Title: A phase II clinical study of SHR-1210 combined with apatinib mesylate for the treatment of extensive-stage small cell lung cancer failing first-line standard therapy (PASSION)

NCT number: NCT03417895

Date: 12 Jun., 2018

A PHASE II CLINICAL STUDY OF SHR-1210 COMBINED WITH APATINIB MESYLATE FOR THE TREATMENT OF EXTENSIVE-STAGE SMALL CELL LUNG CANCER FAILING FIRST-LINE STANDARD THERAPY

(PASSION)

Protocol No.:	SHR-1210-II-206
Study Phase:	II
Investigational Drug No.:	SHR-1210
Medical Director:	[redacted]
Leading Center 1 of Clinical Study:	Cancer Hospital of Chinese Academy of Medical Science
Principal Investigator 1:	Prof. Jie Wang
Leading Center 2 of Clinical Study:	Zhejiang Cancer Hospital
Principal Investigator 2:	Prof. Yun Fan
Version No.:	2.0
Version Date:	12 Jun. 2018

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	14 Nov., 2017	Not applicable
Version 2.0	12 Jun., 2018	

Sponsor's Signature Page

I have read and confirmed this clinical study protocol (protocol number: SHR-1210-II-206, version number: 2.0, version date: 12 Jun., 2018). I agree to fulfill my duties in accordance with Chinese laws, the Declaration of Helsinki, the Chinese GCP, and this study protocol.

Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

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

Principal Investigator's Signature Page (Leading Center)

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

Study Center: _____

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

Principal Investigator's Signature Page (Participating Center)

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

Study Center: _____

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

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PROTOCOL SYNOPSIS

Study Title	A phase II clinical study of SHR-1210 combined with apatinib mesylate for the treatment of extensive-stage small cell lung cancer failing first-line standard therapy (PASSION)
Protocol No.	SHR-1210-II-206
Version No.	2.0
Sponsor	Jiangsu Hengrui Pharmaceuticals Co., Ltd.
Principal Investigators	Prof. Jie Wang, Cancer Hospital of Chinese Academy of Medical Science Prof. Yun Fan, Zhejiang Cancer Hospital
Participating Study Centers	Approximately 20 centers
Study Objectives	**Primary objective:** • To evaluate the safety and efficacy of SHR-1210 combined with apatinib in the treatment of extensive-stage small cell lung cancer failing first-line standard therapy **Secondary objective:** • To evaluate the immunogenicity of SHR-1210 **Exploratory objective:** • To evaluate the correlation between biomarkers (including but not limited to programmed death ligand 1 [PD-L1] and tumor mutation burden [TMB]) and efficacy
Study endpoints	**Primary endpoints:** • Incidence of AE evaluated as per CTCAE 4.03 • Overall response rate (ORR) evaluated as per RECIST v1.1 **Secondary endpoints:** • Incidence of AEs and serious adverse events (SAEs) assessed as per CTCAE 4.03, laboratory test values, ECG, vital signs, and other safety endpoints • Overall survival (OS), 6-month OS rate and progression free survival (PFS) evaluated as per RECIST v1.1, time to response (TTR), duration of response (DoR), disease control rate (DCR) • Immunogenicity evaluation: positive rate of anti-drug antibody (ADA) and neutralizing antibody (NAb) **Exploratory endpoint:** • Tumor biomarkers (including but not limited to expression levels of PD-L1 and TMB in tumor samples)
Study Population	Subjects who have previously received first-line platinum-based treatment for small cell lung cancer and have shown objective radiographic progression. Including patients who meet any of the following conditions: • Sensitive recurrence: progression in ≥ 90 days from the last chemotherapy • Drug-resistant recurrence: progression during chemotherapy or within 90 days from the last chemotherapy

Study Design	This is a randomized, open-label, multi-center phase II clinical study. Eligible subjects after screening will be randomized into the following three groups in a 1:1:1 ratio, with 4 weeks as 1 treatment cycle: A: SHR-1210 200 mg, IV, Q2W + apatinib 375 mg, PO, QD B: SHR-1210 200 mg, IV, Q2W + apatinib 375 mg, PO, QD (5 days on, 2 days off) C: SHR-1210 200 mg, IV, Q2W + apatinib 375 mg, PO, QD (7 days on, 7 days off) The study consists of two stages. In Stage I, subjects will be randomized into 3 different dose groups, with 6 subjects in each group. It is planned that after the last subject in Stage I completes Cycle 1 treatment (28 days), the leading center's principal investigator and the sponsor will jointly perform a safety assessment of subjects enrolled in Stage I, decide the treatment group of Stage II, and choose one group of method of administration and a tolerated dose of apatinib for Stage II treatment. A total of 39 subjects will be enrolled in Stage II. The primary analysis will be performed when the last subject has been treated for 180 days. For any treatment group entering Stage II, if the safety is acceptable and the efficacy meets the corresponding statistical criteria, it indicates potential needs of further development.
Study Drugs and Method of Administration	A: SHR-1210 200 mg, IV, Q2W + apatinib 375 mg, PO, QD B: SHR-1210 200 mg, IV, Q2W + apatinib 375 mg, PO, QD (5 days on, 2 days off) C: SHR-1210 200 mg, IV, Q2W + apatinib 375 mg, PO, QD (7 days on, 7 days off) Note: PO: per os; QD: quaque die; IV: intravenous infusion; Q2W: once every 2 weeks; 5 Days on, 2 Days off: administration for 5 days and interrupt for 2 days; 7 Days on, 7 Days off: administration for 7 days and interrupt for 7 days
Inclusion Criteria	Patients must meet all of the following inclusion criteria to be eligible for this study. 1. All patients should sign the informed consent form (ICF) before starting study-related operations 2. Aged ≥ 18 and ≤ 70 years 3. With histologically or cytologically confirmed SCLC 4. Staged as ED-SCLC according to Veterans Administration Lung Study Group (VALG) staging 5. Have previously received first-line platinum-based treatment for ED-SCLC and have shown objective imaging progression. Including: • Sensitive recurrence: progression in ≥ 90 days from the last chemotherapy • Drug-resistant recurrence: progression during chemotherapy or within 90 days from the last chemotherapy 6. Able to provide tumor tissue samples for diagnosis, either archived samples within 12 months prior to the first dose of study drug or freshly obtained. The specimens shall meet the requirements of formalin-fixed and paraffin-embedded (FFPE) tumor tissue blocks allowing the cutting of 5-10 slices with a thickness of 4-6 μm for staining and testing. Cell smears from fine needle aspiration or centrifuged pleural fluid, bone lesions without soft tissue components or decalcified bone tumor specimens, and drill biopsy tissues are not acceptable, as they are insufficient for biomarker detection 7. ECOG PS of 0-1 8. Expected survival of ≥ 8 weeks

	9. With at least one target lesion without previous radiotherapy (RECIST v1.1) shown by CT or MRI scan ≤ 28 days prior to the first dose of study drug 10. Males and females of reproductive potential must take contraceptive measures from the first dose of study drug to within 24 weeks after the last dose of study drug (see 6.6.2 of the protocol for recommended contraceptive methods) 11. Had no transfusion of blood or blood products within the last 14 days prior to the first dose, not corrected with G-CSF or other hematopoietic colony-stimulating factors. Before the first dose of study drug, laboratory test values must meet the following conditions: (1) Hematology: white blood cell count (WBC) ≥ 3.0×10^9/L; absolute neutrophil count (ANC) ≥ 1.5×10^9/L; platelet (PLT) ≥ 100×10^9/L; hemoglobin content (HGB) ≥ 9.0 g/dL (2) Liver function: for patients without liver metastasis, aspartate transferase (AST) ≤ 2.5 × ULN, and alanine aminotransferase (ALT) ≤ 2.5 × ULN; for patients with liver metastasis, ALT and AST < 5 × ULN, serum total bilirubin (TBIL) ≤ 1.5 × ULN (except for Gilbert syndrome, total bilirubin < 3.0 mg/dL), and albumin (ULB) ≥ 3 g/dL (3) Kidney function: serum creatinine ≤ 1.5 × ULN or creatinine clearance rate (CrCl) ≥ 40 mL/minute (Cockcroft/Gault formula, see Appendix 2); urine protein (UPRO) negative (4) Coagulation function: international normalized ratio (INR) ≤ 1.5, activated partial thromboplastin time (APTT) ≤ 1.5 × ULN (5) Other: lipase ≤ 1.5 × ULN. If lipase is > 1.5 × ULN and no clinical or imaging evidence confirms pancreatitis, the patient can be enrolled; amylase ≤ 1.5 × ULN. If amylase is > 1.5 × ULN and no clinical or imaging evidence confirms pancreatitis, the patient can be enrolled. Alkaline phosphatase (ALP) ≤ 2.5 × ULN; for patients with bone metastasis, ALP ≤ 5 × ULN.
Exclusion Criteria	Patients meeting any one of the followings are not eligible to participate in this study: 1. With histologically or cytologically confirmed mixed SCLC and NSCLC. 2. Patients who have previously received anti-tumor viral treatment. Patients who have previously received T cell costimulation or immune checkpoint therapy, including but not limited to cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) inhibitors, PD-1 inhibitors, PD-L1/2 inhibitors or other drugs targeting T cells. 3. Patients who have previously received anti-vascular endothelial growth factor (VEGF) or vascular endothelial growth factor receptor (VEGFR) therapy. 4. Patients with clinically symptomatic brain metastasis or meningeal metastasis. Treated patients with brain metastasis should meet the following conditions to be enrolled: • No MRI-proven progression ≥ 4 weeks after the end of treatment • Completed treatment within ≥ 28 days prior to the first dose of study drug • No need to receive systemic corticosteroid treatment (> 10 mg/day prednisone or an equivalent dose) in ≤ 14 days prior to the first dose of study drug 5. Radiotherapy of the chest and whole brain should be completed less than 4 weeks prior to the first dose of study drug (patients whose palliative radiotherapy for bone lesions was completed prior to the first dose of study drug are allowed to be enrolled) 6. Clinically symptomatic effusion in the third space, such as pericardial effusion, pleural effusion, and ascites effusion that cannot be controlled by drainage or other treatments

	7. Active, known or suspected autoimmune diseases (see Appendix 4). Patients with vitiligo, type I diabetes, or residual hypothyroidism caused by autoimmune thyroiditis that only requires hormone replacement therapy or is unlikely to recur in the absence of external stimulation can be enrolled 8. Treated with systemic corticosteroids (> 10 mg prednisone or equivalent) or other immunosuppressants within ≤ 14 days prior to the first dose of study drug. In the absence of active autoimmune diseases, inhaled or topical use of steroids and adrenal replacement steroids is permitted 9. Patients who have received or plan to receive live vaccines within 4 weeks prior to the first dose of study drug 10. Interstitial pneumonia (ILD), drug-induced pneumonia, radiation pneumonia requiring steroid therapy, or active pneumonia with clinical symptoms or severe pulmonary dysfunction 11. Patients with active tuberculosis (TB) or a history of active tuberculosis infection ≤ 48 weeks before screening, regardless of whether they have been treated 12. Except for alopecia and fatigue, other toxicities caused by previous anti-tumor treatments should have recovered to CTCAE 4.03 Grade ≤ 1 prior to the first dose of study drug Patients with other toxicities caused by previous anti-tumor treatments that cannot be resolved within expectations and have long-lasting sequelae, such as neurotoxicity caused by platinum-based treatments, are allowed to be enrolled 13. Imaging (CT scan or MRI) showed tumor invasion of large blood vessels, symptoms of hemoptysis of daily hemoptysis ≥ 2.5 mL within 3 months before screening 14. Patients who have undergone minor surgery (including catheterization) within 48 hours before the first dose of study drug 15. Currently or recently (within 10 days prior to the first dose of study drug) using aspirin (> 325 mg/day) or other non-steroidal anti-inflammatory drugs known to inhibit platelet function 16. Currently or recently (within 10 days prior to the first dose of study drug) being treated with full-dose oral or parenteral anticoagulant or thrombolytic agents. But prophylactic use of anticoagulants is allowed 17. Patients with hereditary bleeding tendency or coagulation dysfunction. Patients with clinically significant bleeding symptoms or a clear bleeding tendency within 12 weeks prior to screening, such as hemorrhage of digestive tract, stomach ulcer with hemorrhage, baseline fecal occult blood++ and above, or vasculitis 18. Had arterial/venous thrombosis within 24 weeks prior to signing of ICF, such as cerebrovascular accidents (including transient ischemic attacks, cerebral hemorrhage, and brain infarction), deep vein thrombosis, and pulmonary embolism 19. Uncontrolled hypertension (systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg), a history of hypertensive crisis or hypertensive encephalopathy 20. With a history of the following diseases within 24 weeks prior to the signing of ICF: peptic ulcer, gastrointestinal perforation, corrosive esophagitis or gastritis, inflammatory bowel disease or diverticulitis, abdominal fistula, tracheo-esophageal fistula, or intra-abdominal abscess

	21. Patients with clinical symptoms or diseases of the heart that are not well controlled, such as: (1) > NYHA class 2 cardiac failure; (2) unstable angina; (3) myocardial infarction within 24 weeks; (4) patients with clinically significant supraventricular or ventricular arrhythmia requiring treatment or intervention 22. Known to be allergic to drugs or excipients, known to have severe allergic reactions to any kind of monoclonal antibody 23. Patients complicated with other malignant tumors ≤ 5 years before the first dose, except for cervical carcinoma *in situ*, basal cell or squamous cell skin cancer that can be adequately treated, local prostate cancer after radical resection, and ductal carcinoma *in situ* after radical resection 24. With evidence or history of psychiatric disorders, alcoholism, narcotics or drug abuse 25. Patients who are HBsAg positive with HBV DNA test value exceeding the upper limit of normal (1000 copies/mL or 500 IU/mL), or HCV positive (HCV RNA or HCV Ab test indicates acute and chronic infection); with known HIV-positive medical history or known acquired immune deficiency syndrome (AIDS) 26. Have received any other investigational drug or participated in other interventional clinical study within 4 weeks prior to signing the ICF 27. The investigator determines that the patient may have other factors leading to the discontinuation of the study, such as protocol incompliance, other serious diseases (including mental illness) requiring concomitant treatment, serious laboratory test abnormalities, accompanied by family or social factors that may affect the safety of the subject or the collection of data and samples
Study Withdrawal Criteria	**Reasons for withdrawal may include:** 1. The subject withdraws the ICF and refuses further follow-ups 2. Any clinical adverse drug reactions, laboratory abnormalities, or complications that renders the subject not benefiting from further treatment, as determined by the investigator 3. Other reasons investigator deems necessary for 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	**Criteria for treatment discontinuation are as follows:** 1. Treatment discontinuation requested by subjects 2. Radiographic or clinical evidence of progressive disease, unless the subject meets the criteria for continuing treatment beyond progression (see 6.1.2 of the protocol) 3. Occurrence of pregnancy during the study 4. Any clinical AEs, laboratory abnormalities, or other medical conditions indicating that the subject can no longer benefit from study treatment 5. General deterioration of health status suggesting that the subject cannot continue to involve the study 6. The enrolled subject is found to have important protocol deviations such as ineligibility 7. Lost to follow-up

	8. Termination by sponsor 9. Death 10. Other reasons as determined by the investigator
Determination of Sample Size	Assume that in this study, the expected ORR in each treatment group of SHR-1210 + apatinib combination therapy is ≥ 30% (alternative hypothesis), and that there is no need to continue the study if the ORR is ≤ 15% (null hypothesis), at the significance level of 0.1 and a power of 80%, 40 subjects should be enrolled. If ≥ 9 (22.5%) of the 40 subjects have response, it can be considered that the ORR in this treatment group is 15% and the investigational drug is worthy of continued development. With a dropout rate of 10% taken into account, each treatment group needs to enroll about 45 subjects. A total of 57 subjects are required in Stages I and II.
Data Analysis/ Statistical Methods	**General analysis:** Unless otherwise stated, the following descriptive statistics will be summarized based on data types. • Continuous variables will be summarized using the mean, standard deviation, median, maximum, and minimum. • Categorical variables will be summarized using the frequency and percentage. • For time-to-event data, the survival rate and median survival will be estimated using the Kaplan-Meier method. A corresponding 95% confidence interval will be provided for the aforementioned analyses, when necessary. **Efficacy analysis:** ORR is the primary efficacy endpoint of this study, which refers to the proportion of all enrolled subjects assessed to have complete response (CR) or partial response (PR) as per RECIST 1.1 criteria. Response confirmation should be conducted for CR and PR. The point estimate of ORR and two-sided 95% confidence interval based on the Clopper-Pearson method will be calculated. The statistical analysis of ORR will be based on the full analysis set (FAS) and evaluable set (ES), with FAS as the primary analysis set. The secondary efficacy endpoints of the study include the 6-month OS rate, OS, as well as PFS, TTR, DoR, and DCR evaluated per RECIST v1.1. The statistical analysis of DoR, TTR, and PFS will be based on the FAS and ES, with FAS as the primary analysis set. The statistical analysis of OS will be based on the FAS. PFS, TTR, DoR, and OS will be estimated based on the Kaplan-Meier method, and the corresponding two-sided 95% confidence interval will be calculated. The point estimate of DCR and the 95% confidence interval based on the Clopper-Pearson method will be calculated. **Safety analysis:** The following safety analyses (including but not limited to) will be performed according to the existing report criteria of Hengrui by group: • Analysis of treatment discontinuation, dose reduction, or treatment interruption due to AEs • Incidence and severity of AEs • Causality analysis between AEs and study drug • Analysis of outcomes of AEs • Analysis of SAEs

	• Descriptive statistical summary of laboratory test, vital signs, and ECG data • Incidence of laboratory abnormalities • Analysis of normal and abnormal changes in laboratory parameters, vital signs, and ECG data compared to baseline.
Interim Analysis	This study does not involve an interim analysis
Study Period	Anticipated enrollment of the first subject: Q1 of 2018 Anticipated enrollment of the last subject: Q4 of 2018 Anticipated time of last subject last visit: Q3 of 2019 Anticipated study completion: Q1 of 2020

