Title: An Open-Label, Single Arm, Multi-Center, Phase 2 Study of PD-1 Antibody SHR-1210 in Subjects with Relapsed or Refractory Classic Hodgkin's Lymphoma

NCT number: NCT03155425

Date: 19 Jul., 2017

AN OPEN-LABEL, SINGLE ARM, MULTI-CENTER, PHASE 2 STUDY OF PD-1 ANTIBODY SHR-1210 IN SUBJECTS WITH RELAPSED OR REFRACTORY CLASSIC HODGKIN'S LYMPHOMA

Protocol No.: SHR-1210-II-204
Study Phase: II
Compound Code: SHR-1210
Medical Director: [redacted]
Leading Site of Clinical Study: Beijing Cancer Hospital
Jiangsu Cancer Hospital
Principal Investigators: Prof. Jun Zhu, Prof. Jifeng Feng

Version No.: 3.0
Version Date: 19 Jul., 2017

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
Version 1.0	25 Apr., 2017	Not applicable
Version 2.0	6 May, 2017	See separate document: Amendment Instructions of Protocol Version 2.0
Version 3.0	19 Jul., 2017	See separate document: Amendment Instructions of Protocol Version 3.0

Sponsor's Signature Page

I have read and confirmed this clinical study protocol (protocol no.: SHR-1210-II-204, version no.: 3.0, version date: 19 Jul., 2017). 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 Site)

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 investigational drug; I have read the materials of preclinical studies of the investigational drug 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 authority, 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, and submit it to the ethics committee and to the drug regulatory authority for filing purposes.

Study Site: _____

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

Principal Investigator's Signature Page (Leading Site)

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 investigational drug; I have read the materials of preclinical studies of the investigational drug 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 authority, 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, and submit it to the ethics committee and to the drug regulatory authority for filing purposes.

Study Site: _____

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

Principal Investigator's Signature Page (Participating Site)

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 investigational drug; I have read the materials of preclinical studies of the investigational drug 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 authority, 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, and submit it to the ethics committee and to the drug regulatory authority for filing purposes.

Study Site: _____

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

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PROTOCOL SYNOPSIS

Study Title	An Open-Label, Single Arm, Multi-Center, Phase 2 Study of PD-1 Antibody SHR-1210 in Subjects with Relapsed or Refractory Classic Hodgkin's Lymphoma
Protocol No.	SHR-1210-II-204
Version No.	3.0
Sponsor	Jiangsu Hengrui Pharmaceuticals Co., Ltd.
Principal Investigators	Prof. Jun Zhu, Prof. Jifeng Feng
Participating Study Sites	Approximately 15 sites
Study Objectives	**Primary objective** To evaluate the objective response rate (ORR) of PD-1 antibody SHR-1210 in the treatment of relapsed or refractory classic Hodgkin's lymphoma. **Secondary objectives** • To investigate and evaluate the duration of response (DoR), progression-free survival (PFS), time to response (TTR), and overall survival (OS) of PD-1 antibody SHR-1210 in the treatment of patients with relapsed or refractory classic Hodgkin's lymphoma (cHL). • To evaluate the safety of PD-1 antibody SHR-1210 in patients with relapsed or refractory classic Hodgkin's lymphoma (cHL). • To evaluate the pharmacokinetic (PK) parameters of PD-1 antibody SHR-1210 in patients with relapsed or refractory classic Hodgkin's lymphoma (cHL)
Study Endpoints	**Primary endpoint** • Objective response rate (ORR) assessed by the independent review committee (IRC), including the proportion of complete response (CR) and partial response (PR)

	Secondary endpoints • Objective response rate (ORR) assessed by the investigators, including the proportion of complete response (CR) and partial response (PR) • Duration of response (DoR) • Progression-free survival (PFS) • Time to response (TTR) • Overall survival (OS) • Safety: adverse events (AEs), clinical laboratory measurements • Population estimates of pharmacokinetic (PK) parameters
Study Population	Chinese adult patients with refractory or relapsed cHL.
Study Design	This study is an open-label, single-arm, multi-center, phase II clinical study of PD-1 antibody SHR-1210 in the treatment of patients with refractory or relapsed classic Hodgkin's lymphoma.
Investigational Drug	SHR-1210 Injection
Method of Administration	All subjects will receive an intravenous infusion of SHR-1210 at 200 mg/dose over 30 min (not less than 20 min and not more than 60 min, including rinsing), once every two weeks (q2w), until the following conditions occur: progressive disease, intolerable toxicity, or other reasons specified in the protocol.
Inclusion Criteria	Patients must meet all of the following criteria to be eligible for this study: 1. Age ≥ 18 years old, male or female; 2. With histologically identified cHL; 3. Have relapsed (confirmed progressive disease [PD] after the latest treatment) or refractory (failure to achieve complete response or partial response after the latest treatment) cHL, and must meet any of the following criteria: a) Have not reached response after autologous hematopoietic stem cell transplant or have progressed;

b) Have previously received at least 2 lines of systemic chemotherapy and not suitable for autologous stem cell transplant

4. Have a measurable lesion. Measurable lesions are defined as: the longest diameter > 1.5 cm for lymph node lesions in CT cross-sectional images or the longest diameter > 1.0 cm for extranodal lesions; and the lesions should be FDG-PET positive;
5. With an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1
6. With a life expectancy of ≥ 12 weeks
7. Patients must undergo all laboratory tests during the screening period as required by study protocol, and must complete such tests within 14 days before enrollment. Laboratory tests at screening must meet the following criteria:

   Hematology (without blood transfusion, G-CSF, or corrective treatment within 14 days prior to screening):

   1) Hb ≥ 80 g/L;
   2) ANC ≥ 1.0×10^9/L;
   3) PLT ≥ 75×10^9/L;

   Clinical chemistry:

   1) TBIL < 1.5 × upper limit of normal (ULN);
   2) ALT and AST ≤ 2.5 × ULN;
   3) Serum Cr ≤ 1.25 × ULN or endogenous CrCl ≥ 45 mL/min (Cockcroft-Gault formula)

   Coagulation function (unless the subject is receiving anticoagulant therapy and the coagulation parameters (PT/INR and APTT) at the time of screening are within the expected range of anticoagulant therapy):

   1) International normalized ratio (INR) ≤ 1.5 × ULN;
   2) Activated partial thromboplastin time (APTT) ≤ 1.5 × ULN;
8. Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to the first administration and be willing to take highly effective contraceptive measures during the study and within 60 days after the last dose of the investigational drug (around 5 half-lives of the drug + menstrual cycle). Male patients with female partners of childbearing potential must have undergone surgical sterilization or

	agree to take highly effective contraceptive measures during the study and within 120 days after the last dose of the investigational drug (around 5 half-lives of the drug + sperm production cycle); 9. Patients must participate voluntarily, sign the informed consent form, have good compliance, and cooperate with follow-up visits.
Exclusion Criteria	Patients meeting any of the following are ineligible to participate in this study 1. With nodular lymphocyte predominant Hodgkin's lymphoma or gray zone lymphoma 2. With known central nervous system (CNS) lymphoma 3. Medical history and concurrent diseases 1) With any active, known, or suspected autoimmune disease. Patients who are stable and do not require systemic immunosuppressive treatment may be enrolled; 2) With a condition requiring systemic treatment with either corticosteroids (> 10 mg/day of prednisone or equivalent) or other immunosuppressive medications within 14 days before receiving the investigational drug. In the absence of active autoimmune disease, inhaled or topical use of corticosteroids and an equivalent dose to > 10 mg/day of prednisone for adrenal hormone replacement are permitted; 3) Received tumor antigen vaccines or other immunostimulatory anti-tumor treatments within 3 months before receiving the investigational drug; 4) Prior treatment with anti-PD-1 antibodies, anti-PD-L1 antibodies, anti-PD-L2 antibodies, or anti-CTLA-4 antibodies (or any other antibody targeting T-cell co-stimulation or checkpoint pathways); 5) Currently participating in another clinical study or less than 4 weeks from the end of the last clinical study treatment; 6) With a known history of interstitial pneumonia or highly suspected of interstitial pneumonia; or with conditions that may interfere with the testing or management of suspected treatment-related pulmonary toxicities; 7) With other active malignant tumors requiring treatment at the same time;

8) With a history of malignant tumors, except for patients with skin basal cell carcinoma, superficial bladder cancer, cutaneous squamous cell carcinoma, or cervical carcinoma *in situ* who have undergone possible curative treatment and do not have disease recurrence within 5 years since starting the treatment
9) Less than 4 weeks from prior cancer chemotherapy, radiotherapy, and immunotherapy, including local-regional treatment; patients whose anti-tumor treatment-related adverse reactions (except for alopecia) after previous systemic anti-tumor treatment have not recovered to NCI-CTCAE Grade ≤ 1
10) Have received allogeneic hematopoietic stem cell transplant
11) Have received autologous stem cell transplant within 90 days before the first dose
12) Have undergone major surgery or have severe trauma, with the effects of surgery or trauma eliminated for less than 14 days before enrollment;
13) Patients with active pulmonary tuberculosis (TB) should be excluded. Active TB should be ruled out in patients suspected of such condition, by chest X-ray, sputum test, and examinations of clinical symptoms and signs. Patients with a history of active TB infection within the past year should be excluded, despite being treated; patients with a history of active TB infection more than 1 year ago should also be excluded, unless it is proven that the course and type of prior TB treatment are both appropriate;
14) With severe acute or chronic infections requiring systemic treatment;
15) With heart failure (New York Heart Association Class III or IV) and despite receiving appropriate pharmacological treatment, poorly controlled coronary artery disease or arrhythmia, or a history of myocardial infarction within 6 months before screening;
16) Inoculated with live vaccine within 4 weeks before receiving the investigational drug. Injections of inactivated influenza vaccine for seasonal influenza are permitted, but not live attenuated influenza vaccines for intranasal use.

	4. Physical examination and laboratory tests 1) With a known history of human immunodeficiency virus (HIV) seropositive status or acquired immunodeficiency syndrome (AIDS); 2) With untreated active hepatitis (hepatitis B: HBsAg positive and HBV DNA ≥ 500 IU/mL; hepatitis C: HCV RNA positive with abnormal liver function); co-infection with hepatitis B and hepatitis C; 5. The investigators determine that the patients may have other factors that may result in the premature termination of the study, such as other serious illnesses or serious laboratory abnormalities or family or social factors that could affect the safety of the subject, or study data and sample collection
PK Study	A PK study will be carried out in 12 subjects enrolled in this study (the PK study will only be carried out in Beijing Cancer Hospital, the leading site). 1) There are 4 blood collection time points for the single dose in Cycle 1: within 0.5 h pre-administration on D1, within 5 min and at 2 h (±10 min) after the end of administration on D1, and on D8 (±60 min). 2) In Cycles 2, 4, and 6, a total of 2 blood sampling time points: within 0.5 h pre-administration and 5 min post-administration on D1. **The concentration of the parent drug in the blood sample will be determined, and the primary multiple-dose PK parameters will be investigated, mainly including:** 1) C_{max}: maximum blood concentration; 2) C_{min}: minimum blood concentration; 3) T_{max}: time to the maximum concentration; 4) Elimination half-life ($t_{1/2z}$); 5) Area under the concentration-time curve (AUC_{τ}); 6) Apparent volume of distribution (V_z); 7) Systemic clearance (CL_S); The above PK parameters of SHR-1210 in the human body will be calculated using the non-compartmental model. For multiple-dose pharmacokinetics, drug accumulation will be studied according to the maximum concentration and minimum concentration in multiple cycles.

