uveitis, enteritis, hepatitis, hypophysitis, vasculitis, nephritis, hyperthyroidism, hypothyroidism; adult patient with vitiligo or completely relieved childhood asthma may be enrolled if they do not require any intervention), or known history of allogeneic organ transplantation or allogeneic hematopoietic stem cell transplantation.
8. Complicated with severe infection (such as one requiring intravenous drip infusion of antibiotics, antifungals, or antivirals) within 4 weeks prior to C1D1, or any unexplained fever of > 38.5 °C during screening/prior to the first dose.
9. Hypertension uncontrolled by antihypertensives (systolic pressure > 140 mmHg or diastolic pressure > 90 mmHg).
10. Patients with clinically significant bleeding symptoms or a clear bleeding tendency within 3 months prior to C1D1, such as hemorrhage of digestive tract, stomach ulcer with hemorrhage, fecal occult blood ++ and above at baseline, or vasculitis; or arterial/venous thrombus events, such as cerebrovascular accidents (including transient ischemic attack, cerebral hemorrhage, and cerebral infarction), deep vein thrombus, pulmonary embolism, etc. within 6 months before C1D1; or requiring long-term anticoagulation therapy with warfarin or heparin, or requiring long-term antiplatelet therapy (aspirin ≥ 300 mg/d or clopidogrel ≥ 75 mg/d).
11. Active heart diseases within 6 months before C1D1, including myocardial infarction, severe/unstable angina, etc. Left ventricular ejection fraction < 50% as revealed by echocardiography and poorly controlled arrhythmia (including QTcF interval > 450 ms in males and > 470 ms in females).
12. Having been diagnosed with any other malignancies within 3 years before C1D1, excluding adequately treated basal cell carcinoma and squamous cell skin cancer, and cervical carcinoma in situ.
13. Known allergies to the study drug or their excipients; severe allergic reactions to other monoclonal antibodies.

14. With human immunodeficiency virus (HIV) infection, or active hepatitis B (positive hepatitis B surface antigen and HBV DNA ≥ 500 IU/mL) or hepatitis C (positive for hepatitis C antibody, and HCV-RNA higher than the lower limit of detection of the analytical method).
15. Presence of accompanying diseases (such as poorly controlled hypertension, severe diabetes, neurological or mental illness, etc.) or any other situation that may pose serious risks to the safety of the subjects, confuse the research results, or affect the ability of the subjects to complete the study as judged by the investigator.

8.4 Definition of End of Study

Study completion is defined as 12 months after reaching the 214 events required for the analysis of the primary endpoint (IRC-assessed PFS) or completion of collection of all OS data.

At the end of the study, all subjects who did not progress may continue treatment with the investigational drug after a new informed consent is signed. The drugs may be provided through charity donations or other forms as determined by the sponsor.

8.5 Termination or Suspension of Study

This study can be terminated early or suspended if there are sufficient reasons. This may result from the decision of the regulatory authorities, changes in comments by the Ethics Committee, efficacy or safety issues of the study medications, or the judgment of the sponsor. In addition, Hengrui reserves the right to terminate the research and development of SHR-1210 and apatinib at any time. The party who decides to suspend/terminate the study should notify the investigator, sponsor, and regulatory authorities in writing, documenting the reasons for suspension/termination. The investigator must immediately notify the ethics committee and sponsor, and provide relevant reasons.

The reasons for termination or suspension of the study may include:

- Confirmed unexpected, major, or unacceptable risk to the subjects.
- Existing efficacy data supporting study termination.
- Poor protocol compliance.
- Incomplete or undetectable measures.
- Valueless study results.

The study may continue once that issues related to drug safety, protocol compliance, and data quality have been resolved and approved by the sponsor, ethics committee, or CFDA (now NMPA).

9 COLLECTION AND PROCESSING OF PHARMACOKINETIC AND IMMUNOGENIC BLOOD SAMPLES

9.1 Collection and Processing of Blood Samples

9.1.1 Blood sampling time

Subjects receiving the combination therapy of SHR-1210 and apatinib shall undergo blood sampling for the pharmacokinetics and immunogenicity study of SHR-1210, as well as the pharmacokinetics study of apatinib.

Pharmacokinetics/immunogenicity blood sampling time points of SHR-1210: within 0.5 h pre-administration on C1D1, C2D1, C4D1, C6D1, C9D1, and every 4 cycles thereafter, with 4-6 mL of peripheral venous blood collected at each time point. If SHR-1210 medication is interrupted at the above time points, immunogenicity blood samples of SHR-1210 shall still be collected within the time windows of the corresponding time points. At 30 days after the last dose, 4-6 mL of peripheral venous blood will also be collected.

Pharmacokinetics blood sampling time points of apatinib: within 0.5 h pre-administration and 4 h (±10 min) on C1D1, C2D1, C4D1, and C6D1, with 2 -4 mL of peripheral venous blood collected at each time point.

The time interval between the administration of apatinib on the day of blood sampling and the previous administration should be no less than 20 h. If the administration of apatinib is interrupted at the above sampling time point, there is no need to collect the blood sample related to the pharmacokinetics of apatinib.

9.1.2 Processing and storage of blood samples

Please refer to the Laboratory Manual for operation details and sample storage and transportation conditions.

9.1.3 Blood sample submission

The samples in test tubes should be sent out first in dry ice storage state. The samples in the backup tubes will be sent out after the bioanalytical laboratory confirms the receipt of the test tube samples. Details of shipping frequency and other shipping information are described in the Laboratory Manual.

10 STUDY MEDICATION

10.1 Overview of Study Drugs

10.1.1 Access to drugs

The study drugs are uniformly packaged, tested, and provided by the sponsor (see corresponding Certificate of Analysis).

10.1.2 Dosage form, packaging, and storage of study drugs

Investigational drug: SHR-1210 for injection

Manufacturer: Suzhou Suncadia Biopharmaceuticals Co., Ltd.

Dosage form: lyophilized powder.

Strength: 200 mg (proposed) in 20-mL vials.

Batch No.: see Certificate of Analysis

Route of administration: intravenous infusion.

Shelf life: 2 years (tentative) from the date of manufacture.

Storage conditions: sealed, away from light, stored at 2-8 ℃ in refrigerator. Do not freeze.

Apatinib mesylate tablets

Manufacturer: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Dosage form: tablet.

Strength: 250 mg/tablet; 375 mg/tablet

Batch No.: see Certificate of Analysis

Route of administration: oral administration after meals (best to take the two drugs at the same time each day).

Shelf life: 2 years.

Storage conditions: away from light, sealed, stored below 25℃.

Adriamycin hydrochloride for injection (doxorubicin)

Manufacturer: Hisun-Pfizer Pharmaceuticals Co., Ltd.

Dosage form: injection.

Strength: 10 mg

Batch No.: see Certificate of Analysis

Route of administration: intravenous infusion.

Shelf life: 24 months (tentative).

Storage conditions: kept away from light, sealed, in a cool condition (≤ 20 °C).

Cyclophosphamide for injection

Manufacturer: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Dosage form: injection.

Strength: 1 g; 0.5 g

Batch No.: see Certificate of Analysis

Route of administration: intravenous infusion.

Shelf life: 36 months.

Storage conditions: kept away from light, sealed, in a cool condition (2-8 ℃).

10.1.3 Storage and stability of drugs

The investigator or his/her authorized representative (e.g. pharmacist) shall ensure that all study drugs are stored in a safe zone with qualified storage conditions and controlled access. The storage must be in compliance with regulatory requirements.

Study drugs should be stored under the storage conditions listed in Section 10.1.2. Where the protocol and other information differ, store according to the storage conditions listed on the label.

Daily maximum and minimum temperatures of all storage areas (such as freezer, refrigerator, and room temperature) must be recorded by the study center. The documented period shall begin with the receipt of the study drug until the last subject completes the last visit. Even if a continuous monitoring system is employed, a written log must be kept to ensure a correct record of storage temperature. The temperature monitoring and storage devices (such as refrigerator) should be regularly inspected to ensure proper operation.

Any deviations related to the labeled conditions on the product should be immediately reported upon discovery. The study center shall take active measures to restore the study drugs under the storage conditions described on the label, and the temperature deviation and the measures taken shall be reported to the sponsor.

Study drugs affected by the temperature deviation should be isolated temporarily and may only be used after approval by the sponsor and if it is not a protocol deviation. The use of affected investigational drugs without the approval of the sponsor is considered a protocol deviation. The sponsor will provide a detailed procedure on reporting temperature deviations to the study center.

10.1.4 Preparation of study drugs

Some drugs used in this study are administered via intravenous infusions. Therefore, the drugs should be prepared by a qualified or experienced study staff such as a study nurse. The investigational drug SHR-1210 does not contain preservatives, and must be prepared using aseptic technique. Refer to the brochure for drug preparation.

10.1.5 Administration of study drugs

SHR-1210

Administered via intravenous drip infusion at 200 mg/dose (not less than 20 min and not more than 60 min) on day 1 of each 3-week cycle for a period of up to 2 years.

Apatinib Mesylate Tablets

Administered orally at 500 mg/day once daily with warm water at approximately half an hour after meals (administration time should be the same in each day whenever possible) in 3-week cycles.

Doxorubicin

Administered via intravenous drip infusion at 60 mg/m^2 within 2 h on day 1 of each 3-week cycle. Six cycles are recommended.

If a subject has received more than 450 mg/m^2 of anthracyclines, doxorubicin will no longer be used. Doxorubicin will also be discontinued if the subject experiences a decrease in LVEF from baseline by at least 5% to an absolute value of < 55% with symptoms of chronic heart failure, or a decrease in LVEF from baseline by at least 10% to an absolute value of < 55% without symptoms or signs.

If the subject has received anthracycline treatment before the study, refer to Appendix 3. Dose Conversion of Anthracyclines for the conversion. In the course of the study, if the remaining available dose of doxorubicin (450 mg/m^2 minus the cumulative dose used previously) is ≥ 51 mg/m^2 (i.e., 85% of the initial dose) in a certain cycle, then the doxorubicin + ifosfamide regimen is still used this time. If the remaining available dose of doxorubicin is less than 51 mg/m^2, the ifosfamide monotherapy regimen is used directly.

The body surface area is calculated using the Stevenson's formula: body surface area (m^2) = 0.0061 ×height (cm) + 0.0128 ×weight (kg) - 0.1529. The final dose should be 95-105% of the calculated dose.

Ifosfamide

Combination with doxorubicin: Ifosfamide 2 g/m^2/d on D1-D4, intravenous drip infusion within 4-6 h, in 3-week cycles (i.e., the total dose per cycle shall be 8 g/m^2). Six cycles are recommended.

Ifosfamide monotherapy: 2 g/m^2/ d on D1-D5, intravenous drip infusion within 4-6 h, in 3-week cycles (i.e., the total dose per cycle shall be 10 g/m^2). Six cycles are recommended.

If the above infusion rate is not tolerated by the subject, the investigator may consider adjusting the ifosfamide infusion rate.

The body surface area is calculated using the Stevenson's formula: body surface area (m^2) = 0.0061 ×height (cm) + 0.0128 ×weight (kg) - 0.1529. The final dose should be 95-105% of the calculated dose.

10.1.6 Dose modifications and delay

10.1.6.1 Dose modifications for SHR-1210

Adverse events related to SHR-1210 may be immune-related (irAE), and may develop shortly after the first dose or months after the last dose. SHR-1210 should be interrupted if events listed in Table 4 occur. During the study, the investigator must consult with the sponsor if, based on the benefit to risk ratio of the subject, SHR-1210 should be interrupted or resumed instead of the recommendations found in Table 4 or when the situation is not listed.

When SHR-1210 is discontinued and apatinib is well tolerated, the subject may receive apatinib monotherapy.

Table 4. Criteria for SHR-1210 dose modifications

Treatment-Related Immune-Related Adverse Events (irAEs)	Severity Grades for Treatment Interruption	Resumption	Discontinuation
Diarrhea/Colitis	2-3	Recovered to Grade 0-1	Fail to resolve within 12 weeks from the last dose, or the dose of corticosteroids cannot be reduced to ≤ 10 mg of prednisone or equivalent within 12 weeks.
	4	Discontinuation	Discontinuation
AST, ALT, or bilirubin increased	2	Recovered to Grade 0-1	Fail to resolve within 12 weeks from the last dose.
	3-4	Discontinuation	Discontinuation
Hyperthyroidism	3	Recovered to Grade 0-1	Fail to resolve within 12 weeks from the last dose, or the dose of corticosteroids cannot be reduced to ≤ 10 mg of prednisone or equivalent within 12 weeks.
	4	Discontinuation	Discontinuation
Hypothyroidism	2-4	Treatment can be continued after starting thyroxine replacement therapy	Treatment can be continued after starting thyroxine replacement therapy

Treatment-Related Immune-Related Adverse Events (irAEs)	Severity Grades for Treatment Interruption	Resumption	Discontinuation
Pulmonitis	2	Recovered to Grade 0-1	Fail to resolve within 12 weeks from the last dose, or the dose of corticosteroids cannot be reduced to ≤ 10 mg of prednisone or equivalent within 12 weeks.
	3-4	Discontinuation	Discontinuation
Immune-Related Hypophysitis	2-3	Recovered to Grade 0-1; SHR-1210 treatment can be resumed after starting hormone replacement therapy	Fail to resolve within 12 weeks from the last dose, or the dose of corticosteroids cannot be reduced to ≤ 10 mg of prednisone or equivalent within 12 weeks.
	4	Discontinuation	Discontinuation
Type I diabetes mellitus (new onset) or hyperglycemia	New-onset type I diabetes mellitus or Grade 3-4 hyperglycemia accompanied with evidence of β-cell depletion	After clinical and metabolic conditions are stabilized	Continue SHR-1210 treatment.
Renal Failure or Nephritis	2	Recovered to Grade 0-1	Fail to resolve within 12 weeks from the last dose, or the dose of corticosteroids cannot be reduced to ≤ 10 mg of prednisone or equivalent within 12 weeks.
	3-4	Discontinuation	Discontinuation
Infusion reactions	2	Symptoms disappeared	Re-administer at 50% of the initial rate after symptoms resolve. If no reaction occurs within 30 min, restore the original infusion rate (100%). Closely monitor. If the symptoms recur, the administration of the current SHR-1210 dose will be discontinued.
	3-4	Discontinuation	Discontinuation
Other Treatment-Related Adverse Events	3	Recovered to Grade 0-1	Fail to resolve within 12 weeks from the last dose, or the dose of corticosteroids cannot be reduced to ≤ 10 mg of prednisone or equivalent within 12 weeks.
	4	Discontinuation	Discontinuation

Note: Treatment should be discontinued if any Grade 3 treatment-related AE recurs or any life-threatening event occurs.

For subjects with metastasis to liver and Grade 2 AST or ALT increased at baseline, treatment should be discontinued if a ≥ 50% increase in AST or ALT from baseline persists for at least 1 week.

For subjects with intolerable or persistent Grade 2 treatment-related AEs, the investigator may consider interrupting SHR-1210 treatment if appropriate. For subjects with persistent Grade 2 adverse drug reactions that fail to recover to Grade 0-1 within 12 weeks after the last dose, the treatment should be discontinued.

For subjects with hypertension with a blood pressure not more than 140/90 mmHg whose AE is considered as Grade 3-4 only because of the administration of multiple antihypertensive drugs, treatment interruption is not required.

10.1.6.2 Treatment for Common Adverse Drug Reactions Related to SHR-1210

10.1.6.2.1 Immune-related adverse reactions

Adverse events caused by immuno-oncology (I-O) drugs are different from those of other anti-tumor drugs, especially in terms of severity and duration. SHR-1210 is one such drug, and therefore, early identification and management of adverse events is required to reduce the incidence of severe toxicities. The safety management procedures of similar approved drugs provide references to assist the investigator in assessing and dealing with adverse events involving the following systems: GI tract, kidneys, lungs, liver, endocrine, skin, and nervous system. Safety management rules for immuno-oncology drugs are presented in Appendix 7. Management Principles for Immune Related Adverse Events.