SCHEDULE OF ACTIVITIES

Table 1. Schedule of activities

Stage	Screening Period			Treatment Period (4 weeks/cycle)				End of Treatment[26]	Safety Follow-Up[27]	Survival Follow-Up[28]
				Cycle 1[25]		Cycle 2 and thereafter				
Visit	**1**			**2**	**3**	**N**	**N + 1**			
Day	**-28 to -1**	**-7 to 1**	**-3 to 1**	**1**	**15 (± 3 days)**	**1 (± 3 days)**	**15 (± 3 days)**	**± 3 days**	**90 days (± 7 days)**	**Every 8 weeks (± 7 days)**
Baseline										
Written Informed Consent Form[1]	X									
Inclusion/Exclusion Criteria	X									
Demographics/Medical History/ Medication History[2]	X									
Vital Signs[3]	X			X	X	X	X	X	X	
Weight/Height[4]	X			X	X	X	X	X	X	
Physical Examinations[5]	X			X	X	X	X	X	X	
ECOG Performance Status[6]	X			X	X	X	X	X	X	
Laboratory tests										
12-Lead ECG[7]	X			X	X	X	X	X	X	
Hematology/Clinical Chemistry/ Urinalysis/Routine Stool[8]		X			X	X	X	X	X	
Coagulation Function[9]		X				X		X	X	
Pregnancy Test[10]			X					X		
Thyroid Function[11]	X					X		X	X	
Myocardial Zymogram[12]		X						X		

Stage	**Screening Period**			**Treatment Period (4 weeks/cycle)**				**End of Treatment[26]**	**Safety Follow-Up[27]**	**Survival Follow-Up[28]**
				Cycle 1[25]		**Cycle 2 and thereafter**				
Visit	**1**			**2**	**3**	**N**	**N + 1**			
Day	**-28 to -1**	**-7 to 1**	**-3 to 1**	**1**	**15 (± 3 days)**	**1 (± 3 days)**	**15 (± 3 days)**	**± 3 days**	**90 days (± 7 days)**	**Every 8 weeks (± 7 days)**
Pituitary Adrenal Axis Test[13]	X					X		X		
HIV, HBV, and HCV[14]	X									
Echocardiography[15]	X							X		
Pulmonary Function Test and Arterial Blood Gases[16]	X									
Immunogenicity (ADA, Nab)[17]				X		X		X	X	
AE Assessment[18]	X			X		X		X	X	
Concomitant Medications[19]	X			X		X		X	X	
End of treatment visit										
Survival Status									X	X
Subsequent Anti-Tumor Treatment									X	X
Response Evaluation										
Imaging Evaluation[20]	X			X		X		X		
Infusion of Study Drugs										
SHR-1210[21]				200 mg, IV, Q2W						
Apatinib[22]				375 mg, PO						
Exploration of Biomarkers										
Archived or Fresh Tumor Tissue Sample[23]	X							X		

Stage	Screening Period			Treatment Period (4 weeks/cycle)				End of Treatment[26]	Safety Follow-Up[27]	Survival Follow-Up[28]
				Cycle 1[25]		Cycle 2 and thereafter				
Visit	**1**			**2**	**3**	**N**	**N + 1**			
Day	**-28 to -1**	**-7 to 1**	**-3 to 1**	**1**	**15 (± 3 days)**	**1 (± 3 days)**	**15 (± 3 days)**	**± 3 days**	**90 days (± 7 days)**	**Every 8 weeks (± 7 days)**
Peripheral Blood[24]	X					X		X		

Note:

1. Except for tumor imaging and tumor biopsy within the prescribed time limit before the first dose, the ICF should be signed before any operation specified in the protocol.
2. The medications include treatment for initial diagnosis, including chemotherapy, radiotherapy, and surgical treatment. The time of the last anti-tumor treatment must be recorded.
3. Vital signs include body temperature, pulse, respiratory rate, and blood pressure. Measurements will be conducted during the screening period, before each SHR-1210 administration, at the end of the treatment, and at safety follow-ups. Blood pressure monitoring: cigarettes and caffeine are prohibited within 30 min before each blood pressure measurement, and subjects shall rest for at least 10 min. The blood pressure will be measured at sitting position with elbow on the same level as heart. All measurements should be taken on the same side. During the screening period and before each scheduled SHR-1210 infusion, the investigator will measure the blood pressure of the subject. During the study, the subject will monitor the blood pressure and record on the diary card. Blood pressure shall be measured at least 3 times per week in the first 2 cycles. For subjects with abnormal blood pressure, the blood pressure shall be measured daily; if normal, the blood pressure shall be measured twice per week after Cycle 2.
4. Height will be measured only during the screening period. Weight will be measured during the screening period, before each SHR-1210 administration, at the end of the treatment, and at safety follow-ups.
5. Physical examinations will be conducted during the screening period, before each SHR-1210 administration, at the end of the treatment, and at safety follow-ups.
6. ECOG PS scoring will be conducted during the screening period, before each SHR-1210 administration, at the end of the treatment, and at safety follow-ups.
7. 12-lead ECG examination time: during the screening period, after each SHR-1210 infusion, at the end of treatment, and during safety follow-up. The examination results during screening may be used for the ECG examination at C1D1 visit. Refer to Section 8.2.3 of the protocol for details.

8. Hematology includes: red blood cell count (RBC), hemoglobin (HGB), hematocrit value (HCT), white blood cell count (WBC), platelet (PLT), and white blood cell differential [lymphocyte count (LYM), absolute neutrophil count (ANC), monocyte count (MONO), eosinophil count (EOS), and basophil count (BASO)]. Clinical chemistry includes: liver function [serum total bilirubin (TBIL), alanine aminotransferase (ALT), aspartate transferase (AST), gamma-glutamyltransferase (γ-GT), alkaline phosphatase (ALP), albumin (ALB), total protein (TP), and lactic dehydrogenase (LDH)]; renal function [blood urea nitrogen (BUN) and creatinine (Cr)]; blood electrolytes (Na, K, Cl, Mg, Ca, and P); lipase, amylase, and fasting blood glucose (FBG). Urinalysis includes: pH, urine albumin (UALB), urine protein (UPRO), urine red blood cell (URBC), and urine glucose (UGLU). The subject may be enrolled only if urinalysis shows negative urine protein at screening. Routine stool test: occult blood; re-examination is needed for fecal occult blood+; if fecal occult blood is confirmed, then a gastroenterological endoscopy will be performed. Hematology, clinical chemistry, urinalysis, and routine stool will be performed during the screening period (within 7 days before the first dose of the study drug), before each SHR-1210 administration, at the end of the treatment, and at safety follow-ups. Tests will be performed at each study center.
9. Coagulation function tests include: thrombin time (TT), prothrombin time (PT), activated partial thromboplastin time (APTT), and international normalized ratio (INR). Tests will be performed within 7 days prior to the first dose, before the administration of SHR-1210 on day 1 of each cycle, at the end of the treatment, and at safety follow-ups. Tests will be performed at each study center.
10. Women of childbearing potential will undergo a serum pregnancy test within 3 days prior to the first dose and at the end of the treatment. Tests will be performed at each study center.
11. Thyroid function tests include: thiiodothronine (T3), thyroxine (T4), free thiiodothronine (FT3), free thyroxine (FT4), and thyroid stimulating hormone (TSH). Tests will be performed during the screening period, before the administration of SHR-1210 on day 1 of each cycle, at the end of the treatment, and at safety follow-ups; the results from the screening period may be used for the thyroid function tests at the C1D1 visit. Tests will be performed at each study center.
12. Myocardial zymography: including LDH, AST, creatine kinase (CK), creatine kinase isoenzyme (CK-MB), and ALT. Tests will be performed once within 7 days prior to the first dose and performed again only upon the onset of symptoms of precordial pain and palpitations, and abnormal ECG hereafter, as well as at the end of the treatment.
13. Hypothalamic-pituitary-adrenal (HPA) axis tests: including corticotropin releasing hormone (CRH), adrenocorticotropic hormone (plasma ACTH), and adrenocortical hormones. Adrenocortical hormone tests include serum cortisol, urinary free cortisol (UFC), urinary 17-ketosteroids (17-KS), and urinary 17-ketogenic steroids (17-KGS). For hospitals where conditions permit, the tests are recommended during the screening period, before the administration of SHR-1210 on day 1 of each cycle, and at the end of the treatment.

14. Include HBV, HCV, and HIV antibody tests; requirements for HBV testing: HbsAg shall be tested during the screening period to determine the presence of HBV infection; if positive, HbsAg (quantitative), HbsAb (qualitative), HbcAb (qualitative), HbeAg (qualitative), HbeAb (qualitative), and HBV-DNA (qualitative; quantitative test required if positive) shall be tested. Requirements for HCV testing: HCV-Ab is tested at screening to determine the presence of HCV infection. If positive, HCV-RNA will be tested (qualitative, and if positive, quantitatively). The investigator must arrange for appropriate anti-viral treatment for HBV carriers participating in this study. Tests will be performed at each study center.
15. Echocardiography: Perform once within 28 days before the first dose and at the end of the treatment, and when clinically significant ECG abnormalities are found during the study.
16. Pulmonary function test: Maximum vital capacity, the forced expiratory flow at 25-75% of forced vital capacity (FEF25-75), the peak expiratory flow rate (PEF), the maximum expiratory volume per second, diffusing capacity of the lungs for carbon monoxide (DLCO) and oxygen saturation, which will be performed during the screening period and based on clinical indicators as determined by the investigator thereafter. Arterial blood gas test: optional. This test includes partial arterial pressure of oxygen (PaO_2), partial arterial pressure of carbon dioxide ($PaCO_2$), arterial oxygen saturation (SaO_2), and pH, and can be performed during the screening period. Pulmonary function test and arterial blood gas test indicators will be based on the actual conditions at each site.
17. Immunogenicity blood samples will be collected once within 0.5 h before SHR-1210 infusion on D1 of cycle 1, cycle 2, and the third cycle of every three cycles thereafter (cycles 5, 8, 11, etc.), once at the end of the treatment, and once per month at safety follow-ups after withdrawal for 3 times (if applicable). In case of national holidays, the blood collection time may be adjusted as appropriate. If the subject develops SHR-1210 infusion-related reactions, blood samples should be collected as close as possible to the onset of the event, to the end of the event, and about 30 days after the end of the event, for immunogenicity comparison and analysis. Immunogenicity blood samples should be collected following the study protocol. However, if deemed necessary by the investigator, unscheduled immunogenicity blood samples may be collected. Tests will be performed at the central laboratory. Four (4) mL of blood will be collected each time for immunogenicity.
18. The safety assessment for AEs and laboratory tests will be performed according to NCI CTCAE v4.03. All AEs/SAEs will be recorded in the CRF from the time of signing the ICF to the end of safety follow-up or the start of new anti-tumor therapy (whichever occurs first). The definition, recording, causality assessment, severity assessment, reporting time limit, handling, and follow-up of AE and SAE should refer to the description in Section 9 of the protocol.
19. All drugs related to the treatment of AEs other than solvents within 28 days before the first dose of the study drug until 30 days after and 30-60 days after the end of the treatment should be documented in the CRF, including the name, dose, route of administration, frequency of administration, purpose, and start and end dates.
20. The method used for tumor imaging evaluation during the baseline period must be consistent with the method used for each subsequent follow-up evaluation. Computerized tomography (CT) or magnetic resonance imaging (MRI) scans are recommended. Other involved parts are examined based on the symptoms and signs of each subject. Baseline imaging evaluations should include thoracic, abdominal, and pelvic scans (from apex of lungs to pubic symphysis), brain scan,

bone scan, and scan of all known or suspected lesions. Each subsequent clinical tumor imaging evaluation should include thoracic, abdominal, and pelvic scans; brain and/or bone scans may be performed when clinically indicated. The frequency of imaging monitoring can be increased by the investigator as needed. The baseline tumor evaluation will be performed within 28 days before the first dose. Imaging data obtained before the signing of informed consent form may be used for tumor evaluation during the screening period as long as it meets the requirements of the protocol. During the study, imaging assessment will be performed on C1D28 (± 3 days) and every 8 weeks (± 7 days) after C1D28 until radiographic progressive disease (PD) is documented. An additional imaging evaluation must be performed in 4 weeks (+ 7 days) for confirmation after the initial documentation of response (CR or PR) and imaging PD. If PD is not confirmed, the study medication and imaging evaluation are continued until relapse of PD. Refer to Section 6.1.2 of the protocol for the relapse of PD. Subjects with relapse of PD must discontinue treatment. If the treatment is discontinued for reasons other than radiologically confirmed PD, imaging evaluations shall be performed as much as possible per the scheduled imaging time points until any of the following events occurs: start of new anti-tumor therapy, PD, withdrawal of ICF and/or death. Refer to Section 8 of the protocol for details.

21. 200 mg of SHR-1210, intravenous drip infusion, once every 2 weeks. Subjects who meet specific conditions may continue the medication after PD (refer to Section 6.1.2 of the protocol for continued medication beyond progression).
22. Eligible subjects after screening will be randomized in a 1:1:1 ratio into the following three treatment groups: apatinib 375 mg, PO, QD; apatinib 375 mg, PO, QD (5 Days on, 2 Days off); or apatinib 375 mg, PO, QD (7 Days on, 7 Days off). Apatinib should be administered at a fixed time every day as much as possible. On the day of SHR-1210 infusion, apatinib shall be administered 30 min after the end of SHR-1210 infusion.
23. Subjects are required to provide archived or fresh tumor tissue samples that meet the testing requirements during the screening period. After obtaining the subject's ICF, another biopsy may be performed at the end of treatment. Tumor tissue samples to be provided at screening (required) and the end of treatment shall be 5-10 unstained tissue slices with a thickness of 4-6 μm, among which at least 5 sections are used for PD-L1 testing.
24. After the subject's ICF is obtained, about 16 mL of peripheral blood may be collected for tumor biomarker detection during the screening period, at each tumor evaluation, and the end of the treatment.
25. Randomization must be completed within 24 h before the first dose of the study drug.
26. End of treatment refers to confirmation of progressive disease or withdrawal from study, and shall be carried out within ± 3 days when the decision of treatment discontinuation and/or withdrawal from study is made.
27. Safety follow-ups will be performed 90 ± 7 days after the last dose.
28. Survival follow-ups: Performed once every 8 weeks (± 7 days) after the last dose, and telephone interviews are acceptable.

ABBREVIATIONS

Abbreviations	Full Name
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
AIDS	Acquired Immune Deficiency Syndrome
ALB	Albumin
ALP	Alkaline phosphatase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
AST	Aspartate transferase
BASO	Basophil cell count
CFDA	China food and drug administration
BUN	Blood urea nitrogen
CK	Creatine kinase
CK-MB	Creatine kinase isoenzyme
CR	Complete response
Cr	Creatinine
CRF	Case report form
CTLA-4	Cytotoxic T lymphocyte-associated antigen-4
DCR	Disease control rate
DLT	Dose-limiting toxicity
DoR	Duration of response
EC	Ethics Committee
EDC	Electronic data capture
eCRF	Electronic case report form
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EOS	Eosinophil count
ED-SCLC	Extensive-stage disease small cell lung cancer
FGF	Fibroblast growth factor
FT3	Free triiodothyronine
FT4	Free thyroxine 4
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice

Abbreviations	Full Name
GMP	Good Manufacturing Practices
GLP	Good Laboratory Practices
HCT	Hematocrit value
HGB	Hemoglobin
HRT	Hormone replacement therapy
IB	Investigator's brochure
ICF	Inform consent form
INR	International normalized ratio
IU	International unit
irAE	Immuno-related adverse event
LDH	Lactate dehydrogenase
LD-SCLC	Limited-stage disease small cell lung cancer
LYM	Lymphocyte count
IVIgG	Intravenous immunoglobulin G
MedDRA	Medical Dictionary for Regulatory Activities
MONO	Monocyte count
MTD	Maximum tolerated dose
Na+	Plasma sodium
Nab	Neutralizing antibody
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
PBMCs	Peripheral blood mononuclear cells
PD	Progressive disease
PD-1	Programmed death-1
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PLT	Platelet
PR	Partial response
PT	Prothrombin time
RBC	Red blood cell
Q2W	Every 2 weeks
QD	Once daily
RECIST	Response Evaluation Criteria in Solid Tumors

Abbreviations	Full Name
RPLS	Reversible posterior leukoencephalopathy syndrome
SD	Stable disease
SDV	Source data verification
T3	Triiodothyronine
T4	Thyroxine
TCR	T cell receptor
TBIL	Total bilirubin
TP	Total protein
TSH	Thyroid-stimulating hormone
TT	Thrombin time
TTR	Time to response
UALB	Urinary albumin
UGLU	Urine glucose
UPRO	Urine protein
URBC	Urine red blood cell
VALG	Veterans Administration Lung Study Group
WBC	White blood cell
γ-GT	γ-glutamyltransferase
SAE	Serious adverse event
SCLC	Small cell lung cancer
SAP	Statistical analysis plan
TEAE	Treatment emergent adverse event
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
CrCl	Creatinine clearance rate

1 KEY FUNCTIONAL ROLES

Principal Investigator of Leading Center	Prof. Jie Wang Contact: Cancer Hospital of Chinese Academy of Medical Science [redacted]
Principal Investigator of Cooperative Leading Center	Prof. Yun Fan Contact: Zhejiang Cancer Hospital [redacted]
Sponsor's Medical Director	[redacted], M.D., Clinical Medical Director Jiangsu Hengrui Pharmaceuticals Co., Ltd. [redacted]
Statistician	[redacted], Ph.D., Jiangsu Hengrui Pharmaceuticals Co., Ltd. [redacted]

2 BACKGROUND AND SCIENTIFIC RATIONALE

2.1 Disease Background

Lung cancer is the most common malignant tumor in China. According to data released by the National Center for Cancer Registry in 2016, the incidence of lung cancer ranked first in males and second only to breast cancer in females [1]. The main types include non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC).

2.1.1 Non-small cell lung cancer

NSCLC accounts for approximately 85% of lung cancers[2,3]. NSCLC is classified by histology as adenocarcinoma, squamous carcinoma, large cell carcinoma, neuroendocrine tumor, sarcomatoid carcinoma, and poorly differentiated carcinoma. Among these subtypes, adenocarcinoma accounts for more than 50% and squamous cell carcinoma accounts for 25%[4]. The 5-year survival rate of NSCLC is 2-4%, depending on the lesion site[5]. Factors for poor prognosis include advanced stage at initial diagnosis, poor PS score, and history of surreptitious weight loss. Half of NSCLC patients have distant metastases when initially diagnosed.