Study Withdrawal Criteria	1. Withdrawal of informed consent and refusal of further follow-ups by subjects; 2. Continuing participation in the study is not in the best interests of the patient due to any clinical adverse reactions, laboratory abnormalities, or concurrent diseases, as assessed by the investigators; 3. Other investigator-assessed reasons requiring withdrawal, such as the inability to provide voluntary consent due to imprisonment or quarantine; 4. Lost to follow-up; 5. Death; 6. Study termination by the sponsor.
Study Treatment Discontinuation Criteria	The study treatment must be discontinued when any of the following occurs: 1. Treatment discontinuation requested by subjects; 2. Radiographic or clinical evidence of PD, unless the subject meets the criteria for continuing treatment after progression (see Section 8.6 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. Deterioration of the overall health suggesting treatment continuation impossible; 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 investigators.
Determination of Sample Size	This study uses a single-arm design. The primary objective is to evaluate the efficacy of SHR-1210 in the treatment of relapsed or refractory cHL. The study endpoint is ORR. By referring to historical research data and research results of similar products and given the current clinical practice requirements, the investigational drug can be judged as effective only when the lower limit of the 95% confidence interval for ORR obtained from the

	study data is greater than 40%. Therefore, the sample size for this study is determined based on the following 2 points: 1. the exact method (Clopper-Pearson) is used to calculate the 95% confidence interval for ORR; 2. the lower limit of the confidence interval is greater than 40%. Assuming that the ORR of SHR-1210 in the treatment of relapsed or refractory cHL reaches 65%, a power of 92.90% can be obtained with 50 subjects. Given a dropout rate of 20%, this study intends to enroll 60 subjects.
Data Analysis/ Statistical Methods	**Analysis sets/populations** This study will involve the following analysis sets or populations: • Informed Consent Set (ICS): all subjects who have signed the informed consent form. • Full Analysis Set (FAS): eligible subjects who have received the investigational drug. The FAS is the primary analysis set for efficacy analysis other than the primary efficacy endpoint. • Evaluable Set (ES): a subset of the FAS, defined as subjects with at least one post-baseline efficacy evaluation in the FAS. The ES is the primary analysis set for the primary efficacy endpoint ORR. • Per-Protocol Set (PPS): a subset of the FAS, defined as subjects in the FAS who have experienced no major protocol deviations. PPS is the secondary analysis set for efficacy analysis. Safety Set (SS): all enrolled subjects who have received the investigational drug and have post-administration evaluable safety data. SS is the primary analysis set for safety analysis. • PK Set (PKS): all enrolled subjects who have received the investigational drug and have post-administration evaluable PK data (concentration and/or parameters). **General analysis** Unless otherwise specified, all data in this study will be summarized using descriptive statistics according to the data type. Measurement data will be summarized using mean, standard deviation (SD), median, minimum, and maximum; count data and rank data will be summarized using frequency and

percentage; for time to event data, the Kaplan-Meier method will be used to estimate the median time and its overall 95% confidence interval will be calculated.

Efficacy analysis

For the objective response rate (ORR) based on the IRC's and investigators' assessment, point estimation will be performed, and the exact method (Clopper-Pearson) will be used to estimate the overall 95% confidence interval.

For other secondary efficacy endpoints, including duration of response (DoR), progression-free survival (PFS), time to response (TTR), and overall survival (OS), the Kaplan-Meier method will be used to estimate their median times and the overall 95% confidence intervals will be calculated.

The analysis of the primary efficacy endpoint will be based on the ES, and other efficacy analyses will be repeated based on the primary analysis set FAS and secondary analysis set PPS.

Safety analysis

The safety analysis will be summarized primarily using descriptive statistics. AEs, treatment-emergent AEs (TEAEs), SAEs, laboratory data, vital signs, and other data will be statistically summarized. Also, the exposure to the investigational drug (including treatment cycle, received total dose, and dose intensity) will be statistically summarized. The above data will be analyzed and summarized using Hengrui's current clinical study report standards. Such standards include but are not limited to the following:

Summary of AEs (of all causes and treatment-related);

Incidence and severity of AEs (of all causes and treatment-related);

Correlation analysis between AEs and investigational drug;

Analysis of outcomes of AEs;

Analysis of SAEs;

Descriptive statistical summary of laboratory measurements, vital sign data, and ECG data (post-baseline absolute values and post-baseline changes from baseline);

Classified summary of post-baseline vital sign data and ECG.

	Statistical analysis of PK PK analyses will be based on the PKS, and PK concentration and PK parameters will be summarized using descriptive statistics. Apart from the statistics listed in the general analysis, PK concentration and PK parameter data will be also summarized descriptively using geometric mean (GM), coefficient of variation (CV%), and geometric CV% (GCV%). In addition, for PK concentration data, average and median blood concentration-time curves (concentration-time curves) on linear scale and semi-logarithmic scale can be plotted, and individual subjects' concentration-time curves (linear scale and semi-logarithmic scale) can be plotted at the same time. If PK statistical analysis is outsourced, the statistical analysis plan provided independently by the vendor shall prevail for the specific statistical analysis and method plan.
Study Period	Anticipated enrollment of the first subject: Jun. 2017 Anticipated enrollment of the last subject: Nov. 2017 Anticipated study end time: 24 months after the last subject receives the first administration (about Dec. 2019)

SCHEDULE OF ACTIVITIES

Item	Screening Period[1] (-28 days)	Treatment Cycle (14 days)[2]		End of Treatment[3]	Follow-Up Period	
		D1 of Cycle 1	D1 of Every Cycle (±3 days)		Safety Follow-Up[6]	Survival Follow-Up[22]
Enrollment Assessment						
Signing of Informed Consent	√					
Verification of Eligibility	√					
Demographics	√					
Medical History	√					
History of Anti-Tumor Treatment	√					
Safety Evaluation						
ECOG PS	√	√	√	√	√	
Physical Examination[4]	√	√	√	√	√	
Vital Signs[5]	√	√	√	√	√	
Hematology	√		√	√	√	
Urinalysis[7]	√		√	√	√	
Fecal Occult Blood	√		√	√	√	
Hepatic and Renal Function[8]	√		√	√	√	
Blood Electrolytes[8]	√		√	√	√	
Coagulation Function[9]	√		See Notes	√	√	
Thyroid Function[10]	√		See Notes	√	√	

Item	Screening Period[1] (-28 days)	Treatment Cycle (14 days)[2]		End of Treatment[3]	Follow-Up Period	
		D1 of Cycle 1	D1 of Every Cycle (±3 days)		Safety Follow-Up[6]	Survival Follow-Up[22]
Fasting Blood Glucose	√		√	√	√	
Erythrocyte Sedimentation Rate	√					
LDH	√		√	√	√	
Virological Examination[11]	√		See Notes	√	√	
Blood HCG Test[12]	√	√	See Notes	√		
12-Lead ECG	√		√	√	√	
Echocardiography[13]	√					
Concomitant Medication/Treatment[18]	√	√	√	√	√	
Recording of AEs[19]	√	√	√	√	√	
Efficacy Evaluation						
Tumor CT or MRI Examination[14]	√		See Notes	See Notes	√	√
Tumor FDG-PET Examination[15]	√		See Notes			
Bone Marrow Aspiration and Biopsy[16]	√		See Notes			
IPS Score	√					
B Symptom Assessment[17]	√	√	See Notes	√		

Item	Screening Period[1] (-28 days)	Treatment Cycle (14 days)[2]		End of Treatment[3]	Follow-Up Period	
		D1 of Cycle 1	D1 of Every Cycle (±3 days)		Safety Follow-Up[6]	Survival Follow-Up[22]
PK Evaluation	√					
PK Blood Sampling [20]		See Notes	See Notes			
Study Treatment	√					
Injection of SHR-1210[21]		√	√			
Others						
Survival Information					√	√
Subsequent Anti-Tumor Treatment					√	√

Note: In addition to the examinations and time points shown in this table, the investigators may order additional tests at any time. Test results should be entered into the "Unscheduled Tests" sheet of the eCRF.

[1] Screening period: physical examination, vital signs, laboratory tests (including hematology, urinalysis, fecal occult blood, Hepatic and Renal Function, LDH, erythrocyte sedimentation rate, blood electrolytes, fasting blood glucose, coagulation function, thyroxine, virological examination, etc.), ECG, echocardiography (including LVEF) are tested within 14 days before the start of the study treatment; tumor CT or MRI examination (chest, abdomen, pelvis, and other sites of known lesions), FDG-PET examination, and bone marrow aspiration and biopsy are performed within 28 days before the start of the study treatment; blood HCG test is performed within 7 days before the start of the study treatment.

[2] Treatment cycle: In the event of a dose delay, the scheduled visit items at the same time point should be delayed accordingly to ensure consistency with the actual time of administration. Imaging evaluation (including CT or MRI examination, FDG-PET examination) should be carried out according to the scheduled time point and is not related to administration.

[3] End of study treatment/withdrawal from study: Examinations are not required at this stage if tumor CT or MRI has been performed within 4 weeks and safety evaluation and B symptom assessment have been completed within 7 days prior to treatment discontinuation.

[4] Physical examination: including height, weight, symptoms, and signs. Lymph node regions (for example, submandibular, cervical, supraclavicular, armpit, and groin) and abdominal organs (for example, liver and spleen) are checked within 72 h before each administration.

[5] Vital signs: including body temperature, blood pressure, heart rate, and respiratory rate; measure within 72 h before each administration.

[6] Safety follow-up: until 90 days after the last dose. The first visit should be conducted 30 days (±7 d ays) after the last dose or on the day of treatment discontinuation (if the date of treatment discontinuation is more than 84 days after the date of the last dose). The second visit is conducted approximately 90 days (±7 days) after the last dose. Both vi sits must be conducted at study sites.

[7] Urinalysis: In case of a urine protein ≥ 2+ at screening, a 24-h urine protein quantitation should be added.

[8] Hepatic and Renal Function: including ALT, AST, TBIL, ALP, BUN or serum urea level, creatinine, and albumin; blood electrolytes: including K^+, Na^+, Ca^{++}, Mg^{++}, and Cl^-.

[9] Coagulation function: When international normalized ratio (INR) is not available, prothrombin time (PT) will be used. Measure once every 2 cycles during treatment

[10] Thyroid function: including TSH, FT3, and FT4. Measure once every 4 cycles during treatment

[11] Virological examination: including HIV-Ab, HBV, and HCV infection testing. HBV testing requirements: HbsAg (qualitative), HbsAb (qualitative), HbcAb (qualitative), HbeAg (qualitative), and HbeAb (qualitative) should be tested at screening. If HBV infection is suspected, HBV-DNA should be tested (qualitatively; if positive, then quantitatively). HCV testing requirements: HCV-Ab is tested at screening to determine the presence of HCV infection. If positive, HCV-RNA will be tested (qualitatively; if positive, then quantitatively). For patients with hepatitis virus infection during the screening period, virological examination will be performed every 2 cycles during the treatment period, and the examination will be performed at the end of the treatment and during the safety follow-up; for patients with HBV infection, they will be tested for HBV-DNA (quantitative), and for patients with HCV infection, they will be tested for HCV-RNA (quantitative).

[12] Blood HCG test: Only for women of child bearing potential (WOCBP); test within 7 days before the first dose, and at least once every 4 weeks (±7 days) thereafter, regardless of the dosing cycle.

[13] Echocardiography: Perform according to local standard practice when clinically indicated.

[14] Tumor CT or MRI examination: Evaluate according to IWG2014 criteria, including CT scans with contrast of the chest, abdomen, pelvis, and any other sites of known lesions (such as neck). If the subject is allergic to contrast media or has bronchial asthma, kidney damage, or other diseases that make it difficult to perform contrast imaging, the subject can undergo chest CT without contrast + MRI scans of abdomen, pelvis, and any other sites of known lesions (such as neck). Evaluation will be carried out on D1 (±7 days) of Weeks 9, 17, 25, 37, and 49 after the start of treatment, then every 16 weeks (± 14 days) until Week 97, and then every 26 weeks (±21 days) until PD (for subjects who continue to receive the study treatment a fter radiographic progression, evaluation will be carried out until the investigational drug is discontinued), start of new anti-tumor treatment, or death.

[15] Tumor FDG-PET examination: Perform on D1 (±7 days) of Weeks 17 and 25 after the start of treatment. For subjects who have not obtained two negative FDG-PET results after Week 1 and until Week 49, it is necessary to add a tumor FDG-PET examination on D1 (±7 days) of Week 49. If it is necessary to determine whether a radiographic CR is obtained at other unscheduled FDG-PET evaluation time points after the start of treatment, the FDG-PET evaluation must be performed within 4 weeks after the CT evaluation.

[16] Bone marrow aspiration and biopsy: The subject can start the study treatment before obtaining the bone marrow biopsy result, but the result must be recorded in the subject's CRF. Patients with bone marrow involvement at baseline require bone marrow aspiration or biopsy to confirm CR status. Bone marrow aspiration and biopsy specimens are collected within 2 weeks after the CT scan. There is no need to perform bone marrow assessment after the bone marrow aspiration and biopsy result turns negative.

[17] B symptom assessment: including pyrexia of > 38 ℃ of unknown cause; night sweats; weight loss of > 10% within 6 mont hs before the assessment. The evaluation will be conducted on D1 of Cycle 1, and every 2 cycles thereafter until the discontinuation of study treatment. In addition, the evaluation is performed when the subject obtains PR or CR for the first time; if the subject has obtained PR before CR, the evaluation should be performed again when CR is obtained.

[18] Concomitant medication: Concomitant medications from 14 days before study treatment to 90 days after the last dose of study treatment will be collected. After the last dose, only concomitant medications for treatment-related AEs will be recorded.

[19] AE: As per NCI CTCAE V4.03, all AEs that occur from the signing of the informed consent form to 90 days after the last dose or the start of new anti-tumor treatment should be observed and documented. From 30 days after the last dose, for non-serious AEs, only those related to the investigational drug, including AEs of special interest, will be collected. All AEs should be followed up until Grade 0-1, recovery to baseline levels, or reasonably explained (e.g., lost to follow-up or death).