10.1.6.2.2 Infusion reactions

During the course of this study, the investigator should pay close attention to potential infusion and/or allergic reactions, especially acute immune-mediated adverse reactions (including cytokine storms).

SHR-1210 is a fully humanized monoclonal antibody with little potential for infusion or allergic reactions, and thus, in general, no prophylactic medications are required prior to SHR-1210 infusion. Based on published relevant information, allergic reactions/events are most likely to occur within 24 h after infusion. If an allergic reaction/event occurs, the infusion should be slowed or interrupted based on the subject's condition, and supportive treatment should be given. In addition, prophylactics should be given before further administration. Possible allergic reactions include fever, chills, shiver, headache, rash, arthralgia, hypotension/hypertension, and bronchospasm.

Management of allergic reactions should be based on the medical practice and guidelines of the study center. The treatment recommendations for infusion reactions are shown below for reference.

Table 5. Treatment recommendations for infusion reactions related to SHR-1210

CTCAE Grade	Clinical Symptoms	Recommended Management	SHR-1210 Treatment
Grade 1	Mild and transient reactions	Bedside observation and close monitoring until recovery. Pre-dose prophylactics are recommended for subsequent administration: 50mg of diphenhydramine or equivalent, and/or 325-1000 mg of acetaminophen can be given at least 30 minutes before the administration of SHR-1210.	Continued use
Grade 2	Moderate reactions requiring treatment or interruption; rapidly resolve after symptomatic treatment (such as antihistamines, non-steroidal antiphlogistics, anesthetics, bronchodilators, intravenous fluids, etc.)	Intravenous administration of normal saline, 50 mg of diphenhydramine IV or equivalent and/or 325-1000 mg of acetaminophen; bedside observation and close monitoring should be given until recovery. Corticosteroids or bronchodilators can be considered based on clinical needs; The amount of study drug infused should be recorded in the original medical record; Pre-dose prophylactics are recommended for subsequent administration: 50mg of diphenhydramine or equivalent, and/or 325-1000 mg of acetaminophen can be given at least 30 minutes before the administration of SHR-1210. Corticosteroids (equivalent to 25 mg of hydrocortisone) can be used when necessary.	Interrupt. Re-administer at 50% of the initial rate after symptoms resolve. Restore the original infusion rate if no complications occur within 30 minutes. Closely monitor. If the symptoms recur, no more infusion shall be given.
Grade ≥ 3	Grade 3: Severe reaction without rapid recovery with treatment and/or interruption; or symptoms recur after alleviation; or the subject develops sequelae that requires hospitalization. Grade 4: Life-threatening.	Immediately discontinue SHR-1210; Administer normal saline by intravenous infusion. Bronchodilators are recommended. Subcutaneous injection of 0.2-1 mg of 1:1000 adrenaline solution or slow intravenous infusion of 0.1-0.25 mg of 1:10,000 adrenaline solution is recommended. Intravenous infusion of diphenhydramine 50 mg and methylprednisolone 100 mg (or equivalent dose) can be given if necessary. Medical practices and guidelines for treating allergic reactions at the study center are followed. Bedside observation and close monitoring until recovery.	Discontinuation

10.1.6.3 Apatinib Dose Modification

Dose modifications due to apatinib-related toxicity include: dose delay (for up to 28 days), dose reduction (first dose modification: 375 mg qd, second dose modification: 250 mg qd), and permanent treatment discontinuation.

In case of Grade ≥ 3 apatinib-related toxicity, administration should be delayed until recovery, and then the original dose should be resumed or the dose should be reduced by one dose level. The minimum dose allowable is 250 mg/d. If the dose is still intolerable at the reduced dose of 250 mg/d, apatinib should be permanently discontinued (refer to Table 6 for the recommended dose modification method). When apatinib is discontinued and SHR-1210 is well tolerated, the subject may receive SHR-1210 monotherapy.

In case of Grade ≥ 3 AEs unrelated to apatinib, the investigator shall decide on dose delay based on the actual situation.

If apatinib causes Grade 2 ALT or AST increased for ≥ 7 days, the investigator can interrupt the apatinib treatment as appropriate.

Dose increase of apatinib is not allowed during the study period.

For subjects with hypertension with a blood pressure not more than 140/90 mmHg whose AE is considered as Grade 3-4 only because of the administration of multiple antihypertensive drugs, treatment interruption is not required.

Table 6. Recommended dose modification of apatinib

Apatinib Treatment-related toxicity	Grade	Dose delay	Criteria for resuming	Dose Modification Method	Criteria for Discontinuation
Hematologic Toxicity	Grade 1-2	No	—	—	—
	Grade 3-4	Yes	Toxicity returns to Grade ≤ 2	At the original dose or at a reduced dose level	Apatinib interruption for more than 28 days
Non-Hematologic Toxicity	Grade 1-2	No	—	—	—
	Grade 3-4	Yes	Toxicity returns to Grade ≤ 1	At the original dose or at a reduced dose level	Apatinib interruption for more than 28 days

10.1.6.4 Dose modification of doxorubicin/ifosfamide

For subjects receiving doxorubicin combined with ifosfamide, dose modification can be made based on toxicities.

Table 7. Recommended dose modification of doxorubicin/ifosfamide

Chemotherapy-related toxicity	Grade	Dose delay	Criteria for resuming	Dose Modification Method	Criteria for Discontinuation
Hematologic Toxicity	Grade 1-2	No	—	—	—
	Grade 3-4	Yes	Toxicity returns to Grade ≤ 1	At the original dose or at a reduced dose level	Chemotherapy interruption for more than 6 weeks
Non-Hematologic Toxicity	Grade 1-2	No	—	—	—
	Grade 3-4	Yes	Toxicity returns to Grade ≤ 1	At the original dose or at a reduced dose level	Chemotherapy interruption for more than 6 weeks

For non-severe or non-fatal toxicities (e.g., alopecia, appetite change and nail discoloration), dose modification may not be necessary as judged by the investigator.

Dose modification caused by toxicities of a single drug in the combination therapy will not affect the usage of other drugs according to the plan.

For subjects with hypertension with a blood pressure not more than 140/90 mmHg whose AE is considered as Grade 3-4 only because of the administration of multiple antihypertensive drugs, treatment interruption is not required.

Table 8. Dose modification of doxorubicin/ifosfamide

Drug	Initial Dose	Next Dose (85% of the initial dose)	Dose after the Next Dose
Doxorubicin	60 mg/m^2, q3w	51 mg/m^2, q3w	Discontinuation
Ifosfamide	2 g/m^2 on D1-D4 q3w for combined medication or 2 g/m^2 on D1-D5 q3w for monotherapy	1.7 g/m^2 on D1-D4 q3w for combined medication or 1.7 g/m^2 on D1-D4 q3w for monotherapy	Discontinuation

Chemotherapy-related toxicities cannot resolve within the same treatment cycle. Thus, the administration of doxorubicin/ifosfamide can be delayed for no more than 6 weeks (±3 days). If the toxicities still do not resolve by 6 weeks, the chemotherapy will be discontinued, unless the investigator considers that the subjects can benefit from continued chemotherapy.

10.2 Drug Management, Dispensation and Return

The management, dispensation, and retrieval of study drugs should be the responsibility of designated study staff. The investigator must ensure that all study drugs are used for subjects participating in this clinical study. The dosage and administration are shown in Section 10.1.5. Remaining or expired drugs should be returned to the sponsor and may not be used for non-participants.

When the drug is transported to the sub-center, a drug receipt form shall be signed in duplicate, one copy for the study center and one copy for the sponsor. When returning remaining drugs and empty packaging, both parties must sign the drug retrieval form. The dispensation and return of every drug should be immediately documented on designated forms.

The CRA is responsible for monitoring the supply, use, and storage of study drugs, and disposal of remaining medications.

10.2.1 Disposal of study drugs

The sponsor or his/her authorized personnel will provide guidance on the destruction of unused study drugs. If the study center is authorized to destroy the study drugs, the investigator must ensure that the destruction of the study drugs complies with applicable environmental regulations and company policies, and provide relevant procedures for destruction. The investigator should record all destruction activities.

10.3 Concomitant Medications

Concomitant medications refer to any drugs/treatments that are given for the interest of subjects as determined by the investigator.

All concomitant medications, blood products, and non-drug interventions (e.g., paracentesis) that are given to the subjects from 28 days prior to the first dose to the end of the safety visit must be strictly documented in the CRF according to GCP requirements. If a subject starts a new anti-tumor therapy during the safety follow-up period, only concomitant medications used for treatment-related AEs will be collected.

Prohibited medications and vaccines specified in the study protocol are strictly prohibited during the entire course of study. If the subject develops a comorbidity requiring treatment with a prohibited drug, the investigator should consult with the sponsor before discontinuing the study treatment or using the prohibited drug. Whether the subject will continue the study treatment or receive a prohibited drug should be jointly decided by the investigator, the sponsor, and the subject.

In addition to the following contents, for subjects who receive apatinib, doxorubicin, and ifosfamide, the latest package insert of marketed drugs or medical practices regarding contraindications and precautions shall also be taken for reference.

10.3.1 Other anti-tumor/cancer or study drugs

Other anti-tumor treatments not specified in the protocol are not permitted while subjects are receiving study treatment, including CDFA (NMPA)-approved Chinese herbal preparations for anti-tumor treatments (see Appendix 9. Prohibited Traditional Chinese Medicines During the Study Period) and immunomodulators (including but not limited to interferon, interleukin-2, and thymosin).

Participation in other drug/medical device clinical studies is not permitted.

Subjects can receive bisphosphonates for the treatment of bone metastases. If systemic treatment or local analgesia is not effective in controlling painful lesions of bone metastases, a small area of palliative radiotherapy (the area of the radiotherapy must be < 5% of the bone marrow region, and the percent bone marrow in human is shown in Appendix 8. Percent Bone Marrow Content in Human Skeleton) is allowed. Except for the above-mentioned treatments for bone metastases, other anti-tumor treatments such as chemotherapy, molecular targeted therapy, hormone therapy, immunotherapy, biological therapy, radiotherapy, and surgical treatment are not permitted.

10.3.2 Medications to be used with caution in subjects receiving apatinib

10.3.2.1 Drugs that may have interactions with apatinib mesylate

In vitro metabolic enzymes studies have shown that apatinib is mainly metabolized by CYP3A4. When apatinib is used concomitantly with strong inhibitors of CYP3A4 (itraconazole, clarithromycin, voriconazole, telithromycin, saquinavir, and ritonavir), the plasma concentration of apatinib may rise. When apatinib is used concomitantly with CYP3A4 inducers (dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital, and rifapentine), the plasma concentration of apatinib may decrease. When other combined medications are needed, it is recommended to choose alternative drugs that do not inhibit or induce CYP3A4. If a strong inducer or inhibitor of CYP3A4 enzyme must be used concomitantly, it is necessary to consider whether to modify the dose based on clinical observation.

10.3.2.2 Drugs that prolong the QT interval of the heart

As tinib drugs may cause toxicities of prolonged QT interval in clinical applications, drugs that may prolong the QT interval should be used with caution during the study. These mainly include, but are not limited to, the following categories of drugs:

- Antibiotics: fluoroquinolones: sparfloxacin, gatifloxacin, levofloxacin, moxifloxacin, ofloxacin, ciprofloxacin; macrolides: erythromycin, clarithromycin, telithromycin, azithromycin, roxithromycin, and metronidazole.
- Antiarrhythmics: quinidine, procainamide, disopyramide, flecainide, propafenone, amiodarone, dronedarone, sotalol, dofetilide, and ibutilide.
- Drugs used to relieve angina: ranolazine and ivabradine.
- Antipsychotics: risperidone, fluphenazine, droperidol, haloperidol, thioridazine, pimozide, olanzapine, and clozapine.
- Antifungal drugs: voriconazole and posaconazole.
- Antimalarial drugs: mefloquine and chloroquine.
- Antihistamines: terfenadine, astemizole, and hydroxyzine.
- Gastrointestinal drugs: antiemetics: ondansetron, granisetron, dolasetron, droperidol (0.625-1.25 mg may be a safe dose), and hydroxyzine; prokinetics: cisapride, domperidone, and metoclopramide.
- Antidepressants: amitriptyline, imipramine, clomipramine, dosulepin, and doxepin.

10.3.3 Hematopoietic growth factor

According to the current edition of the "American Society of Clinical Oncology Clinical Practice Guideline", granulocyte colony stimulating factor is used as prophylaxis for neutropenia.

The probability that doxorubicin + ifosfamide causes febrile neutropenia is ≥ 20%, and it is recommended to use recombinant human granulocyte stimulating factor (such as mecapegfilgrastim) for prophylaxis. Whether to continue to use recombinant human granulocyte stimulating factor (such as mecapegfilgrastim) in the future depends on the outcome of previous use.

10.3.4 Dexrazoxane

Dexrazoxane is recommended when the cumulative dose of doxorubicin reaches 300 mg/m^2, but is not recommended when the cumulative dose has not reached 300 mg/m^2, so as not to affect the efficacy.

10.3.5 Mesna

The toxicity of acrolein, a degradation product of ifosfamide, to the urinary system is mainly hemorrhagic cystitis, while Mesna reacts with acrolein and becomes non-toxic products that are excreted in the urine, reducing the incidence of hemorrhagic cystitis. The recommended dose for single-dose injection of Mesna is 20% (w/w) of ifosfamide, injected at the start of ifosfamide infusion, at 4 h after the infusion, and at 8 h after the infusion (the total dose is 60%). The recommended infusion time is the scheduled time ±10 min.

The recommended dose of ifosfamide in the protocol is 2 g/m^2, and the recommended dose of mesna is 400 mg/m^2 per injection (the actual dose should not be less than the recommended dose).

10.3.6 Treatment for vomiting

Chemotherapy with anthracycline and ifosfamide may pose a risk of vomiting. The investigator shall determine the prophylactic drugs to be used.

The use of antiemetic drugs as a primary prevention method is not allowed for the investigational treatment group.

10.3.7 Anti-inflammatory treatment

Anti-inflammatory medications or narcotic analgesics can be given if there are no known or foreseeable drug interactions and if these drugs are not prohibited in the protocol.

10.3.8 Corticosteroids

Long-term, systemic use of corticosteroids for palliative or supportive treatment are prohibited. Emergency use, topical application, inhalation, eye drops, or local injections of corticosteroids are permitted.

10.3.9 Surgery

Any non-therapeutic tumor surgery conducted during the study period shall have its theoretical basis and necessity. The interval between the surgery and the treatment with study drug must not affect the recovery of the wound and the investigation on hemorrhage of unknown cause. An interruption of study treatment 1 week before the surgery is recommended. Re-initiation of study treatment after surgery will be determined on the basis of clinical assessment of wound healing and postoperative recovery.

10.4 Subject Compliance

Subjects in the investigational treatment group will be required to return or count all study drugs that have not been administered in the previous cycle before the start of the next cycle. The corresponding number of apatinib tablets will be documented and archived. The medication information in the subject's diary card will also be checked for consistency.

For SHR-1210, doxorubicin, and ifosfamide, the study center shall prepare the drugs complete the documentation as per the product brochure or package insert. The documentation system of the study center should include all relevant or required information with regards to preparation and administration.

11 STUDY PROCEDURES

Before the start of the study, subjects must read and sign the current version of ICF approved by the independent ethics committee/institutional review board (IEC/IRB). All the study procedures must be completed within the time window specified in the study schedule. The informed consent form shall be signed within 28 days before C1D1. Subjects who have failed previous screening may be screened again in this study. The informed consent form must be re-signed and a new subject number should be given for re-screening. If the re-screening fails, no further screening will be performed. Data from virology, echocardiography, and imaging assessment (tested at this study center only) performed prior to the signing of informed consent for clinical needs may be used if they are within the specified window period.

11.1 Screening

Unless otherwise stated, the following procedures must be completed within 28 days prior to the start of study treatment during at the screening visit (Day-28 to Day-1):

- Obtain informed consent form signed by the subject.
- Collecting demographics: gender, date of birth, ethnicity, etc.