Adenocarcinoma and squamous cell carcinoma have different characteristics. First, squamous cell carcinoma is commonly the central type and mostly in the bronchial epithelium, whereas non-squamous carcinoma is commonly the peripheral type and mostly in the lung parenchyma. Evaluation of the histological type of NSCLC further shows the difference between squamous cell carcinoma (keratinization, intracellular bridges, and central necrosis) and adenocarcinoma (glandular structure). Immunohistochemical labeling further supports the diagnosis of NSCLC when the tumor specimens are limited in quantity or the degree of differentiation is low. TTF-1 is expressed highly in adenocarcinoma but rarely in squamous cell carcinoma. On the contrary, p63, CK5/6, and 34BE12 are highly expressed in squamous cell carcinoma but rarely in adenocarcinoma[6].

The driver genes of NSCLC include EGFR, ALK, and KRAS. These driver genes have different mutation rates in adenocarcinoma and squamous cell carcinoma. For example, 10-40% of adenocarcinoma patients are EGFRm+. Approximately 7% of adenocarcinoma patients are ALK fusion gene positive. And approximately 30% of adenocarcinoma patients are KRASm+. But these gene mutations are rare in patients with squamous cell carcinoma[4,6,7].

See Table 2 for the treatment of different types of NSCLC recommended by the FDA and EMA. No immunotherapy drug is available in China for the treatment of advanced NSCLC (Stage IV) with negative driver genes according to the guidelines of the Chinese Society of Clinical Oncology (CSCO) issued in 2017. For the second-line treatment of non-squamous cell carcinoma, mono-chemotherapy with docetaxel or pemetrexed is recommended for patients with a PS score of 0-1. The best supportive treatment is recommended for patients with a PS score of 3-4, who are encouraged to participate in clinical studies. Mono-chemotherapy with docetaxel is recommended as second-line treatment of squamous cell carcinoma. Patients who are not suitable for cytotoxic chemotherapy may choose afatinib, vinorelbine, or gemcitabine. Few second-line treatment options are available for NSCLC, and new treatment methods are urgently needed. Most immunotherapy, anti-VEGFI therapy, immunotherapy-based combination therapy, or anti-VI(R)-based combination therapy are still under clinical studies.

Table 2. Individualized treatment of NSCLC

Histology	Molecular Pathology	PD-L1 Expression*	First line	Maintenance	Second Line
Squamous cell cancer	NA	< 50%	Platinum-based chemotherapy ± necitumumab (EMA)	Necitumumab	Immunotherapy Chemotherapy Docetaxel + ramucirumab Afatinib
	NA	≥ 50%	Pembrolizumab	Pembrolizumab	Platinum-based chemotherapy
Non-squamous cell cancer	EGFRm+	NA	Erlotinib + bevacizumab Erlotinib Afatinib Gefitinib	Erlotinib + bevacizumab Erlotinib Afatinib Gefitinib	Osimertinib Platinum-based chemotherapy
	ALK+	NA	Crizotinib (also applicable to ROS1+) Ceritinib (FDA and EMA)	Crizotinib (also applicable to ROS1+) Ceritinib (FDA and EMA)	Ceritinib Alectinib (failure of first-line treatment with crizotinib) Platinum-based chemotherapy
	Wild-type	< 50%	Platinum-based chemotherapy (± bevacizumab)	Pemetrexed (continued or transferred to maintenance treatment) Bevacizumab (continued maintenance treatment)	Immunotherapy Chemotherapy Docetaxel + ramucirumab Docetaxel + nintedanib (adenocarcinoma, EMA) Erlotinib (EMA)
	Wild-type	≥ 50%	Pembrolizumab	Pembrolizumab	Platinum-based

Note: This table is from Reference 8.* Dako 22C3 kit is used for the detection of PD-L1.

2.1.2 Small cell lung cancer

SCLC accounts for 10-15% of new lung cancers. It is a highly aggressive neuroendocrine tumor. It is significantly different from NSCLC clinically and pathologically, characterized by rapid growth, proneness to drug resistance, and early metastasis. Almost all patients with SCLC have a history of heavy tobacco use[9,10]. Traditionally, SCLC is classified into limited-stage disease (LD-SCLC, where tumor tissue surrounds a radiotherapy field) and extensive-stage disease (ED-SCLC, where tumor tissue exceeds the boundary of a radiotherapy field)[11]. Most patients have ED-SCLC when first diagnosed. Platinum (cisplatin or carboplatin) combined with etoposide for 4-6 cycles is still the first-line standard treatment for LD-SCLC and ED-SCLC. The combination of platinum, etoposide, and thoracic radiotherapy can reach an ORR of 70-90% in LD-SCLC. The combination of platinum and etoposide can reach an ORR of 60-70% in ED-SCLC. The mOS is 14-20 months and 9-11 months, respectively. After proper treatment, the 2-year survival rate is 40% and < 5%, respectively[12]. Concomitant thoracic radiotherapy can increase the local control rate by 25% in LD-SCLC [13,14]. The combination of radiotherapy and chemotherapy are recommended for LD-SCLC patients with negative cytological results or uncertain pleural effusion without pericardial effusion[15,16].

After the first-line treatment with the combination of platinum and etoposide, approximately 80% of LD-SCLC patients and almost all ED-SCLC patients develop progressive disease[17]. Subjects whose last dose of first-line chemotherapy is longer than 180 days ago may use platinum-based two-drug chemotherapy again. Other patients can only be treated with topotecan monotherapy, the only second-line medicine approved by the FDA. The approval of the second-line treatment of topotecan was based on a phase III study in subjects with recurrent SCLC to compare the efficacy and safety of topotecan monotherapy and the CAV regimen, i.e., cyclophosphamide, adriamycin, and vincristine. The results showed similar efficacy between the two groups in terms of the ORR (24.3% vs. 18.3%, p = 0.285), mPFS (13.3 wks vs. 12.3 wks, p = 0.552), and mOS (25 wks vs. 24.7 wks, p = 0.795). In terms of safety, the incidence of non-hematologic toxicity in the topotecan group was lower than that in the CAV group, mostly Grade 1-2. In terms of hematologic toxicity, there were more Grade > 4 neutropenia cases in the CAV group than in the topotecan group, but the incidences of Grade > 4 thrombocytopenia and Grade 3-4 anemia were higher in the topotecan group [18]. Based on 21 meta-analyses published during 1984-2011, the mOS of second-line treatments of SCLC was 6.7 months[19]. In summary, SCLC has huge unmet clinical needs.

2.2 Immune Checkpoint Therapy

In the process of tumor occurrence and development, tumor cells undergo many hereditary and epigenetic changes compared with normal cells, and theoretically have enough antigens to be recognized by the human immune system, which can trigger an immune response to inhibit tumor growth. However, tumors can suppress the immune response through multiple pathways to evade the attack from immune system[20].

In the process of effective anti-tumor immunity, T cells as core executors are first recognized by antigen recognition signals mediated by T cell receptor (TCR), while numerous costimulatory signals and coinhibitory signals finely regulate the intensity and quality of T cell responses[21], of which the inhibitory signal is the checkmate inhibitor. Under physiological circumstances, these immune checkpoints are involved in maintaining immune tolerance to self-antigens on the one hand to avoid autoimmune diseases; on the other hand, they can avoid tissue damage caused by excessive activation of immune responses[22]. However, tumor cells can use these immune checkpoints to inhibit T cell activation, thereby evading immune killing.

2.2.1 PD-1/PD-L1 and tumors

The induction of effective anti-tumor immune responses is a complex process involving multiple steps. The key step depends on the ability of the major executor, effector T-cells, to effectively recognize and kill tumor cells, while the activation of T-cells is the premise for their anti-tumor effects.

Programmed death-1 (PD-1) is one of the many immune checkpoints that can inhibit T cell activation. It is one of the important inhibitory receptors on the surface of T cells and is homologous with CD28 and CTLA-4. It is named for its initial discovery in apoptotic T cell lymphoma and its ability to promote programmed cell death. PD-1 is expressed on activated T cells, depleted T cells, activated B cells, natural killer cells, dendritic cells, and activated monocytes, but not on the surface of resting lymphocytes[23,24]. Up-regulation of PD-1 expression on the surface of activated lymphocytes can lead to inhibition of acquired or innate immune responses, as PD-1-mediated immunosuppression can be triggered when the phosphorylase binds to the immunoreceptor tyrosine-based inhibitory motif and conversion motif of PD-1 in the cytoplasm[23]. PD-1 has two major ligands, programmed death factor ligand 1 (PD-L1 [B7-H1]) and programmed death factor ligand 2 (PD-L2 [B7-DC])[25,26].

The PD-1/PD-L1 binding plays an important role in regulating T cell activation and maintaining peripheral immune tolerance (the role of PD-1 in the process of T cell activation, aging, and response is shown in Figure 1 below[8]). When T cells do not express PD-1, they interact with antigen-presenting cells to activate and proliferate T cells and secrete activated cytokines to act on tumor cells, mainly manifested as killing of tumor cells (Figure 1A); activated T cells begin to express PD-1, and when they bind to ligand PD-L1 on antigen-presenting cells or tumor cells, the inhibitory signals transmitted by PD-1 will inhibit the proliferation of T cells and the secretion of active cytokines, so that the function of T cells is reduced, and most tumor cells evade immune cell attack through this mechanism (Figure 1B); if the interaction between PD-1 and PD-L1 is blocked by drugs, the activity of T cells and the ability to kill cancer cells can be restored (Figure 1C)[27].

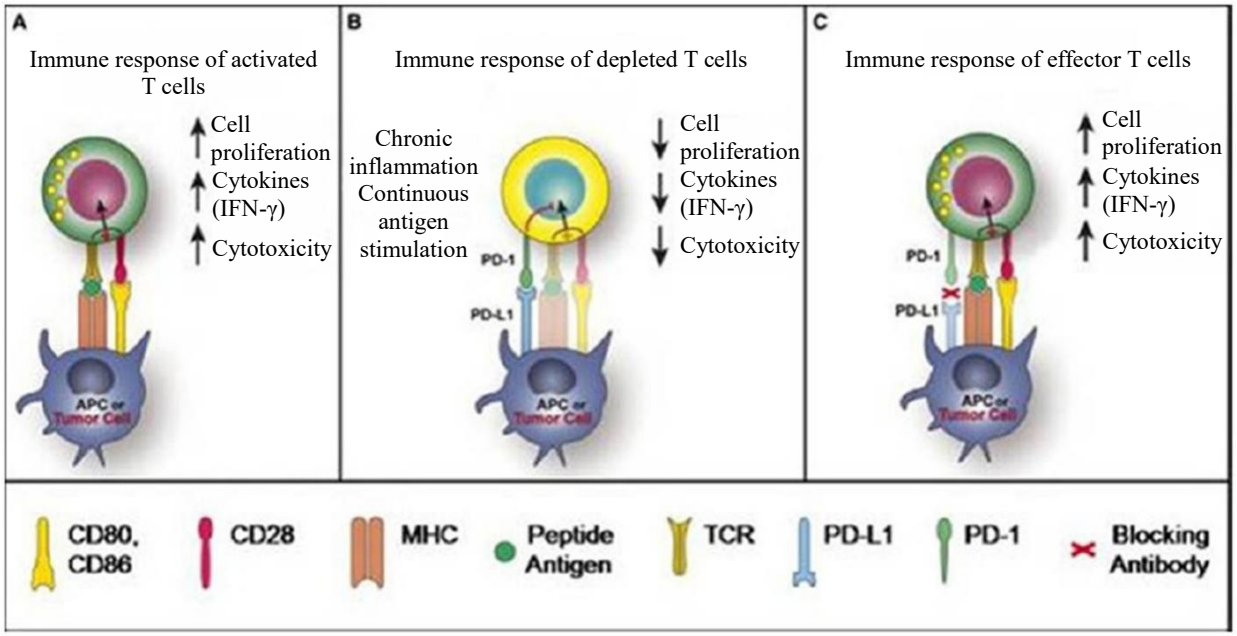


Figure 1. PD-1's role in T cell activation, aging, and response

2.2.2 Anti-PD-1/PD-L1 agents

PD-L1 is widely expressed in solid tumors and hematological tumors (Table 3)[28]. A variety of tumor types rank among the top ten in incidence/mortality in China, such as lung cancer, colon cancer, gastric cancer, esophageal cancer, breast cancer, and liver cancer[29]. Anti-PD-1 agents play a therapeutic role by blocking the binding of PD-L1 on tumor cells and PD-1 of T cells, blocking its inhibition on T cells. Compared with traditional cytotoxic chemotherapy, PD-1 targeted therapy has higher specificity, lower toxicity, and applicability to a variety of tumor types.

Table 3. PD-L1 expression in multiple types of tumors

Types of Tumors	Positive Rate of PD-L1 (%)
Malignant glioma	100
Nasopharyngeal Carcinoma	68-100
Melanoma	40-100
Bladder cancer	28-100
Non-Small Cell Lung Cancer	35-95
Small Cell Lung Cancer	28.6%
Multiple Myeloma	93
Hepatic Cancer	45-93
Ovarian Cancer	33-80
Colon Cancer	53
Gastric Cancer	42
Esophageal Cancer	42
Pancreatic Cancer	39
Breast Cancer	31-34
Renal Cancer	15-24
Lymphoma	17-94
Leukaemia	11-42

Note: * The data comes from the 2016 World Conference on Lung Cancer.

See Table 4 for anti-PD-1/PD-L1 monoclonal antibodies that have been marketed as of 27 Sep., 2017.

Table 4. Marketed anti-PD-1/PD-L1 monoclonal antibodies

Generic Name (Trade Name)	Company	Target	Category	Time of Marketing	Current Indication(s)
Nivolumab (OPDIVO)	BMS	PD-1	IgG-4	2014	Melanoma, non-small cell lung cancer, renal cell carcinoma, classic Hodgkin's lymphoma, head and neck squamous cell carcinoma, urothelial carcinoma, colorectal cancer (MSI-H or dMMR), and liver cancer
Pembrolizumab (KEYTRUDA)	Merck	PD-1	IgG-4	2014	Melanoma, non-small cell lung cancer, head and neck squamous cell carcinoma, classic Hodgkin's lymphoma, urothelial carcinoma, MSI-H tumor, and gastric cancer
Atezolizumab (Tecentriq)	Roche	PD-L1	IgG-1	2016	Urothelial cancer, non-small cell lung cancer

Generic Name (Trade Name)	Company	Target	Category	Time of Marketing	Current Indication(s)
Durvalumab (Imfinzi)	AZ	PD-L1	IgG-1	2017	Urothelial carcinoma
Avelumab (Bavencio)	Merck & Pfizer	PD-L1	IgG-1	2017	Merkel cell carcinoma

As of 27 Sep., 2017

2.3 Scientific Rationale

2.3.1 Basis of SHR-1210 combined with apatinib in the second-line treatment of SCLC

Peripheral blood mononuclear cells (PBMCs) in SCLC patients show that there are more effector T cells in LD-SCLC patients than in ED-SCLC patients. SCLC patients with a long survival have a high ratio of effector T cells to regulatory T cells[30]. In the phase I study of nivolumab 1, 3, and 10 mg/kg dose groups for the treatment of SCLC, the ORRs were 6%, 27%, and 17%, respectively, and the 24-week PFS rates were 25%, 44%, and 31%, respectively[31,32]. The CheckMate 032 study is a phase I/II open-label study comparing the ORRs of nivolumab 1 mg/kg, nivolumab 1 mg/kg combined with anti-CTLA-4 monoclonal antibody ipilimumab 3 mg/kg, and nivolumab 3 mg/kg combined with ipilimumab 1 mg/kg in SCLC patients who have previously undergone first-line or second-line standard treatment. The results showed that, regardless of PD-L1 expression, ORRs were 10%, 23%, and 19%, respectively; mPFSs were 1.4, 2.8, and 1.4 months, respectively; mOSs were 5.7, 7.7, and 7.2 months, respectively; and the 1-year OS rates were 33%, 43%, and 35%, respectively. Common adverse events included asthenia, diarrhea, vomiting, skin rash, and serum lipase increased. The incidence of Grade ≥ 3 adverse events in the combination group was greater than that in the monotherapy group[33]. The KEYNOTE 028 study is a phase Ib study evaluating pembrolizumab 10 mg/kg Q2W monotherapy as second-line treatment of advanced solid tumors. In SCLC patients with high PD-L1 expression, the ORR was 29.2% and the mPFS was 1.8 months. Common adverse events included joint pain, faintness, skin rash, diarrhea, and asthenia. The incidence of Grade ≥ 3 toxicity was 8.3%, with 1 case of enteritis resulted in death[34].

In vivo studies have shown that very early angiogenesis is caused by the imbalance of angiogenesis and anti-angiogenic mediators. Multiple factors, overlapping signal pathways and mechanisms are involved in angiogenesis. Hypoxia during tumor growth stimulates angiogenesis by inducing the production of VEGF. The binding of VEGF and VEGFR activates the VEGF signaling pathway. Fibroblast growth factor (FGF) and angiopoietin-2 continuously stimulate angiogenesis. Therefore, the angiogenesis signaling pathway plays a vital role in the process of SCLC metastasis[35].

The phase I clinical study of ramucirumab combined with pembrolizumab in the first-line, second-line, and subsequent lines of treatments of gastric cancer (including gastroesophageal junction tumors) showed ORRs of 14% (4/28) and 7% (3/4), respectively, mPFSs of 5.6 (95% CI: 2.4-NR) months and 2.6 (95% CI: 1.5-4.2) months, respectively, and 6-month PFS rates of 35% and 26.1%, respectively; in the second-line and subsequent lines of treatment, the mOS was 6.2 (95% CI: 4.4-12.6) months. The safety and tolerability were similar to those of monotherapies. Grade ≥ 3 adverse events included asthenia, hypertension, and enteritis, without additional toxicity[36]. The phase II study in naive patients with metastatic renal carcinoma compared the efficacy and safety of atezolizumab combined with bevacizumab vs. atezulizumab monotherapy vs. sunitinib monotherapy, with the subjects in the atezulizumab monotherapy and sunitinib monotherapy groups crossing over to the atezolizumab combined with bevacizumab group for continued treatment after progressive disease assessment per RECIST v1.1. The results showed that the combination group was superior to the sunibinib group. Although atezulizumab monotherapy and sunitinib monotherapy had limited efficacy, the subjects still benefited after crossover to the combination group. The overall ORR of the crossover group was 26% (28% in the sunitinib group and 24% in the atezolizumab group), and the total mPFS was 8.8 months; the safety was consistent with the monotherapy and combination therapy groups. Grade ≥ 3 adverse events included asthenia, arthralgia, nausea, proteinuria, diarrhea, and vomiting[37]. Currently, studies evaluating the efficacy and safety of VEGF/VEGFR inhibitors combined with immune checkpoint inhibitors combined with or without chemotherapy have been carried out in multiple tumors such as NSCLC and SCLC.