[20] PK blood collection: In Cycle 1, within 0.5 h pre-administration and within 5 min and at 2 h (± 10 min) post-administration on D1, and on D8 (± 60 min). In Cycles 2, 4, and 6, within 0.5 h pre-administration and 5 min post-administration on D1 (only for subjects participating in the PK study).

[21] SHR-1210 injection: Record the start and end time of the infusion of the investigational drug.

[22] Survival follow-up: The survival follow-up period will start after the end of the safety follow-up period. Survival follow-up will be conducted once every 3 months (±14 days), either via telephone or in -person visit.

ABBREVIATIONS

Abbreviation	Full Name
Ab	Antibody
ADA	Anti-drug antibody
ADL	Activities of daily living
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
APTT	Activated partial thromboplastin time
AUC	Area under the curve
BUN	Blood urea nitrogen
CD-ROM	Compact disc read-only memory
CIOMS	Council for International Organizations of Medical Sciences
CL	Clearance
CFDA	China Food and Drug Administration (now NMPA)
cHL	Classic Hodgkin's lymphoma
CNS	Central nervous system
Cr	Creatinine
CR	Complete response
CRA	Clinical research associate
CRC	Clinical research coordinator
CRO	Contract research organization
CT	Computed tomography
CV	Coefficient of variation
DNA	Deoxyribonucleic acid
DoR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
eCRF	Electronic case report form
FAS	Full analysis set
GCP	Good Clinical Practice
GCV	Geometric coefficient of variation
GLP	Good Laboratory Practices
GM	Geometric mean

Abbreviation	Full Name
GMP	Good Manufacturing Practices
Hb	Hemoglobin
HbsAg	Hepatitis B surface antigen
HbcAb	Hepatitis B core antibody
HbeAg	Hepatitis B e antigen
HBV	Hepatitis B virus
HCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HL	Hodgkin's lymphoma
ICH	International Conference on Harmonization
ICS	Informed consent set
INR	International normalized ratio
IPS	International Prognostic Score
irAE	Immune-related adverse event
IRB/IEC	Institutional review board/independent ethics committee
IRC	Independent Review Committee
LDH	Lactate dehydrogenase
Ldi	Longest transverse diameter of a lesion
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI-CTC	National Cancer Institute Common Toxicity Criteria
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
	Standard deviation
SDi	Shortest axis perpendicular to the Ldi
SDV	Source data verification
SOP	Standard operating procedure
SPD	Sum of the product of the perpendicular diameters for multiple lesions
TEAE	Treatment-emergent adverse event
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed death-1
PD	Progressive disease

Abbreviation	Full Name
PPD	Cross product of the Ldi and perpendicular diameter
PFS	Progression-free survival
PI	Principal investigator
PK	Pharmacokinetics
PLT	Platelet
PPS	Per-protocol set
PR	Partial response
PT	Prothrombin time
q2w	Every 2 weeks
RNA	Ribonucleic acid
SS	Safety set
TTP	Time to progression
TTR	Time to response
ULN	Upper limit of normal
WOCBP	Woman of childbearing potential

1. KEY FUNCTIONAL ROLES

Principal Investigators	Prof. Jun Zhu Contact: Beijing Cancer Hospital [redacted]	Prof. Jifeng Feng Contact: Jiangsu Cancer Hospital [redacted]
Sponsor's Medical Director	[redacted], M.D., Clinical Medical Director Contact: [redacted]	
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2. INTRODUCTION: BACKGROUND AND SCIENTIFIC RATIONALE

2.1. Background

Hodgkin's lymphoma (HL) is a tumor that originates from lymphocytes, and R-S cells are its characteristic pathological manifestation, while painless lymphadenopathy is its common clinical manifestation. WHO divides HL into classic Hodgkin's lymphoma (cHL) and nodular lymphocyte predominant Hodgkin's lymphoma (NLPHL). According to GLOBOCAN 2012, the number of new HL cases is 66,000 per year [1]. The National Cancer Institute of the United States estimated that the number of new HL cases in 2016 was about 8500, and the total number of HL patients in 2013 was 193,545 [2]. China lacks complete epidemiological data of HL, but the National Cancer Center of China estimated that there would be 88,200 new lymphoma patients in 2016 [3], and HL accounted for 8.54% of all lymphoma patients [4]. The cause of HL is still unknown. The etiology study of Epstein-Barr virus has received the most attention. The genome fragments of Epstein-Barr virus can be detected in the RS cells of about half of the patients.

The initial treatment of HL can achieve a high cure rate, but 5%-10% of patients are still resistant to the initial treatment, and 10%-30% of patients will relapse after a complete response (CR). High-dose chemotherapy combined with ASCT is the standard treatment for refractory or relapsed HL [5]. HL patients who relapse after ASCT usually have a poor prognosis. Studies have reported that the median time to progression (TTP) for treatment after ASCT failure was only 3.8 months, and the median overall survival (OS) was 26 months [6]. After ASCT failure, the treatment options are very limited. Among the cytotoxic drugs, only vinorelbine and gemcitabine show certain activity, but the duration of their effects is relatively short and complicated with obvious hematological toxicity. In recent years, some new drugs have also been explored in patients with relapsed or refractory HL. The detailed information can be seen in Table 1:

Table 1. Summary of treatments for relapsed or refractory HL

Drug Name	Drug Classification	Number of Subjects	Past ASCT (%)	ORR (%)
Brentuxiamb Vedotin[7]	ADC	102	100	75
Panobinostat[8]	HADC Inhibitors	129	100	27
Mocetinostat[9]	HADC Inhibitors	51	84	27
Lenalidomide[10]	IMiDs	38	87	19
Everolimus[11]	mTOR Inhibitors	57	58	42

In foreign countries, brentuximab vedotin has been approved for relapsed HL patients after ASCT, and the median OS is 22.4 months [12], while the median PFS of treatment after the failure of brentuximab vedotin is only 3.5 months [13].

The *Science* selected cancer immunotherapy as the most important scientific breakthrough in 2013. In recent years, immune checkpoint inhibitors represented by PD-1/PD-L1 monoclonal antibodies have achieved great success in the field of cancer treatment, especially in the treatment of melanoma, non-small cell lung cancer, kidney cancer, head and neck cancer, and Hodgkin's lymphoma. In a phase Ib clinical study of PD-1 antibody nivolumab developed by BMS, among 23 patients with relapsed or refractory cHL who were given 3 mg/kg of nivolumab once every 2 weeks, the ORR was as high as 87% and the 24-week PFS rate was 86% [14]. In a subsequent phase II study, 80 patients with cHL who failed both ASCT and brentuximab vedotin were enrolled and were given 3 mg/kg of nivolumab once every 2 weeks, and the ORR was 66.3%. The most common treatment-related AEs (≥ 15%) included asthenia (25%), injection related reaction (20%), and rash (16%). The most common treatment-related Grade 3/4 AEs were neutropenia (5%) and lipase concentration increased (5%). The most common SAE was fever [15]. Based on the results of these two trials, the FDA has approved nivolumab for the treatment of cHL after ASCT and brentuximab vedotin treatments. Pembrolizumab, a PD-1

antibody from Merck, was investigated in 31 cHL patients who had failed brentuximab vedotin treatment in the phase I study, and the patients were given 10 mg/kg of pembrolizumab once every 2 weeks, achieving an ORR of 65% (CR 16%, PR 48%) [16]. In a subsequent phase II study, pembrolizumab 200 mg was used once every 3 weeks to treat a total of 210 patients with relapsed/refractory cHL, with an ORR of about 70% and an proportion of CR of about 20%. The FDA has also approved it for the treatment of relapsed or refractory cHL [17]. In China, ASCT has not been widely used, and no brentuximab vedotin or PD-1 antibodies have been approved for the treatment of HL. Therefore, Chinese HL patients urgently need effective treatment options after the failure of initial treatment.

2.2. Scientific Rationale

2.2.1. Study rationale

Programmed death-1 (PD-1) is a protein receptor expressed on the surface of T cells. It binds to programmed death-ligand 1 (PD-L1) to transmit inhibitory signals and reduce the proliferation of T cells. Many human solid tumors express PD-L1, which is one of the reasons for their evasion of immune killing. The genetic variation at the 9p24.1 locus is a feature of malignant cells in classic Hodgkin's lymphoma and leads to the overexpression of PD-L1 and immune escape [18]. Epstein-Barr virus infection will also increase the expression of PD-L1 in EBV + Hodgkin's lymphoma [19]. The overexpression of PD-L1 in Hodgkin's lymphoma may indicate the sensitivity of this disease to PD-1 blockade. PD-1 antibodies nivolumab and pembrolizumab have shown good efficacy and safety in clinical studies of classic Hodgkin's lymphoma.

2.2.2. Rationale for drug development

Hengrui used PD-1 as a target and recombinant PD-1 protein as an immunogen to obtain a series of PD-1 antibodies in mice. Through a large number of *in vitro* binding assays, *in vitro* ligand blocking assays, T cell proliferation assays, animal studies, and antibody druggability assessments, an antibody prototype was selected. Then, a humanized design of the murine antibody prototype was carried out through computer simulations, resulting in several humanized anti-PD-1 monoclonal antibodies. Finally, SHR-1210, an antibody with the highest activity, was selected for further development. Preclinical study data showed that SHR-1210 has *in vivo* and *in vitro* anti-tumor effects similar to those of nivolumab and pembrolizumab on the market. Moreover, 3 phase I clinical studies of SHR-1210 are being carried out in Chinese solid tumor patients, and the dose escalation phase has been completed. No dose-limiting toxicity was found, and the maximum tolerated dose (MTD) was not reached, indicating good tolerability. This study aims to further explore the efficacy and safety of SHR-1210 in classic Hodgkin's lymphoma with potential benefit.

2.2.3. Basis of dosing regimen

PD-1 immune checkpoint inhibitors exert their effect on relieving immunosuppression by blocking the binding of PD-1/PD-L1. Therefore, the receptor occupancy of these inhibitors is the basic pharmacological mechanism that reflects the ultimate anti-tumor effects. Phase I PK studies showed that blood concentrations dropped to 1000 ng/mL or below on D15 after a single dose of 1 mg/kg and a fixed dose of 60 mg, and remained between 4000-9000 ng/mL after a single dose of 3 mg/kg and a fixed dose of 200 mg. Receptor occupancy assays suggested that a blood concentration of at least 2000 ng/mL is required to maintain the receptor saturation. Clinical results also suggested that a fixed dose of 200 mg every 2 weeks can maintain a saturated receptor occupancy. In phase I studies, the incidence of AEs did not increase with the dose, whether the drug was administered by weight or by dose fixed. Based on results from the studies described above and the convenience of clinical administration, a fixed dose of 200 mg every 2 weeks is selected as the treatment regimen for this study.

2.3. Potential Risks and Benefits

Relapsed or refractory HL lacks effective treatment drugs. In recent years, studies have found that PD-1 antibodies nivolumab and pembrolizumab have shown good efficacy in patients with classic Hodgkin's lymphoma, and both nivolumab and pembrolizumab have been approved by the FDA for the treatment of relapsed or refractory classic Hodgkin's lymphoma. SHR-1210 is a humanized PD-1 antibody independently developed by Hengrui. Preclinical data suggested that SHR-1210 has efficacy and anti-tumor effect similar to those of nivolumab and pembrolizumab. An ongoing phase I clinical study in China has found that SHR-1210 also shows certain efficacy in solid tumors of different types, and it has entered the phase III clinical study. The possible benefit for subjects enrolled in this study is partial or complete response. The maintenance of stable disease may also be a benefit for subjects with relapsed or refractory cHL. The treatment data of these subjects may guide the clinical treatment and development of SHR-1210 for cHL. The AEs with a high incidence in phase I studies were mainly reactive cutaneous capillary endothelial proliferation, rash, pyrexia, ALT increased, AST increased, and hypothyroidism, but most of them were Grade I-II and could be recovered without interrupting the continued use of the investigational drug. In addition, subjects undergoing biopsy may be at risk of bleeding and pain. For more detailed safety information, please refer to the second edition of SHR-1210 Investigator's Brochure and Informed Consent Form.

3. OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary objective

To evaluate the efficacy, namely objective response rate (ORR), of PD-1 antibody SHR-1210 in the treatment of relapsed or refractory classic Hodgkin's lymphoma.