- Tumor diagnosis: the location of the primary lesion, the date of pathological diagnosis, the pathological diagnosis (must be consistent with the term of the 2013 version of the WHO guidelines on soft tissue tumors), the time of progressive disease or recurrence, and the progressive disease (locally advanced, unresectable, or distantly metastatic).
- History of cancer treatment
  - ✓ History of tumor surgery: type, name, and date of surgery;
  - ✓ History of radiotherapy: site, total dose, and start and end dates;
  - ✓ History of neoadjuvant chemotherapy or chemotherapy: chemotherapy regimen, cycle, start and end dates, best response, reason for discontinuation of chemotherapy, whether recurrence happens within 6 months, and cumulative total dose of doxorubicin;
  - ✓ History of adjuvant chemotherapy: chemotherapy regimen, cycle, start and end dates, reason for discontinuation of chemotherapy, whether recurrence happens within 6 months, and cumulative total dose of doxorubicin;
- Medical history, surgical history, medication history (concomitant medications within 28 days before C1D1), history of drug or alcohol abuse, history of drug allergy, etc.;
- Virology: HBsAg (quantitative HBV DNA test if positive); HCV-Ab (quantitative HCV-RNA test if positive) and HIV-Ab: within 28 days before the first dose.
- Echocardiography: Including left ventricular ejection fraction (LVEF) assessment. Echocardiography will be performed once within 28 days prior to the first dose, and performed if clinically indicated thereafter.
- Imaging evaluation: CT or MRI of lesions in the head, chest, abdomen, pelvis, and other sites. Sites with bone metastasis as shown by bone scans, PET-CT, or clinical indications must also be reexamined by CT or MRI at baseline.
- Collection of adverse events: Collect adverse events starting from the signing of ICF.
- Concomitant medications/treatments: Concomitant medications/treatments within 28 days prior to the first dose of the study drug should be documented.

The following screening procedures should be completed within 7 days before the start of study treatment:

- ECOG PS.
- Vital signs: pulse, respiratory rate, temperature, and blood pressure.

- Comprehensive physical examination: height, weight, general condition, head and face, neck, chest, abdomen, perineum, extremities, etc.
- Hematology: Red blood cell count (RBC), hemoglobin (Hb), blood platelet count (PLT), white blood cell count (WBC), absolute neutrophil count (ANC), and lymphocyte count (LYM).
- Urinalysis: WBC, RBC, and urine protein. If urine protein is ≥ 2+, then a quantitative 24-h urine protein test should be added.
- Fecal occult blood (OB): within 7 days before the first dose.
- Blood biochemistry: Alanine transaminase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (γ-GT), total bilirubin (TBIL), direct bilirubin (DBIL), alkaline phosphatase (AKP), blood urea nitrogen (BUN) or urea, total protein (TP), albumin (ALB), creatinine (Cr), blood glucose (GLU), serum potassium (K+), serum natrium (Na+), serum calcium (Ca2+), serum magnesium (Mg2+), and blood chloride (Cl-).
- Coagulation function: Activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), fibrinogen (FIB), and international normalized ratio (INR).
- Thyroid function: Including serum thyroid stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4). If FT3 and FT4 cannot be obtained, T3 and T4 are allowed for substitution;
- Myocardial zymogram: lactate dehydrogenase (LDH), creatine kinase (CK), and hybrid creatine kinase (CK-MB)
- 12-Lead ECG: Attentions should be paid to heart rate, QT, QTcF, and PR intervals. The investigator may decide to add other investigations if the results are abnormal.
- Pregnancy test (serum pregnancy test will be performed for women of childbearing potential).
- Quality of life score.

11.2 Treatment Period

11.2.1 Treatment period for the investigational treatment group

The treatment period for the investigational treatment group will start from the first dose of the subject. The first dose of the study drugs should be given as close as possible to the time of completing the screening examinations and confirming the subjects' eligibility for the study. Each treatment cycle lasts for 21 days.

- **The following should be completed on C1D1:**
  - Dispensation of study drugs in the investigational treatment group: Apatinib tablets are permitted to be dispensed on the day before or on the day of administration.
  - Treatment with SHR-1210 and apatinib
  - Pharmacokinetics and immunogenicity test for the investigational treatment group: Approximately 4-6 mL of peripheral venous blood will be collected within 0.5 h before the administration of SHR-1210 on C1D1 for pharmacokinetics/immunogenicity test of SHR-1210; Approximately 2-4 mL of peripheral venous blood will be collected within 0.5 h before and at 4 h (± 10 min) after the administration of apatinib on C1D1 for pharmacokinetics test of apatinib.
  - Adverse event
  - Recording of concomitant medications and concomitant treatments
  - Dispensation and filling in of the subject diary card
- **The following should be completed on day 1 of each cycle from cycle 2 onwards:**
  - ECOG PS
  - Vital signs
  - Physical examination
  - Hematology
  - Fecal occult blood
  - Blood biochemistry
  - 12-Lead ECG
  - Dispensation and retrieval of study drugs of the investigational treatment group: Apatinib tablets are allowed to be dispensed at the scheduled time point within ± 3 days; remaining apatinib must be retrieved before each dispensation. Unscheduled drug dispensation and retrieval are permitted.
  - Pharmacokinetics/immunogenicity test: Within 0.5 h pre-administration on C2D1, C4D1, C6D1, C9D1 and every 4 cycles thereafter, with 4-6 mL of peripheral venous blood collected at each time point for pharmacokinetics/immunogenicity studies of SHR-1210; 4-6 mL of peripheral venous blood will be collected once 30 days after the last dose. Approximately 2-4 mL of peripheral venous blood will be collected within 0.5 h before and at 4 h (± 10 min) after the administration of apatinib on C2D1, C4D1, and C6D1 for pharmacokinetics study of apatinib.

- Collection of AEs
- Documentation of concomitant medications/concomitant treatments
- Dispensation and filling in of the subject diary card

◆ **The following should be completed on day 1 of every 2 cycles from cycle 3 onwards:**

- Urinalysis
- Coagulation function
- Thyroid function
- Blood pregnancy test
- Tumor imaging examination: Imaging examinations will be performed once every 2 cycles (6 weeks) in the first 16 treatment cycles of the study treatment period and once every 4 cycles (12 weeks) thereafter. Imaging conditions should be the same as those at baseline (including slice thickness and contrast agent). The time window for imaging examination is ± 7 days. Additional imaging evaluations may be performed if PD is suspected (e.g., worsening of symptoms)
- Quality of life score

11.2.2 Treatment period for the control group

The treatment period will start from the first dose of the subject in the control group. The first dose of the study drugs should be given as close as possible to the time of completing the screening examinations and confirming the subjects' eligibility for the study. Each treatment cycle lasts for 21 days.

◆ **The following should be completed on C1D1:**

- Treatment with doxorubicin + ifosfamide or ifosfamide monotherapy
- Adverse event
- Recording of concomitant medications and concomitant treatments

◆ **The following should be completed on day 1 of each cycle from cycle 2 onwards (additional chemotherapy cycles may be administered if deemed beneficial by the investigator):**

- ECOG PS
- Vital signs
- Physical examination

- Hematology
- Urinalysis
- Fecal occult blood
- Blood biochemistry
- Coagulation function
- Myocardial zymogram
- 12-Lead ECG
- Echocardiography
- Blood pregnancy test: Once every 2 cycles from cycle 3 onwards
- Treatment with doxorubicin + ifosfamide or ifosfamide monotherapy
- Collection of AEs
- Documentation of concomitant medications/concomitant treatments
- Tumor imaging examination: Imaging examinations will be performed once every 2 cycles (6 weeks) in the first 16 treatment cycles of the study treatment period and once every 4 cycles (12 weeks) thereafter. Imaging conditions should be the same as those at baseline (including slice thickness and contrast agent). The time window for tumor evaluation is ± 7 days. Additional tumor evaluations may be performed if PD is suspected (for example, worsening of symptoms).
- Quality of life score: Quality of life scoring will be performed once every 2 cycles in the first 16 treatment cycles from cycle 3 onwards and once every 4 cycles from cycle 17 onwards.

11.3 Follow-Up Period

11.3.1 Safety follow-up for the investigational treatment group

The safety follow-up for the combined medication of SHR-1210 and apatinib will start from the last dose of study treatment. Follow-ups will be performed once every 30 days (±5 days) until 90 days after the last dose.

The first safety follow-up (30 ±5 days) will be carried out at the study center where the evaluations specified in the protocol are completed. The second (60 ±5 days) and the third (90 ±5 days) follow-up will be made via phone calls. The information on new anti-tumor treatment, survival, concomitant medications/concomitant treatments, and adverse events will be collected.

- At the first safety follow-up (30 ± 5 days), subjects should return to the study center to complete the following assessments:
  - ECOG PS
  - Vital signs
  - Physical examination
  - Hematology
  - Urinalysis
  - Fecal occult blood
  - Blood biochemistry
  - Thyroid function
  - Coagulation function
  - Myocardial zymogram
  - 12-Lead ECG
  - Imaging examination: Subjects who discontinue the study treatment for reasons other than radiographic progression will still be followed up according to the established cycle. If no imaging examination is performed within 4 weeks before the last dose, an imaging examination must be performed within 30 days after the last dose.
  - Pharmacokinetics and immunogenicity test: 4-6 mL of peripheral venous blood will be collected 30 days (± 5 days) after the last dose for pharmacokinetics and immunogenicity tests of SHR-1210.
  - Adverse events: Recorded from the date of signing the informed consent form to the end of the safety follow-up period. If a new anti-tumor treatment is initiated during this period, only treatment-related AEs will be collected after the start of the new anti-tumor treatment.
  - Concomitant medications/treatments
  - New anti-tumor treatment
  - Quality of life score
- For the second (60 days after the last dose) and the third safety follow-ups (90 days after the last dose), the subjects' subsequent anti-tumor treatment, survival, adverse events, and concomitant medications/treatments will be collected via phone interviews.

11.3.2 Safety follow-up for the control group

The safety follow-up period for the combined medication of doxorubicin and ifosfamide will start from 21 days (±5 days) after the last dose.

- At the safety follow-up (21 ± 5 days), subjects should return to the study center to complete the following assessments:
  - ECOG PS
  - Vital signs
  - Physical examination
  - Hematology
  - Urinalysis
  - Fecal occult blood
  - Blood biochemistry
  - Thyroid function
  - Coagulation function
  - Myocardial zymogram
  - 12-Lead ECG
  - Echocardiography
  - Imaging examination: Subjects who discontinue the study treatment for reasons other than radiographic progression will still be followed up according to the established cycle if no imaging assessment is performed within 4 weeks before the last dose. An imaging examination must be performed within 21 days after the last dose.
  - Adverse events: Recorded from the date of signing the informed consent form to the end of the safety follow-up period. If a new anti-tumor treatment is initiated during this period, only treatment-related AEs will be collected after the start of the new anti-tumor treatment
  - Concomitant medication/treatments: Those within 28 days before the first dose of study medication to the new anti-tumor treatment will be documented; afterward, only concomitant medications for treatment-related AEs are documented.
  - New anti-tumor treatment
  - Quality of life score

11.3.3 Survival follow-up

The survival follow-up period starts after the end of the safety follow-up period. The survival follow-up period ends upon the subject's death, lost to follow-up, withdrawal of informed consent, or study termination by sponsor. During this period, an effective follow-up such as telephone follow-up will be conducted once every 2 months to collect information on subject survival and subsequent treatments (if the subject has started a new anti-tumor treatment, the therapeutic regimen and the start and end time should be recorded).

11.4 Criteria for Crossover Treatment of Control Group

Subjects who are willing to and eligible for crossover treatment may be crossed over to receive the treatment of SHR-1210 combined with apatinib.

11.4.1 Screening Period

Unless otherwise stated, the following procedures must be completed within 7 days prior to the start of study treatment during at the screening visit (Day-7 to Day-1):

- Obtain informed consent form signed by the subject.
- Virology: HBsAg (quantitative HBV DNA test if positive); HCV-Ab (quantitative HCV-RNA test if positive) and HIV-Ab: within 28 days before the first dose.
- Echocardiography: Including left ventricular ejection fraction (LVEF) assessment. Echocardiography will be performed once within 28 days prior to the first dose, and performed if clinically indicated thereafter.
- Imaging evaluation: CT or MRI of lesions in the head, chest, abdomen, pelvis, and other sites. Sites with bone metastasis as shown by bone scans, PET-CT, or clinical indications must also be reexamined by CT or MRI at baseline but no longer undergo bone scan or PET-CT for efficacy follow-up.
- Collection of adverse events: Collect adverse events starting from the signing of ICF.
- Concomitant medications/treatments: Concomitant medications/treatments within 28 days prior to the first dose of the study drug should be documented.
- ECOG PS.
- Vital signs: pulse, respiratory rate, temperature, and blood pressure.
- Comprehensive physical examination: height, weight, general condition, head and face, neck, chest, abdomen, perineum, extremities, etc.

- Hematology: Red blood cell count (RBC), hemoglobin (Hb), blood platelet count (PLT), white blood cell count (WBC), absolute neutrophil count (ANC), and lymphocyte count (LYM).
- Urinalysis: WBC, RBC, and urine protein. If urine protein is ≥ 2+, then a quantitative 24-h urine protein test should be added.
- Fecal occult blood (OB): within 7 days before the first dose.
- Blood biochemistry: Alanine transaminase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (γ-GT), total bilirubin (TBIL), direct bilirubin (DBIL), alkaline phosphatase (AKP), blood urea nitrogen (BUN) or urea, total protein (TP), albumin (ALB), creatinine (Cr), blood glucose (GLU), serum potassium (K+), serum natrium (Na+), serum calcium (Ca2+), serum magnesium (Mg2+), and blood chloride (Cl-).
- Coagulation function: Activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), fibrinogen (FIB), and international normalized ratio (INR).
- Thyroid function: Including serum thyroid stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4). If FT3 and FT4 cannot be obtained, T3 and T4 are allowed for substitution;
- 12-Lead ECG: Attentions should be paid to heart rate, QT, QTcF, and P-R intervals. The investigator may decide to add other investigations if the results are abnormal.
- Echocardiography
- Pregnancy test (serum pregnancy test will be performed for women of childbearing potential).
- Quality of life score.

11.4.2 Treatment period

The content of the visit is the same as 11.2.1 Treatment period for the investigational treatment group.

11.4.3 Follow-up period

The content of the visit is the same as 11.3.1 Safety follow-up for the investigational treatment group.

11.5 Unscheduled Visit

The following shall be documented during unscheduled visits when subjects develop AEs during the study:

- Concomitant medications/treatments;
- Adverse events;
- All examinations performed related to adverse events (including radiographic examinations, if any).

12 EVALUATIONS

12.1 Efficacy Evaluation

In addition to the investigator's assessments of the tumor imaging results in this study, the sponsor will also collect all imaging results (except for the imaging results of the control group after crossover treatment), and use them for blinded independent review (all per RECIST v1.1). The specific procedures for independent review are described in the "Third-Party Independent Review Charter" for this study, written by the central imaging.

PFS: the time between the date of enrollment and the date of the first documented tumor progression (as per RECIST v1.1, regardless of whether treatment is continued), or death from any cause, whichever occurs first.

In addition, subjects in the investigational treatment group will continue the study treatment after progressive disease. The investigator will perform subsequent imaging assessments as per iRECIST (see Appendix 11; independent imaging evaluation is still carried out as per RECIST v1.1) for exploratory evaluation of PFS in the investigational treatment group as per iRECIST. PFS is defined as the period of time from the date of the subject's enrollment to the first iUPD that can be subsequently confirmed or the date of death due to any cause, whichever occurs first. The imaging evaluation criteria of the control group after crossover treatment are the same as those of the investigational treatment group, but no independent review of central imaging will be performed. The subjects after crossover will be analyzed based on the PFS data as per RECIST v1.1 and iRECIST.

OS: the time from the date of enrollment to the date of death from any cause. Subjects whose final status is "survived" are censored, and the date of censoring is the date of the last follow-up.