Apatinib mesylate (trade name: Aitan®) was developed by Jiangsu Hengrui Pharmaceuticals Co., Ltd. and was approved for marketing by the China Food and Drug Administration (CFDA; now National Medical Products Administration, or NMPA) in 2014. Apatinib is a small molecular targeted drug and exerts anti-angiogenic effect to treat cancer by inhibiting VEGFR. Recombinant humanized anti-PD-1 monoclonal antibody injection (SHR-1210), a new class 1 therapeutic biological product developed by Jiangsu Hengrui Pharmaceuticals Co., Ltd., has not been marketed both in China and abroad. Jiangsu Hengrui Pharmaceuticals Co., Ltd. has initiated Phase I/II clinical studies of SHR-1210 in several types of tumors in both Australia and China, and preliminarily validated the safety, tolerability and efficacy of SHR-1210 monotherapy in the treatment of advanced solid tumors.

Considering the role of immune-related therapies in SCLC, as well as the role of immune checkpoint inhibitors combined with VEGF and VEGFR-2 inhibitors in patients with gastric cancer and kidney cancer, the benefits of SHR-1210 combined with apatinib in the second-line treatment of SCLC are reasonable and worth looking forward to.

2.3.2 Basis for SHR-1210 administration at the fixed dose of 200 mg

PD-1 immune checkpoint inhibitors exert their effect on 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, serum drug concentrations dropped below 1000 ng/mL on Day 15 after a single dose of SHR-1210 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 suggest that to maintain the receptor saturation, a serum drug concentration of at least 2000 ng/mL is required. Clinical data also suggest that a fixed dose of 200 mg every 2 weeks can maintain a saturated receptor occupancy. In Phase I studies, the incidence of adverse events did not increase with dose, whether the drug was administered by weight or by a fixed dose. Based on results from the studies described above, and taking into account the convenience of clinical administration, a fixed dose of 200 mg Q2W was selected.

2.3.3 Basis for continued medication beyond progression

Increasingly more clinical evidence shows that, after immunostimulant therapy in some patients, progressive disease (through traditional response evaluation, per RECIST v1.1) precedes objective clinical response and/or stable disease. This phenomenon was observed in approximately 10% of patients in the phase I study of nivolumab[38]. Two hypotheses attempt to explain this phenomenon. One is that the enhanced inflammatory response in the tumor leads to an increase in the size of the tumor. Over time, the seemingly worsening part and the inflammatory part disappear, and the therapeutic effect begins to appear. The other is that the growth rate of tumors exceeds the rate of immune anti-tumor. After a sufficiently long period of time, the anti-tumor activity finally dominates and the therapeutic effect begins to appear. Therefore, subjects who are clinically evaluated as beneficial and well tolerated are allowed to undergo immune checkpoint inhibitors again after the initial progressive disease as defined per RECIST v1.1. Such subjects shall discontinue the study treatment after relapse of progressive disease.

2.3.4 Basis for selecting PD-L1 as the exploratory biomarker

As described in 2.2.2 of the protocol, PD-L1 is up-regulated in a variety of solid tumors. PD-L1 expression is closely related to shortened survival and poor prognosis in various cancers, including lung cancer, liver cancer, gastric cancer, esophageal cancer, urothelial cancer, renal cancer, pancreatic cancer, and ovarian cancer[28]. In *in vitro* studies, tumor cells expressing PD-L1 promote the apoptosis of activated tumor cell-specific T cells, while tumor cells avoid the killing effect of effector T cells. In a number of clinical studies of nivolumab and pembrolizumab, the expression level of PD-L1 in tumor tissues was positively correlated with the efficacy. Based on the above evidence, the expression level of PD-L1 in tumor tissues may be related to the efficacy of SHR-1210, and preliminary biomarker exploration is necessary.

2.4 Preclinical Studies

Refer to Investigator's Brochure (IB) (version number: 2.0, version date: 24 Nov., 2016) for the pharmacology studies, toxicology studies, and pharmacokinetics studies of SHR-1210. Refer to IB (version number: 2.0, version date: 8 Dec., 2016) for the pharmacokinetics studies, toxicology studies, and pharmacokinetics studies of apatinib mesylate tablets.

2.5 Clinical Studies

Refer to the IB of SHR-1210 (version number: 2.0, version date: 24 Nov., 2016) and the IB of apatinib mesylate tablets (version number: 2.0, version date: 8 Dec., 2016).

2.6 Potential Risks and Benefits

Only topotecan (intravenously or orally administered) has been approved by the FDA for the treatment of ED-SCLC after failure of first-line standard therapies. No immunotherapy is commercially available currently. SHR-1210 is a humanized PD-1 antibody independently developed by Hengrui. Preclinical data suggested that it has similar pharmacodynamics and anti-tumor effects to nivolumab and pembrolizumab. The studies on the PD-1/PD-L1-based combination therapy that have been published and undergoing abroad suggest that patients may benefit and the safety is controllable. For more detailed safety information of SHR-1210, please refer to the IB (version number: 2.0, version date: 24 Nov., 2016) and the informed consent form (ICF).

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Primary objective

- To evaluate the safety and efficacy of SHR-1210 combined with apatinib in the treatment of ED-SCLC failing first-line standard therapy

3.1.2 Secondary objective

- To evaluate the immunogenicity

3.1.3 Exploratory objective

- To evaluate the correlation between biomarkers (including but not limited to PD-L1 and TMB) and efficacy

3.2 Study Endpoints

3.2.1 Primary endpoints

- Incidence of AEs evaluated per CTCAE 4.03, especially the incidence of AEs meeting any of the following criteria:
  - Hematologic toxicity
    - Grade 4, or
    - Grade ≥ 3 thrombocytopenia with hemorrhage, or
    - Grade ≥ 4 neutropenia with pyrexia and infection
  - Grade ≥ 3 non-hematologic toxicity (except for laboratory abnormalities), hypertension, rash, diarrhea, nausea and vomiting that cannot be controlled after symptomatic treatment
  - Grade ≥ 3 laboratory abnormalities that lead to medical interventions or hospitalization, or last for ≥ 7 days
  - Any Grade 5 AEs
- ORR evaluated as per RECIST v1.1

3.2.2 Secondary endpoints

- Incidence of AE and SAE assessed as per CTCAE 4.03, laboratory measurements, ECG, vital signs, and other safety endpoints
- OS, 6-month OS rate, and PFS, TTR, DoR, and DCR evaluated as per RECIST v1.1
- Immunogenicity evaluation: positive rates of ADA and NAb

3.2.3 Exploratory endpoint

- Tumor biomarkers (including but not limited to expression levels of PD-L1 and TMB in tumor samples)

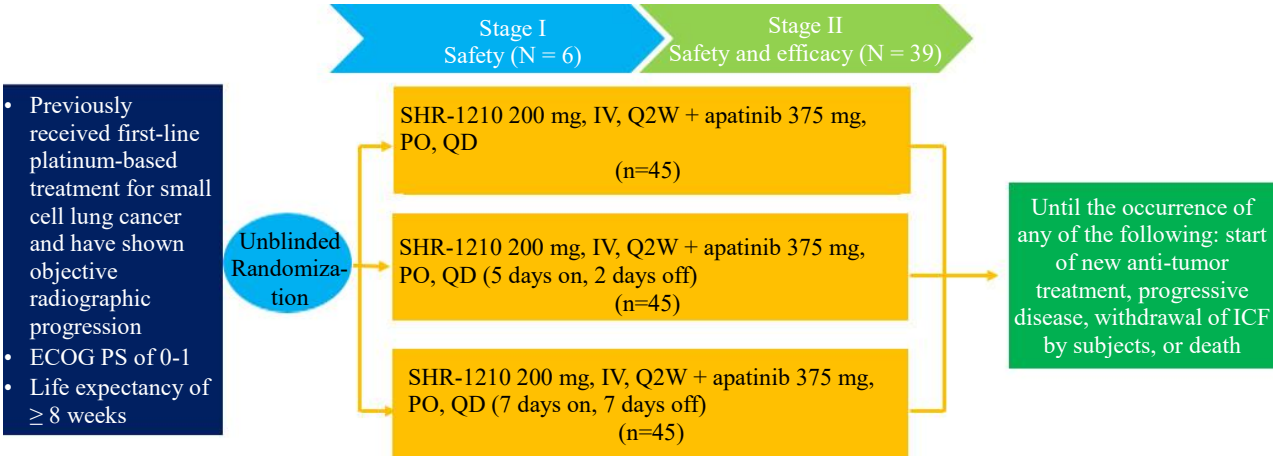
4 STUDY DESIGN

This is a randomized, open-label, multi-center phase II clinical study. Eligible subjects after screening will be randomized into the following 3 groups in a 1:1:1 ratio, with 4 weeks as a treatment cycle. Refer to Figure 2 for the study design. Refer to Figure 3 for the study process.

The study consists of two stages. In Stage I, subjects will be randomized into 3 different dose groups, with 6 subjects in each group. It is planned that after the last subject in Stage I completes Cycle 1 treatment (28 days), the leading center's principal investigator and the sponsor will jointly perform a safety assessment of subjects enrolled in Stage I, decide the treatment group of Stage II, and choose one group of method of administration and a tolerated dose of apatinib for Stage II treatment.

A total of 39 subjects will be enrolled in Stage II. The primary analysis will be performed when the last subject has been treated for 180 days.

For any treatment group entering Stage II, if the safety is acceptable and the efficacy meets the corresponding statistical criteria, it indicates potential needs of further development.



Note: Subjects with PD for the first time must be confirmed; for medication after the initial PD, refer to Section 6.1.2 of the protocol; for imaging confirmation and subsequent evaluation of the initial PD, refer to Section 8.1.2 of the protocol

Figure 2. Design of the phase II study of SHR-1210 combined with apatinib

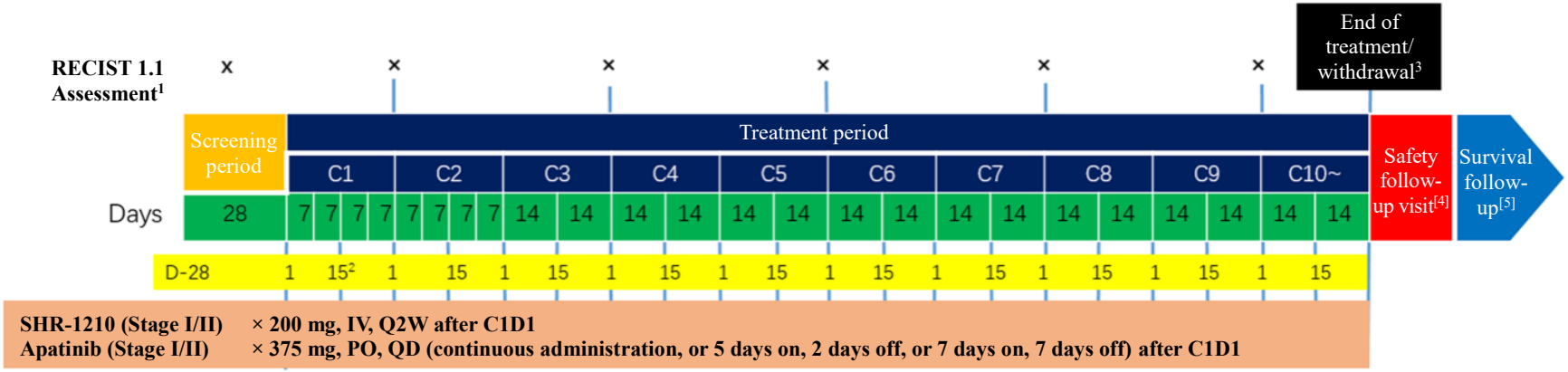


Figure 3. Process of the study of SHR-1210 combined with apatinib

5 STUDY POPULATION

5.1 Inclusion Criteria

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

1. All patients must sign an ICF prior to starting any study-related procedures
2. Aged ≥ 18 and ≤ 70 years
3. Histologically or cytologically confirmed small cell lung cancer
4. Staged ED-SCLC according to VALG staging
5. Have previously received first-line platinum-based treatment for ED-SCLC and have shown objective imaging progression. Including:
   - Sensitive recurrence: progression in ≥ 90 days from the last chemotherapy
   - Drug-resistant recurrence: progression during chemotherapy or within 90 days from the last chemotherapy
6. Able to provide tumor tissue samples for diagnosis, either archived samples within 12 months prior to the first dose of study drug or freshly obtained. The specimens shall meet the requirements of formalin-fixed and paraffin-embedded (FFPE) tumor tissue blocks allowing the cutting of at least 5-10 slices with a thickness of 4-6 μm for staining and testing. Cell smears from fine needle aspiration or centrifuged pleural fluid, bone lesions without soft tissue components or decalcified bone tumor specimens, and drill biopsy tissues are not acceptable, as they are insufficient for biomarker detection
7. ECOG PS of 0-1
8. Life expectancy of ≥ 8 weeks
9. With at least one target lesion without previous radiotherapy (RECIST v1.1) shown by CT or MRI scan ≤ 28 days prior to the first dose of study drug
10. Males and females of reproductive potential must take contraceptive measures from the first dose of study drug to within 24 weeks after the last dose of study drug (see 6.6.2 of the protocol for recommended contraceptive methods)
11. Had no transfusion of blood or blood products within 14 days prior to the first dose, not corrected with G-CSF or other hematopoietic colony-stimulating factors. Before the first dose of study drug, laboratory test values must meet the following conditions:
    (1) Hematology: WBC ≥ 3.0×10^9/L; ANC ≥ 1.5×10^9/L; PLT ≥ 100×10^9/L; HGB ≥ 9.0 g/dL

(2) Liver function: AST ≤ 2.5 × ULN, ALT ≤ 2.5 × ULN for patients without liver metastasis; ALT and AST < 5 × ULN for patients with liver metastasis; TBIL ≤ 1.5 × ULN (TBIL < 3.0 mg/dL in patients with Gilbert syndrome); and ALB ≥ 3 g/dL

(3) Renal function: Cr ≤ 1.5 × ULN or CrCl ≥ 40 mL/min (using Cockcroft/Gault formula, see Appendix 2); negative UPRO

(4) Coagulation function: INR ≤ 1.5, APTT ≤ 1.5 × ULN

(5) Others: Lipase ≤ 1.5 × ULN. Patients with lipase > 1.5 × ULN without clinical or radiographic evidence of pancreatitis may be enrolled; Amylase ≤ 1.5 × ULN. Patients with amylase > 1.5 × ULN without clinical or radiographic evidence of pancreatitis may be enrolled. ALP ≤ 2.5 × ULN; for patients with bone metastases, ALP ≤ 5 × ULN

5.2 Exclusion Criteria

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

1. With histologically or cytologically confirmed mixed SCLC and NSCLC.
2. Patients who have previously received anti-tumor viral treatment. Patients who have previously received any T cell costimulation or immune checkpoint therapy, including but not limited to CTLA-4 inhibitors, PD-1 inhibitors, PD-L1/2 inhibitors, or other drugs targeting T cells.
3. Patients who have previously received anti-VEGF/VEGFR therapy.
4. Patients with clinically symptomatic brain metastasis or meningeal metastasis. Treated patients with brain metastasis should meet the following conditions to be enrolled:
    - No MRI-proven progression ≥ 4 weeks after the end of treatment
    - Completed treatment within ≥ 28 days prior to the first dose of study drug
    - No need to receive systemic corticosteroid treatment (> 10 mg/day prednisone or an equivalent dose) in ≤ 14 days prior to the first dose of study drug
5. Radiotherapy of the chest and whole brain should be completed less than 4 weeks prior to the first dose of study drug (patients whose palliative radiotherapy for bone lesions was completed prior to the first dose of study drug are allowed to be enrolled)
6. Clinically symptomatic effusion in the third space, such as pericardial effusion, pleural effusion, and ascites effusion that cannot be controlled by drainage or other treatments

7. Active, known or suspected autoimmune diseases (see Appendix 4). Patients with vitiligo, type I diabetes, or residual hypothyroidism caused by autoimmune thyroiditis that only requires hormone replacement therapy or is unlikely to recur in the absence of external stimulation can be enrolled
8. Have used corticosteroids (> 10 mg/day prednisone or equivalent dose) or other immunosuppressive agents within ≤ 14 days prior to the first dose of study drug. In the absence of active autoimmune diseases, inhaled or topical use of steroids and adrenal replacement steroids is permitted
9. Patients who have received or plan to receive live vaccines within 4 weeks prior to the first dose of study drug
10. With interstitial lung disease (ILD), drug-induced pneumonitis, radiation pneumonitis requiring steroid treatment, active pneumonitis with clinical symptoms, or severe pulmonary dysfunction
11. Patients with TB or history of active TB infection within ≤ 48 weeks before screening, regardless of treatment status
12. Except for alopecia and fatigue, other toxicities caused by previous anti-tumor treatments should have recovered to CTCAE 4.03 Grade ≤ 1 prior to the first dose of study drug Patients with other toxicities caused by previous anti-tumor treatments that cannot be resolved within expectations and have long-lasting sequelae, such as neurotoxicity caused by platinum-based treatments, are allowed to be enrolled
13. Imaging (CT scan or MRI) showed tumor invasion of large blood vessels, symptoms of hemoptysis of daily hemoptysis ≥ 2.5 mL within 3 months before screening
14. Patients who have undergone minor surgery (including catheterization) within 48 hours before the first dose of study drug
15. Currently or recently (within 10 days prior to the first dose of study drug) using aspirin (> 325 mg/day) or other non-steroidal anti-inflammatory drugs known to inhibit platelet function
16. Currently or recently (within 10 days prior to the first dose of study drug) being treated with full-dose oral or parenteral anticoagulant or thrombolytic agents. But prophylactic use of anticoagulants is allowed
17. Patients with hereditary bleeding tendency or coagulation dysfunction. Patients with clinically significant bleeding symptoms or a clear bleeding tendency within 12 weeks prior to screening, such as hemorrhage of digestive tract, stomach ulcer with hemorrhage, baseline fecal occult blood++ and above, or vasculitis

18. Had arterial/venous thrombosis within 24 weeks prior to signing of ICF, such as cerebrovascular accidents (including transient ischemic attacks, cerebral hemorrhage, and brain infarction), deep vein thrombosis, and pulmonary embolism
19. Uncontrolled hypertension (systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg), a history of hypertensive crisis or hypertensive encephalopathy
20. With a history of the following diseases within 24 weeks prior to the signing of ICF: peptic ulcer, gastrointestinal perforation, corrosive esophagitis or gastritis, inflammatory bowel disease or diverticulitis, abdominal fistula, tracheo-esophageal fistula, or intra-abdominal abscess
21. With clinical symptoms or diseases of the heart that are not well controlled, such as: (1) NYHA Class II or above heart failure (2) unstable angina (3) myocardial infarction within 24 weeks (4) patients with clinically significant supraventricular or ventricular arrhythmia requiring treatment or intervention
22. Known to be allergic to drugs or excipients, known to have severe allergic reactions to any kind of monoclonal antibody
23. Patients complicated with other malignant tumors ≤ 5 years before the first dose, except for cervical carcinoma *in situ*, basal cell or squamous cell skin cancer that can be adequately treated, local prostate cancer after radical resection, and ductal carcinoma *in situ* after radical resection
24. With evidence or history of psychiatric disorders, alcoholism, narcotics or drug abuse
25. Patients with positive HBsAg and HBV DNA exceeding the upper limit of normal (1000 copies/mL or 500 IU/mL) or positive HCV (HCV RNA or HCV Ab test shows acute/chronic infection); known history of positive HIV or known to have AIDS
26. Have received any other investigational drug or participated in other interventional clinical study within 4 weeks prior to signing the ICF
27. The investigator determines that the patient may have other factors leading to the discontinuation of the study, such as protocol incompliance, other serious diseases (including mental illness) requiring concomitant treatment, serious laboratory test abnormalities, accompanied by family or social factors that may affect the safety of the subject or the collection of data and samples

5.3 Randomization Standard

Subjects who do not meet the eligibility criteria shall not be enrolled in this study with no exceptions. In the event that an ineligible subject is randomized, or the treatment erroneously starts, or an enrolled subject no longer meets the eligibility criteria before starting the study treatment, the sponsor's medical representative and the investigator must jointly discuss whether the subject should continue or withdraw from the study. The sponsor should ensure that appropriate documentation is retained with regards to such decisions.