3.1.2. Secondary objectives

- To investigate and evaluate the duration of response (DoR), progression-free survival (PFS), time to response (TTR), and overall survival (OS) of PD-1 antibody SHR-1210 in the treatment of patients with relapsed or refractory classic Hodgkin's lymphoma (cHL).
- To evaluate the safety of PD-1 antibody SHR-1210 in patients with relapsed or refractory classic Hodgkin's lymphoma (cHL).
- To evaluate the pharmacokinetic (PK) parameters of PD-1 antibody SHR-1210 in patients with relapsed or refractory classic Hodgkin's lymphoma (cHL).

3.2. Study Endpoints

3.2.1. Primary endpoint

- Objective response rate (ORR) assessed by the Independent Review Committee (IRC), including the proportion of complete response (CR) and partial response (PR)

3.2.2. Secondary endpoints

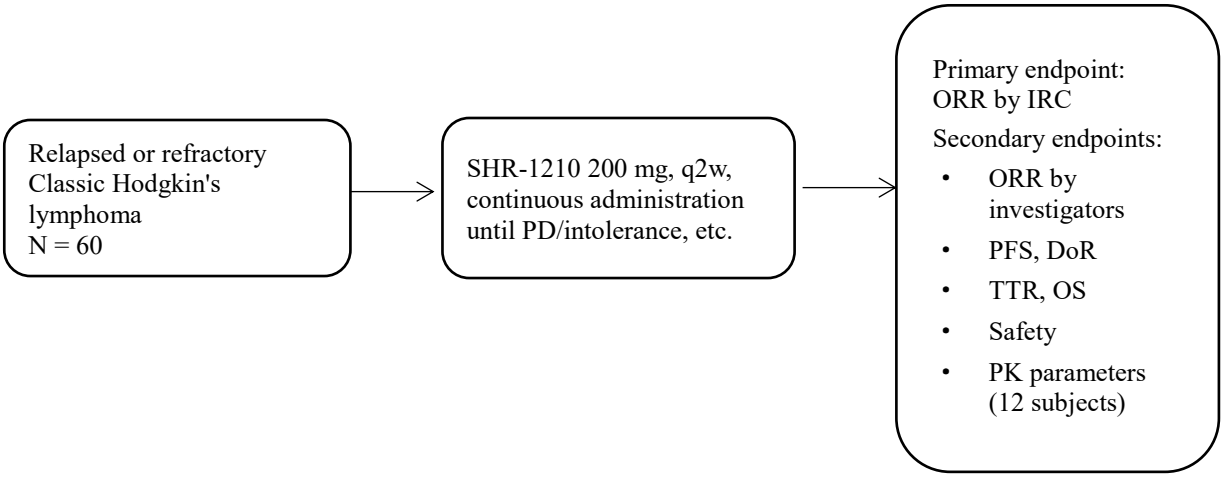
- ORR assessed by the investigators, including the proportion of CR and PR
- Duration of response (DoR)
- Progression-free survival (PFS)
- Time to response (TTR)
- Overall survival (OS)
- Safety: adverse events (AEs), clinical laboratory measurements
- Population estimates of pharmacokinetic (PK) parameters

4. STUDY DESIGN

This study adopts an open-label, single-arm, and multi-center design to evaluate the efficacy and safety of SHR-1210 in patients with relapsed or refractory classic Hodgkin's lymphoma, and to evaluate the PK parameters of 12 subjects at the same time. Sixty subjects who meet the enrollment conditions will be enrolled and given SHR-1210 at 200 mg/dose on D1 of each 2-week cycle, until the following conditions occur: progressive disease (PD), intolerable toxicity, or other reasons specified in the protocol. After treatment, the subjects will enter the follow-up period to receive safety follow-up or survival follow-up.

SHR-1210 is an immune checkpoint inhibitor. According to the experience with similar drugs, some subjects may experience delayed or early pseudo progression after receiving the immunotherapy agents. Therefore, subjects with first PD are allowed to continue to receive treatment under the premise of no obvious clinical deterioration per the judgment of the condition by the investigators, until PD is still determined in the next imaging evaluation.

The diagram of study design is shown as follows:



5. SELECTION AND WITHDRAWAL OF SUBJECTS

5.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for this study.

1) Age ≥ 18 years old, male or female;
2) With histologically identified cHL;
3) Have relapsed (confirmed progressive disease [PD] after the latest treatment) or refractory (failure to achieve complete response or partial response after the latest treatment) cHL, and must meet any of the following criteria:

a) Have not reached response after autologous hematopoietic stem cell transplant or have progressed

b) Have previously received at least 2 lines of systemic chemotherapy and not suitable for autologous stem cell transplant

4) Have a measurable lesion(s). Measurable lesion is defined as: the longest diameter > 1.5 cm for lymph node lesions in CT cross-sectional images or the longest diameter > 1.0 cm for extranodal lesions; and the lesions should be FDG-PET positive;

5) With an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1

6) With a life expectancy of ≥ 12 weeks

7) Patients must undergo all laboratory tests during the screening period as required by study protocol, and must complete such tests within 14 days before enrollment. Laboratory tests at screening must meet the following criteria:

   Hematology (without blood transfusion, G-CSF, or corrective treatment within 14 days prior to screening):

   A. Hb ≥ 80 g/L;

   B. ANC ≥ 1.0×10^9/L;

   C. PLT ≥ 75×10^9/L;

   Clinical chemistry:

   A. TBIL < 1.5 × upper limit of normal (ULN);

   B. ALT and AST ≤ 2.5 × ULN;

   C. Serum Cr ≤ 1.25 × ULN or endogenous CrCl ≥ 45 mL/min (Cockcroft-Gault formula)

   Coagulation function (unless the subject is receiving anticoagulant therapy and the coagulation parameters (PT/INR and APTT) at the time of screening are within the expected range of anticoagulant therapy):

   A. International normalized ratio (INR) ≤ 1.5 × ULN;

   B. Activated partial thromboplastin time (APTT) ≤ 1.5 × ULN;

9) Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to the first administration and be willing to take highly effective contraceptive measures during the study and within 60 days after the last dose of the investigational drug

(around 5 half-lives of the drug + menstrual cycle). Male patients with female partners of childbearing potential must have undergone surgical sterilization or agree to take highly effective contraceptive measures during the study and within 120 days after the last dose of the investigational drug (around 5 half-lives of the drug + sperm production cycle);

10) Patients must participate voluntarily, sign the informed consent form, have good compliance, and cooperate with follow-up visits.

5.2. Exclusion Criteria

Patients meeting any of the following criteria will be excluded:

1) With nodular lymphocyte predominant Hodgkin's lymphoma or gray zone lymphoma
2) With known central nervous system (CNS) lymphoma
3) Medical history and concurrent diseases
   a) With any active, known, or suspected autoimmune disease. Patients who are stable and do not require systemic immunosuppressive treatment may be enrolled;
   b) With a condition requiring systemic treatment with either corticosteroids (> 10 mg/day of prednisone or equivalent) or other immunosuppressive medications within 14 days before receiving the investigational drug. In the absence of active autoimmune disease, inhaled or topical use of corticosteroids and an equivalent dose to > 10 mg/day of prednisone for adrenal hormone replacement are permitted;
   c) Received tumor antigen vaccines or other immunostimulatory anti-tumor treatments within 3 months before receiving the investigational drug;
   d) Prior treatment with anti-PD-1 antibodies, anti-PD-L1 antibodies, anti-PD-L2 antibodies, or anti-CTLA-4 antibodies (or any other antibody targeting T-cell co-stimulation or checkpoint pathways);
   e) Currently participating in another clinical study or less than 4 weeks from the end of the last clinical study;
   f) With a known history of interstitial pneumonia or highly suspected of interstitial pneumonia; or with conditions that may interfere with the testing or management of suspected treatment-related pulmonary toxicities;
   g) With other active malignant tumors requiring treatment at the same time;
   h) With a history of malignant tumors, except for patients with skin basal cell carcinoma, superficial bladder cancer, cutaneous squamous cell carcinoma, or cervical carcinoma *in situ* who have undergone possible curative treatment and do not have disease recurrence within 5 years since starting the treatment

i) Less than 4 weeks from prior cancer chemotherapy, radiotherapy, and immunotherapy, including local-regional treatment; patients whose anti-tumor treatment-related adverse reactions (except for alopecia) after previous systemic anti-tumor treatment have not recovered to NCI-CTC AE Grade ≤ 1

j) Have received allogeneic hematopoietic stem cell transplant

k) Have received autologous stem cell transplant within 90 days before the first dose

l) Have undergone major surgery or have severe trauma, with the effects of surgery or trauma eliminated for less than 14 days before enrollment;

m) Patients with active pulmonary tuberculosis (TB) should be excluded. Active TB should be ruled out in patients suspected of such condition, by chest X-ray, sputum test, and examinations of clinical symptoms and signs. Patients with a history of active TB infection within the past year should be excluded, despite being treated; patients with a history of active TB infection more than 1 year ago should also be excluded, unless it is proven that the course and type of prior TB treatment are both appropriate;

n) With severe acute or chronic infections requiring systemic treatment

o) With heart failure (New York Heart Association Class III or IV) and despite receiving appropriate pharmacological treatment, poorly controlled coronary artery disease or arrhythmia, or a history of myocardial infarction within 6 months before screening;

p) Inoculated with live vaccine within 4 weeks before receiving the investigational drug. Injections of inactivated influenza vaccine for seasonal influenza are permitted, but not live attenuated influenza vaccines for intranasal use.

4) Physical examination and laboratory tests

a) With a known history of human immunodeficiency virus (HIV) seropositive status or acquired immunodeficiency syndrome (AIDS);

b) With untreated active hepatitis (hepatitis B: HBsAg positive and HBV DNA ≥ 500 IU/mL; hepatitis C: HCV RNA positive with abnormal liver function); co-infection with hepatitis B and hepatitis C;

5) The investigators determine that the patients may have other factors that may result in the premature termination of the study, such as other serious illnesses or serious laboratory abnormalities or family or social factors that could affect the safety of the subject, or study data and sample collection

5.3. Study Withdrawal Criteria

Reasons for withdrawal may include:

- Withdrawal of informed consent and refusal of further follow-ups by subjects;
- Continuing participation in the study is not in the best interests of the patient due to any clinical adverse reactions, laboratory abnormalities, or concurrent diseases, as assessed by the investigators;
- 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.

5.4. Criteria for Treatment Discontinuation

Criteria for treatment discontinuation are as follows:

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

1. Treatment discontinuation requested by subjects;
2. Radiographic or clinical evidence of PD, unless the subject meets the criteria for continuing treatment after progression;
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. Deterioration of the overall health suggesting treatment continuation impossible;
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 investigators.

5.5. Procedures for Withdrawal or Discontinuation

The efficacy and safety examinations to be completed upon study withdrawal as specified in the protocol must be completed as much as possible. In addition, the safety follow-up should be completed along with fully documented AEs and their outcomes. The investigators can recommend or provide new or alternative treatments to a subject based on the condition of the subject. Subjects showing no PD need to be continuously followed-up for imaging evaluation until the subjects begin new anti-tumor treatment or show PD.

Subject's survival status should still be followed up even when the subject refuses to visit study sites, unless the subject withdraws consent to provide further information or consent to be further contacted. In such case, no study assessment is performed, nor any data are collected.

5.6. Re-Screening Criteria for Subjects

In this study, re-screening is allowed, i.e., subjects who have entered the screening process but have not met the enrollment conditions and have not started treatment may be re-enrolled. When re-screening, the informed consent form must be re-signed and a new subject number will be given.

5.7. Premature Termination or Suspension of Study

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

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

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

Once the aforementioned issues involving drug safety, protocol compliance, and data quality are resolved, the study can be continued upon approval from the sponsor, EC, or CFDA (now NMPA).

6. PHARMACOKINETIC STUDY DESIGN

6.1. Collection and Processing of Blood Samples

6.1.1. Blood sampling time

A PK study will be carried out in 12 subjects enrolled in this study (in Beijing Cancer Hospital, the leading site).

- There were 4 blood collection time points for the single dose in Cycle 1: within 0.5 h pre-administration on D1, within 5 min and at 2 h (± 10 min) after the end of administration on D1, and on D8 (± 60 min);
- Within 0.5 h pre-administration and 5 min post-administration on D1 of Cycles 2, 4, and 6.

6.1.2. Processing and storage of blood samples

At each of the above time points, 4 mL of venous blood is collected into a serum separation tube to obtain the serum, which is then transferred into cryotubes (aliquoted equally into the test tubes and backup tubes). The cryotubes are stored in a low temperature freezer at ≤ -60 ℃ until they are transported to the central laboratory for PK testing. Please refer to the Laboratory Manual for specific operation details.

6.2. Shipping of Clinical Samples

The samples in test tubes should be sent out first in dry ice storage state. The samples in 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.

7. STUDY MEDICATION

7.1. Overview of Investigational Drug

7.1.1. Access to investigational drug

SHR-1210 is manufactured by Suzhou Suncadia Biopharmaceuticals Co., Ltd.