ORR: the proportion of treated subjects whose best overall response (BoR) is complete response (CR) or partial response (PR) as per RECIST1.1.

DCR: the proportion of treated subjects whose best overall response is complete response (CR), partial response (PR), or stable disease (SD) as per RECIST v1.1.

DoR: the period of time from the first documented tumor response (as per RECIST v1.1) to the first documented objective progression (as per RECIST v1.1) or death of any cause.

iORR: the proportion of treated subjects whose best overall response (BoR) is complete response (CR) or partial response (BOR) as per iRECIST v1.1.

iDCR: the proportion of treated subjects whose best overall response is complete response (CR), partial response (PR), or stable disease (SD) as per iRECIST v1.1.

iDoR: the period of time from the first documented tumor response (as per iRECIST v1.1) to the date of the first iUPD that can be subsequently confirmed or the date of death from any cause.

12.2 Safety Evaluation

12.2.1 Pregnancy test

Female subjects of childbearing potential will receive a sub-serum pregnancy test before the start of administration. When the pregnancy test shows negative during the screening period, appropriate contraceptive measures shall be taken.

Pregnancy test will also be performed routinely once every two cycles during the treatment period and at the end of study treatment, or additionally when a menstrual cycle is missed or when signs of pregnancy are suspected. If the HCG test is positive, the subject discontinues the dose but will continue to be observed for follow-up of the pregnancy event.

12.2.2 Adverse event

The evaluation of an adverse event (AE) includes the type, incidence, severity (according to NCI-CTCAE v4.03), and start and end time of the AE, as well as whether the AE is a SAE, the correlation of the AE to the study drug, and the outcome of the AE.

AEs that occur during the study, including signs and symptoms at screening, will be recorded on the AE page of the CRF.

12.2.3 Laboratory safety assessment

The blood samples for hematology and blood biochemistry tests will be collected according to the Schedule of Activities, and will be analyzed at the local laboratory.

Table 9. Laboratory tests

Hematology	**Blood biochemistry**	Serum natrium	FT4 (or T4)
Red blood cell	ALT	Serum calcium	**Myocardial zymogram**
Hemoglobin	AST	Serum magnesium	Lactate dehydrogenase
Blood platelet	Glutamyl transpeptidase	Blood chlorine	Creatine kinase
White blood cell	Total bilirubin	**Coagulation function**	Hybrid creatine kinase
Absolute neutrophil count	Direct bilirubin	APTT	**Pregnancy Test**
Lymphocyte count	Alkaline phosphatase	PT	Serum pregnancy test
Urinalysis	Blood urea nitrogen (or urea)	TT	
White blood cell	Total protein	FIB	
Red blood cell	Albumin	INR	
Urine protein	Creatinine	**Thyroid function**	
Fecal occult blood	Glucose	TSH	
Occult blood	Serum potassium	FT3 (or T3)	

12.2.4 Vital signs and physical examination

Physical examinations and vital sign examinations are completed by the research physician.

Vital signs include temperature, blood pressure, pulse, and respiratory rate.

Physical examination: height, weight, general condition, head and neck, chest, abdomen, perineum, and extremities. Height will be measured during screening only.

12.2.5 12-Lead electrocardiography (ECG)

12-Lead ECG shall be performed at the time points specified in the "Schedule of Activities". Subjects are required to rest quietly for at least 10 minutes in a supine position prior to undergoing the ECG. The ECG includes at least: heart rate, QT, and P-R intervals. QTcF can be calculated as: $QTcF = QT/(60/\text{heart rate})^{0.33}$.

12.2.6 Echocardiography

Echocardiography will be performed by qualified physicians. LVEF is also measured.

12.3 Collection and Processing of Immunogenicity and Drug Trough Concentration Blood Samples

Peripheral blood of subjects receiving SHR-1210 combined with apatinib will be used for immunogenicity and PK concentration testing. Refer to the "Laboratory Manual" for details.

12.4 Independent Data Monitoring Committee

In this study, an Independent Data Monitoring Committee (IDMC) will be established to evaluate the safety and efficacy of the study drug at the data review meetings on a regular basis. An interim analysis will be performed when about 143 (67%) OS events will be collected. The IDMC will make recommendations on whether to continue or terminate the study based on the safety and efficacy data and results. The IDMC review meeting will be held at the time specified in the charter of the IDMC. The study enrollment will continue during IDMC meetings.

After the data review, the IDMC will provide suggestions on whether to continue the study, whether to modify the protocol, or whether to discontinue the study. Finally, Jiangsu Hengrui Pharmaceuticals Co., Ltd. will decide whether to adopt the IDMC suggestions.

See details in IDMC charter.

13 ADVERSE EVENTS REPORTING

13.1 Adverse Events (AEs)

13.1.1 Definition of adverse event

An AE refers to any untoward medical condition in a clinical study subject who receives a pharmaceutical product, and the condition does not necessarily have a causality with the treatment. AEs can include any unfavorable and unintended symptoms, signs, abnormal laboratory finding, or diseases, including the following:

1) Worsening of pre-existing (prior to entering clinical study) medical conditions/diseases (including worsening symptoms, signs, or laboratory abnormalities);
2) Any new AE: Any new adverse medical conditions (including symptoms, signs, and newly diagnosed diseases);
3) Clinically significant abnormal laboratory findings.

All AEs should be collected in detail by the investigators, including: the name of the AE and description of all relevant symptoms, onset time, severity, causality assessment, duration, measures taken, as well as final results and outcomes.

13.1.2 AE severity grading criteria

The severity of AEs will be graded as per NCI-CTCAE v4.03. Refer to the following criteria for AEs not listed in the table of NCI CTCAE v4.03:

Table 10. CTC-AE severity grading criteria

Grade	Clinical Description of Severity
1	Mild; asymptomatic or mild clinical symptoms; clinical or laboratory test abnormality only; intervention not indicated.
2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily life, e.g., cooking, shopping, using the telephone, counting money, etc.
3	Severe or medically significant but not immediately life-threatening; leading to hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (ADL). Self-care ADL: refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden
4	Life-threatening consequences; urgent intervention indicated
5	Resulting in death

13.1.3 Determination of the relationship between AEs and the study drug

AEs include all unexpected clinical manifestations. All AEs that occur after the signing of the ICF must be reported regardless of whether the AEs are related to the study drug, whether the subject is allocated to the treatment group, and whether the subject receives the drug. Any discomforts complained by the subject or changes in objective laboratory measurements during the treatment period should be truthfully recorded. The severity, duration, measures taken, and the outcome of AEs should also be documented. The study physician shall assess the relationship between the AE and the study drugs by considering the time sequence between the administration of study drug and the occurrence of AE, characteristics and toxicology of the study drug, concomitant medications, underlying diseases, medical history, family history, as well as dechallenge and rechallenge. The causality assessment will be provided using the following five categories "definitely related, possibly related, unlikely related, definitely unrelated, and indeterminable". "Indeterminable" to be adverse drug reaction.

13.2 Serious Adverse Event (SAE)

13.2.1 Definition of SAE

A SAE refers to a medical occurrence during the study that results in hospitalization, prolonged hospitalization, disability, incapacity, life-threatening or death, or congenital malformation.

The following medical events are included:

- Events resulting in death;
- Life-threatening events (defined as when the subject is at immediate risk of death at the time of the event);
- Events resulting in hospitalization or prolonged hospitalization;

- Events resulting in permanent or serious disability/incapacity/impairment of work ability;
- Congenital anomalies or birth defects;
- Other important medical events (defined as events that may jeopardize the subject or require interventions to prevent any of the above).

13.2.2 Hospitalization

AEs resulting in hospitalization (even if for less than 24 hours) or prolonged hospitalization during the clinical study should be considered as SAEs.

Hospitalization does not include the following:

- Hospitalization at a rehabilitation institution
- Hospitalization at a sanatorium
- General emergency admission
- Day surgery (e.g., outpatient/same-day/ambulatory surgery)
- Social reasons (medical insurance reimbursement, etc.)

Hospitalization or prolonged hospitalization unrelated to the worsening of an AE is not a SAE. For example:

- Hospitalization due to the pre-existing disease without new AEs and aggravation of the pre-existing disease (e.g., hospitalization to examine laboratory abnormalities that have persisted from before the study until now);
- Hospitalization for management reasons (e.g., annual physical examination);
- Hospitalization during the study as specified in the study protocol (e.g., as required by the protocol);
- Elective hospitalization unrelated to worsening of AEs (e.g., elective surgery);
- Scheduled treatment or surgery that should be documented throughout the entire study protocol and/or in the subjects' individual baseline information;
- Hospitalization merely for use of blood products.

Diagnostic or therapeutic invasive (e.g., surgery) and non-invasive procedures should not be reported as AEs. However, when a condition resulting in such procedures meets the definition of AE, it should be reported as such. For example, acute appendicitis during the AE reporting period should be reported as an AE, and the resulting appendicectomy shall be recorded as the treatment of the AE.

13.2.3 Progressive disease

Progressive disease is defined as the worsening of the subject's conditions caused by the indications of the study, including radiological progressions and progressions in clinical symptoms and signs. New metastases relative to the primary tumor or progressions of the previous metastases are recognized as PD. Life-threatening events, hospitalization or prolonged hospitalization, or events resulting in permanent or severe disability/incapacity/impairment of work ability, congenital anomalies or birth defects arising from the symptoms and signs of PD are not reported as SAEs. Death caused by the symptoms and signs of PD will be reported as a SAE.

13.2.4 Potential drug-induced liver injury

Drug-induced liver injury will be considered if AST and/or ALT levels are abnormal accompanied with abnormal elevation of total bilirubin, the following criteria are met, and when there are no other causes of liver injury. These cases should always be considered as important medical events.

Potential drug-induced liver injury is defined as follows:

Baseline Period	**Normal (AST/ALT and TBIL)**	**Abnormal (AST/ALT and TBIL)**
Treatment period	• ALT or AST ≥ 3 × ULN • with TBIL ≥ 2 × ULN • and ALP ≤ 2 × ULN • and no hemolysis	• AST or ALT ≥ 2 × baseline level, and ≥ 3 × ULN; or AST or ALT ≥ 8 × ULN • with TBIL increase ≥ 1 × ULN or ≥ 3 × ULN

After being notified of the abnormal results, the subjects should return to the study center for an assessment as soon as possible (preferably within 48 h). Assessments include the laboratory tests, detailed medical history, and physical assessment, and the possibility of hepatic tumor (primary or secondary) should be considered.

Except for reexaminations of AST and ALT, other laboratory tests include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, γ-glutamyltransferase, PT/INR, and alkaline phosphatase. Detailed medical history should include history of alcohol use, acetaminophen, soft drugs, various supplements, family diseases, occupational exposure, sexual behavior, travel, contact with jaundice patients, surgery, blood transfusion, hepatic diseases, and allergies. Further tests may include the testing for acute hepatitis A, B, C and E, and hepatic imaging (such as biliary tract). If the above laboratory criteria are confirmed upon re-examination, the possibility of potential drug-induced liver injury should be considered in the absence of any other causes of abnormal liver function, without waiting for all liver function test results. Potential drug-induced liver injury should be reported as a SAE.

13.2.5 SAE reporting

In the event of a SAE, whether it is the first report or a follow-up report, the investigator must complete the "Serious Adverse Event Report Form" immediately, with a signature and date, and notify the sponsor within 24 h of knowing of the event. Relevant authorities must be informed of such SAE in a timely manner according to regulatory requirements.

SAEs that occur after the safety follow-up period which are suspected to be related to the study drugs should be collected.

The symptoms, severity, causality with the study drug, time of onset, time of treatment, measures taken, time and method of follow-up, and outcome should be documented in detail in the SAE report. If the investigator believes that a SAE is not related to the investigational drug but potentially related to study conditions (such as the termination of the previous treatment, or comorbidities during the study), this causality should be explained in the description section of the SAE report form. If the severity of an ongoing SAE or its relationship to the study drug changes, a follow-up report should be submitted immediately. If an error is found in a previously reported SAE, such SAE may be revised, revoked, or downgraded in follow-up reports and reported in accordance with the SAE reporting procedure.

The sponsor's email address for safety data of this study is: hengrui_drug_safety@hrglobe.cn

13.2.6 Time limit for collection and follow-up of AEs/SAEs

All AEs/SAEs will be collected from the signing of the informed consent form. The time limit and follow-up periods for new events are described in the table below.

Table 11. Principles of AE/SAE collection and follow-up

Classification	Onset Time	Follow-up Time
Unrelated AEs	Until the end of safety follow-up period or start of a new anti-tumor treatment (whichever comes first)	Until the end of safety follow-up period
Treatment-related AEs	Until the end of safety follow-up period	Until resolved, remission, or recovered to baseline levels or Grade ≤ 1, steady state, or reasonably explained (e.g., lost to follow-up, death).
Unrelated SAEs (including SIEs)	Until the end of safety follow-up period or start of a new anti-tumor treatment (whichever comes first)	Until the end of safety follow-up period
Treatment-related SAEs (including SIEs)	No time limit	Until resolved, remission, or recovered to baseline levels or Grade ≤ 1, steady state, or reasonably explained (e.g., lost to follow-up, death).

13.3 Pregnancy

If a female subject becomes pregnant during the clinical study (until the end of the safety follow-up period or start of a new anti-tumor treatment), the subject must withdraw; if the partner of a male subject becomes pregnant during the clinical study, the subject may continue the study. The investigators must fill out the "Pregnancy Report/Follow-up Form for Hengrui's Clinical Studies" and report to the sponsor within 24 hours after becoming aware of the pregnancy, and report to the ethics committee promptly.

The investigator should follow up the outcome of the pregnancy until 1 month after delivery, and report the outcome to the sponsor.

Pregnancy outcomes such as stillbirth, spontaneous abortion, and fetal malformation are considered SAEs and need to be reported according to the time requirements for SAEs.

If the subject also experiences a SAE during the pregnancy, the CFDA (now NMPA) Serious Adverse Event Report Form should also be filled out and reported according to the SAE reporting procedure.

13.4 Adverse Events of Special Interest

When an AE of special interest specified in the study protocol occurs, the investigator must fill out the "Report of Adverse Event of Special Interest for Hengrui's Clinical Studies" and report to the sponsor within 24 h of being notified. If the AE of special interest is also a SAE, the "NMPA Serious Adverse Event Report Form" should also be completed and submitted to the relevant authorities according to SAE reporting procedure.

- Grade ≥ 3 infusion reactions;
- Grade ≥ 3 irAEs;

14 DATA ANALYSIS/STATISTICAL METHODS

14.1 Sample Size

In this study, IRC-assessed PFS will be used as the primary endpoint for superiority test with the control group. An interim analysis will be performed to determine the efficacy of the drugs and to determine whether to terminate or continue the study. The parameters for sample size calculation are as follows:

- Enrollment rate = 3 subjects/month (150 subjects/year), enrollment time = 20 months (the overall time will be 26 months)
- Randomization in a 1:1 ratio; one-sided $\alpha = 0.025$; the power of the test is 90%;

- Hazard ratio (investigational treatment group/control group [HR]) = 0.64 (estimated median PFS is 4.5 months in the control group and 7.0 months in the investigational treatment group)
- An interim analysis will be performed when 67% of PFS events (143) are collected to determine whether the drug is effective or ineffective, and to decide whether to terminate or continue the study.

Based on the above parameters, at least 214 PFS events shall be collected according to the log-rank test for PFS comparison in the two groups and the O'Brien & Fleming spending function (EAST6.4.1) in the α spending function method proposed by Lan-DeMets, i.e., approximately 262 subjects are needed. Considering a 10% dropout rate, 292 subjects are finally required for enrollment.

14.2 Statistical Analysis Plan

The primary objective is to evaluate whether SHR-1210 combined with apatinib is superior to doxorubicin combined with ifosfamide in improving the PFS (assessed by the IRC as per RECIST v1.1) of subjects with soft tissue sarcoma. In this study, SAS 9.4 or above will be used for data processing and analysis.