Subjects who have failed previous screening may be screened again in this study. The informed consent form should be re-signed and a new subject number should be given for re-screening. The treatment will start within 24 hours after randomization.

5.4 Withdrawal from Study or Treatment Discontinuation

5.4.1 Study withdrawal criteria

Reasons for withdrawal may include:

1. The subject withdraws the ICF and refuses further follow-ups
2. Any clinical adverse drug reactions, laboratory abnormalities, or complications that renders the subject not benefiting from further treatment, as determined by the investigator
3. Other reasons investigator deems necessary for 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

5.4.2 Criteria for treatment discontinuation

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

1. Subject requests to discontinue the study treatment
2. Radiographic or clinical evidence of progressive disease, unless the subject meets the criteria for continuing treatment beyond progression (see 6.1.2 of the protocol)
3. Occurrence of pregnancy during the study
4. Any clinical AEs, laboratory abnormalities, or other medical conditions indicating that the subject can no longer benefit from the treatment

5. General deterioration of health status suggesting that the subject cannot continue to involve the study
6. The enrolled subject is found to have important protocol deviations such as ineligibility
7. Lost to follow-up
8. Study termination by the sponsor
9. Death
10. Other reasons as determined by the investigator

5.4.3 Procedures for withdrawal or discontinuation

The end-of-treatment efficacy and safety examinations, safety follow-up, and survival follow-up as specified in the protocol must be completed as much as possible, and the AEs and their outcomes should be fully documented. The investigator can recommend or provide new or alternative treatments to a subject based on the condition of the subject. For subjects who discontinue the treatment for reasons other than radiologically confirmed PD, imaging evaluations shall be performed as much as possible per the scheduled time points until any of the following events occurs: start of new anti-tumor therapy, PD, withdrawal of ICF, or death.

Subject's survival status should still be followed up even when the subject refuses to visit the study center, 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. The sponsor can retain and continue to use all data collected prior to withdrawal of ICF, unless the subject requests a retraction of collected data.

5.5 Termination or Suspension of Study

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

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

1. Confirmed unexpected, major, or unacceptable risk to the subjects
2. Existing efficacy data supporting study termination
3. Poor protocol compliance
4. Incomplete or undetectable data
5. Valueless study results

6 STUDY DRUGS

6.1 Treatment Regimen

6.1.1 Administration regimen

Study drugs refer to SHR-1210 and apatinib, and other drugs during the study are non-study drugs. Refer to Table 5 for the treatment regimen. For the ease of liquid preparation, the protocol allows a deviation of ±5% between the actual dosage and the theoretical dosage each time.

The study drugs will be administered until PD (refer to Section 6.1.2 for continued medication beyond progression), intolerable toxicity, withdrawal of ICF, other reasons that require treatment discontinuation (whichever occurs first)

Table 5. Treatment regimen

Phase	Drug	Dose	Route of Administration	Administration Cycle
II	SHR-1210	200 mg	IV	Q2W
	Apatinib, combined	**375 mg**	PO	QD
	SHR-1210	200 mg	IV	Q2W
	Apatinib, combined	**375 mg**	PO	QD (5 days on, 2 days off)
	SHR-1210	200 mg	IV	Q2W
	Apatinib, combined	**375 mg**	PO	QD (7 days on, 7 days off)

Note:

1. On the day of SHR-1210 infusion, apatinib shall be administered 30 min after the end of SHR-1210 infusion.
2. SHR-1210 is administered through intravenous drip infusion at 200 mg once every 2 weeks with 4 weeks as 1 treatment cycle.
3. Apatinib is administered orally once daily after meal with 4 weeks as 1 treatment cycle. Subjects are randomized into the three groups in a 1:1:1 ratio. Drugs should be administered at a fixed time every day as much as possible.
4. PO: per os; QD: quaque die; IV: intravenous infusion; Q2W: once every 2 weeks; 5 Days on, 2 Days off: administration for 5 days and interrupt for 2 days; 7 Days on, 7 Days off: administration for 7 days and interrupt for 7 days

6.1.2 Continued medication beyond progression

Subjects are allowed to continue the original regimen of study treatment after the initial PD confirmed as per RECIST v1.1, provided that the following conditions are met:

1. Investigator-assessed clinical benefit, and
2. Tolerability in the subject

Investigator-assessed clinical benefit and tolerability in the subject are based on the following considerations:

1. No significant clinical symptoms and changes in laboratory parameters
2. No change (deterioration) in the score of performance status
3. No rapid tumor progression and no tumor progression involving vital organs/sites (such as metastases to central nervous system, respiratory failure due to tumor compression, and spinal cord compression)

For subjects who continue the original regimen of study treatment after progression, the investigator must reassess the benefits and risks of the subject. The ICF must be re-signed. The longest duration of SHR-1210 administration is 2 years.

An additional imaging evaluation must be performed in 4 weeks (+ 7 days) for confirmation after the initial documentation of imaging PD. If PD is not radiographically confirmed, the original study medication and imaging evaluation can be continued until relapse of PD (refer to Section 8.1.2 of the protocol). Subjects with relapse of PD must discontinue treatment.

6.1.3 Continued treatment after study completion

Study completion is defined as 180 days after the first dose of the last subject.

Upon completion of the study, subjects who still benefit clinically may continue the study treatment provided by Hengrui until the criteria for discontinuation are met, and will be continuously followed for OS events. The study drug is provided through extension studies, rollover studies approved by the health regulatory authorities and ethics committee, or other ways determined by Hengrui.

Hengrui reserves the right to stop providing the study drugs in any of the following cases: a) rejection of marketing application by health regulatory authorities; b) termination of the study due to safety issues; c) subjects able to obtain the study drugs from a public or privately-sponsored medical plan; or d) available replacement therapies in the local market.

6.2 Study Drugs

6.2.1 Description

The following study drugs will be supplied by the sponsor in a centralized manner. Refer to Table 6 for the description of study drugs.

Table 6. Description of study drugs

Name	SHR-1210 for injection	Apatinib mesylate tablets
Manufacturer	Suzhou Suncadia Biopharmaceuticals Co., Ltd.	Jiangsu Hengrui Pharmaceuticals Co., Ltd.
Appearance	White or off-white lyophilized powder	Film-coated tablet, white or off-white after peeling off coating
Route of Administration	Intravenous injection	Oral
Strength	200 mg/20 mL vial	250 mg/tablet; 375 mg/tablet
Storage and Stability	Placed in a 2-8 °C medical refrigerator during storage and the shelf life is tentatively set to 2 years. Do not freeze	Sealed and stored below 25 °C and kept away from light. Valid for 2 years

6.2.2 Packaging and labeling of study drugs

The sponsor will package and label the study drug in accordance with local regulatory requirements.

6.3 Study Drug Preparation

The study drugs should be prepared by qualified or experienced study staff (such as physicians, pharmacists, or medical assistants) according to the drug brochures or package inserts (approved by national authorities or study center operating guidelines).

6.3.1 SHR-1210

SHR-1210 is a lyophilized powder for injection that needs to be prepared before its administration via intravenous drip infusion. Refer to Drug Manual for the preparation of SHR-1210.

6.4 Dose Modifications and Delay

6.4.1 General rules for dose modification

- Reasons for dose modification or dose delay, actions taken, and results should be recorded in the medical record and eCRF of the subject.
- For the accompanying symptoms that existed at baseline, the investigator shall determine whether to adjust the dose according to the grade of adverse drug reactions. For example, at baseline, a subject's Grade 1 "asthenia" at baseline that becomes Grade 2 "asthenia" during the study treatment period is one level increase of "asthenia". The dose should be adjusted as a Grade 1 toxicity

- If several adverse drug reactions of different grades or severity occur at the same time, the dose will be adjusted based on the highest level observed.
- If the dose is adjusted only due to abnormal hematological values, the dose will be adjusted based on the hematological values before the start of the treatment cycle.
- When the investigator judges that the adverse drug reaction is unlikely to further develop into a serious or life-threatening event, the current dose will be continued without dose modification or treatment interruption. In addition, no dose modification or treatment interruption is administered for anemia (non-hemolytic) because its symptoms can be relieved through blood transfusion.
- If, per the investigator's judgment, the toxic reaction is caused by a therapeutic drug, there is no need to adjust the dose of other drugs.
- Before PD, permanent discontinuation of a medication will not affect the continued administration of other treatments.
- If any treatment but not all drugs is interrupted due to adverse drug reactions of a drug, the treatment is still counted as a treatment cycle.

6.4.2 Apatinib

Dose interruption of apatinib is allowed for up to 4 weeks (from the actual time of last dose); otherwise the treatment of apatinib shall be discontinued. A maximum of one dose modification is allowed; otherwise the subject will be considered intolerable and the treatment of apatinib shall be discontinued. Refer to Table 7 for the requirements of dose modification of apatinib.

Table 7. Requirements of dose modification of apatinib

Adverse Drug Reaction	Grade	Whether to Interrupt Treatment	Rules for Dose Modification
Hematologic	Grade 1-2	No	—
	Grade 3	Yes	• For the first occurrence, interrupt the treatment until the adverse drug reactions recover to Grade ≤ 2, and resume the treatment at the original dose • For the second occurrence, interrupt the treatment until the adverse drug reactions recover to Grade ≤ 2, and resume the treatment at a reduced dose of 250 mg/d • For recurrence after dose reduction, the investigator should evaluate the risks/benefits of the continued apatinib treatment and determine whether the drug should be permanently discontinued

Adverse Drug Reaction	Grade	Whether to Interrupt Treatment	Rules for Dose Modification
	Grade 4	Yes	• Resume the treatment at a reduced dose of 250 mg/d after the adverse drug reactions recover to Grade ≤ 2 • For the recurrence of Grade 4 toxicity after dose reduction, the treatment shall be permanently discontinued
Non-Hematological	Grade 1	No	—
	Grade 2 (lasting for ≥ 7 d)	Yes	• Resume the treatment at the original dose after the adverse drug reactions recover to Grade ≤ 1
	Grade 3	Yes	• For the first occurrence, interrupt the treatment until the adverse drug reactions recover to Grade ≤ 1, and resume the treatment at the original dose • For the second occurrence, interrupt the treatment until the adverse drug reactions recover to Grade ≤ 1, and resume the treatment at a reduced dose of 250 mg/d • For recurrence after dose reduction, the investigator should evaluate the risks/benefits of the continued apatinib treatment and determine whether the drug should be permanently discontinued
	Grade 4	Yes	• Resume the treatment at a reduced dose of 250 mg/d after the adverse drug reactions recover to Grade ≤ 1 • For the recurrence of Grade 4 toxicity after dose reduction, the treatment shall be permanently discontinued

In the case of the following circumstances, the measures to be taken for apatinib (the following grades are per CTCAE v4.03) are described as follows; if necessary, relevant departments should be consulted:

Hemorrhage

- Grade 3 or 4 bleeding should be treated accordingly and apatinib treatment should be permanently discontinued

Thrombosis/embolism

- For arterial thrombosis of any grade, apatinib treatment should be permanently discontinued
- For Grade 4 venous thrombosis, apatinib treatment should be permanently discontinued
- For Grade 3 venous thrombosis, apatinib treatment should be interrupted. For anticoagulant therapy at the planned therapeutic dose for ≤ 2 weeks, apatinib treatment should be interrupted until the end of anticoagulant therapy. For anticoagulant therapy at

the planned therapeutic dose for > 2 weeks, apatinib treatment should be interrupted for 2 weeks until the following criteria are met, and the study treatment may be resumed during the anticoagulant treatment:

- Before the resumption of study medication, the INR should be within the target range (usually 2-3)
- Subjects should not have Grade 3 or 4 bleeding events since study enrollment
- No finding of tumor invasion or adjacency to large blood vessels in previous tumor evaluations

Note: Therapeutic dose of anticoagulant therapy is defined as the gradual escalation of the dose of warfarin or other anticoagulants to a dose level that maintains an INR not less than 1.5 (usually 2-3). The dose of warfarin should be recorded in the eCRF, and the INR should be monitored throughout the treatment period for subjects receiving anticoagulant therapy.

Hypertension

The blood pressure should be regularly measured in order to monitor the occurrence and deterioration of the subject's hypertension.

- Grade 1: Prehypertension (systolic blood pressure of 120-139 mmHg, diastolic blood pressure of 80-89 mmHg), no intervention is needed.
- Grade 2: First-stage hypertension (systolic blood pressure of 140-159 mmHg, diastolic blood pressure of 90-99 mmHg), medical intervention is required; repeated or persistent (≥ 24 h), an increase in symptomatic systolic blood pressure by > 20 mmHg, or an increase in blood pressure within the normal range to > 140/90mmHg. Apatinib treatment should be interrupted. An antihypertensive drug may be used for treatment. Once the blood pressure is controlled to < 140/90 mmHg, the subject may continue the apatinib treatment.
- Grade 3: Second-stage hypertension (systolic blood pressure of ≥ 160 mmHg, diastolic blood pressure of ≥ 100 mmHg), more than one antihypertensive drug or a higher intensity treatment are required. For persistent or symptomatic hypertension, apatinib treatment should be interrupted; if hypertension is still uncontrollable after 4 weeks of treatment, apatinib treatment should be permanently discontinued.
- Grade 4: Life-threatening (malignant hypertension or persistent nerve damage, hypertensive crisis) emergency intervention, life-threatening (such as hypertensive crisis). For Grade 4 hypertension, apatinib treatment should be permanently discontinued. The dose of antihypertensive drugs used should be recorded at each visit.

The dose of antihypertensive drugs used should be recorded at each subject visit of the subjects. If hypertension still persists when the treatment is discontinued, blood pressure and the use of antihypertensive drugs should be monitored every 3 months until the blood pressure returns to normal or the study completion.

Reversible posterior leukoencephalopathy syndrome (RPLS)

Symptoms and signs consistent with RPLS are rarely reported in subjects receiving the drug treatment. This is a rare neurological disease. The symptoms and signs are: epilepsy, headache, mental status changes, visual disturbance, or cortical blindness, with or without hypertension. Once a subject develops RPLS, apatinib treatment should be permanently discontinued.

Proteinuria

Follow the schedule of study procedures for urinalysis, if:

- < 2+, continue the administration of apatinib as planned, no additional tests are required
- ≥ 2+, immediately monitor the 24-hour urine protein. 24-hour urine protein:
  - < 1 g, continue apatinib treatment as planned
  - 1-3.4 g, interrupt the apatinib medication until the 24-hour urine protein is < 1 g, and then resume the apatinib treatment. For the second occurrence, interrupt apatinib treatment until the 24-hour urine protein is < 1 g, and reduce the dose to 250 mg/d. For recurrence after dose reduction, the investigator should evaluate the risks/benefits of the continued apatinib treatment and determine whether the drug should be permanently discontinued
  - ≥ 3.5 g or occurrence of nephrotic syndrome, apatinib treatment is permanently discontinued

6.4.3 SHR-1210

Dose increase or reduction for SHR-1210 is prohibited. Only interruption or permanent discontinuation is allowed. Dose interruption of SHR-1210 is allowed for up to 8 weeks (from the actual time of last dose); otherwise the treatment of SHR-1210 shall be discontinued. For SHR-1210 interruption that exceeds 8 weeks, the investigator should discuss with the sponsor's medical department if he/she judges that the subjects can benefit from continued treatment.

Refer to Table 8 for the requirements on dose modification of SHR-1210. Refer to Appendix 6 for the guidelines on dose modifications and handling of toxicities of SHR-1210. Refer to Table 9 for the treatment of SHR-1210 related infusion reactions.