7.1.2. Dosage form, packaging, and label of investigational drug

Investigational drug: SHR-1210 Injection

Manufacturer: Suzhou Suncadia Biopharmaceuticals Co., Ltd.

Dosage form: lyophilized powder

Strength: 200 mg in 20 mL vials

Batch no.: see Certificate of Analysis

Method of administration: intravenous drip infusion

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

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

Label: refer to the pharmacy manual, and the actual label shall prevail

7.1.3. Storage and stability of investigational drug

The investigators or the authorized representative thereof (e.g., pharmacist) will ensure that all investigational drugs are stored in a secure and access-controlled area conforming to storage conditions and regulatory requirements.

The investigational drug should be stored under the storage conditions listed in Section 7.1.2. Where the protocol differs from other information, SHR-1210 will be stored according to the storage conditions listed on the label.

Daily maximum and minimum temperatures of all storage zones (such as cold storage) must be recorded by study sites. Documentation should begin with the receipt of the investigational 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. Study sites should take active measures to restore the investigational drug under the storage conditions described on the label, and the temperature deviation and the measures taken should be reported to the sponsor.

Investigational drugs affected by the temperature deviation should be isolated temporarily and may only be used after approval by the sponsor, and such case is not considered 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 study sites.

7.1.4. Preparation of investigational drug

Drugs used in this study are all administered via intravenous drip infusion. Therefore, these drugs should be prepared by 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 pharmacy manual for drug preparation.

7.1.5. Administration of investigational drug

SHR-1210: 200 mg/dose, intravenous drip infusion over 30 min (not less than 20 min and not more than 60 min) on D1 of each 2-week cycle. The treatment will continue until the occurrence of confirmed PD, intolerable toxicity, or other reasons specified in the protocol.

For Cycle 2 and subsequent cycles, the drug can be administered 3 days before or after the day of scheduled administration. Administration beyond 3 days after the scheduled dosing day will be considered as a dose delay. Subsequent dosing will be carried out based on the actual date of the previous dosing. All required examinations and evaluations must be completed prior to each dose.

7.1.6. Dose modification and delay

7.1.6.1. Dose modification

AEs related to SHR-1210 may be immune-related AEs (irAEs), and may develop shortly after the first dose or months after the last dose. SHR-1210 should be interrupted if events listed in the following table occur. During the study, the investigators 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 2 or when the situation is not listed.

Table 2. SHR-1210 dose modification criteria

Treatment-Related Immune-Related Adverse Event (irAE)	Severity Grade for Treatment Interruption	Resumption	SHR-1210 Treatment
Diarrhea/Colitis	2-3	Recovery to Grade 0-1	Treatment should be discontinued if the AE does not resolve within 12 weeks after 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	Recovery to Grade 0-1	Treatment should be discontinued if the AE fails to resolve within 12 weeks after the last dose.
	3-4	Discontinuation	Discontinuation

Treatment-Related Immune-Related Adverse Event (irAE)	Severity Grade for Treatment Interruption	Resumption	SHR-1210 Treatment
Hyperthyroidism	3	Recovery to Grade 0-1	Treatment should be discontinued if the AE does not resolve within 12 weeks after 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		Treatment can be continued after starting thyroxine replacement therapy	Treatment can be continued after starting thyroxine replacement therapy
Pneumonia	2	Recovery to Grade 0-1	Treatment should be discontinued if the AE does not resolve within 12 weeks after 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	Recovery to Grade 0-1; SHR-1210 treatment can be continued after starting endocrine replacement therapy	Treatment should be discontinued if the AE does not resolve within 12 weeks after 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	Recovery to Grade 0-1	Treatment should be discontinued if the AE does not resolve within 12 weeks after 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 Reaction	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

Treatment-Related Immune-Related Adverse Event (irAE)	Severity Grade for Treatment Interruption	Resumption	SHR-1210 Treatment
Other Treatment-Related AEs	3	Recovery to Grade 0-1	Treatment should be discontinued if the AE does not resolve within 12 weeks after 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 patients 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 investigators may consider interrupting SHR-1210 treatment if appropriate. For subjects with persistent Grade 2 adverse reactions that fail to return to Grade 0-1 within 12 weeks after the last dose, treatment should be discontinued.

7.2. Management, Dispensation, and Return of Investigational Drug

Designated personnel are responsible for the management, dispensation, and return of investigational drugs. The investigators must ensure that all investigational drugs are used by enrolled subjects only and the dose and route of administration comply with Section 6.1.5. Remaining or expired drugs should be returned to the sponsor and may not be used for non-participants.

When the investigational drug is transported to study sites, a drug receipt form should be signed by both parties in duplicate, one copy for study sites and the other for the sponsor. When returning remaining drugs and empty packaging, both parties must sign the drug return 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 investigational drugs, and disposal of remaining drugs.

7.2.1. Disposal of investigational drug

The sponsor or authorized personnel is responsible for disposing investigational drugs. Drug disposal should be well documented.

7.3. Concomitant Treatment

7.3.1. Permitted concomitant medications

- Topical use of corticosteroids, such as ophthalmic, nasal, intra-articular, and inhaled administrations, are permitted.
- Use of immunosuppressive agents (such as prednisone of > 10 mg/d or an equivalent dose of glucocorticoids) to handle the AEs in the study.

- Prophylactic use of short-term glucocorticoids, such as for the prevention of contrast agent allergy; short-term glucocorticoids that are used to treat non-autoimmune diseases, such as delayed allergic reactions caused by exposure to allergens.
- The use of inactivated seasonal influenza vaccines is allowed; the use of live attenuated vaccines needs to be decided upon discussion with the sponsor.

7.3.2. Prohibited concomitant medications

- Chemotherapy, radiotherapy, hormone therapy, or immunotherapy
- Immunosuppressants;
- Modern TCM preparations approved by the NMPA for anti-tumor treatment;
- Inoculation of live vaccines within 4 weeks before the first dose and during the study. Live vaccines include but are not limited to, rubeola, epidemic parotitis, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid vaccines. Injections of inactivated influenza vaccine for seasonal influenza are permitted, but not live attenuated influenza vaccines for intranasal use;

7.4. Recommendations on the Handling of Immune-Related Adverse Events

Subjects should receive appropriate supportive treatment measures deemed necessary by the investigators. Supportive treatment measures for managing immune-related AEs (irAEs) are listed below, including oral or intravenous corticosteroids and other anti-inflammatory medications when symptoms are not relieved after the use of corticosteroids. Corticosteroids may need to be tapered over several cycles since symptoms may worsen during dose reduction. Other reasons requiring other supportive treatments, such as metastatic disease or bacterial or viral infections, should be ruled out where possible. When the investigators are sure that the AE is related to SHR-1210, the supportive treatment listed below may be followed. Otherwise, the supportive treatment listed below is not required.

1. Diarrhea/Colitis

Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, hematochezia, or mucus stools, with or without pyrexia) and intestinal perforations (such as peritonitis and intestinal obstruction).

- Subjects with diarrhea/colitis should drink an adequate amount of fluids. Fluids and electrolytes should be administered intravenously if adequate oral intake is not possible. GI consultation and endoscopy should be considered to confirm or rule out colitis for subjects with Grade 2 or greater diarrhea.

- Oral corticosteroids should be prescribed for Grade 2 diarrhea/colitis.
- Subjects with Grade 3 or 4 diarrhea/colitis should be treated with intravenous corticosteroids followed by oral high-dose corticosteroids.
- Corticosteroids should begin to taper after symptoms improve to Grade 1 or lower. Taper will last for no less than 4 weeks.

2. AST, ALT, or bilirubin increased

- Subjects should receive intravenous or oral corticosteroids for Grade 2 events. Liver function should be monitored with an increased frequency until it/they recover(s) to baseline (testing once per week considered).
- Corticosteroids via intravenous route for 24-48 h should be given for Grade 3-4 events.
- Corticosteroids should begin to taper after symptoms improve to Grade 1 or lower. Taper will last for no less than 4 weeks.

3. Hyperthyroidism/hypothyroidism

Thyroid disorder may occur at any time during the course of the treatment period. Monitor changes in subjects' thyroid function (when starting treatment, regularly during the treatment period) as well as clinical signs and symptoms of thyroid disease.

- For subjects with Grade 2 hyperthyroidism, it is recommended to use non-selective beta-blockers (such as propranolol) as initial treatment.
- Subjects with Grade 3-4 hyperthyroidism should receive intravenous corticosteroids followed by oral corticosteroids. Corticosteroids should begin to taper after symptoms improve to Grade 1 or lower. Taper will last for no less than 4 weeks. During the tapering process, appropriate hormone replacement therapy may be required.
- Thyroid hormone replacement therapy may be considered for Grade 2-4 hypothyroidism (such as levothyroxine).

4. Pneumonia

- Subjects with Grade 2 pneumonia should receive systemic corticosteroids. Corticosteroids should begin to taper after symptoms improve to Grade 1 or lower. Taper will last for no less than 4 weeks.
- If subjects receive long-term corticosteroids, antibiotic prophylaxis should be used.

5. Immune-Related Hypophysitis

- Persistent corticosteroid treatment should be used for Grade 2 hypophysitis. Corticosteroids should begin to taper after symptoms improve to Grade 1 or lower. Taper will last for no less than 4 weeks. During the tapering process, appropriate hormone replacement therapy may be required.
- Subjects with Grade 3 or 4 hypophysitis should receive intravenous corticosteroids followed by oral corticosteroids. Corticosteroids should begin to taper after symptoms improve to Grade 1 or lower. Taper will last for no less than 4 weeks. During the tapering process, appropriate hormone replacement therapy may be required.

6. Type I diabetes mellitus

Insulin replacement therapy is recommended for T1DM and Grade 3-4 hyperglycemia accompanied by metabolic acidosis or ketonuria. Then, subjects' blood glucose, and full metabolic panel, urinary ketones, HbA1C, and C-peptide should be evaluated.

7. Renal Failure or Nephritis

- Subjects with Grade 2 events should receive corticosteroids.
- Subjects with Grade 3-4 events should receive systemic corticosteroids.
- Corticosteroids should begin to taper after symptoms improve to Grade 1 or lower. Taper will last for no less than 4 weeks.

8. Infusion Reaction

CTCAE Grade	Clinical Symptom	Clinical Management	SHR-1210 Treatment
Grade 1	Mild and transient reactions	Bedside observation and close monitoring until recovery. Premedications are recommended for subsequent infusion: diphenhydramine 50 mg or equivalent, and/or acetaminophen 325-1000 mg, given at least 30 min before SHR-1210 infusion.	Continue
Grade 2	Moderate reactions requiring treatment or interruption; rapidly resolve after symptomatic treatment (such as antihistamines, non-steroidal	Intravenous drip infusion of normal saline, IV of diphenhydramine 50 mg or equivalent and/or acetaminophen 325-1000 mg; Bedside observation and close monitoring until recovery. Corticosteroids or bronchodilators can be considered based on clinical needs; The amount of investigational drug infused should be recorded in the original medical record;	Interrupt. 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

CTCAE Grade	Clinical Symptom	Clinical Management	SHR-1210 Treatment
	antiphlogistics, anesthetics, bronchodilators, and intravenous fluids)	Premedications are recommended for subsequent infusion: diphenhydramine 50 mg or equivalent, and/or acetaminophen 325-1000 mg, given at least 30 min before SHR-1210 infusion. Use corticosteroids (equivalent to hydrocortisone 25 mg) when necessary.	SHR-1210 dose will be discontinued.
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 require hospitalization. Grade 4: life-threatening	Immediately discontinue SHR-1210; Administer normal saline by intravenous drip infusion. • Bronchodilators are recommended: subcutaneous injection of 1:1000 adrenaline solution 0.2-1 mg or slow intravenous infusion of 1:10,000 adrenaline solution 0.1-0.25 mg, and/or diphenhydramine 50 mg + methylprednisolone 100 mg or equivalent by intravenous injection when necessary; • Based on the guidelines for anaphylaxis of study sites; Bedside observation and close monitoring until recovery.	Discontinuation

8. STUDY PROCEDURES

8.1. Screening Period

The screening period is the time from the signing of the informed consent form until start of study treatment or screen failure. Subjects must sign the informed consent form before undergoing screening procedures for this study. Data from laboratory tests and imaging evaluation performed prior to informed consent for routine clinical practice may be used if they are within the specified window period.

Unless otherwise stated, the screening should be completed within 28 days before starting the investigational drug.