Detailed summaries and methods of statistical analyses for the data collected from the study shall be included in the statistical analysis plan (SAP), which shall be finalized and filed by the sponsor. The SAP should be revised accordingly if there are any changes to the study protocol that may have a major impact on the SAP, as determined by the sponsor or principal investigator. Relevant content in statistical analysis plan that is relevant to this protocol may be revised. However, if revised content involves the main and/or key factors of the protocol (such as the definition of endpoints or their analysis), such content in the protocol will be revised.

14.3 Analysis Population

This study will involve the following analysis sets:

- Full analysis set (FAS): All enrolled subjects who have received at least one dose of the study drug. This analysis set will be used for the efficacy analysis.
- Per-protocol Set (PPS): A subset of the FAS. Subjects with major protocol deviations judged to have a significant impact on treatment efficacy will be excluded from this analysis set. The list of subjects included into or excluded from the PPS should be reviewed and determined by the sponsor and the investigator before the database is locked.
- Safety Set (SS): All enrolled subjects who have received at least one dose of the study drug and had post-administration safety data.

- PK concentration analysis set: All subjects who have undergone blood sampling for trough concentration testing of SHR-1210.

Other analysis populations: In this study, some analysis populations depend on the study endpoint. For example, the analysis population of DoR is the subjects with response, and the analysis population of PFS after crossover is the subjects who have received the crossover treatment.

14.4 Statistical Methods

14.4.1 Basic methods

In this study, unless otherwise stated, all data will be summarized using descriptive statistics in accordance with the following general principles.

The quantitative variables will be summarized using mean, standard deviation, median, maximum, and minimum. The categorical variables will be summarized using frequency and percentage. For time-event data, the survival rate will be estimated using the Kaplan-Meier method and the survival curve will be plotted.

14.4.2 Primary efficacy endpoint analysis

The primary endpoint of the study is the IRC-assessed PFS (as per RECIST v1.1). The primary analysis will be based on the FAS set. The survival functions of PFS of the two groups will be compared using stratified log-rank tests with and without random stratification factors. The Kaplan-Meier method will be used to estimate the PFS rate, plot the survival curve, and estimate the median PFS, and its 95% CI will be calculated (Brookmeyer-Crowley method). The analysis with stratification factors will be used as the primary analysis.

In addition, as a supporting analysis and under the assumption of proportional hazards, the Cox models with and without stratification factors will be used to estimate the hazard ratio (HR) and calculate the corresponding 95% CI (Wald method).

The analysis methods for PPS will be the same as those for FAS.

Refer to section 14.4.6 for the interim analysis of PFS. The final analysis will be performed when 214 PFS events are collected, with a one-sided testing level of 0.023 to maintain the planned 0.025 (see Table 12). When the P-value (one-sided) based on the log-rank test of PFS is < 0.023, the comparison of anti-PD-1 antibody SHR-1210 combined with apatinib mesylate (investigational treatment group) vs. doxorubicin combined with ifosfamide (control group) is statistically significant. When the actual number of observed events does not reach or exceed 214 in the final analysis, automatic adjustments may be performed using EAST (e.g., "last look" item in the EAST IM tool) to control the overall type I errors.

14.4.3 Secondary efficacy endpoint analysis

The analysis of secondary efficacy endpoints will be based on the FAS.

For the secondary endpoint PFS assessed by the investigator (as per RECIST v1.1), the analytical method will be the same as that of the primary endpoint mentioned above.

The secondary endpoint OS will be statistically described using the similar method for the primary endpoint. For DoR, the Kaplan-Meier method will be used to plot the survival curve and estimate the median DoR and its 95% confidence interval will be calculated (Brookmeyer-Crowley method).

For the objective response rate (ORR) and disease control rate (DCR), the rates in the two groups and their two-sided 95% CI (Clopper-Pearson method) will be estimated, and the inter-group difference of rates and its two-sided 95% CI will be calculated (CMH method).

Other endpoints will be statistically summarized in accordance with general principles.

14.4.4 Handling of missing data

In this study, the missing data of the efficacy endpoints will not be treated specially, and the missing values will not be estimated in the safety evaluation.

14.4.5 Safety analysis

AEs that occur during the study will be coded according to MedDRA. The frequency and incidence of AEs will be summarized by system organ class and preferred term. The relevance and severity of AEs will be further tabulated for description. Descriptive statistics will be used to summarize other safety endpoints. Summarize the incidence of AEs, adverse drug reactions, AEs resulting in withdrawal from the study, AEs resulting in death, and SAEs. Severity of adverse events and adverse drug reactions: For the same AE with multiple occurrences in the same subject, the highest severity will be included in the analysis; for different AEs occurring in the same subject, the most severe AE will be included in the analysis.

Laboratory tests: Abnormal laboratory values will be summarized using descriptive statistics.

Vital signs: Measured values and changes will be summarized using mean, maximum, minimum, median, and SD.

Physical examination and 12-Lead ECG will be summarized descriptively.

Baseline is defined as the most recent test data before the first dose.

14.4.6 Interim analysis

In this study, one interim analysis will be carried out for the primary efficacy endpoint PFS. To control the overall type I errors, the O'Brien-Fleming spending function of the alpha spending function method will be used. The boundary of superiority determined using this method is as follows:

Table 12. Termination criteria and α spending in the interim analysis and final analysis of PFS

Time Point	PFS Number of events	Termination boundary value of HR (Investigational treatment group/control group)	One-sided nominal significance level Nominal α (one-sided)
		Effective (≤ lower limit)	
Interim (1st)	143 (67%)	-2.506 (HR = 0.658)	0.006
Final	214 (100%)	-1.993 (HR = 0.761)	0.023

Note: HR = Hazard ratio (investigational treatment group/control group); α = Alpha; PFS = Progression free survival; NA = Not applicable;

The results will be based on the z-scores calculated by EAST 6.4.1, and the O'Brien & Fleming spending function method of the α spending function method proposed by Lan-DeMets will be used for boundary testing and analysis.

The interim analysis will be performed when 67% of PFS events (166) will be collected to evaluate the efficacy of the drugs and to determine whether to terminate the study. When the z-score of PFS based on the log-rank test result exceeding the unbound effective boundary is -2.506 (P-value [one-sided] < 0.006), the study will end early because it is effective. If the efficacy is not established, the study will continue. If, in the interim analysis, the actual number of observed events does not reach or exceed 143, the boundary should be timely monitored and adjusted using EAST (e.g., using IM tool for monitoring). The final analysis will not be performed until 214 PFS events are collected (see 14.4.2).

The results of interim analysis will be reviewed by the IDMC, which will recommend whether to continue the study.

14.4.7 Subgroup analysis

Subgroup analyses will be performed for primary endpoint PFS according to (including but not limited to) the following factors, and the forest plot on HR will be produced:

Stratification factors:

- Age (< 65 years old vs. ≥ 65 years old)
- Gender

- ECOG PS (0 vs. 1 vs. 2)
- Site of primary lesion
- Pathological type
- Histological Classification
- Presence of lung metastases
- Presence of liver metastases
- Previous chemotherapy

14.4.8 Multiple comparison/multiplicity

The primary endpoint of the study is the IRC-assessed PFS (as per RECIST v1.1). The primary analysis of this endpoint will be based on the FAS, and a stratified log-rank method will be used to test the difference in survival function between the two groups. The overall alpha levels will be strictly controlled using the O'Brien-Fleming method for alpha spending during the interim and final analyses, as described in Section 14.4.6.

14.4.9 Exploratory analysis

Statistical description will be given for the production of anti-SHR-1210 antibodies (ADA) at time points of measurement, as well as the drug concentrations of SHR-1210 and apatinib.

For the investigator-assessed PFS and DoR (as per iRECIST) in the investigational treatment group, the PFS and DoR (as per RECIST v1.1 and iRECIST) after crossover treatment in the control group, and the OS, the Kaplan-Meier method will be used to plot the survival curves and estimate the medians and their 95% confidence intervals will be calculated (Brookmeyer-Crowley method).

For the investigator-assessed ORR and DCR (as per iRECIST) in the investigational treatment group and the ORR and DCR (as per RECIST v1.1 and iRECIST) after crossover treatment in the control group, the rates and their 95% confidence intervals will be estimated (Clopper-Pearson method).

The safety and quality of life scores of the control group after crossover treatment will be summarized using descriptive statistics in accordance with general principles.

15 DATA MANAGEMENT

15.1 Data Recording

Data will be collected and managed using the electronic case report form (eCRF).

15.1.1 Source documents and records

Source documents of the clinical study should be retained in their entirety. The investigator is responsible for filling out and keeping the source documents. Medical records should be neat and legible such that the sponsor's monitor can verify data with the eCRF during each inspection.

15.1.2 eCRF entry

Clinical study data will be collected using the HRTAU EDC system.

Entry: The data in the eCRF are from and should be consistent with the source documents, such as the original medical records and laboratory test reports. Any observations or test results in the trial should be entered in the eCRF in a timely, accurate, complete, clear, normative and verifiable manner. Data should not be changed arbitrarily. All items in the CRF should be filled out, with no blank or omissions.

Modifications: The system instructions must be followed when correcting the eCRF data as needed, and the reason for data correction must be recorded. The logic verification program in the system will verify the integrity and logic of the clinical study data entered into the EDC system and generate an error message prompt for questionable data. The PI or CRC will be permitted to modify or explain the problematic data. If necessary, multiple inquiries can be raised until the event of problematic data is resolved.

15.1.3 eCRF review

The investigator must complete, review, and submit the eCRF after the end of each subject's treatment course. The investigator or the data input staff (CRC) should promptly respond to queries raised by the monitor, data manager, and medical reviewer. After data cleaning is completed, the investigator will sign the completed eCRF for verification.

15.2 Data Monitoring

The monitor shall ensure that the data in the eCRF is consistent with the source data. This process is also known as source data verification (SDV), including the following contents: verify whether the study protocol is adhered to; whether the records on CRF is correct and complete, and consistent with the original medical records and laboratory test results, and whether there are errors or omissions in the data. According to the monitoring plan, the CRA will verify the completeness, consistency, and accuracy of study data in the database. The CRA will discuss any queries with study personnel and direct them to add or correct the data whenever necessary.

15.3 Data Management

15.3.1 EDC database establishment

The data manager will establish a study data collection system and database according to the study protocol, which will be available for online usage before the first subject is enrolled. Before use, all EDC users should receive adequate training and get the corresponding account to log into the system. (Access to EDC system will only be granted to the study center staff who have completed the training.)

15.3.2 Data entry and verification

The investigator or CRC should input data into the EDC system in accordance with the requirements of the visit procedures and the eCRF completion guide. After submitting the eCRF, the CRA, data manager, and medical personnel should review the data. Questions during the review will be submitted to the investigator or CRC in the form of queries. After data cleaning is completed, the investigator should sign the completed eCRF for verification.

15.3.3 Database lock

After SDV is completed by the CRA, the data manager and medical reviewer will conduct a final quality control of all data in the database, summarize all protocol deviations and violations during the study, and hold the data review meeting. The database will be locked after quality requirements are met. The data manager will export the data to the statistics department for data analysis.

15.3.4 Data archiving

After the study is completed, the eCRFs of the subjects must be generated from the EDC system in the PDF format and kept on non-rewritable CD-ROMs, which will be archived by the sponsor and various institutions for auditing and/or inspection.

All materials shall be preserved and managed in accordance with GCP requirements, and necessary documents of clinical studies shall be preserved until 2 years after the investigational drug is approved for marketing or 5 years after the termination of the clinical study.

16 SOURCE DATA AND DOCUMENTS

According to ICH E6, relevant regulations, and requirements for subjects' personal information protection of the study centers, each study center must properly keep all the treatment and scientific research records related to this study. As a part of the study that Jiangsu Hengrui Pharmaceuticals Co., Ltd. sponsors or participates in, each study center must allow the authorized representative of Jiangsu Hengrui Pharmaceuticals Co., Ltd. and regulatory authorities to inspect the clinical records (which may be copied if permissible by law) for quality review, audit, and evaluations of safety, study progress, and data validity.

Source data are information required to reconstruct and evaluate the clinical study, and are the original documentation of clinical findings, observations, and other activities. These source documents and data records include but are not limited to: hospital record, laboratory records, memos, subject diary cards, pharmacy dispensing records, recordings of advisory meetings, recorded data from automated devices, copies or transcripts that are verified to be accurate and intact, microfiche, photographic negatives, microfilms or magnetic disks, X-ray films, and subject's documents and records that are kept in the pharmacies, laboratories, and medical technology departments that are involved in this study.

17 QUALITY ASSURANCE AND QUALITY CONTROL

To ensure study quality, the sponsor and the investigator will jointly discuss and formulate a clinical study plan before the formal study initiation. All study personnel participating in the study will receive GCP training.

All the study centers must comply with the SOPs for the management of the study drug, including receipt, storage, dispensing, return, and destruction (if applicable).

According to the GCP guidelines, necessary measures must be taken at the design and implementation phases of the study to ensure that all collected data are accurate, consistent, intact, and reliable. All observed results and abnormal findings in the clinical study must be verified and recorded in a timely manner to ensure data reliability. All devices, equipment, reagents, and standards used in various tests in the study must have stringent specifications and be operated under normal conditions.

The investigator will input data required by the protocol into the eCRF. The CRA will check whether the eCRF is completely and accurately filled and guide the study center personnel for necessary revision and addition.

The drug regulatory authorities, independent ethics committee/institutional review board (IEC/IRB), sponsor's monitor and/or auditor may carry out systemic inspection of study-related activities or documents to assess whether the study is implemented based on the study protocol, SOPs, and relevant regulations (such as Good Laboratory Practices [GLP] and Good Manufacturing Practices [GMP]) and whether the study data is recorded in a prompt, truthful, accurate, and complete manner. The audit should be performed by personnel not directly involved in this clinical study.

18 REGULATORY ETHICS, INFORMED CONSENT, AND SUBJECT PROTECTION

18.1 Regulatory Considerations

According to the corresponding regulatory requirements in China, an application should be submitted to the CFDA (now NMPA) before starting a new drug study and the study can only be carried out after approval is obtained. The clinical approval number of SHR-1210 is 2016L01455. The clinical approval numbers of apatinib mesylate tablets are 2014L00876 and 2014L00877.

The legal basis for the design of this protocol is as follows:

1) Provisions for Drug Registration
2) Good Clinical Practice
3) Technical Guidelines for Clinical Pharmacokinetic Study of Chemical Drugs
4) Consensus on ethical principles based on international ethics guidelines, including the Declaration of Helsinki and the Council for International Organizations of Medical Sciences (CIOMS) International Ethics Guidelines
5) ICH Guidelines
6) Other applicable laws and regulations

18.2 Ethical Standards

This study protocol must first be reviewed and approved in writing by the IEC/IRB of the Hospital before being implemented. The study protocol, protocol revisions, ICF, and other relevant documents such as recruitment advertisements should be submitted to the ethics committee. This clinical study must comply with the "Declaration of Helsinki", NMPA's (former CFDA) "Good Clinical Practice" (GCP), and other relevant regulations. Before the study is initiated, approval must be obtained from the IEC/IRB of the hospital.

The study protocol must not be unilaterally modified without approvals from both the sponsor and investigator. The investigator can modify or deviate from the study protocol before obtaining an approval from the IEC/IRB only when in purpose of eliminating direct and immediate harm to the subject. Besides, the deviation or change and the corresponding reason, and the recommended protocol modification should be submitted to the IEC/IRB for review. The investigator must provide explanations and document any protocol deviation.

During the study, any changes to this study protocol must be submitted to the IEC/IRB. If necessary, corresponding changes should be simultaneously made to other study documents and submitted and/or be approved according to the pertinent requirements of the IEC/IRB. The

investigator is responsible for submitting the interim reports regularly according to the pertinent requirements of the IEC/IRB. After the end of the study, the completion should be informed to the IEC/IRB.