In addition, treatment should be discontinued permanently if PD is determined by the investigator as per the RECIST v1.1 criteria (unless subjects meet the criteria for continued treatment after PD as described in Section 6.1.2 of the protocol). For treatment interruption due to medical events, surgeries, or unexpected (holidays) events unrelated to the study treatment, the subject should resume study treatment within 2 weeks after interruption (i.e., originally scheduled administration time), unless otherwise jointly determined by the investigator and the sponsor. The reasons for treatment interruption should be documented in the eCRF.

Table 8. Principles for SHR-1210 dose modification

Adverse Drug Reaction	**Severity**	**Dose Modification**
Pneumonia	Grade 2 pneumonia	Treatment interruption[a]
	Grade 3 or 4 pneumonia	Permanent discontinuation
Diarrhea/Entercolitis	Grade 2 or 3 diarrhea or entercolitis	Treatment interruption[a]
	Grade 4 diarrhea or entercolitis	Permanent discontinuation
Dermatitis	Grade 3 dermatitis	Treatment interruption[a]
	Grade 4 dermatitis	Permanent discontinuation
Hepatitis	For subjects with normal baseline ALT, AST, or TBIL, Grade 2 AST, ALT, or TBIL increased, or For subjects with baseline AST, ALT, or TBIL > ULN, AST, ALT, or TBIL increased by ≥ 50% persisting for < 7 days	Treatment interruption[a]
	For subjects with normal baseline ALT, AST, or TBIL, Grade 3 or 4 AST, ALT, or TBIL increased, or For subjects with baseline AST, ALT, or TBIL > ULN, AST, ALT, or TBIL increased by ≥ 50% persisting for ≥ 7 days	Permanent discontinuation
Hypophysitis	Grade 2 hypophysitis	Treatment interruption[b]
	Grade 3 or 4 hypophysitis	Permanent discontinuation
Adrenal cortical insufficiency	Grade 2 adrenal cortical insufficiency	Treatment interruption[b]
	Grade 3 or 4 adrenal cortical insufficiency	Permanent discontinuation
Hyperthyroidism	Grade 3 or 4 hyperthyroidism	Permanent discontinuation

Adverse Drug Reaction	Severity	Dose Modification
Type 1 diabetes	Grade 3 hyperglycemia	Treatment interruption[b]
	Grade 4 hyperglycemia	Permanent discontinuation
Kidney dysfunction	Grade 2 or 3 creatinine increased	Treatment interruption[a]
	Grade 4 creatinine increased	Permanent discontinuation
Neurotoxicity	Grade 2 neurotoxicity	Treatment interruption[a]
	Grade 3 or 4 neurotoxicity	Permanent discontinuation
Infusion reactions	Grade 3 or 4 infusion reaction	Permanent discontinuation
Other AEs	First occurrence of other Grade 3 AE	Treatment interruption[a]
	Second occurrence of the same Grade 3 AE	Permanent discontinuation
	Grade 3 AEs that cannot recover to Grade 0-2/baseline level within 7 days or recover to Grade 0-1/baseline level within 14 days	Permanent discontinuation
	Grade 4 AE	Permanent discontinuation[c]

Note:

a: Resume the medication after the symptoms improve to Grade 0-1 or the baseline level.

b: For hypophysitis, adrenal insufficiency, and type 1 diabetes, medication may be resumed if the AEs are fully controlled and only require physiological hormone replacement therapy.

c: For Grade 4 abnormal laboratory findings, the decision of treatment discontinuation should be based on the accompanying clinical symptoms/signs and the clinical judgment of the investigator.

Table 9. Treatment recommendations for infusion reactions of SHR-1210

CTCAE Grade	Dose Modification	Treatment of Toxicity
Any Grade		- Treat according to local clinical practice - Monitor the subject's infusion-related reactions (e.g., pyrexia or shivers, flushing and/or pruritus, changes in heart rate and blood pressure, dyspnea, chest discomfort, and rash) and allergic reactions (e.g., generalized urticaria, angioedema, asthma, hypotension, and tachycardia)

CTCAE Grade	Dose Modification	Treatment of Toxicity
Grade 1	The infusion rate may be reduced by 50% or the infusion can be temporarily interrupted until the infusion reaction is relieved	For Grade 1 or 2: - Give acetaminophen and/or antihistamines at the discretion of the investigator based on local clinical practice - Consider prophylactic medication before subsequent courses of treatment according to local clinical practice
Grade 2	The infusion rate may be reduced by 50% or the infusion can be temporarily interrupted until the infusion reaction is relieved. The subsequent infusion rate can be adjusted to 50% of the initial rate	
Grade 3/4	Permanent discontinuation	For Grade 3 or 4: - Deal with severe infusion-related reactions according to local clinical practice (e.g., administration of epinephrine, diphenhydramine, ranitidine, and glucocorticoids)

6.5 Concomitant Medications

The use of drugs or vaccines explicitly prohibited in the exclusion criteria is prohibited during the entire study. If any explicitly prohibited drug or vaccine is clinically indicated during the study, the interruption of study treatment may be required. The investigator shall discuss with the sponsor's medical department. The decision whether the subject continues to participate in the study treatment or vaccination arrangements needs to be jointly decided by the investigator, the sponsor, and the subject. The investigator and/or the subject's attending physician shall make the final decision on supportive therapy or vaccination.

All drugs related to the treatment of AEs other than solvents within 28 days before the first dose of the study drug until 30 days after and 30-60 days after the end of the treatment should be documented in the CRF, including the name, dose, route of administration, frequency of administration, purpose, and start and end dates.

6.5.1 Permitted concomitant medications and/or treatment

During the treatment period, the investigator, per his/her judgment, may give the subject the best supportive treatment for the health of the subject. The clinical comorbidities and various AEs should be actively treated, especially immune-related adverse events (irAEs).

Subjects are allowed to receive bisphosphonate for the treatment of bone metastases. If systemic or local analgesia is not effective in controlling painful lesions of bone metastases, a small area of palliative radiotherapy irradiation (the area of the radiotherapy must be < 5% of the bone marrow region) is allowed.

Palliative treatment for lesions outside the lungs is allowed during the study (when the treatment of the subjects is needed to improve symptoms upon the onset of PD), including the treatments for pleural effusion, ascites, pericardial effusion, and radiotherapy for brain lesions. During such treatment, the study drugs should be interrupted until the end of the recovery period of palliative treatment.

6.5.2 Prohibited concomitant medications and/or treatment

Subjects are prohibited from the following therapies during the treatment period of this study:

- Systemic chemotherapy and biological therapy (anti-tumor drugs with immunomodulatory effects, including but not limited to interferon, interleukin-2, thymosin, and immune cell therapy)
- Immunotherapy not specified in this protocol;
- The use of other drugs not specified in the protocol, including Chinese patent medicines with clear anti-tumor indications (refer to Appendix 5)
- Radiotherapy (Note: As long as it is not a lung or target lesion, the sponsor may approve and allow radiotherapy to symptomatic isolated lesions or to the brain)
- Inoculation of live vaccines within 28 days before the first dose of the study medication and during the course of the study. Live vaccines include but are not limited to the following: rubeola, epidemic parotitis, rubella, chickenpox, yellow fever, rabies, BCG, and typhoid (oral) vaccines. Seasonal inactivated flu vaccines for injection are permitted but intranasal live attenuated flu vaccines (e.g., FluMist®) are not permitted
- Corticosteroids. Inhaled steroids are permitted as part of a fixed treatment for asthma or chronic obstructive pulmonary disease (COPD). Corticosteroids to treat potential irAE are permitted. After consultation with the sponsor, physiological doses of corticosteroids are permitted. Corticosteroids may be used prophylactically to prevent allergic reactions (such as intravenous contrast agent)

Based on the investigator's assessment, subjects who need to use any of the above therapies for clinical treatment should be excluded from the study. Subjects can receive other medications as deemed medically necessary by the investigator

It is important for the investigator to review each drug (prescription and over-the-counter) the subject receives before the start of the study and at each study visit.

- At each visit, the subject must be asked about any new medication received since the last visit

- In order to reduce the risk of drug interactions, all measures must be taken to limit the number of concomitant medications that are indeed necessary.
- During the administration period, drugs with hepatotoxicity should be avoided (i.e., drugs with hepatotoxicity warning in the package insert). The investigators are encouraged to review the potential hepatotoxicity of each drug at www.livertox.nih.gov.

6.5.3 Drugs that must be used with caution

1. Drugs that may have drug-drug interactions with apatinib

In vitro studies have shown that apatinib is primarily metabolized by the liver P450 enzyme CYP3A4. Apatinib has a strong inhibitory effect on CYP3A4 and CYP2C9, and has a moderate inhibitory effect on CYP2C19. CYP3A4 inducers (dexamethasone, carbamazepine, rifampicin and phenobarbital) and inhibitors (ketoconazole, itraconazole, erythromycin and clarithromycin), CYP3A4 substrates (simvastatin, cyclosporine and pimozide), and other drugs metabolized via CYP3A4 (such as benzodiazepines, dihydropyridine, calcium ion antagonist and HMG-COA reductase inhibitors) should be used with caution during the treatment. Omeprazole should be used with caution during the treatment (except when omeprazole must be used to treat serious adverse drug reactions).

The substrates of CYP2C9 and CYP2C19 should be used with caution, as shown in Table 10.

Table 10. CYP2C9 and CYP2C19 substrates that should be used with caution

P450 Enzyme	Substrate
CYP2C9	Diclofenac, phenytoin, piroxicam, S-warfarin, and tolbutamide
CYP2C19	Diazepam, imipramine, lansoprazole, and S-mephenytoin

2. Drugs that prolong the QT interval of the heart

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

- Antibiotics: fluoroquinolones: sparfloxacin, gatifloxacin, levofloxacin, moxifloxacin, ofloxacin, ciprofloxacin; macrolides: erythromycin, clarithromycin, telithromycin, azithromycin, roxithromycin, and metronidazole
- Antiarrhythmics: quinidine, procainamide, disopyramide, flecainide, propafenone, amiodarone, dronedarone, sotalol, dofetilide, and ibutilide
- Drugs used to relieve angina pectoris: ranolazine, ivabradine

- Antipsychotics: risperidone, fluphenazine, droperidol, haloperidol, thioridazine, pimozide, olanzapine, and clozapine
- Antifungal drugs: voriconazole, posaconazole
- Antimalarial drugs: mefloquine, chloroquine
- Antihistamines: terfenadine, astemizole, hydroxyzine
- Gastrointestinal drugs: antiemetics: ondansetron, granisetron, dolasetron, droperidol (0.625 to 1.25 mg may be a safe dose), hydroxyzine; prokinetics: cisapride, domperidone, metoclopramide
- Antidepressants: amitriptyline, imipramine, clomipramine, dosulepin, and doxepin

3. CYP3A4 substrates prohibited during the study (drugs with narrow safety windows and may cause serious adverse drug reactions when their metabolism is affected) include but are not limited to:

- Hypoglycemic agents: tolbutamide, chlorpropamide
- Ergot derivatives: dihydroergotamine, ergometrine, ergotamine, methyl ergometrine (potential risk of ergot poisoning, including severe vasospasm leading to peripheral and cerebral ischemia)
- Antipsychotic: pimozide (can potentially increase the risk of prolonged QT interval)
- Antiarrhythmics: amiodarone (prohibited within 6 months prior to randomization), bepridil, flecainide, lidocaine, mexiletine, quinidine, and propafenone
- Immunomodulators: cyclosporine, tacrolimus, sirolimus (may potentially increase the risk of nephrotoxicity and neurotoxicity)
- Miscellaneous: quetiapine, risperidone, clozapine, tomoxetine hydrochloride

4. If warfarin is used for anticoagulation during the study, the dose should be reduced and closely monitored, and the study drug should be discontinued if necessary.
5. During the treatment period, anti-tumor drugs and adjuvant drugs related to anti-tumor treatments, such as anti-tumor traditional Chinese medicine (refer to Appendix 6) and immunological agents, shall be discontinued.

6.6 Medication During Pregnancy, Childbearing Age, and Lactation

The following lists the special restrictions on concomitant medications during the study period. Medication during pregnancy, childbearing age, and lactation

6.6.1 Pregnancy

SHR-1210 is an IgG4 that can cross the placental barrier. It has been suspected/confirmed to have teratogenicity/fetal toxicity. Pregnant women must not be enrolled in the study.

6.6.2 Childbearing potential

Women of childbearing potential must have a negative serum pregnancy test within 3 days prior to the first dose of the study drug.

Female subjects of childbearing age and male subjects with partners of childbearing age should be sterilized or agree to take highly effective contraceptive measures during the study period and 24 days after the last study dose.

After consulting with the subject, the investigator or designated personnel will select appropriate contraceptive methods for the subject and his/her partner from the following contraceptive methods, and confirm the subject's awareness of correct and consistent use the contraceptive method. At time points shown in the Schedule of Activities, the investigator shall notify the subject of the persistent and correct use of contraception. The subject should be aware that the investigator must be notified immediately once the selected method of contraception is stopped, or when the subject or the partner is suspected or confirmed of pregnancy.

An effective contraception method refers to a method with an annual failure rate of < 1% when correctly used independently or with other methods, including:

1. Commonly used hormonal contraceptive methods associated with the suppression of ovulation (e.g., oral, inserted, injectable, implants, subcutaneous) should meet the requirement that the female subject or partner of male subject has been using this method for a period of time with proven effectiveness, and plans to continue using it correctly throughout the study.
2. Correctly inserted intrauterine devices.
3. Male/female condom combined with topical spermicides (i.e., foams, gels, films, creams, or suppositories).
4. Male sterilization by vasectomy.
5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusion (the occlusion should be proven effective by relevant instruments).

Menopause refers to 12 months of amenorrhea in women ≥ 45 years old without biological or physiological reasons:

1. Women ≤ 55 years old must have a serum follicle-stimulating hormone (FSH) test, i.e., FSH > 40 mIU/mL to prove menopause
2. Women who use hormone replacement therapy (HRT) may artificially suppress FSH levels and require a certain washout period to obtain a normal physiological level of FSH. The investigator is recommended to determine the washout period based on the level of FSH. Any serum FSH > 40 mIU/mL during the washout period is considered menopause. Recommended duration of the washout period:

- ≥ 1 week for vaginal hormone products (rings, ointments, and gels)
- ≥ 4 weeks for transdermal products
- ≥ 8 weeks for oral products

6.6.3 Lactation

Whether SHR-1210 is secreted in breast milk is unknown. Considering that many drugs are present in breast milk, SHR-1210 may be potentially toxic to infants. Thus, lactating women who are breast feeding must not be enrolled in this study.

6.7 Subject Compliance

The medication compliance of the subject undergoing study treatment at the study center will be monitored through the following visits:

- Tablets: Subjects will be required to return all unused study drugs from the previous cycle before the commencement of the next cycle. The number of tablets returned by the subjects will be counted, recorded, and archived.
- Drugs for intravenous infusion: The study center shall prepare the drugs and complete the documentation as per the product brochure or package insert of the study drugs. The documentation system of the study center should include all relevant or required information with regards to preparation and administration.

6.8 Return and Disposal of Drugs

In this study, the containers, vials, infusion bags, and syringes of study drugs that are used and partially used may be destroyed on-site according to the guidelines and operating procedures established by the study center and local institutions.

All unused study drugs shall be returned to the sponsor for destruction after the study is completed/terminated or after the expiry date. The return of the study drugs will be arranged by the clinical research associate designated by the sponsor.

6.9 Handling of Complaints

To ensure the safety of subjects and the quality of monitoring, and to assist in the improvement of processes and drugs, the sponsor will collect product complaints related to the study drugs used in the clinical study.

Complaints related to concomitant medications will be reported directly to the manufacturer according to the product information.

The investigator or designated person thereof is responsible for completing the following product complaint procedures in accordance with the relevant requirements of this study:

- Use a study-specific complaint form to record the reported product complaints and relevant complete descriptions.
- Fax the completed product complaint form to the sponsor or designated person thereof within 24 hours.

If the investigator is required to return the product for investigation, the investigator should return a copy of the product complaint form together with the product.

7 STUDY PROCEDURES

7.1 Procedures of Subject Enrollment and Randomization

7.1.1 Subject enrollment

The investigator will enroll the subjects following the steps below:

1. Obtain an ICF with the subject's signature before proceeding with any study-related procedures.
2. The principal investigator or designated person thereof with appropriate training will formally determine the eligibility of the subject after reviewing the inclusion/exclusion criteria.

The sponsor will monitor the enrollment of each cohort such that the sample size of each cohort meets the study requirements.

Subjects who do not meet the relevant criteria of this study (screening failure) may be rescreened. If re-screening of subjects is considered, the investigator must contact the sponsor's medical department. Each subject may be re-screened once. For rescreening, the subject must re-sign the ICF and will be assigned another subject ID.

In the first stage, if the subject develops PD, withdraws the ICF, develops intolerability without completing the 28-day observation before withdrawal, or does not meet the inclusion/exclusion criteria, the principal investigator of the leading center and the sponsor may decide whether to enroll additional subjects as appropriate.

7.1.2 Handling procedures for mistakenly enrolled subjects

The inclusion/exclusion criteria must be strictly followed. In the case where subjects who do not meet the inclusion/exclusion criteria are enrolled, the sponsor's medical department and the investigator shall discuss and determine whether to allow the subjects to continue to participate in the study, i.e., whether or not to administer the study drugs. If the investigator believes that it is medically appropriate for the subject to continue participating in the study, and the sponsor's medical department agrees with the investigator's decision, the subject may continue participating in the study and undergo the study treatment. If the investigator believes that it is medically appropriate for the subject to continue participating in the study, but the sponsor's medical department does not agree with the investigator's decision, the subject shall not continue participating in the study (whether or not to undergo the study treatment). Only after the investigator receives written approval from the sponsor can the subjects who are unqualified for the inclusion/exclusion criteria be enrolled for continued participation in the study.

7.1.3 Randomization and blinding

This study is open-label and does not involve blinding. Eligible subjects after screening will be randomized into the following three treatment groups in a 1:1:1 ratio: SHR-1210 200 mg, IV, Q2W + apatinib 375 mg, PO, QD; SHR-1210 200 mg, IV, Q2W + apatinib 375 mg, PO, QD (5 Days on, 2 Days off); or SHR-1210 200 mg, IV, Q2W + apatinib 375 mg, PO, QD (7 Days on, 7 Days off).

7.2 Main Study Procedures

7.2.1 Screening period (visit 1)

Refer to Table 11 for procedures of visits during the screening period.