- Obtain informed consent form signed by the subject.
- Demographics: gender, date of birth, ethnicity, height, weight, etc.
- Medical history collection:
    - Diagnosis: date of pathological diagnosis, pathological type, clinical stage, B symptoms, and IPS score
    - Treatment history:

- History of radiotherapy: site, dose, and start and completion dates
- History of chemotherapy: regimen, cycles, and start and completion dates
- History of concomitant disease, prior medications, and drug allergies

- Safety assessment (within 14 days prior to the first study dose):
  - ECOG PS;
  - Physical examination: including height, weight, symptoms, and signs. Lymph node regions (for example, submandibular, cervical, supraclavicular, armpit, and groin) and abdominal organs (for example, liver and spleen);
  - Vital signs: body temperature, blood pressure, heart rate, and respiratory rate;
  - Hematology: RBC count, hemoglobin, platelet count, WBC count, neutrophil count, and lymphocyte count;
  - Urinalysis: WBCs, RBCs, and urine protein; if urine protein ≥ 2+, 24-h urine protein quantitation is required;
  - Fecal occult blood;
  - Hepatic and Renal Function: including ALT, AST, TBIL, ALP, BUN or serum urea level, creatinine, and albumin;
  - Blood electrolytes: including K^+, Na^+, Ca^{++}, Mg^{++}, and Cl^-;
  - Coagulation function: When international normalized ratio (INR) is not available, prothrombin time (PT) will be used;
  - Thyroid function: including TSH, FT3, and FT;
  - Fasting blood glucose;
  - Erythrocyte sedimentation rate;
  - LDH;
  - Virological examination: including HIV-Ab, HBV, and HCV infection testing. HBV testing requirements: HbsAg (qualitative), HbsAb (qualitative), HbcAb (qualitative), HbeAg (qualitative), and HbeAb (qualitative) should be tested at screening. If HBV infection is suspected, HBV-DNA should be tested (qualitatively; if positive, then quantitatively). HCV testing requirements: HCV-Ab is tested at screening to determine the presence of HCV infection. If positive, HCV-RNA will be tested (qualitatively; if positive, then quantitatively).

  - Blood HCG test: Only for women of childbearing potential (WOCBP); test within 7 days before the first dose;
  - 12-lead ECG;
  - Echocardiography;
  - Concomitant medication/treatment: Concomitant medications within 14 days before the first dose will be recorded;
  - AEs: Document from the signing of informed consent form.
- Efficacy Evaluation
  - Tumor CT or MRI examination: chest, abdomen, pelvis, and other sites of known lesions (perform within 28 days before starting treatment; results of imaging examination performed prior to signing informed consent may be used for tumor assessment at screening if the requirements are met).
  - Tumor FDG-PET examination: Perform within 28 days before starting treatment; results of imaging examination performed prior to signing informed consent may be used for tumor assessment at screening if the requirements are met.
  - Bone marrow aspiration and biopsy. Perform within 28 days before starting treatment; results of bone marrow aspiration and biopsy performed prior to signing informed consent may be used for tumor assessment at screening if the requirements are met.

8.2. Treatment Period

All examinations and evaluations during the treatment period should be completed prior to the administration.

- ECOG PS: Perform within 72 h prior to each dose
- Physical examination: including height, weight, symptoms, and signs. Lymph node regions (for example, submandibular, cervical, supraclavicular, armpit, and groin) and abdominal organs (for example, liver and spleen) are checked within 72 h before each administration;
- Vital signs: including body temperature, blood pressure, heart rate, and respiratory rate; measure within 72 h before each administration;

- Blood HCG test: Only for women of childbearing potential (WOCBP); test within 7 days before the first dose, and at least once every 4 weeks (± 7 days) thereafter, regardless of the dosing cycle;
- B symptom assessment: including pyrexia of > 38 °C of unknown cause, night sweats, or weight loss of > 10% (the evaluation will be conducted on D1 of Cycle 1, and every 2 cycles thereafter until the discontinuation of study treatment);
- PK blood collection: In Cycle 1, within 0.5 h pre-administration and within 5 min and at 2 h (± 10 min) post-administration on D1, and on D8 (± 60 min). In Cycles 2, 4, and 6, within 0.5 h pre-administration and within 5 min post-administration on D1 (only for subjects participating in the PK study);
- Injection of SHR-1210:
- Adverse event
- Concomitant medication/treatment

The following relevant examinations must be completed pre-administration in Cycle 2 and subsequent cycles (complete within 72 h pre-administration):

- Hematology: RBC count, hemoglobin, platelet count, WBC count, neutrophil count, and lymphocyte count;
- Urinalysis: WBCs, RBCs, and urine protein; if urine protein ≥ 2+, 24-h urine protein quantitation is required;
- Fecal occult blood;
- Hepatic and Renal Function: including ALT, AST, TBIL, ALP, BUN or serum urea level, creatinine, and albumin;
- Blood electrolytes: including K^+, Na^+, Ca^{++}, Mg^{++}, and Cl^-;
- Coagulation function: When international normalized ratio (INR) is not available, prothrombin time (PT) will be used; once every 2 cycles;
- Thyroid function: including TSH, FT3, and FT; once every 4 cycles
- Fasting blood glucose;
- LDH;

- Virological examination: Only for patients with hepatitis virus infection. Virological examination will be performed every 2 cycles during the treatment period; for patients with HBV infection, they will be tested for HBV-DNA (quantitative), and for patients with HCV infection, they will be tested for HCV-RNA (quantitative);
- 12-lead ECG;
- Tumor CT or MRI examination: Evaluation will be carried out on D1 (± 7 days) of Weeks 9, 17, 25, 37, and 49 after the start of treatment, then every 16 weeks (± 14 days) until Week 97, and then every 26 weeks (± 21 days) until PD (for subjects who continue to receive study treatment after radiographic progression, evaluation will be carried out until the investigational drug is discontinued), start of new anti-tumor treatment, or death;
- Tumor FDG-PET examination: Perform on D1 (± 7 days) of Weeks 17 and 25 after the start of treatment. For subjects who have not obtained two negative FDG-PET results after Week 1 and until Week 49, it is necessary to add a tumor FDG-PET examination on D1 (± 7 days) of Week 49. If it is necessary to determine whether a radiographic CR is obtained at other unscheduled FDG-PET evaluation time points after the start of treatment, the FDG-PET evaluation must be performed within 4 weeks after the CT evaluation;
- Bone marrow aspiration and biopsy: Patients with bone marrow involvement at baseline require bone marrow aspiration and biopsy to confirm CR status. Bone marrow aspiration and biopsy specimens are collected within 2 weeks after the CT scan. There is no need to perform bone marrow assessment after the bone marrow aspiration and biopsy result turns negative. The subject can start the study treatment before obtaining the bone marrow biopsy result, but the result must be recorded in the subject's CRF.

8.3. End of Treatment

The following examinations are required if tumor CT or MRI has not been performed within 4 weeks and safety evaluation and B symptom assessment have not been completed within 7 days prior to discontinuing the study treatment:

- ECOG PS:
- B symptom assessment: including pyrexia of > 38 °C of unknown cause; night sweats; weight loss of > 10% (symptoms in the past 6 months are evaluated);

- Physical examination: including height, weight, symptoms, and signs. Lymph node regions (for example, submandibular, cervical, supraclavicular, armpit, and groin) and abdominal organs (for example, liver and spleen);
- Vital signs: body temperature, blood pressure, heart rate, and respiratory rate;
- Hematology: RBC count, hemoglobin, platelet count, WBC count, neutrophil count, and lymphocyte count;
- Urinalysis: WBCs, RBCs, and urine protein; if urine protein ≥ 2+, 24-h urine protein quantitation is required;
- Fecal occult blood;
- Hepatic and Renal Function: including ALT, AST, TBIL, ALP, BUN or serum urea level, creatinine, and albumin;
- Blood electrolytes: including K^+, Na^+, Ca^{++}, Mg^{++}, and Cl^-;
- Coagulation function: When international normalized ratio (INR) is not available, prothrombin time (PT) will be used;
- Thyroid function: including TSH, FT3, and FT;
- Fasting blood glucose;
- LDH;
- Virological examination: Only for patients with hepatitis virus infection. For patients with HBV infection, they will be tested for HBV-DNA (quantitative), and for patients with HCV infection, they will be tested for HCV-RNA (quantitative);
- 12-lead ECG;
- Blood HCG test: for women of childbearing potential (WOCBP) only;
- Tumor CT or MRI examination.

8.4. Follow-Up Period

Subjects enter the follow-up period after the end of treatment. The first visit should be conducted 30 days (± 7 days) after the last dose or on the day of treatment discontinuation (if the date of treatment discontinuation is more than 42 days after the date of the last dose). The second visit is conducted approximately 90 days (± 7 days) after the last dose. Both visits must be conducted at study sites.

- ECOG PS:
- Physical examination: including height, weight, symptoms, and signs. Lymph node regions (for example, submandibular, cervical, supraclavicular, armpit, and groin) and abdominal organs (for example, liver and spleen);
- Vital signs: including body temperature, blood pressure, heart rate, and respiratory rate; measure within 72 h before each administration;
- Hematology: RBC count, hemoglobin, platelet count, WBC count, neutrophil count, and lymphocyte count;
- Urinalysis: WBCs, RBCs, and urine protein; if urine protein ≥ 2+, 24-h urine protein quantitation is required;
- Fecal occult blood;
- Hepatic and Renal Function: including ALT, AST, TBIL, ALP, BUN or serum urea level, creatinine, and albumin;
- Blood electrolytes: including K^+, Na^+, Ca^{++}, Mg^{++}, and Cl^-;
- Coagulation function: When international normalized ratio (INR) is not available, prothrombin time (PT) will be used;
- Thyroid function: including TSH, FT3, and FT;
- Fasting blood glucose;
- LDH;
- Virological examination: Only for patients with hepatitis virus infection. For patients with HBV infection, they will be tested for HBV-DNA (quantitative), and for patients with HCV infection, they will be tested for HCV-RNA (quantitative);
- AEs: All AEs should be collected until 90 days after the last dose or the start of new anti-tumor treatment. From 30 days after the last dose, for non-serious AEs, only those related to the investigational drug, including AEs of special interest, will be collected. Each recorded AE should be followed up until recovered to baseline level or Grade 0-1, stabilized, or reasonably explained (such as lost to follow-up and death).
- Concomitant medications: collect until 90 days after the last dose of study treatment. After the last dose, only concomitant medications for treatment-related AEs will be recorded.
- Survival follow-up:

- Subjects who discontinue study treatment due to "PD" will begin survival follow-up, which will be conducted every 3 months (± 14 days), either via telephone or in-person visit.
- Subjects who discontinue the study treatment due to reasons other than "PD" will enter the tumor progression follow-up, and continue to receive tumor evaluation in accordance with the efficacy evaluation visit frequency (tumor CT or MRI examination, tumor FDG-PET examination) as stipulated in the protocol, until PD, start of new anti-tumor treatment, or death; after tumor progression, the survival follow-up will be carried out once every 3 months (± 14 days), either via telephone or in-person visit.

8.5. Unscheduled Visit

The following items should be documented at unscheduled visits for subjects developing AEs during the study:

- Results of relevant examinations
- AEs
- Concomitant medications

8.6. Criteria for Continuing Treatment Beyond Progression

Some subjects receiving immunotherapy can still benefit clinically after radiographic progression. The study treatment may be continued after PD defined per Lugano 2014 criteria for subjects who meet the criteria below:

- The investigators deem 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 significant deterioration in subject's performance status, and no significant worsening of cancer-related symptoms
- Before continuing the study treatment, it must be reviewed and approved by the medical monitor

If it is decided that the subject will continue the study treatment after progression, the subject should continue to be treated, evaluated, and followed up according to the protocol requirements.

Subjects should withdraw from study treatment if further progression is observed at the next assessment. The initial date of investigator-assessed progression should be used for all statistics analyses involving progression, 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 PD, the progression will be reported as "general deterioration". More objective evidences (such as imaging confirmation) of progression of these subjects should be obtained after treatment discontinuation.

For subjects who withdraw from the study due to intolerable toxicity without radiographic PD observed, the imaging examination should be performed at the same frequency, until PD or start of other anti-tumor treatment. The radiographic evidence of PD of these subjects must be obtained whenever possible.

9. ASSESSMENTS

9.1. Assessment of Efficacy

The Lugano 2014 criteria are used to evaluate the objective response rate (ORR), including the CR and PR cases.

ORR: Defined as the proportion of subjects whose best response reaches CR or PR from the first dose to the occurrence of PD or the start of new anti-tumor treatment, whichever comes first

PFS: Defined as the time from the date of the first dose to the first documented PD or all-cause death, whichever occurs first. If the subject has not had PD or died by the data cut-off date, the cut-off date is the date of the subject's last efficacy evaluation. If the subject has not received tumor evaluation, the cut-off date is the date of the first dose, and PFS lasts for 1 day.

DoR: Defined as the time from the date of the first CR or PR to the date of initial assessment of PD or all-cause death, whichever comes first. If the subject has not had PD or died by the data cut-off date, the censoring date is the date of the subject's last efficacy evaluation. Only applicable to subjects with CR/PR.