18.3 Independent Ethics Committee

The protocol, ICF, recruitment material, and all subject materials must be reviewed and approved by the IEC/IRB. Subjects may be enrolled only after the protocol and ICF have been approved. Any revisions to the protocol must be reviewed and approved by the EC prior to being implemented. All revisions to the ICF must be approved by the IEC/IRB, who will decide whether the subjects who have signed the previous version of the ICF are required to sign the new one.

18.4 Informed Consent

All subjects participating in the study sponsored by Hengrui shall provide the informed consent. The investigator shall follow applicable regulatory requirements and conduct the study in full compliance with ICH E6. Before the start of the study, the investigator shall obtain written approval of the study protocol from the IRB, ICF signed in writing, and other written information required to be provided to the subjects.

18.4.1 ICF and other written information for subjects

The ICF describes the study drugs and study process in detail and fully explains the risks of the study to the subjects. Written documentation of informed consent must be obtained before starting any study-related procedures.

18.4.2 Informed consent process and records

Informed consent will begin before an individual decides to participate in the clinical study and continues during the entire clinical study. The risks and potential benefits of participating in the study should be discussed fully and in detail with the subjects or their legal representatives. Subjects will be asked to read and review the ICF that has been approved by the IEC/IRB. The investigator will explain the clinical study to the subjects and answer any questions posed by the subjects. Subjects can only participate in the study after they have signed the ICFs. During the clinical study, subjects can withdraw the informed consents at any time. One copy of the signed ICF will be kept by the subjects. Even if a patient refuses to participate in this study, his or her rights will be fully protected, and the nursing quality will not be affected.

18.5 Confidentiality of Subject Information

The confidentiality of subject information will be strictly enforced by the investigator, participated study personnel, and sponsor and its representative. In addition to the clinical information, confidentiality also simultaneously covers biological samples and genetic tests of the subjects.

Therefore, the study protocol, documents, data, and other information generated from these materials will be kept strictly confidential. All relevant study or data information should not to be disclosed to any unauthorized third-party without prior written approval from the sponsor.

Other authorized representatives of the sponsor, IRB or regulatory authorities, and the representatives of the pharmaceutical company that provides the study drugs can examine all the documents and records that are maintained by the investigator, including but are not limited to the medical records and subject's administration records. The study center should allow access to these records.

The contact information of the subjects will be safely kept in each study center and only used internally during the study. When the study is ended, all the records will be kept in a secure place based on the time limit specified by local IRB and regulations.

The study data of the subjects collected for statistical analysis and scientific reports will be uploaded and stored at the sponsor or a third-party company entrusted by the sponsor. This should not include the contact information or identification information of subjects. Instead, individual subjects and their study data will be given a unique study identification number. The study data entry and study management system used by the study personnel at the study centers will be confidential and password-protected.

18.5.1 Use of samples, specimens, or data

- Planned use: The samples and data collected in accordance with the protocol will be used for the content specified in the protocol and will not be used for any unrelated purposes.
- Storage: Samples and data are numbered for storage. The data in the computer will also be password-protected. Only the study personnel can have access to these samples and data.

19 PUBLICATION OF STUDY RESULTS

The study results belong to Jiangsu Hengrui Pharmaceuticals Co., Ltd. If the investigator plans to publish any research-related data and information, Hengrui should be provided with the manuscript, abstract, or full text of all planned publications (poster, invited lectures, or guest lectures) at least 30 days prior to the submission of documents for publication or other forms of publication.

20 CLINICAL STUDY PROGRESS

Anticipated enrollment of the first subject: Sep. 2018

Anticipated enrollment of the last subject: Dec. 2020

Anticipated study completion: Sep. 2022

21 REFERENCES

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Appendix 1. The WHO Soft Tissue Tumor Classification (2013 Edition)

Adipocytic Tumors	**Benign**	**Intermediate (locally aggressive)**	**Malignant**
	Lipoma	Atypical lipomatous tumor	Dedifferentiated liposarcoma
	Lipomatosis	Well-differentiated liposarcoma	Myxoid liposarcoma
	Lipomatosis of nerve		Pleomorphic liposarcoma
	Lipoblastoma/lipoblastomatosis		Mixed-type liposarcoma
	Angiolipoma		Liposarcoma, not otherwise specified
	Mylipoma		
	Chondroid lipoma		
	Extrarenal angiomyolipoma		
	Extra-adrenal medullary lipoma		
	Spindle/pleomorphic lipoma		
	Hibernoma		
Fibroblast/myofibroblast tumors	**Benign**	**Intermediate (locally aggressive)**	**Malignant**
	Nodular fasciitis	Palmar/plantar fibromatoses	Adult fibrosarcoma
	Proliferative fasciitis	Desmoid-type fibromatoses	Myxofibrosarcoma
	Proliferative myositis	Lipofibromatosis	Low-grade fibromyxoid sarcoma
	Myositis ossificans	Giant cell fibroblastoma	Hyalinizing spindle cell tumor
	Fibro-osseous pseudotumor of digits	**Intermediate (occasionally metastatic)**	Sclerosing epithelioid fibrosarcoma
	Ischaemic fasciitis	Dermatofibrosarcoma protuberans	
	Elastofibroma	Fibrosarcomatoid dermatofibrosarcoma protuberans	
	Fibrous hamartoma of infancy	Pigmented dermatofibrosarcoma protuberans	
	Fibromatosis colli	Solitary fibrous tumor	
	Juvenile hyaline fibromatosis	Solitary fibrous tumor, malignant	

Adipocytic Tumors	**Benign**	**Intermediate (locally aggressive)**	**Malignant**
	Inclusion body fibromatosis	Inflammatory myofibroblastic tumor	
	Fibroma of tendon sheath	Low grade myofibroblastic sarcoma	
	Desmoplastic fibroblastoma	Myxoinflammatory fibroblastic sarcoma	
	Mammary-type myofibroblastoma	Atipical myxoinflammatory fibroblastic tumor	
	Calcifying aponeurotic fibroma	Infantile fibrosarcoma	
	Angiomyofibroblastoma		
	Cellular angiofibroma		
	Nuchal-type fibroma		
	Gardner fibroma		
	Calcifying fibrous tumor		
So-called fibrohistio cytic tumors			
Tenosynovial giant cell tumor, localized-type, and diffuse-type, malignant			
Plexiform fibrohistiocytic tumor			
Giant cell tumor of soft tissues			
Deep benign fibrous histiocytoma			
Smooth muscle tumors	**Benign**		**Malignant**
	Deep leiomyoma		Leiomyosarcoma (not including skin)
Pericytic (perivascular) tumors			
Glomus tumor and variants			
Glomangiomatosis			
Malignant glomus tumor			
Myopericytoma			
Myofibroma			
Myofibromatosis			
Angioleiomyoma			

Adipocytic Tumors	**Benign**	**Intermediate (locally aggressive)**	**Malignant**
Skeletal muscle tumors	**Benign**		**Malignant**
	Rhabdomyoma		Embryonic rhabdomyosarcoma (including grape clusters, anaplastic)
	Adult-type		Alveolar rhabdomyosarcoma (including solid, anaplastic)
	Fetal-type		Pleomorphic rhabdomyosarcoma
	Genital-type		Spindle cell/sclerosing rhabdomyosarcoma
Vascular tumors	**Benign**	**Intermediate (locally aggressive)**	**Malignant**
	Haemangiomas	Kaposiform haemangioendothelioma	Epithelioid haemangioendothelioma
	Synovial	**Intermediate (occasionally metastatic)**	Angiosarcoma of soft tissue
	Venous	Retiform haemangioendothelioma	
	Arteriovenous	Papillary intralymphatic angioendothelioma	
	Intramuscular	Composite haemangioendothelioma	
	Epithelioid haemangioma	Pseudomyogenic (epithelioid sarcoma-like) haemangioendothelioma	
	Angiomatosis	Kaposi sarcoma	
	Lymphangioma		
Chondro-osseous tumors			
Soft tissue chondroma			
Extraskeletal mesenchymal chondrosarcoma			
Extraskeletal osteosarcoma			
Gastrointestinal stromal tumors			
Gastrointestinal stromal tumor			
Gastrointestinal stromal tumor, uncertain malignant potential			
Gastrointestinal stromal tumor, malignant			

Adipocytic Tumors	**Benign**	**Intermediate (locally aggressive)**	**Malignant**
Nerve sheath tumors	**Benign**		**Malignant**
	Schwannoma (including variants)		Malignant peripheral nerve sheath tumor
	Melanotic Schwannoma		Epithelioid malignant peripheral nerve sheath tumor
	Neurofibroma (including variants)		Malignant triton tumor
	Plexiform neurofibroma		Malignant granular cell tumor
	Perineurioma		Ectomesenchymoma
	Malignant perineurioma		
	Granular cell tumor		
	Dermal nerve sheath myxoma		
	Solitary circumscribed neuroma		
	Ectopicmeningioma		
	Nasal glial heterotopia		
	Benign triton tumor		
	Hybrid nerve sheath tumors		
Tumors of uncertain differentiation	**Benign**	**Intermediate (locally aggressive)**	**Malignant**
	Acral fibromyxoma	Hemosiderotic fibrohistiocytic lipomatous tumor	Synovial sarcoma, NOS
	Intramuscular myxoma, including cellular variant	**Intermediate (occasionally metastatic)**	Synovial sarcoma, spindle cell
	Juxta-articular myxoma	Atypical fibroxanthoma	Synovial sarcoma, biphasic
	Deep ("aggressive") angiomyxoma	Angiomatoid fibrous histocytoma	Epithelioid sarcoma
	Pleomorphichyalinizing angiectatic tumor	Ossifying fibromyxoid tumor	Alveolar soft-part sarcoma
	Ectopic haemartomatous thymoma	Ossifying fibromyxoid tumor, malignant	Clear cell sarcoma of soft tissue
		Mixed tumor, NOS	Extraskeletal myxoid chondrosarcoma
		Mixed tumor, NOS, malignant	Extraskeletal Ewing sarcoma
		Myoepithelioma	Desmoplastic small round cell tumor

Adipocytic Tumors	**Benign**	**Intermediate (locally aggressive)**	**Malignant**
		Phosphaturic mesenchymal tumor, benign	Extra-renal rhabdoid tumor
		Phosphaturic mesenchymal tumor, malignant	Malignant mesenchymoma
Neoplasms with perivascular epithelioid cell differentiation, PEComa			
PECOma, NOS, benign			
PECOma, NOS, malignant			
Intimal sarcoma			
Undifferentiated/Unclassified Sarcomas			
Undifferentiated spindle cell sarcoma			
Undifferentiated pleomorphic sarcoma			
Undifferentiated round cell sarcoma			
Undifferentiated epithelioid cell sarcoma			
Undifferentiated sarcoma, NOS			

Appendix 2. Common Soft Tissue Sarcomas with Poor Chemotherapy Sensitivity

- Alveolar soft-part sarcoma
- Clear cell sarcoma of soft tissue
- Dedifferentiated liposarcoma
- Atypical lipomatous tumor
- Well differentiated liposarcoma

Appendix 3. Dose Conversion of Anthracyclines[7-8]

	Conversion Ratio
Doxorubicin	1
Epirubicin	0.5
Pirarubicin	1
Liposomal Doxorubicin	0.625

Appendix 4. ECOG PS

Grade	Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair 50% or more of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

Appendix 5. Cockroft-Gault Formula (for Calculating Creatinine Clearance)

Serum creatinine: mg/dL

$$\text{Creatinine Clearance in Males}\left(\frac{\text{ml}}{\text{min}}\right) = \frac{(140 - \text{Age}) \times \text{Weight}}{72 \times \text{Serum creatinine}}$$

$$\text{Creatinine Clearance in Females}\left(\frac{\text{ml}}{\text{min}}\right) = \frac{0.85 \times (140 - \text{Age}) \times \text{Weight}}{72 \times \text{Serum creatinine}}$$

Serum creatinine: μmol/L

$$\text{Creatinine Clearance in Males}\left(\frac{\text{ml}}{\text{min}}\right) = \frac{(140 - \text{Age}) \times \text{Weight}}{0.818 \times \text{Serum creatinine}}$$

$$\text{Creatinine Clearance in Females}\left(\frac{\text{ml}}{\text{min}}\right) = \frac{0.85 \times (140 - \text{Age}) \times \text{Weight}}{0.818 \times \text{Serum creatinine}}$$

Age in years, weight in kilogram (kg).

Appendix 6. Response Evaluation Criteria in Solid Tumors

Response Evaluation Criteria in Solid Tumors Version 1.1 (Excerpt)

Note: This appendix is translated internally and is for reference only. Please refer to the English version during practice.

1 BACKGROUND

Omitted

2 PURPOSE

Omitted

3 MEASURABILITY OF TUMOR AT BASELINE

3.1 Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

3.1.1 Measurable

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter is to be recorded) with a minimum size of:

- CT scan 10 mm (the thickness of CT scan layer shall not be more than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray;
- Malignant lymph nodule: pathologically enlarged and measurable, single lymph nodule must be ≥ 15 mm in short axis by CT scan (CT scan slice thickness no greater than 5 mm). At baseline and during follow-up, only the short axis will be measured and followed.

3.1.2 Non-measurable

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodule with a short axis ≥ 10 mm and < 15 mm) as well as truly non-measurable lesions. Non-measurable lesions include: meningeal disease, ascites, pleural or pericardial effusion, inflammatory breast cancer, lymphangitis carcinomatosa of the skin or lung, abdominal masses unable to be diagnosed or followed by imaging techniques, and cystic lesions.

3.1.3 Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions;
- Lytic lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by tomography techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above;
- Blastic lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts;
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other locoregional therapy, are usually considered non-measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

3.2 Specifications by Methods of Measurements

3.2.1 Measurement of lesions

All measurements should be recorded in metric notation if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 28 days (4 weeks) before the beginning of the treatment.

3.2.2 Method of assessment

The same method and technique should be used to assess lesions at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). For the case of cutaneous lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. When lesions can be evaluated by both imaging and clinical examination, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, especially when tumor progression is an important clinical endpoint, since CT is more sensitive, particularly in identifying new lesions. Chest X-ray is only applicable when the measured lesion boundary is clear and the lungs are well ventilated.

CT and MRI: CT is currently the best available and reproducible method for response evaluation. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for whole body scans).

Ultrasound: Ultrasound should not be used as a method to measure lesion size. Ultrasound examinations are operation-dependent, and cannot be reproduced at a later date. It cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead.

Endoscopy and laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm CR when biopsies are obtained, or to determine relapse in trials where recurrence following CR or surgical excision is an endpoint.

Tumor biomarkers: Tumor biomarkers alone cannot be used to assess objective tumor response. However, if the marker levels exceed the upper normal limit at baseline, they must return to the normal levels for evaluation of complete response. Because tumor biomarkers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line studies in ovarian cancer.

Cytology/histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual benign tumor tissue is commonly observed in lesions of germ cell neoplasm). When effusions are known to be a potential adverse effect of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met the criteria for response or stable disease in order to differentiate between response (or stable disease) and PD.

4 TUMOR RESPONSE EVALUATION

4.1 Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable lesions at baseline should be included in protocols where objective response is the primary endpoint. Measurable lesion is defined by the presence of at least one measurable lesion. In trials where the primary endpoint is tumor progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if enrollment is restricted to those with measurable lesions or whether patients with non-measurable lesions are also eligible.

4.2 Baseline Documentation of 'Target' and 'Non-Target' Lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ), representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where subjects have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal tissues which may be visible by imaging even if not involved by tumor metastasis. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes needs to be measured at baseline. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by tumor metastasis. Nodule size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial,

sagittal or coronal). The smallest of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm ×30 mm with a short axis of 20 mm qualifies as a malignant and measurable node. In this example, 20 mm should be recorded as the node measurement. Nodes with a short axis ≥ 10 mm but < 15 mm should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and are thus not to be recorded or followed up.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference.

All other lesions including pathological lymph nodes should be identified as non-target lesions, and while measurements are not required, they should be recorded at baseline. These lesions should be recorded as "present", "absent", or in rare cases "unequivocal progression". It is possible to record multiple target lesions involving the same organ as a single item on the case record form (e.g. "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

4.3 Response Criteria

4.3.1 Evaluation of target lesions

Complete response (CR): Disappearance of all target lesions. Any pathological lymph nodules (whether target or non-target) must have reduction in short axis to < 10mm.