Table 11. Procedures of visits during the screening period

Period	Screening Period			Note
Day	-28 to -1	-7 to -1	-3 to -1	
Baseline				
ICF	X			Subjects who do not meet the relevant criteria of this study (screening failure) may be rescreened. See Section 7.1.1 of the protocol for rescreening procedures

Period	Screening Period			Note
Day	-28 to -1	-7 to -1	-3 to -1	
Inclusion/Exclusion Criteria	X			
Demographics/Medical History/Medication History	X			The medications include treatment for initial diagnosis, including chemotherapy, radiotherapy, and surgical treatment. The time of the last anti-tumor treatment must be recorded.
Vital Signs	X			Vital signs include body temperature, pulse, respiratory rate, and blood pressure. See Section 8.2.4 of the protocol for detailed requirements
Weight/Height	X			
Physical Examination	X			See Section 8.2.2 of the protocol
ECOG PS	X			
Laboratory tests				
12-Lead ECG	X			Refer to Section 8.2.3 of the protocol for details
Hematology/Clinical Chemistry/ Urinalysis/Routine Stool		X		See Section 8.2.1 of the protocol
Coagulation Function		X		
Pregnancy Test			X	Serum pregnancy test
Thyroid Function	X			See Section 8.2.7 of the protocol
Myocardial Zymogram		X		See Section 8.2.7 of the protocol
Pituitary Adrenal Axis Test	X			Applicable to hospitals where conditions permit
HIV, HBV, and HCV	X			See Section 8.2.7 of the protocol
Echocardiography	X			See Section 8.2.7 of the protocol
Pulmonary function test and arterial blood gases	X			See Section 8.2.7 of the protocol
AE Assessment	X			All AEs from the time of signing the ICF to the end of safety follow-up or the start of new anti-tumor therapy (whichever occurs first) and all SAEs from signing of ICF to the end of safety follow-up will be recorded in the CRF
Concomitant Medications	X			Drugs related to the treatment of AEs other than solvents within 28 days before the first dose of the study drug until 30 days after and 30 to 60 days after the end of the treatment should be documented
Response Evaluation				

Period	Screening Period			Note
Day	-28 to -1	-7 to -1	-3 to -1	
Imaging Assessment	X			See Section 8.1 of the protocol
Exploration of Biomarkers				
Archived or Fresh Tumor Tissue Sample	X			5-10 unstained tissue slices with thickness of 4-6 μm
Peripheral Blood	X			Collect 16 mL of peripheral blood for tumor biomarker detection

7.2.2 Treatment period (visits 2 to N)

Refer to Table 12 for procedures of visits during the treatment period.

Table 12. Procedures of visits during the treatment period

Period	Treatment Period				Note
	Cycle 1		Cycle 2 and thereafter		
Day	1	15 (± 3 days)	1 (± 3 days)	15 (± 3 days)	
Vital Signs	X	X	X	X	Vital signs include body temperature, pulse, respiratory rate, and blood pressure. Before each SHR-1210 administration. See Section 8.2.4 of the protocol for detailed requirements
Body Weight	X	X	X	X	Before each SHR-1210 administration
Physical Examination		X	X	X	Before each SHR-1210 administration. See Section 8.2.2 of the protocol
ECOG PS	X	X	X	X	Before each SHR-1210 administration
Laboratory Tests					
12-Lead ECG	X	X	X	X	After each SHR-1210 infusion. See Section 8.2.3 of the protocol for detailed requirements
Hematology/Clinical Chemistry/Urinalysis/Routine Stool		X	X	X	Before each SHR-1210 administration. See Section 8.2.1 of the protocol
Coagulation Function			X		Before each SHR-1210 administration
Thyroid Function	X		X		Before each SHR-1210 administration
Myocardial Zymogram					Performed when clinically indicated per the investigator's judgment

Period	Treatment Period				Note
	Cycle 1		Cycle 2 and thereafter		
Day	**1**	**15 (± 3 days)**	**1 (± 3 days)**	**15 (± 3 days)**	
Pituitary Adrenal Axis Test			X		Applicable to hospitals where conditions permit; before each SHR-1210 administration
Echocardiography					Performed when clinically indicated per the investigator's judgment
Pulmonary function test and arterial blood gases					Performed when clinically indicated per the investigator's judgment
Immunogenicity (ADA, Nab)	X		X		Sampling will performed once within 0.5 h prior to SHR-1210 infusion on D1 of Cycle 1, Cycle 2, and every 3 cycles thereafter (Cycles 5, 8, 11, and so forth). If the subject develops SHR-1210-related infusion reactions, blood samples should be collected as close as possible to the onset of the event, to the end of the event, and about 30 days after the end of the event, for immunogenicity comparison and analysis. Tests will be performed at the central laboratory
AE Assessment	X		X		All AEs from the signing of the ICF to the end of safety follow-up or the start of a new anti-tumor treatment (whichever comes first) and all SAEs from the signing of the ICF to the end of safety follow-up should be recorded in the CRF
Concomitant Medications	X		X		Drugs related to the treatment of AEs other than solvents within 28 days before the first dose of the study drug until 30 days after and 30 to 60 days after the end of the treatment should be documented
Response Evaluation					
Imaging Assessment	X		X		See Section 8.1 of the protocol
Infusion of Study Drugs					
SHR-1210	IV, Q2W				See Section 6.1.1 of the protocol for the administration regimen. Subjects who meet specific conditions may continue the medication after PD (refer to Section 6.1.2 of the protocol for continued medication beyond progression).

Period	Treatment Period				Note
	Cycle 1		Cycle 2 and thereafter		
Day	1	15 (± 3 days)	1 (± 3 days)	15 (± 3 days)	
Apatinib	PO				See Section 6.1.1 of the protocol for the administration regimen.
Exploration of Biomarkers					
Peripheral Blood	X				Collect approximately 16 mL of peripheral blood for tumor biomarker detection during each tumor evaluation period

7.2.3 End of treatment

End of treatment refers to confirmation of progressive disease or withdrawal from the study. The end-of-treatment visit should be performed within ±3 days of the decision of treatment discontinuation and/or withdrawal from the study (refer to Table 13).

Table 13. Procedures of the end-of-treatment visit

Period	End of treatment	Note 28 Days (± 7 Days)
Day	± 3 days	
Vital Signs	X	Vital signs include body temperature, pulse, respiratory rate, and blood pressure. See Section 8.2.4 of the protocol for detailed requirements
Body Weight	X	
Physical Examination	X	See Section 8.2.2 of the protocol
ECOG PS	X	
Laboratory tests		
12-Lead ECG	X	Refer to Section 8.2.3 of the protocol for details
Hematology/Clinical Chemistry/Urinalysis/Routine Stool	X	See Section 8.2.1 of the protocol
Coagulation Function	X	
Pregnancy Test		Serum pregnancy test
Thyroid Function	X	
Myocardial Zymogram	X	
Pituitary Adrenal Axis Test	X	Applicable to hospitals where conditions permit
Echocardiography	X	
Pulmonary function test and arterial blood gases		Performed when clinically indicated per the investigator's judgment
Immunogenicity (ADA, Nab)	X	

Period	End of treatment	Note 28 Days (± 7 Days)
Day	± 3 days	
AE Assessment	X	All AEs from the time of signing the ICF to the end of safety follow-up or the start of new anti-tumor therapy (whichever occurs first) and all SAEs from signing of ICF to the end of safety follow-up will be recorded in the CRF
Concomitant Medications	X	Drugs related to the treatment of AEs other than solvents within 28 days before the first dose of the study drug until 30 days after and 30 to 60 days after the end of the treatment should be documented
Response Evaluation		
Imaging Assessment	X	See Section 8.1 of the protocol
Exploration of Biomarkers		
Archived or Fresh Tumor Tissue Sample	X	5-10 unstained tissue slices with the thickness of 4-6 μm, among which at least 5 slices will be used for PDL1 testing
Peripheral Blood	X	16 mL of peripheral blood will be collected for tumor biomarker detection

7.2.4 Safety follow-up

Safety follow-ups will be performed 90 ±7 days after the last dose (refer to Table 14).

Table 14. Procedures of the safety follow-ups

Period	Safety Follow-Up	Note
Day	28 Days (± 7 Days)	
Vital Signs	X	Vital signs include body temperature, pulse, respiratory rate, and blood pressure. See Section 8.2.4 of the protocol for detailed requirements
Body Weight	X	
Physical Examination	X	See Section 8.2.2 of the protocol
ECOG PS	X	
Laboratory tests		
12-Lead ECG	X	Refer to Section 8.2.3 of the protocol for details
Hematology/Clinical Chemistry/Urinalysis/Routine Stool	X	See Section 8.2.1 of the protocol
Coagulation Function	X	
Thyroid Function	X	
Immunogenicity (ADA, Nab)	X	

Period	Safety Follow-Up	Note
Day	**28 Days (± 7 Days)**	
AE Assessment	X	All AEs from the time of signing the ICF to the end of safety follow-up or the start of new anti-tumor therapy (whichever occurs first) and all SAEs from signing of ICF to the end of safety follow-up will be recorded in the CRF
Concomitant Medications	X	Drugs related to the treatment of AEs other than solvents within 28 days before the first dose of the study drug until 30 days after and 30 to 60 days after the end of the treatment should be documented
End of treatment visit		
Survival Status	X	
Subsequent Anti-Tumor Treatment	X	
Response Evaluation		
Imaging Assessment	X	If the treatment is discontinued for reasons other than radiologically confirmed PD, imaging evaluations shall be performed as much as possible per the scheduled time points until any of the following events occurs: start of new anti-tumor therapy, PD, withdrawal of ICF, or death.

7.2.5 Survival follow-up

Survival follow-ups will be performed once every 8 weeks (±7 days) after the last dose and telephone interviews are acceptable.

7.3 Procedures of Continued Medication After Progressive Disease

See Section 6.1.2 of the protocol for the procedures of continued medication after PD. Refer to Table 1 Schedule of Study Procedures for details.

8 STUDY ASSESSMENT

8.1 Efficacy Evaluation

This study does not involve central imaging review. The primary analysis of this study will be based on the tumor assessment conducted by the study centers per RECIST v1.1 (refer to Appendix 3). The ORR, PFS, TTR, DoR, DCR, 6-month OS rate, and OS after medication are evaluated.

8.1.1 Sites of radiographic scans

The method used for tumor imaging evaluation during the baseline period must be consistent with the method used for each subsequent follow-up evaluation. Computerized tomography (CT) or magnetic resonance imaging (MRI) scans is recommended. Other involved parts are examined

based on the symptoms and signs of each subject. Baseline imaging evaluations should include thoracic, abdominal, and pelvic scans (from apex of lung to pubic symphysis), brain scan, bone scan, and scan of all known or suspected lesions. Each subsequent clinical tumor imaging evaluation should include thoracic, abdominal, and pelvic scans; brain and/or bone scans may be performed when clinically indicated. The frequency of imaging monitoring can be increased by the investigator as needed.

8.1.2 Evaluation time points

The baseline tumor evaluation will be performed within 28 days before the first dose. Imaging data obtained before the signing of informed consent form may be used for tumor evaluation during the screening period as long as it meets the requirements of the protocol.

During the study, imaging assessment will be performed on C1D28 and every 8 weeks (±7 days) after C1D28 until radiographic PD is documented. An additional imaging evaluation must be performed in 4 weeks (+ 7 days) for confirmation after the initial documentation of response (CR or PR) and imaging PD.

Criteria for relapse of PD:

1. At 2 consecutive visits, the sum of the diameters of the target lesions increased by ≥ 20% from the lowest value (the smallest sum of diameters may occur at baseline or subsequent visits) and the absolute value increased by ≥ 5 mm, and/or
2. At the time point of confirming PD, non-target lesions or new lesions have significantly progressed (exacerbated) relative to the first time point when progression of non-target lesions are discovered or new lesions are discovered (such that if the target lesions appeared CR, PR, or SD, the total tumor burden has increased sufficiently to discontinue treatment), and/or
3. Compared to the first time point when new lesions are discovered, new lesions appeared at the time point of confirming PD.

If PD is not confirmed, the study medication and imaging evaluation are continued until relapse of PD. Refer to Section 6.1.2 of the protocol for the relapse of PD. Subjects with relapse of PD must discontinue treatment. If the treatment is discontinued for reasons other than radiologically confirmed PD, imaging evaluations shall be performed as much as possible per the scheduled time points until any of the following events occurs: start of new anti-tumor therapy, PD, withdrawal of ICF, or death. Refer to Section 7 of the protocol for details.

If the investigator is unable to determine whether the disease is progressing, especially if the determination of non-target lesions and new lesions is uncertain, the subject may continue the treatment, and when clinically indicated or at the next scheduled assessment, the subject will be reassessed for the disease status. If PD is confirmed by scan reexamination, the date of progression should be the date of initial discovery.

The interruption of one or more study drug(s) does not affect the evaluation frequency per RECIST v1.1.

8.2 Safety Evaluation

8.2.1 Routine laboratory safety evaluation

Table 15. Routine laboratory safety evaluation

Hematology	RBC, HGB, HCT, WBC, PLT, LYM, ANC, MONO, EOS, and BASO
Coagulation Function	TT, PT, APTT, and INR
Clinical Chemistry	TBIL[a], ALT, AST, γ-GT, ALP, ALB, TP, LDH, BUN, Cr, Na, K, Cl, Mg, Ca, P, lipase, amylase, and FBG
Urinalysis	PH, UALB, UPRO[b], URBC[c], and UGLU
Routine Stool Test	Occult blood

[a.] If TBIL ≥ 2 × ULN (without evidence of Gilbert syndrome), then direct bilirubin and indirect bilirubin shall be tested separately.

[b.] The white blood cells should be examined microscopically (if appropriate), and the red blood cells should be examined with a high-power field of view.

8.2.2 Physical examination

A complete physical examination includes: general conditions, respiratory tract, cardiovascular system, abdomen, skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, musculoskeletal (including spine and limbs), genitals/anus, and nervous system evaluation.

Refer to the schedule of visits in Table 1 for the time points of examinations. Refer to Appendix 1 for ECOG PS scoring criteria.

8.2.3 12-Lead ECG

The resting 12-lead ECG will be analyzed in the local laboratory according to the visit schedule.

The 12-lead ECG examination will be performed after the subject rests for at least 5 min in the lying position. All 12-lead ECGs should be recorded while the subject is lying and resting. When clinically needed, for example when a cardiac AE is noted, further ECG examinations will be

performed. On the day of the examination, the investigator completes the ECG assessment and records the assessment results on the electrocardiogram. The same assessment method should be used throughout the study period.

The ECG will be recorded at a speed of 25 mm/s. The investigator should evaluate all ECGs based on clinically significant abnormalities/clinically non-significant abnormalities. The investigator should record clinically significant abnormal findings as AEs in the eCRF.

8.2.4 Vital signs

Vital signs will be measured as described in the study visit schedule. Vital signs include body temperature, pulse rate, respiratory rate, and blood pressure.

The investigator may perform additional vital sign assessment and monitoring according to standard clinical practice or based on clinical needs.

In the event of an AE/SAE, additional vital sign records may be collected on the eCRF (if applicable). The date and time of collection and measurement will be recorded in the appropriate section of the eCRF.

8.2.4.1 Pulse and blood pressure

Pulse and blood pressure are measured during the screening period and before the scheduled SHR-1210 infusion.

Blood pressure monitoring: cigarettes and caffeine are prohibited within 30 min before each blood pressure measurement, and subjects shall rest for at least 10 min. The blood pressure will be measured at sitting position with elbow on the same level as heart. All measurements should be taken on the same side.

During the screening period and before each scheduled SHR-1210 infusion, the investigator will measure the blood pressure of the subject. During the study, the subject will monitor the blood pressure and record on the diary card. Blood pressure shall be measured at least 3 times per week in the first 2 cycles. For subjects with abnormal blood pressure, the blood pressure shall be measured daily; if normal, the blood pressure shall be measured twice per week after Cycle 2.

8.2.4.2 Body temperature and respiration

Body temperature and respiration are measured during the screening period and before the scheduled SHR-1210 infusion.

8.2.5 Weight and height

Height will be measured only during the screening period. Weight will be measured during the screening period, before SHR-1210 administration at each visit, at the end of the treatment, and at safety follow-ups.

8.2.6 Pregnancy test

Women of childbearing potential undergo a serum human chorionic gonadotropin (hCG) pregnancy test within 3 days before the first dose of the study drug. Subjects with a positive result are not eligible or must discontinue participation in the study. Retests will be performed when pregnancy is suspected during the study period.

8.2.7 Other safety examinations

- Hepatitis B tests: HBsAg, HBsAb, HBcAb, HBeAg, and HBeAb.
- HIV antibodies and HCV antibodies
- Thyroid function: T3, T4, TSH, FT3, and FT4
- Myocardial zymography: LDH, AST, CK, CK-MB, and ALT
- Pituitary adrenal axis test: Including tests of CRH, plasma ACTH, and adrenocortical hormone. Adrenocortical hormone tests include serum cortisol, UFC, 17-KS, and 17-KGS
- Echocardiography
- Pulmonary function test: maximum vital capacity, the forced expiratory flow at 25-75% of forced vital capacity (FEF25-75), the peak expiratory flow rate (PEF), the maximum expiratory volume per second, diffusing capacity of the lungs for carbon monoxide (DLCO) and oxygen saturation, which will be performed during the screening period and based on clinical indicators as determined by the investigator thereafter. Subject to the actual conditions of each site.
- Arterial blood gas test: optional. This test includes partial arterial pressure of oxygen (PaO_2), partial arterial pressure of carbon dioxide ($PaCO_2$), arterial oxygen saturation (SaO_2), and pH, and can be performed during the screening period. Subject to the actual conditions of each site.

8.3 Pharmacokinetics

Not applicable.

8.4 Pharmacodynamics

Not applicable.

8.5 Immunogenicity

Immunogenicity blood samples will be collected once within 0.5 h before SHR-1210 infusion on D1 of cycle 1, cycle 2, and the third cycle of every three cycles thereafter (cycles 5, 8, 11, etc.), once at the end of the treatment, and once per month at safety follow-ups after withdrawal for

3 times (if applicable). In case of national holidays, the blood collection time may be adjusted as appropriate. If the subject develops SHR-1210-related infusion reactions, blood samples should be collected as close as possible to the onset of the event, to the end of the event, and about 30 days after the end of the event, for immunogenicity comparison and analysis. Immunogenicity blood samples should be collected following the study protocol. However, if deemed necessary by the investigator, unscheduled immunogenicity blood samples may be collected.