TTR: Defined as the time from D1 of administration to the first evaluation of PR or CR, whichever comes first. Only applicable to subjects with CR/PR.

9.2. Assessment of Safety

9.2.1. Safety parameters

Safety parameters for this study include clinical symptoms, vital signs, physical examination, and laboratory tests (hematology, urinalysis, blood biochemistry, thyroid function, coagulation function, etc.).

AEs are evaluated according to NCI CTCAE V4.03, including type, incidence, severity, start and end date, whether it is an SAE, correlation with the investigational drug, and outcome.

AEs that occur during the study, including signs and symptoms at screening, will be recorded in the AE page of the electronic case report form (eCRF).

The latest version of MedDRA is used to medically code the collected AEs, which are finally presented in the form of listing.

9.3. Assessment of Pharmacodynamics

PK assessment is conducted by measuring the concentration of the parent drug in the blood sample, and the PK parameters of SHR-1210 in the human body will be calculated using the non-compartmental model. For multiple-dose pharmacokinetics, drug accumulation will be studied according to the maximum concentration and minimum concentration in multiple cycles. The primary multiple-dose PK parameters will be investigated, mainly including:

1) C_{max}: maximum blood concentration;
2) C_{min}: minimum blood concentration;
3) T_{max}: time to the maximum concentration;
4) Elimination half-life ($t_{1/2z}$);
5) Area under the concentration-time curve (AUC_{τ});
6) Apparent volume of distribution (V_z);
7) Systemic clearance (CL_S).

10. ADVERSE EVENT REPORTING

10.1. Adverse Event (AE)

10.1.1. Definition of adverse event

An AE refers to any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. In this study, all AEs occurring from signing the informed consent form to 90 days after the last dose will be collected. From 30 days after the last dose, for non-serious AEs, only those related to the investigational drug will be collected.

AEs can include any unfavorable and unintended symptoms, signs, laboratory abnormalities, 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 laboratory abnormalities.

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, correlation with the investigational drug, duration, measures taken, as well as final results and outcomes.

10.1.2. AE severity grading criteria

Please refer to NCI-CTC AE V4.03 for grading criteria. Refer to the following criteria for AEs not listed in NCI-CTC AE V4.03:

Table 3. 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 non-invasive interventions required; limiting age-appropriate instrumental activities of daily living (ADL), e.g., cooking, shopping, using the telephone, counting money, etc.
3	Severe or medically significant symptoms but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care 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	Leading to death

10.1.3. Determination of the relationship between AEs and investigational drug

AEs will be collected from the signing of the informed consent form to 90 days after the last study dose or the start of new anti-tumor treatment, regardless of whether the event is related to the investigational drug or whether any medication is taken against the AE. From 30 days after the end of treatment, for non-serious AEs, only those related to the investigational drug will be collected. Any discomforts complained by the subject or changes in objective laboratory measurements during the treatment period should be faithfully recorded. The severity, duration, measures taken, and outcome of AEs should also be documented. The study physician should comprehensively assess the relationship between the AE and the investigational drug by considering the temporal relationship between the administration of investigational drug and the occurrence of AE, the characteristics of the investigational drug, the toxicological and pharmacological effects of the investigational 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: "related, possibly related, unlikely related, not related, and unassessable". Events that are assessed to be "related", "possibly related", and "unassessable" will be listed as adverse drug reactions. When calculating the incidence of AEs, the total of these three categories will be used as the numerator and the total number of subjects for safety assessments will be used as the denominator.

10.2. Serious Adverse Event (SAE)

10.2.1. Definition of SAE

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

10.2.2. Hospitalization

AEs leading to hospitalization (even if for less than 24 h) 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 an SAE. For example:

- Hospitalization due to the pre-existing disease without new AEs or 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 should be recorded as the treatment of the AE.

10.2.3. Progressive disease

PD 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 lesions relative to the primary tumor, or progression of the previous lesions, are recognized as PD. Life-threatening events, hospitalization or prolonged hospitalization, or events leading to 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 an SAE.

10.2.4. 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 TBIL, 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 values ≥ 3 × ULN; or AST or ALT ≥ 8 × ULN • With TBIL increase ≥ 1 × ULN or TBIL ≥ 3 × ULN

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

Except for the reexaminations of AST and ALT, albumin, creatine kinase, TBIL, direct and indirect bilirubin, γ-GT, prothrombin time (PT)/international normalized ratio (INR), and ALP should also be examined. 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 an SAE.

10.2.5. Other anti-tumor treatment

SAEs should be collected from the signing of the informed consent form until 90 days after the last dose of the investigational drug. Within 90 days after the last dose, SAEs that occur after the start of new anti-tumor treatment should also be reported.

10.2.6. SAE reporting

The collection period for SAEs begins with the signing of the informed consent form until 90 calendar days (inclusive) after the last study dose. In case of an SAE, whether it is an initial report or a follow-up report, the investigators must complete the "NMPA Serious Adverse Event Report Form" promptly with signature and date provided. The SAE must be reported to the provincial, autonomous regional, and municipal drug regulatory authorities, NMPA, and health administrations within 24 h of knowing the event. In addition, the sponsor should be notified and the event should be reported to the EC in time. The contact information for reporting is shown in Table 5.

SAEs that occur after 90 days post the last study dose are generally not reported unless they are suspected to be related to the investigational drug. The symptoms, severity, correlation with the investigational 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 investigators believe that an 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 investigational 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.

Table 4. Contacts for SAE reporting

Institution	Contact	Fax/Tel./Address
Hospital	Ethics Committee	Tel./Fax:
Jiangsu Hengrui Pharmaceuticals Co., Ltd.	Drug Safety Group (SAE), Oncology Business Unit	Email: hengrui_drug_safety@shhrp.com
Division of Drug Research Supervision, Department of Drug and Cosmetics Registration, China Food and Drug Administration (now NMPA)		Address: Building 2, No. 26 Xuanwumen West Street, Xicheng District, Beijing, China Postal code: 100053 Tel.: 010-88330732 Fax: 010-88363228
Medical Administration Bureau, Health Administration		Address: No. 38 North Lishi Road, Xicheng District, Beijing, China (100810) Tel.: 010-68792201 Fax: 010-68792734 (preferred)
Food and Drug Administration of Provinces, Autonomous Regions, and Municipalities	Refer to the reporting requirements of the drug administration of corresponding province, autonomous region, or municipality	

10.2.7. Follow-up of AEs/SAEs

All AEs/SAEs should be followed up until they are resolved, return to baseline levels or Grade ≤ 1, reach a stable state, or are reasonably explained (e.g., lost to follow-up or death).

10.3. Pregnancy

During the study, if a female subject becomes pregnant, she will immediately discontinue the study treatment. The investigators will report it to the sponsor within 24 h and fill out the "Pregnancy Report/Follow-Up Form for Hengrui Clinical Studies".

During the study, if the partner of a male subject becomes pregnant, the subject can continue in the study. The investigators must report to the sponsor within 24 h and fill out the "Pregnancy Report/Follow-Up Form for Hengrui Clinical Studies".

The investigators 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 an SAE during the pregnancy, the "NMPA Serious Adverse Event Report Form" should also be filled out and reported according to the SAE reporting procedure.

10.4. Adverse Event of Special Interest

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

- Grade ≥ 3 infusion reaction;
- Grade ≥ 2 diarrhea/colitis, uveitis, and interstitial pneumonia;
- Other Grade ≥ 3 immune-related AEs;
- Any events that meet Hy's Law (ALT/AST > 3 × ULN accompanied with TBIL > 2 × ULN and without other causes).

11. INDEPENDENT REVIEW

On-site imaging review will be performed at each study site, and the independent review committee (IRC) will perform central review on the primary efficacy endpoint, ORR.

On-site imaging review will be performed by an experienced and qualified study physician designated by each study site. All the imaging data related to efficacy assessment should be archived on CD and sent by each study site to the IRC for evaluation at regular intervals.

Central review will be performed blindly by two independent radiologists. In the event of disagreement between these two independent radiologists, a third radiologist should make the final judgment. Refer to the IRC Charter for details.

Radiographic efficacy evaluations will be performed at each study site and by independent radiologists according to Lugano 2014 criteria.

12. DATA ANALYSIS/STATISTICAL METHODS

Data analysis will be completed by Hengrui. Data analysis will be carried out without distinction of study sites (Data from all participating study sites will be combined). The primary analysis will be performed when the last subject has been treated for 6 months.

Patients who have failed the screening (those who do not receive any treatment despite signing informed consent) will not be included in any analysis. However, they will be reported in a separate listing.

Reasons for withdrawal will be summarized and listed. The listing should include: date of first and last administration, duration of investigational drug exposure, and date of withdrawal.

12.1. Sample Size Determination

This study uses a single-arm design. The primary objective is to evaluate the efficacy of SHR-1210 in the treatment of relapsed or refractory cHL. The study endpoint is ORR. By referring to historical research data and research results of similar products and given the current clinical practice requirements, the investigational drug can be judged as effective only when the lower limit of the 95% confidence interval for ORR obtained from the study data is greater than 40%. Therefore, the sample size for this study is determined based on the following 2 points: 1. the exact method (Clopper-Pearson) is used to calculate the 95% confidence interval for ORR; 2. the lower limit of the confidence interval is greater than 40%. Assuming that the ORR of SHR-1210 in the treatment of relapsed or refractory cHL reaches 65%, a power of 92.90% can be obtained with 50 subjects. Given a dropout rate of 20%, this study intends to enroll 60 subjects.

12.2. Statistical Analysis Plan

Statistical summaries and analytical methods of data collected from this study will be detailed in another individual statistical analysis plan (SAP). The finalized SAP will be kept by the sponsor. This SAP may contain revisions to the relevant contents in the protocol. However, when the revised content involves the main and/or key factors in the protocol, such as the definition of endpoints and the corresponding analysis, such a revision should be reflected in the protocol amendment version.

12.3. Statistical Hypothesis and Decision Rules

The alternative hypothesis of this study is that the ORR of SHR-1210 for relapsed or refractory cHL is greater than 40%. A lower limit of the 95% confidence interval for overall ORR greater than 40% estimated from the study data indicates that the investigational drug is effective

12.4. Analysis Populations

This study will involve the following analysis sets or populations:

- Informed Consent Set (ICS): all subjects who have signed the informed consent form.
- Full Analysis Set (FAS): eligible subjects who have received the investigational drug. The FAS is the primary analysis set for efficacy analysis other than the primary efficacy endpoint.
- Evaluable Set (ES):
  a subset of the FAS, defined as subjects with at least one post-baseline efficacy evaluation in the FAS. The ES is the primary analysis set for the primary efficacy endpoint ORR
- Per-Protocol Set (PPS): a subset of the FAS, defined as subjects in the FAS who have experienced no major protocol deviations. PPS is the secondary analysis set for efficacy analysis.
- Safety Set (SS): all enrolled subjects who have received the investigational drug and have post-administration evaluable safety data. SS is the primary analysis set for safety analysis.
- PK Set (PKS): all enrolled subjects who have received the investigational drug and have post-administration evaluable PK data (concentration and/or parameters).

12.5. Statistical Methods

The content and methods of analysis in this study will be explained in the following sections hierarchically.

12.5.1. General analysis

Unless otherwise specified, all data in this study will be summarized using descriptive statistics according to the data type. Measurement data will be summarized using mean, standard deviation (SD), median, minimum, and maximum; count data and rank data will be summarized using frequency and percentage; for time to event data, the Kaplan-Meier method will be used to estimate the median time and its overall 95% confidence interval will be calculated.

12.5.2. Basic analysis

The basic analysis will be based on the FAS. The analysis will include but is not limited to the following:

- Subject disposition and populations;

- Subjects' basic characteristics (including demographics, life history, medical history, and medication history);
- The analysis of dose interruption, dose reduction, and study withdrawal of subjects as well as corresponding reasons.

Descriptive summary will be made in the form of listing or using the statistical methods listed in Section 12.5.1.

12.5.3. Handling of missing data

Except for missing dates in this study, missing data will not be processed. PFS and other time to event data will be judged according to Hengrui's censoring rules and the censoring time will be calculated. Missing date will be processed according to Hengrui's missing date imputation criteria.

12.5.4. Efficacy endpoint analysis

For the objective response rate (ORR) based on the IRC's and investigators' assessment, point estimation will be performed, and the exact method (Clopper-Pearson) will be used to estimate the overall 95% confidence interval as its primary analysis.

For other secondary efficacy endpoints, including duration of response (DoR), progression-free survival (PFS), time to response (TTR), and overall survival (OS), the Kaplan-Meier method will be used to estimate their median times and the overall 95% confidence intervals will be calculated.