Partial response (PR): At least a 30% decrease in the sum of diameters of target lesions, compared with baseline.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition, the sum must also demonstrate an absolute increase of at least 5 mm (the appearance of one or more new lesions is also considered PD).

Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

4.3.2 Special notes on the assessment of target lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis < 10 mm. CRFs or other data collection methods may

therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must have a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become too small to measure: While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure". When this occurs it is important that a value be recorded on the CRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement shall be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm can be assigned. (Note: It is less likely that this rule will be used for lymph nodules since they usually have a definable size when normal and are frequently surrounded by adipose tissues as in the retroperitoneum; however, if a lymph nodule is believed to be present and is faintly seen but too small to measure, a default value of 5 mm can be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false evaluation based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce: When non-nodal lesions fragmented, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the coalesced lesion.

4.3.3 Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete response (CR): Disappearance of all non-target lesions and normalization of tumor biomarker level. All lymph nodules must be non-pathological in size (short axis < 10 mm).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor biomarker level above the normal limits.

Progressive disease (PD): Unequivocal progression of existing non-target lesions. Note: the appearance of one or more new lesions is also considered PD.

4.3.4 Special notes on assessment of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows: When the patient also has measurable disease, to achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that the overall tumor load has increased sufficiently to the point where treatment must be discontinued. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease: This circumstance arises in some phase III trials when it is not a criterion of study inclusion to have measurable disease. The same general concepts apply here as noted above; however, in this instance there is no measurable disease assessment. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease load based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease. For example, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large", an increase in lymphangitic disease from "localized" to "widespread", or may be described in protocols as "sufficient to require a change in treatment". Examples include an increase in a pleural effusion from trace to large, an increase in lymphangitic disease from localized to widespread, or may be described in protocols as "sufficient to require a change in therapy". If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

4.3.5 New lesions

The appearance of new malignant lesions denotes PD; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of radiographically detected lesions; however, the finding of a new lesion should be unequivocal. For example, it should not be attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some new bone lesions that may be simply healing, or re-occurrence of pre-existing lesions). This is particularly important

when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a new cystic lesion, which it is not.

A lesion identified on a follow-up study that is not scanned at baseline will be considered a new lesion and will indicate PD. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example, because of its small size, continued treatment and follow-up evaluation are required to clarify if it represents a truly new disease. If repeated scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial identification.

While FDG-PET response evaluations generally need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible new disease). New lesions on the basis of FDG-PET imaging can be identified according to the following process:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up:
- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, PD is confirmed.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the imaging examination, this is not PD.

4.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the trial until the end of trial taking into account any necessary requirement for confirmation. On occasion a response may not be documented until after the end of treatment, so protocols should be clear if post-treatment assessments are to be considered in the evaluation of best overall response. Protocols must specify how any new treatment introduced before progression will affect best response evaluation. The patient's best overall response evaluation will depend on the findings of both target and non-target

diseases and will also take into consideration the characteristics of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized studies where response is the primary endpoint, confirmation of PR or CR is needed to determine either one is the BOR.

4.4.1 Time point response

It is assumed that at each time point specified in protocol, an efficacy response occurs. Table 1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

Table 1. Time point response: subjects with target (+/- non-target) disease

Target Lesion	Non-Target Lesion	New Lesion	Overall Response
CR	CR	Non	CR
CR	Non-CR/Non-PD	Non	PR
CR	Not evaluable	Non	PR
PR	Non-PD or not all evaluable	Non	PR
SD	Non-PD or not all evaluable	Non	SD
Not all evaluable	Non-PD	Non	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable

If patient does not have measurable lesions (no target lesions), refer to Table 2.

Table 2. Time point response: subjects with non-target lesion only

Non-Target Lesion	New Lesion	Overall Response
CR	Non	CR
Non-CR/Non-PD	Non	Non-CR/Non-PD[a]
Not all evaluable	Non	Not evaluable
Equivocal PD	Yes or No	PD
Any	Yes	PD

[a]: "Non-CR/non-PD" is preferred over SD for non-target disease. Since SD is increasingly used as an endpoint for response evaluation, non-CR/non-PD response is developed to address the absence of lesion measurability.

4.4.2 Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable at that time point. If only a subset of lesion measurements is made at an evaluation, usually the case is also considered not evaluable at that time point, unless a convincing argument can be made that

the contribution of the individual missing lesion(s) has/have no effect on the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had three measured lesions with a baseline sum of 50 mm and only two lesions with a sum of 80 mm were assessed at a subsequent follow-up, the patient has achieved PD status, regardless of the contribution of the missing lesion.

4.4.3 Best overall response: all time points

The BOR is determined once all the data for the patient are known.

BOR determination in studies where confirmation of complete or partial response is not required: BOR in these studies is defined as the best response across all time points (for example, a patient who has SD in evaluation at Cycle 1, PR at Cycle 2, and PD at the last cycle has a BOR of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time calculated from baseline. If the minimum time is not met when SD is otherwise the BOR, the patient's BOR depends on the subsequent assessments. For example, a patient who has SD at Cycle 1, PD at Cycle 2 and does not meet minimum duration for SD, will have a BOR of PD. The same patient lost to follow-up after the first SD assessment would be considered not evaluable.

BOR determination in studies where confirmation of complete or partial response is required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the BOR can be interpreted as in Table 3.

Table 3. Best overall response when confirmation of CR and PR required

Overall Response at First Time Point	Overall Response at Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	SD (provided minimum criteria for SD duration met, otherwise, PD)
CR	PD	SD (provided minimum criteria for SD duration met, otherwise, PD)
CR	NE	SD (provided minimum criteria for SD duration met, otherwise, NE)
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD (provided minimum criteria for SD duration met, otherwise, PD)

Overall Response at First Time Point	Overall Response at Subsequent Time Point	Best Overall Response
PR	NE	SD (provided minimum criteria for SD duration met, otherwise, NE)
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable.
[a]: If a CR is truly met at first time point, then efficacy of any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, will still be evaluated as PD at that point (since disease will reappear after CR). Best response will depend on whether minimum duration for SD is met. However, sometimes CR may be claimed when subsequent scans suggest small lesions are likely still present and in fact the subject has PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

4.4.4 Special notes on response evaluation

When nodal disease is included in the sum of target lesions and the nodules decrease to a normal size < 10 mm, they may still have a measurement reported on scans. This measurement should be recorded even though the nodules are normal in order not to overstate progression should it be based on increase in size of the nodules. As noted earlier, this means that subjects with CR may not have a total sum of zero on the CRF.

In trials where confirmation of response is required, repeated "NE" time point evaluations may complicate best response evaluation. The analysis plan for the trial must address how missing data/evaluations will be addressed in determination of response and progression. For example, in most studies it is reasonable to consider a subject with time point responses of PR-NE-PR as a confirmed response.

Subjects with an overall deterioration of health status requiring discontinuation of treatment without objective evidence of PD at that time should be reported as symptomatic deterioration. Efforts should be made to evaluate objective progression even after discontinuation of treatment. Symptomatic deterioration is not a description of an objective response: it is a reason for discontinuation of treatment. The objective response status of such subjects is to be determined by evaluation of target and non-target lesion as shown in Tables 1-3.

Conditions that are defined as early progression, early death and not evaluable are study specific and shall be clearly described in each protocol (depending on treatment duration and treatment cycle).

In some circumstances it may be difficult to distinguish residual lesions from normal tissues. When the evaluation of complete response depends upon this definition, it is recommended to perform a biopsy before evaluating the efficacy of complete remission of local lesions. FDG-PET may be used to confirm a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this

circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled evaluation. If at the next scheduled evaluation, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

4.5 Frequency of Tumor Re-Evaluation

Frequency of tumor re-evaluation during treatment should be protocol-specific and consistent with the type and schedule of treatment. However, in the phase II studies where the beneficial effect of treatment is not known, follow-ups for every 6-8 weeks (timed to coincide with the end of a cycle) is reasonable. Interval adjustments can be justified in specific regimens or circumstances. The protocol should specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumor type under study) and how often evaluations are repeated. Normally, all target and non-target sites are evaluated at each assessment. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when CR is identified in target disease or when progression in bone is suspected.

After the treatment, the need for tumor re-evaluations depends on whether the trial has made the response rate or the time to an event (progression/death) an endpoint. If time to an event (e.g. TTP/DFS/PFS) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomized comparative studies in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6-8 weeks on treatment or every 3-4 months after treatment) and should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment group in the timing of disease assessment.

4.6 Confirmatory Evaluation/Duration of Response

4.6.1 Confirmation

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, i.e., in randomized trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation

of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6-8 weeks) that is defined in the study protocol.

4.6.2 Duration of overall response

The duration of overall response will be measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study). The duration of overall complete response will be measured from the time criteria are first met for CR until the first date that recurrent or progressive disease is truly documented.

4.6.3 Duration of stable disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD). The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving SD for a minimum period of time is an endpoint in a particular study, the protocol should specify the minimal time interval required between two measurements for determination of SD.

Note: The duration of response and stable disease as well as the progression free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

4.7 PFS/TTP

4.7.1 Phase II studies

This guideline is focused primarily on the use of objective response endpoints for phase II clinical studies. In some circumstances, response rate may not be the optimal method to assess the potential anti-cancer activity of new agents/regimens. In such cases PFS/PPF at landmark time points, might be considered appropriate alternatives to provide an initial signal of biologic effect of new agents. It is clear, however, that in an uncontrolled trial, these measures are subject to

criticism since an apparently promising observation may be related to biological factors such as patient selection and not the impact of the intervention. Thus, phase II screening studies utilizing these endpoints are best designed with a randomized control. Exceptions may exist where the behavior patterns of certain cancers are so consistent (and usually consistently poor) that a non-randomized trial is justifiable. However, in these cases it will be essential to document with care the basis for estimating the expected PFS or PPF in the absence of a treatment effect.

Appendix 7. Management Principles for Immune Related Adverse Events

The principles specified in this section can be used as reference for the investigator when managing immune-related AEs. Investigators can select their own dosing regimens according to clinical reality.

The general principle is that AEs should be carefully evaluated and the differential diagnosis be made in accordance with the standard medical practice. Non-inflammatory causes should be considered and properly handled.

Corticosteroids are preferable drug for immuno-oncology treatment-related AEs. An oral dose equivalent to the recommended IV dose can be considered for ambulatory patients with low grade toxicity. The low bioavailability of oral administration should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with an internist or surgeon is recommended, especially before an invasive diagnostic or therapeutic procedure.

The frequency and severity of related adverse events included in these protocols will depend on the cancer immunotherapy or regimen being used.

Appendix 7.1. Management Principles for Gastrointestinal Adverse Events

Inflammatory causes of disease should be excluded. Opioids/anesthetics may mask the symptoms of perforation. Do not use infliximab in the case of perforation/sepsis.

Diarrhea/Colorectitis Grade (NCICTCAEv4)	Handling	Follow-Up
Grade 1 Diarrhea: Defecation frequency exceeds baseline by < 4 times/day; Colitis: no symptom.	◆ Continue the immunotherapy according to the study protocol; ◆ Symptomatic treatment.	◆ Closely monitor aggravated symptoms. ◆ Educate subjects to report aggravated symptoms immediately. If it is aggravated: ◆ Provide treatment according to the method for grade 2 or grade 3/4 situations.
Grade 2-3 Diarrhea (Grade 2): Defecation frequency exceeds baseline for 4-6 times/day; intravenous infusion of < 24 h is required; daily living is not affected; Colitis (Grade 2): abdominal pain; hematochezia. Diarrhea (Grade 3): Defecation frequency exceeds baseline for ≥ 7 times/day; fecal incontinence; intravenous infusion of ≥ 24 h is required; daily living is affected; Colitis (Grade 3): severe abdominal pain; indications for medical intervention; peritoneal signs;	◆ Delay the immunotherapy according to the study protocol; ◆ Symptomatic treatment.	If it is improved to Grade 1: ◆ Resume the immunotherapy according to the study protocol. If it lasts for > 5-7 days or relapses: ◆ Intravenous administration of 0.5-1.0 mg/kg/d methylprednisolone or an equivalent orally administrated dose; ◆ When the symptoms improve to grade 1, reduce the dose of steroids for at least 1 month and consider prophylactic antibiotics to prevent opportunistic infections, then resume the immunotherapy as per study protocol. If the symptoms aggravated or persisted after > 3-5 days of oral administration of steroids: ◆ Provide treatment according to the method for grade 3/4 situations.
Grade 4 Grade 4: life-threatening; perforation.	◆ Terminate the immunotherapy according to the study protocol; ◆ Intravenous administration of 1.0-2.0 mg/kg/d methylprednisolone or an equivalent IV dose; ◆ Add prophylactic antibiotics to prevent opportunistic infections; ◆ Consider lower GI endoscopy.	If symptoms improve: ◆ Continue steroid treatment until the symptoms return to grade 1, then gradually reduce the dose of steroids for at least 1 month. If it lasts for > 3-5 days or relapses after improvement: ◆ Add 5 mg/kg infliximab (if there are no contraindications). Note: Do not use infliximab in the case of perforation/sepsis.

Once a subject given intravenous injections of steroids shows a sustained clinical improvement, the subject can switch to an equivalent dose of oral corticosteroids (e.g., prednisone) by the time or before the dose of steroid injections starts to be gradually reduced. When switching to oral corticosteroids with an equivalent dose, it should be considered that the bioavailability of oral corticosteroids is relatively low.

Appendix 7.2 Management Principles for Pulmonary Adverse Events

Inflammatory causes of disease should be excluded. If it is due to a non-inflammatory cause, a symptomatic treatment should be given while the immunotherapy should be continued. Imaging evaluation and consultations with the respiratory department should be performed.

Grade of Pulmonitis (NCICTCAEv4)	Handling	Follow-Up
Grade 1 Only radiographic changes	◆ Consider delaying the immunotherapy; ◆ Monitor symptoms every 2-3 days; ◆ Consider consulting with respirologist and infectious diseases specialist.	◆ Repeat imaging examinations at least every 3 weeks. <u>If it is aggravated:</u> ◆ Provide treatment according to the method for grade 2 or grade 3/4 situations.
Grade 2 Mild to moderate new symptoms	◆ Delay the immunotherapy according to the study protocol; ◆ Consult with respirologist and infectious diseases specialist; ◆ Intravenous administration of 1.0 mg/kg/d methylprednisolone or an equivalent orally administrated dose; ◆ Consider bronchoscopy and lung biopsy.	◆ Repeat imaging examinations every 1-3 days. <u>If symptoms improve:</u> ◆ When symptoms return to near baseline levels, reduce the dose of steroids for at least 1 month and then resume the immunotherapy as per study protocol while considering prophylactic antibiotics. <u>If the symptoms are not improved or aggravated after 2 weeks:</u> ◆ Provide treatment according to the method for grade 3/4 situations.
Grade 3-4 Severe new symptoms; new onset/aggravation of hypoxia; life-threatening.	◆ Terminate the immunotherapy according to the study protocol; ◆ Consult with respirologist and infectious diseases specialist; ◆ Intravenous administration of 2-4 mg/kg/d methylprednisolone or an equivalent IV dose; ◆ Add prophylactic antibiotics to prevent opportunistic infections; ◆ Consider bronchoscopy and lung biopsy.	<u>If symptoms improve to the baseline level:</u> ◆ Gradually reduce the dose of steroids for at least 6 weeks. <u>If the symptoms are not improved or aggravated after 48 h:</u> ◆ Add other immunosuppressants (e.g., infliximab, cyclophosphamide, intravenous immunoglobulin or mycophenolate mofetil).

Once a subject given intravenous injections of steroids shows a sustained clinical improvement, the subject can switch to an equivalent dose of oral corticosteroids (e.g., prednisone) by the time or before the dose of steroid injections starts to be gradually reduced. When switching to oral corticosteroids with an equivalent dose, it should be considered that the bioavailability of oral corticosteroids is relatively low.