The analysis of the primary efficacy endpoint will be based on the ES, and other efficacy analyses will be repeated based on the primary analysis set FAS and secondary analysis set PPS.

12.5.5. Safety analysis

The safety analysis will be summarized primarily using descriptive statistics. AEs, treatment-emergent AEs (TEAEs), SAEs, laboratory data, vital signs, and other data will be statistically summarized. Also, the exposure to the investigational drug (including treatment cycle, received total dose, and dose intensity) will be statistically summarized. The above data will be analyzed and summarized using Hengrui's current clinical study report standards. Such standards include but are not limited to the following:

Summary of AEs (of all causes and treatment-related);

Incidence and severity of AEs (of all causes and treatment-related);

Correlation analysis between AEs and investigational drug;

Analysis of outcomes of AEs;

Analysis of SAEs;

Descriptive statistical summary of laboratory measurements, vital sign data, and ECG data (post-baseline absolute values and post-baseline changes from baseline);

Classified summary of post-baseline vital sign data and ECG.

12.5.6. Interim analysis

This study does not involve an interim analysis.

12.5.7. Subgroup analysis

As a supporting analysis for the primary endpoint ORR, this study will analyze the following subgroups based on the FAS: age (≤ 45 vs. > 45 years), IPS score (≤ 3 vs. > 4), and baseline disease status (relapsed vs. refractory). The analytical method is the same as that of ORR. If necessary, the results will be presented with a forest plot.

12.5.8. Multiple comparison/multiplicity

This study does not involve conventional hypothesis testing, and the main results will be presented in the form of confidence intervals, without involving the issue of multiplicity.

12.5.9. Statistical analysis of PK

PK analyses will be based on the PKS, and PK concentration and PK parameters will be summarized using descriptive statistics. Apart from the statistics listed in the general analysis, PK concentration and PK parameter data will also be summarized descriptively using geometric mean (GM), coefficient of variation (CV%), and geometric CV% (GCV%). In addition, for PK concentration data, average and median blood concentration-time curves (concentration-time curves) on linear scale and semi-logarithmic scale can be plotted, and individual subjects' concentration-time curves (linear scale and semi-logarithmic scale) can be plotted at the same time. If PK statistical analysis is outsourced, the statistical analysis plan provided independently by the vendor shall prevail for the specific statistical analysis and method plan.

13. DATA MANAGEMENT

13.1. Data Recording

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

13.1.1. Filing of study medical records

As source documents, the medical records should be completely retained. The investigators should be responsible for filling and keeping the study medical record. The subject information on the cover of the medical record should be checked each time before filling the record. The medical record should be written in a neat and legible way so that the sponsor's CRA could verify the data with eCRF during each monitoring visit.

13.1.2. 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 study 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 eCRF should be filled out, with no blank or omission.

Modification: 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 error message prompt for questionable data. PI or clinical research coordinator (CRC) is permitted to modify or explain the problematic data. If necessary, multiple queries can be raised until the event of problematic data is resolved.

13.1.3. eCRF review

The investigators or designated personnel should fill out, review, and submit the eCRF in a timely manner. The investigators or clinical research coordinator (CRC) should promptly respond to queries raised by CRA, data manager, and medical reviewer. After data cleaning is completed, the investigators will sign the completed eCRF for verification.

13.2. Data Monitoring

Implemented by: clinical research associate (CRA).

Monitoring content: To confirm that whether the study protocol is adhered to; whether the records in eCRF are correct and complete, and consistent with the source documents such as study medical records and laboratory test reports, 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. Ensure that the data in the eCRF are consistent with source data. This process is also known as source data verification (SDV).

13.3. Data Management

13.3.1. 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.

13.3.2. Data entry and verification

The investigators 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 investigators or CRC in the form of queries. After data cleaning is completed, the investigators should sign the completed eCRF for verification.

13.3.3. Database lock

After SDV is completed by CRA, data manager and medical reviewer will conduct the final quality control of all data in the database, summarize all protocol deviations during the study, and hold a data verification 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.

13.3.4. Data archiving

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

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

13.3.5. Protocol deviation

Protocol deviation refers to any practice that does not comply with study protocol or GCP. This non-compliance may occur in the subject and may also occur in the investigators or other study personnel. Study sites should prepare corresponding corrective measures and implement them immediately if a protocol deviation occurs.

Study sites have the responsibility to maintain constant vigilance, complete the identification of protocol deviations in a timely manner, and complete the actions required by the protocol, to identify and report protocol deviations in a timely manner. All protocol deviations must be documented in the source documents. Protocol deviations must be submitted to local IRB in accordance with local ethical regulations. The principal investigators or study personnel of study sites are responsible for understanding and complying with local ethical standards.

14. SOURCE DATA AND DOCUMENTS

According to ICH E6, relevant regulations, and requirements for subject's personal information protection of study sites, each study site must properly keep all the treatment and scientific records related to this study. As a part of the study that Hengrui sponsors or participates in, each study site must allow the authorized representative of Hengrui 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.

15. QUALITY ASSURANCE AND QUALITY CONTROL

To ensure study quality, the sponsor and the investigators 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 sites must comply with the SOPs for the management of the investigational drug, including receipt, storage, dispensation, 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 investigators 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 site personnel for necessary revision and addition.

The drug regulatory authorities, institutional review board (IRB)/independent ethics committee (IEC), sponsor's CRA and/or auditor may carry out systematic inspection of study-related activities and 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, faithful, accurate, and complete manner. The audit should be performed by personnel not directly involved in this clinical study.

16. REGULATORY ETHICS, INFORMED CONSENT, AND SUBJECT PROTECTION

16.1. Regulatory Considerations

According to the corresponding regulatory requirements in China, an application should be submitted to the NMPA before starting a new drug study and the study can only be carried out after approval is obtained. The clinical approval number for SHR-1210 is 2016L01455.

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

16.2. Ethical Standards

The investigators will ensure that this study is fully implemented in accordance with the requirements for fully protection of the safety and rights of the subjects.

This study protocol must first be reviewed and approved in writing by the EC of the hospital before being implemented. The study protocol, protocol amendments, informed consent form, and other relevant documents such as recruitment advertisements should be submitted to the EC. This clinical study must be conducted in accordance with the Declaration of Helsinki, NMPA's Good Clinical Practice (GCP), and applicable laws and regulations. Before the study is initiated, approval must be obtained from the EC of the hospital.

The study protocol must not be unilaterally modified without approvals from both the sponsor and investigators. The investigators can modify or deviate from the study protocol before obtaining an approval from the EC/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 amendment should be submitted to the EC/IRB for review. The investigators must provide explanations and document any protocol deviation.

During the study, any changes to this study protocol must be submitted to the EC. If necessary, corresponding changes should be simultaneously made to other study documents and be submitted and/or approved according to the pertinent requirements of the EC. The investigators are responsible for submitting the interim reports regularly according to the pertinent requirements of the EC. After the end of the study, the completion should be informed to the EC.

16.3. Independent Ethics Committee

The protocol, informed consent form, recruitment material, and all subject materials must be reviewed and approved by the EC. Subjects may be enrolled only after the protocol and informed consent form have been approved. Any revisions to the protocol must be reviewed and approved by the EC prior to being implemented. All revisions to the informed consent form must be approved by the EC.

16.3.1. Informed consent form and other written information for subjects

The informed consent form describes the investigational drug 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.

16.3.2. 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 legally acceptable representatives. Subjects will be asked to read and review the informed consent form that has been approved by the EC. The investigators 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 informed consent forms. During the clinical study, subjects can withdraw the informed consents at any time. One copy of the signed informed consent form 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.

16.4. Confidentiality of Subject Information

The confidentiality of subject information will be strictly enforced by the investigators, 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, documentation, 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 investigational drug can examine all the documents and records that are maintained by the investigators, including but not limited to medical records and subject's administration records. Study sites should allow access to these records.

The contact information of the subjects will be safely kept in each study site 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.

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 study sites should be confidential and password-protected.

16.4.1. Use of samples, specimens, or data

This section should include the following:

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

17. PUBLICATION OF STUDY RESULTS

The study results belong to Jiangsu Hengrui Pharmaceuticals Co., Ltd. If the investigators plan 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.

18. CLINICAL STUDY PROGRESS

Anticipated enrollment of the first subject: Jun. 2017

Anticipated enrollment of the last subject: Nov. 2017

Anticipated study completion: Dec. 2019

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APPENDIX I. 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 self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, 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.
5	Death.

APPENDIX II. CREATININE CLEARANCE CALCULATION

Creatinine Clearance Calculation Using the **Cockcroft-Gault** Formula

Serum Creatinine Concentration (mg/dL):

$$\text{Creatinine clearance in males (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight})^{a}}{72 \times \text{serum creatinine}}$$

$$\text{Creatinine clearance in females (mL/min)} = \frac{0.85 \times (140 - \text{age}) \times (\text{weight})^{a}}{72 \times \text{serum creatinine}}$$

Serum Creatinine Concentration (μmol/L):

$$\text{Creatinine clearance in males (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight})^{a}}{0.818 \times \text{serum creatinine}}$$

$$\text{Creatinine clearance in females (mL/min)} = \frac{0.85 \times (140 - \text{age}) \times (\text{weight})^{a}}{0.818 \times \text{serum creatinine}}$$

a Age in years, weight in kg.

APPENDIX III. STAGING OF HODGKIN'S LYMPHOMA

Stage I Single lymph node involvement (I) or local involvement of a single extralymphatic organ or site (I_E).

Stage II Involvement of two or more lymph node regions (II) on the same side of the diaphragm or localized involvement of a single extralymphatic organ or site in association with regional lymph node involvement, with or without involvement of other lymph node regions on the same side of the diaphragm (II_E).

Note: The number of involved lymph node regions can be represented by subscripts (for example, II_3).

Stage III Involvement of lymph node regions above or below the diaphragm (III); involvement of lymph node groups above and below the diaphragm and outside of the lymph nodes in a nearby organ or site (III_E); involvement of lymph node groups above and below the diaphragm and in the spleen (III_S); or involvement of lymph node groups above and below the diaphragm, outside the lymph nodes in a nearby organ or site, and in the spleen (III_{E+S}).

Stage IV Diffuse (multiple sites) involvement of one or more extralymphatic organs with or without related lymph node involvement or involvement of solitary extralymphatic organs with involvement of distant lymph nodes (non-lymphatic areas).

A Absence of systemic symptoms

B Pyrexia of > 38 ℃ of unknown cause; night sweats; weight loss of > 10% (within 6 months before diagnosis)

APPENDIX IV. INTERNATIONAL PROGNOSTIC SCORE (IPS)

1 point for each of the following factors:

Albumin < 4 g/dL

Hemoglobin < 10.5 g/dL

Male

Age ≥ 45 years old

Stage IV lesion

WBC increased (WBC count of at least 15000/mm^3)

Lymphocyte decreased (lymphocyte count less than 8% of total WBCs, and/or lymphocyte count less than 600/mm^3)

APPENDIX V. RESPONSE EVALUATION CRITERIA

Lugano 2014 Revised Criteria for Response Assessment of Lymphoma		
Response and Site	**Metabolic Response (PET-CT)**	**Radiologic Response (CT)**
CR	CMR (complete metabolic response)	CRR (complete radiologic response)
Lymph nodes and extranodal sites	Score 1, 2, or 3 with or without a residual mass on PET 5-point scale. It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extranodal sites of disease
Nonmeasured lesions	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
PR	PMR (partial metabolic response)	PRR (partial radiologic response)
Lymph nodes and extranodal sites	Score 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size. At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites; when a lesion is too small to measure on CT, assign 5 mm ×5 mm as the default value; when no longer visible, 0 ×0 mm; for a node > 5 mm ×5 mm, but smaller than normal, use actual measurement for calculation;
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan.	Not applicable

Lugano 2014 Revised Criteria for Response Assessment of Lymphoma		
Response and Site	**Metabolic Response (PET-CT)**	**Radiologic Response (CT)**
SD	No metabolic response	SD
Lymph nodes and extranodal sites	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment.	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
PD	Metabolic progression	Radiologic progression
Individual target nodes/nodal masses and extranodal lesions	Score 4 or 5 with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment.	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm; In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to > 16 cm); if no prior splenomegaly, must increase by at least 2 cm from baseline; New or recurrent splenomegaly.
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	A new node > 1.5 cm in any axis; a new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma; Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease;

SPD: sum of the product of the perpendicular diameters for multiple lesions; PPD: cross product of the LDi and perpendicular diameter; LDi: longest transverse diameter of a lesion; SDi: shortest axis perpendicular to the LDi

PET 5-Point Scale

Score	**PET/CT Examination Result**
1	No uptake above background
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately > liver
5	Uptake markedly higher than liver and/or new lesions