Appendix 7.3. Management Principles for Hepatic Adverse Events

Non-inflammatory causes of disease should be excluded. If it is due to a non-inflammatory cause, a symptomatic treatment should be given while the immunotherapy should be continued. Consider imaging examinations to rule out obstruction/tumor progression.

Elevation Grade in the Hepatic Function Test (NCICTCAEv4)	Handling	Follow-Up
Grade 1 AST/ALT > 3 × ULN and/or TBIL > 1 × ULN but ≤ 1.5 × ULN	◆ Continue the immunotherapy according to the study protocol.	◆ Continue hepatic function monitoring as per study protocol. If it is aggravated: ◆ Provide treatment according to the method for grade 2 or grade 3/4 situations.
Grade 2 AST/ALT > 3 × ULN, but ≤ 5 × ULN and/or TBIL> 1.5 × ULN but ≤ 3 × ULNN	◆ Delay the immunotherapy according to the study protocol; ◆ Increase the monitoring frequency to once every 3 days.	If symptoms recover to the baseline level: ◆ Resume routine monitoring and resume the immunotherapy according to the study protocol. If elevation persists for > 5-7 days or aggravates: ◆ Intravenous administration of 0.5-1 mg/kg/d methylprednisolone or an equivalent orally administrated dose. If LFT recovers to Grade 1 or to the baseline level, reduce the dose of steroids for at least 1 month, and consider prophylactic antibiotics to prevent opportunistic infection and then resume the immunotherapy according to study protocol.
Grade 3-4 ALT/AST > 5 × ULN and/or TBIL > 3 × ULN	◆ Terminate the immunotherapy according to the study protocol*; ◆ Increase the monitoring frequency to once every 1-2 days; ◆ Intravenous administration of 1.0-2.0 mg/kg/d methylprednisolone or an equivalent dose via intravenous injection**; ◆ Add prophylactic antibiotics to prevent opportunistic infections; ◆ Consultation with the gastroenterology department.	If it recovers to Grade 2: ◆ Reduce the dose of steroids for at least 1 month. If not improving, or even aggravating or recurring after > 3-5 days: ◆ Add 1 g of mycophenolate mofetil, bid; ◆ If the symptoms are not relieved within 3-5 days, other immunosuppressants are considered based on local guidelines.

Once a subject given intravenous injections of steroids shows a sustained clinical improvement, the subject can switch to an equivalent dose of oral corticosteroids (e.g., prednisone) by the time or before the dose of steroid injections starts to be gradually reduced. When switching to oral corticosteroids with an equivalent dose, it should be considered that the bioavailability of oral corticosteroids is relatively low.

*** If AST/ALT ≤ 8 × ULN and TBIL ≤ 5 × ULN, the immunotherapy can be delayed rather than discontinued.**

****For grade 4 hepatitis, the recommended starting dose of methylprednisolone via intravenous injection is 2 mg/kg/d.**

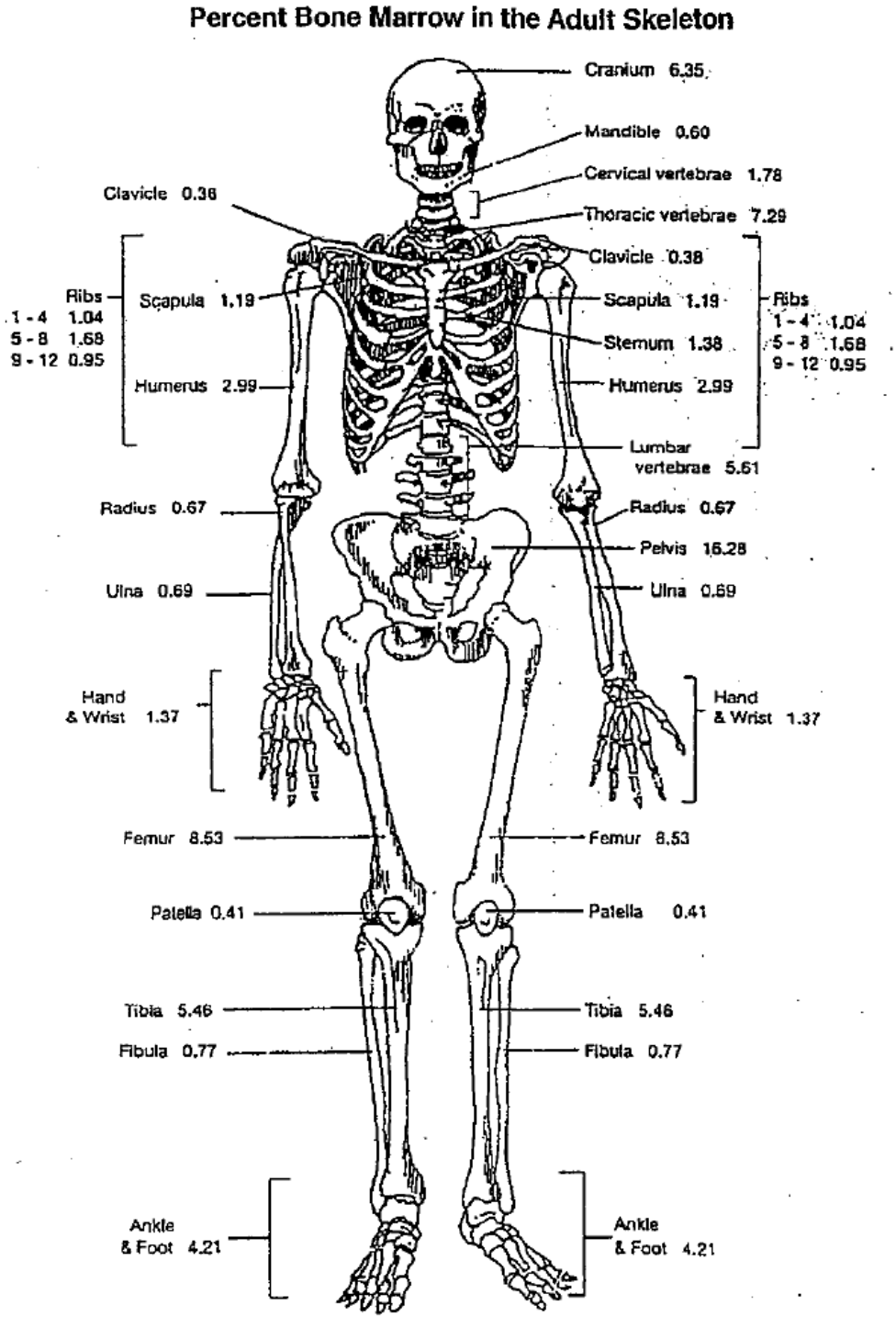
Appendix 7.4. Management Principles for Endocrine Adverse Events

Non-inflammatory causes of disease should be excluded. If it is due to a non-inflammatory cause, a symptomatic treatment should be given while the immunotherapy should be continued. Visual field tests, endocrinology consultation and imaging examinations are considered.

TSH Increased/Thyroxine Decreased	◆ Continue the immunotherapy according to the study protocol; ◆ Treatment may be continued through initiation of thyroid hormone replacement therapy if thyroxine is reduced.
Immune-Related Hypophysitis	◆ Assess endocrine functions; ◆ Consider pituitary scans; ◆ Continue the medication for Grade 1; ◆ Delay the immunotherapy according to the study protocol for Grade 2-3; ◆ Treatment discontinuation for Grade 4
Suspected Adrenal Crisis (e.g., severe dehydration, hypotension, and shock that does not match the severity of the disease)	◆ Terminate the immunotherapy according to the study protocol; ◆ Exclude sepsis; ◆ Intravenous administration of a stress dose of steroids containing mineralocorticoids; ◆ Intravenous infusion; ◆ Consult an endocrinologist; ◆ If adrenal crisis is ruled out, treat the symptomatic endocrinopathy using the methods described above.

Once a subject given intravenous injections of steroids shows a sustained clinical improvement, the subject can switch to an equivalent dose of oral corticosteroids (e.g., prednisone) by the time or before the dose of steroid injections starts to be gradually reduced. When switching to oral corticosteroids with an equivalent dose in the lungs and liver, it should be considered that the bioavailability of oral corticosteroids is relatively low.

Appendix 8. Percent Bone Marrow Content in Human Skeleton



Woodward Holoday E. A summary of the data of Mechanik on the distribution of human bone marrow. Phys Med Biol. 1960;5:57-59

Appendix 9. Prohibited Traditional Chinese Medicines During the Study Period

Traditional Chinese medicines prohibited during the study include but are not limited to the following:

- ✓ Huatan Huisheng tablet
- ✓ Brucea Javanica oil soft capsule
- ✓ Mandarin melon berry syrup
- ✓ Cantharidin
- ✓ Cinobufotalin
- ✓ Bufotoxin
- ✓ Kang'ai injection
- ✓ Kanglaite injection
- ✓ Zhongjiefeng injection
- ✓ Aidi injection
- ✓ Awei Huapi ointment
- ✓ Kangaiping pill
- ✓ Fukang capsule
- ✓ Xiaoaiping
- ✓ Pingxiao capsule
- ✓ Pingxiao tablet
- ✓ Shendan Sanjie capsule
- ✓ Ankangxin capsule
- ✓ Boshengaining
- ✓ Zedoary turmeric oil and glucose injection
- ✓ Kanglixin capsule
- ✓ Cidan capsule

Appendix 10. EORTC QLQ-C30 Scale

EORTC Quality of Life Measurement Scale QLQ-C30 (V3.0) (Chinese Version)

(When there is inconsistency with the official scale, the official scale prevails)

We would like to know about you and your health status. Please answer all the questions yourself. Please circle the number that best applies to you. There are no "right" or "wrong" answers. The information you provide will be kept strictly confidential.

Please fill in your code (no.): _____

Date of birth (DD/MM/YYYY): _____

Today's date (DD/MM/YYYY): _____

	None	A little bit	Quite a bit	Very much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, bathing or using the toilet?	1	2	3	4

During the past week:	None	A little bit	Quite a bit	Very much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Continued on next page

During the past week:	None	A little bit	Quite a bit	Very much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?				

For the following questions, please circle the number from 1 to 7 that best applies to you

29. How would you rate your overall <u>health condition during the past week</u>?

1	2	3	4	5	6	7
Very bad						Very good

30. How would you rate your overall <u>quality of life</u> during the past week?

1	2	3	4	5	6	7
Very bad						Very good

Appendix 11. iRECIST Response Evaluation Criteria in Solid Tumors

iRECIST Response Evaluation Criteria in Solid Tumors (Excerpt)

(Seymouretal: Supplementary Appendix to: iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol, 2017; 18(3): e143-e152.)

Note: This appendix is translated internally and is for reference only. Please refer to the English version during practice.

3 iRECIST Response Evaluation

iRECIST can be used to assess overall efficacy. In immunotherapy, the infiltration of immune cells may cause temporary enlargement of the tumor tissue, and may also cause the tumor tissue that would otherwise be undetectable large enough to be detectable. In many respects, the provisions of iRECIST are the same as those of RECIST v1.1, but some of the contents have been adjusted to accurately reflect whether the tumor is really progressing when the tumor burden increases or new lesions appear.

The main differences between iRECIST and RECIST v1.1 are detailed below. Reactions judged using iRECIST are marked with the prefix "i". The overall response and the BOR of iRECIST at a certain time point are recorded separately.

3.1 Progression Confirmation

Unlike RECIST v1.1, iRECIST requires further confirmation of progressive disease (PD), using iUPD to represent unconfirmed progression, and iCPD to represent confirmed progression. The confirmatory imaging evaluation will be performed 4 weeks (but no more than 8 weeks) after iUPD.

Compared with the previous imaging evaluation, if the tumor burden increases further and meets at least one of the following criteria, iCPD is confirmed:

- Among the tumor burdens (including target lesions, non-target lesions, or new lesions) judged to be progressive (iUPD) as per RECIST v1.1, the burden continued to increase compared with the burden at iUPD.
    - The absolute value of the sum of diameters of target lesions continues to increase by at least 5 mm;
    - Non-target lesions continue to progress significantly, accompanied by an increase in tumor burden;

- Enlargement of new lesions which occurred recently (the absolute value of the sum of diameters of new target lesions must increase by at least 5 mm) or appearance of other new lesions

➢ Progression in lesions not previously identified as progressive (target lesions, non-target lesions, or new lesions) (as per RECIST v1.1), including the appearance of new lesions.

If iUPD is not confirmed in the next evaluation, it should be judged as other results (if it still meets the PD criteria and does not aggravate, it is judged as iUPD; compared with the baseline, if it meets the evaluation criteria of SD, PR, or CR, then it is judged as iSD , iPR, or iSD, respectively). As shown in Table 2, if a previous iUPD is not confirmed as iCPD in the next evaluation, then the response evaluation (including the best overall response) at the next time point can be iCR, iPR, or iSD.

3.2 New Lesions

New lesions should be evaluated and measured as per RESIST1.1 [up to 5 lesions, no more than 2 lesions per organ, and the long diameter of the lesion shall be at least 10 mm (for lymph node lesions, the short diameter shall be at least 15 mm)]. New lesions will be recorded as new target lesions (NLT) and new non-target lesions (NLNT) to clearly distinguish them from baseline target lesions and non-target lesions.

New lesions can be judged as NLT or NLNT and used as the basis for the judgment of iUPD (or iCPD). However, the measurement of the new target lesions should not be included in the measured sum of the original target lesions at baseline. Instead, these measurements will be collected separately in the case record form.

Since the appearance of new lesions is assessed as iUPD, and the next evaluation will be performed in at least 4 weeks (up to 8 weeks), progression can be confirmed when any of the following situations occurs: the sum of diameters of new target lesions has increased by at least 5 mm; or the new non-target lesions have enlarged (no significant progression required); appearance of other new lesions.

Table 3. Evaluation of immune response at various time points

Original target lesion*	**Original non-target lesion***	**New Lesion**	**Judgment of overall response at this time point**	
			Not iUPD last time**	**iUPD last time**; *****
iCR	iCR	None	iCR	iCR
iCR	Non-iCR/Non-iUPD	None	iPR	iPR
iPR	Non-iCR/Non-iUPD	None	iPR	iPR
iSD	Non-iCR/Non-iUPD	None	iSD	iSD

Original target lesion*	**Original non-target lesion***	**New Lesion**	**Judgment of overall response at this time point**	
			Not iUPD last time**	**iUPD last time**; *****
iUPD has no progression or has decreased	iUPD has no progression or has decreased	Yes	NA	The increase in the size or number of new lesions (the sum of diameters of new target lesions increases by ≥ 5 mm or new non-target lesions increase) is iCPD. If the changes in new lesions do not reach the above level, they are still iUPD.
iSD	iUPD	None	iUPD	The original non-target lesions, if further increasing in size (no need become significant PD as per RECIST v1.1), are iCPD; otherwise, the iUPD conclusion is maintained.
iUPD	Non-iCR/Non-iUPD	None	iUPD	The original target lesions, if further increasing in size by ≥ 5 mm, are iCPD; otherwise, they are iUPD.
iUPD	iUPD	None	iUPD	If the original target lesions increase in size by ≥ 5 mm, or the original non-target lesions increase in size (no need to increase significantly), they are iCPD; if there is no increase, they are iUPD.
iUPD	iUPD	Yes	iUPD	If the original target lesions increase in size by ≥ 5 mm, or the original non-target lesions increase in size (no need to increase significantly), or the new lesions increase in size or number, they are iCPD; otherwise, they are iUPD.
Non-iUPD/PD	Non-iUPD/PD	Yes	iUPD	The new lesions, if with an increase in size or number, are iCPD; otherwise, they are iUPD.
*As per RECIST v1.1. If there is no pseudoprogression, the criteria for CR, PR, and SD as per RECIST v1.1 and iRECIST are the same; ** Any lesion type; *** Judged in the evaluation prior to this time point.				