Each subject shall be tested for anti-drug antibody (ADA) titer. ADA-positive serum samples will be further tested for neutralizing antibodies (NAb). Four (4) mL of blood will be collected each time for immunogenicity. Please refer to the Laboratory Manual provided by the sponsor-designated central laboratory for sampling methods, sample storage, transportation, and analysis.

8.6 Biomarker Analysis

Subject to the permission of the ethics committee, all subjects who meet the inclusion criteria shall provide diagnostic tumor tissues at baseline. Acceptable tumor tissues include 5-10 unstained 4-6 μm slices prepared with archived tumor tissues or freshly obtained during the screening period.

After the subject's ICF is obtained and after the study medication, another biopsy is preformed before PD or treatment discontinuation to provide tumor tissue to the central laboratory for testing and analysis of the relationship between the change in PD-L1 expression before and after the administration and the efficacy. These samples may also be used for exploratory biomarker analysis, including but not limited to PD-L1 expression.

After the subject's ICF is obtained, about 16 mL of peripheral blood may be collected for tumor biomarker detection during the screening period, at each tumor evaluation, and the end of the treatment.

Refer to the Laboratory Manual for sample processing, handling, and transportation.

8.7 Storage and Destruction of Biological Samples

The samples will be disposed of or destroyed, and pooled and anonymized. Additional analysis may be performed on the anonymized and pooled samples to further evaluate and validate the analysis method. Any results obtained from these analyses may be reported separately from CSR.

The sample reproducibility analysis (if performed) will be performed simultaneously with the biological sample analysis. These evaluation results will not be reported in the clinical study report, but will be separately given in a biological sample analysis report.

9 SAFETY EVALUATION

9.1 AE

9.1.1 Definition of AE

AE refers to any untoward medical condition in a clinical study subject who receives a pharmaceutical product, and the condition does not necessarily have a causality with the treatment. All AEs from signing of the informed consent form to the end of the safety follow-up period (90 days after the last dose) or the start of other anti-tumor treatments will be collected in this study. AEs can include any unfavorable and unintended symptoms, signs, abnormal laboratory findings, or diseases, including the following:

1) Worsening of pre-existing (prior to entering the clinical trial) medical conditions/diseases (including worsening symptoms, signs, or laboratory abnormalities);

2) Any new AE: Any new adverse medical conditions (including symptoms, signs, and newly diagnosed diseases);

3) Clinically significant abnormal laboratory findings.

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

9.1.2 AE severity grading criteria

Please refer to NCI CTCAE 4.03 for grading standards. Refer to the following criteria for AEs not listed in NCI-CTCAE 4.03:

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; limited age-appropriate instrumental activities of daily living (ADL), e.g., cooking, shopping, using the telephone, counting money.
3	Severe or medically significant symptoms but not immediately life-threatening; hospitalization or prolonged 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	Resulting in death

9.1.3 Causality assessment of AEs

AEs include all unexpected clinical manifestations. All such events occurring after the signing of the ICF must be reported as AEs regardless of whether they are related to the study drugs or even whether the subject has received the drugs. All subject complaints and abnormal changes in laboratory tests during the treatment period will be documented truthfully. The severity, duration,

measures taken, and outcome of the AE will be noted. The investigator shall assess the causality between the AE and the study drug, such as whether there is a plausible temporal relationship with the study drug, the characteristics of the study drug, the toxicological and pharmacological effects of the study drug, whether there are concomitant medications, the subject's underlying diseases, medical history, family history, as well as dechallenge and rechallenge. The potential relationship between the AE and the study drug will be assessed with 5 grades of causality: "definitely related", "possibly related", "unlikely related", "not related", and "indeterminable". Events deemed "definitely related", "possibly related", "unlikely related", and "indeterminable" will be listed as adverse drug reactions. When calculating the incidence of AEs, the total of these four categories shall be used as the numerator and the total number of subjects for safety assessments shall be used as the denominator.

9.2 Serious Adverse Event (SAE)

9.2.1 Definition of SAE

An SAE is any untoward medical occurrence at any dose. The following medical events are included:

- Events resulting in death;
- Life-threatening events (defined as when the subject is at immediate risk of death at the time of the event);
- Events resulting in hospitalization or prolonged hospitalization;
- Events resulting in permanent or serious disability/incapacity/impairment of work ability;
- Congenital anomalies or birth defects;
- Other important medical events (defined as events that may jeopardize the subject or require interventions to prevent any of the above).

9.2.2 Hospitalization

AEs that result in 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 pre-existing disease without the occurrence of new AEs or worsening of the pre-existing diseases (e.g., in order to examine the persistent laboratory abnormalities that started before the study);
- Hospitalization for management reasons (e.g., annual physical examination);
- Hospitalizations during the study as specified in the protocol (e.g. hospitalization performed in accordance with study protocol);
- Elective hospitalization unrelated to worsening of AEs (e.g., elective surgery);
- Scheduled treatment or surgical procedures, which should be documented in the individual subject's baseline information;
- Hospitalization merely for use of blood products.

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

9.2.3 Progressive disease

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

9.2.4 Potential drug-induced liver injury

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

Potential drug-induced liver injury is defined as follows:

Baseline Period	Normal (AST/ALT and TBIL)	Abnormal (AST/ALT and TBIL)
Treatment Period	• ALT or AST > 3 ×ULN • with TBIL ≥ 2 × ULN • and ALP ≤ 2 × ULN • and no hemolysis	• AST or ALT ≥ 2 × baseline level, and 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 the study center for an assessment as soon as possible (preferably within 48 h). Assessments include the laboratory tests, detailed medical history, and physical assessment, and the possibility of hepatic tumor (primary or secondary) should be considered.

Except for 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.

9.2.5 Other anti-tumor treatments

For subjects starting other anti-tumor treatments, unless suspected to be related to the study drugs, adverse events except death will be reported until the start of the new anti-tumor treatment. Deaths that occur within the SAE reporting period after study treatment is completed should be reported regardless of whether the subject has received other treatments.

9.2.6 SAE reporting

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

Email the SAE reports to: hengrui_drug_safety@hrglobe.cn

SAEs that occur after the safety follow-up period will generally not be reported unless suspected to be treatment-related. Symptoms, severity, causality with the study drugs, time of occurrence, duration of treatment, measures taken, follow-up time and methods, and outcomes of SAEs shall be documented. If an SAE is potentially related to the study conditions (e.g., discontinuation of previous therapy, or comorbidities during the study procedure) rather than the study treatment as deemed by the investigator, this relationship shall be detailed in the narrative section of the SAE report form. If the severity of an ongoing SAE or its relationship to the study drug changes, a follow-up report should be submitted immediately. If an error is found in a previously reported SAE, such SAE may be revised, revoked, or downgraded in follow-up reports and reported in accordance with the SAE reporting procedure.

9.2.7 Follow-up of AEs/SAEs

All the AEs/SAEs should be followed up until they resolve, recover to baseline levels or Grade ≤ 1, steady state, or reasonably are explained (e.g., lost to follow-up, death).

During each visit, the investigator should ask about the situation of AEs/SAEs that occur after the last visit and provide follow-up information in a timely manner based on the sponsor's query request. Principles of collection and follow-up of AEs/SAEs after the last dose at the end of treatment are shown in the table below.

Principles of AE/SAE collection and follow-up

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

9.3 Pregnancy

During the study, if a female subject becomes pregnant, she must immediately discontinue the study drug treatment. The investigator must report the event to the sponsor within 24 h of being notified 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 investigator must report the event to the sponsor within 24 h of being notified and fill out the "Pregnancy Report/Follow-up Form for Hengrui Clinical Studies".

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

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

If the subject also experiences 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.

9.4 Adverse Events of Special Interest

For adverse event of special interest (AESIs) specified in the study protocol, the investigator must complete the "Report of Adverse Event of Special Interest for Hengrui Clinical Studies" and report to the sponsor within 24 h of knowing of the event. 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 SAE reporting procedure.

- Grade ≥ 3 infusion reaction
- Grade ≥ 3 other immune-related AEs

10 DATA ANALYSIS/STATISTICAL METHODS

10.1 Sample Size

In this study, based on historical study data and study results of drugs of the same class and combined with clinical needs, a single-stage assessment method will be adopted to explore the efficacy of SHR-1210 combined with apatinib on ORR in ED-SCLC after failure of the first-line standard therapy.

Assume that in this study, the expected ORR in each treatment group of SHR-1210 + apatinib combination therapy is ≥ 30% (alternative hypothesis), and that there is no need to continue the study if the ORR is ≤ 15% (null hypothesis), at the significance level of 0.1 and a power of 80%, 40 subjects should be enrolled. If ≥ 9 (22.5%) of the 40 subjects have response, it can be considered that the ORR in this treatment group is 15% and the study drug is worthy of continued development.

With a dropout rate of 10% taken into account, each treatment group needs to enroll about 45 subjects. A total of 57 subjects are required in Stages I and II.

10.2 Statistical Analysis Plan

Detailed summaries and methods of statistical analyses for the data collected from the study will be included in the statistical analysis plan (SAP), which will be finalized and filed by the sponsor. The SAP should be revised accordingly if there are any changes to the study protocol that may have an obvious impact on the SAP, as determined by the sponsors or principal investigators. The SAP must be finalized before database locking.

10.3 Statistical Hypotheses

This study does not involve any statistical hypotheses and inference.

A single-stage assessment method will be adopted to explore the efficacy of SHR-1210 combined with apatinib on ORR in ED-SCLC after failure of the first-line standard therapy. The potential need for further development is indicated when the predefined number of responses (objective response) of a treatment group is reached (see Section 10.1 for details).

10.4 Analysis Sets

The analysis sets in this study include:

Full analysis set (FAS): an analysis set determined based on the intent-to-treat principle. This analysis set includes all subjects who have been randomized and have received at least one dose of the study drug. In the FAS-based analysis, subjects will be analyzed by groups after randomization (regardless of the actual treatment they receive).

Per-protocol set (PPS): a subset of the FAS. Subjects with protocol violations that are judged to have a significant effect on the efficacy will be excluded from this set. The list of subjects included into or excluded from the PPS should be reviewed and determined by the sponsor and the investigator before the database is locked.

Evaluable set (ES): a subset of the FAS, defined as the all enrolled subjects receive at least one dose of the study drugs and receive post-baseline tumor assessment at least once.

Safety set (SS): All subjects who have been randomized and have received at least one dose of the study drug. Analyses based on the safety set will be carried out according to the actual treatment received by the subjects.

ADA set (ADAS): All enrolled subjects who have received at least one dose of the study drug and have baseline and at least one post-baseline ADA evaluation data.

Tumor biomarkers set (TMKS): Subjects who have been randomized and received at least one dose of the study drugs, and have tumor biopsy samples make up the PD-L1 or TMB set.

10.5 Statistical Methods

10.5.1 Basic methods

Unless otherwise specified, standard descriptive statistics will be summarized by different type of variables:

- Continuous data will be summarized using mean, standard deviation, median, maximum, and minimum;
- Categorical data will be summarized using frequency and percentage;
- For time-to-event data, Kaplan-Meier method will be used to estimate the survival function and median time to event onset, and a survival curve will be plotted.

The baseline is generally defined as the last pre-administration observation before the first dose (including the very day).

10.5.2 Primary efficacy endpoint analysis

ORR is the primary efficacy endpoint of the study. It refers to the proportion of all enrolled subjects with CR or PR evaluated by RECIST v1.1. Response confirmation should be conducted for CR and PR. The point estimate of ORR and two-sided 95% confidence interval based on the Clopper-Pearson method will be calculated. The statistical analysis of ORR will be based on the FAS and ES, with FAS as the primary analysis set.

10.5.3 Secondary efficacy endpoint analysis

The secondary efficacy endpoints of this study include OS, 6-month OS rate, PFS, TTR, DoR, and DCR evaluated as per RECIST v1.1

The statistical analysis of DoR, TTR, and PFS will be based on the FAS and ES, with FAS as the primary analysis set. The statistical analysis of OS will be based on the FAS.

PFS, TTR, DoR, and OS will be estimated based on the Kaplan-Meier method, and the corresponding two-sided 95% confidence interval will be calculated.

The point estimate of DCR and the 95% confidence interval based on the Clopper-Pearson method will be calculated.

10.5.4 Safety analysis

The safety analysis will be summarized primarily using descriptive statistics. The analysis set is SS.

All AEs will be coded according to the latest version of MedDRA. AEs will be statistically summarized by AEs, SAEs, treatment-related AEs, AEs resulting in dose modification, and AEs resulting in study withdrawal. All AEs will also be graded by NCI CTCAE (v4.03). Grade ≥ 3 AEs will be statistically summarized. In addition, safety data such as laboratory tests and vital signs will also be statistically summarized.

The safety data will be analyzed and summarized using Hengrui's current clinical study report standards. Such standards include but are not limited to the following:

- Analysis of treatment discontinuation, dose reduction, or treatment interruption due to AEs
- Incidence and severity of AEs
- Causality analysis between AEs and study drug
- Analysis of outcomes of AEs
- Analysis of SAEs
- Descriptive statistical summary of laboratory test, vital signs, and ECG data
- Incidence of laboratory abnormalities
- Analysis of normal and abnormal changes in laboratory parameters, vital signs, and ECG data compared to baseline

10.5.5 Exploratory analysis

The expression levels of PD-L1 and TMB will be analyzed using descriptive statistics. The analysis will be based on the TMKS.

The immunogenicity will be analyzed using descriptive statistics. The analysis will be based on the ADAS.

10.5.6 Subgroup analysis

The analysis of the primary endpoint ORR will be carried out in the following subgroups:

- Sensitive recurrence (progression in ≥ 90 days from the last chemotherapy)
- Drug-resistant recurrence (progression during chemotherapy or within 90 days from the last chemotherapy)

Other subgroup analyses will be detailed in SAP.

10.5.7 Multiple comparison/Multiplicity

Not applicable.

11 DATA MANAGEMENT

11.1 Data Recording

Study data will be collected and managed using the eCRF.

11.1.1 Study medical recording

As source documents of the study, medical records should be retained in their entirety. The investigator 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.

11.1.2 eCRF entry

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 true manner. Data should not be changed arbitrarily. All items in the CRF should be filled out, with no blank or omissions.

Modifications: The system instructions must be followed when correcting the eCRF data as needed, and the reason for data correction must be recorded. The logic verification program in the system will verify the integrity and logic of the study data entered into the electronic data capture (EDC) system and generate an error message prompt for questionable data. The PI or data entry personnel (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.

11.1.3 eCRF review

The investigator must complete, review, and submit the eCRF within 3 working days after the end of each subject's treatment course. The investigator or the data input staff (CRC) should promptly respond to queries raised by the monitor, data manager, and medical reviewer. After data cleaning is completed, the investigator will sign the completed eCRF for verification.

11.2 Data Monitoring

Implemented by: CRA.

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

11.3 Data Management

11.3.1 EDC database establishment

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

11.3.2 Data entry and verification

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

11.3.3 Data review and database locking

After the study is completed, the study director, sponsor, statistician, and data manager will conduct a joint data review before statistical analysis mainly to determine the analysis data set (including FAS, PPS, and SS) for each case, the judgment of missing values, and the handling of outliers. All decisions made under data review must not be modified, and any decision must be documented.

After the established database is considered correct by review, the database will locked. After the database is locked, the data must be properly stored for future reviews, and the database should be statistically analyzed by the statistician.

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

11.3.4 Data archiving

After the study is completed, subject's 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 shall be preserved and managed in accordance with GCP requirements, and necessary documents of clinical studies shall be preserved until 2 years after the study drug is approved for marketing or 5 years after the termination of the clinical study.

12 SOURCE DATA AND DOCUMENTS

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

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

13 QUALITY ASSURANCE AND QUALITY CONTROL

To ensure study quality, the sponsor and investigator will together discuss and formulate the clinical study plan before the official commencement of the study. GCP training will be conducted for relevant investigators participating in the study.

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

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

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

The drug regulatory authorities, Institutional Review Board (IRB)/Independent Ethics Committee (IEC), sponsor's monitor and/or auditor may carry out systemic inspection of study-related activities or documents to assess whether the study is implemented based on the study protocol, SOPs, and relevant regulations (such as Good Laboratory Practices [GLP] and Good Manufacturing Practices [GMP]) and whether the study data is recorded in a prompt, truthful, accurate, and complete manner. The audit shall be conducted by persons not directly involved in the study.

14 REGULATIONS, ETHICS, ICF, AND SUBJECT PROTECTION

14.1 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 clinical study can only be carried out after an 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

14.2 Ethical Standards

The investigator will ensure that the trial in this study is fully implemented in accordance with the requirements for subject protection in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56 and/or ICH E6.

This study protocol must first be reviewed and approved by the Ethics Committee of the Cancer Hospital before being implemented. The study protocol, protocol revisions, ICF, and other relevant documents such as recruitment advertisements should be submitted to the ethics committee. This clinical study must comply with the Declaration of Helsinki, Good Clinical Practice (GCP) enacted by the NMPA, and other relevant regulations. Before the study is initiated, approval must be obtained from the ethics committee of the hospital.

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

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

14.3 Independent Ethics Committee

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

14.4 ICF

14.4.1 ICFs and other written information for subjects

The ICF shall describe the study drugs and study process in detail and fully explain the risks of the study to the subjects. Written documentation of the ICF must be obtained before starting any study-related procedures.

14.4.2 Informed consent process and recording

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

14.5 Confidentiality of Subject Information

The confidentiality of subject information will be strictly enforced by the investigator, participated study personnel, and sponsor and its representative. In addition to the clinical information, confidentiality also simultaneously covers biological samples and genetic tests of the subjects. Therefore, the study protocol, documents, data, and other information generated from these materials will be kept strictly confidential. All relevant study or data information should not to be disclosed to any unauthorized third-party without prior written approval from the sponsor.

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

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

This should not include the contact information or identification information of subjects. Instead, individual subjects and their study data will be given a unique study identification number. The study data entry and study management system used by the study personnel at the study centers shall be confidential and password-protected.

14.6 Sample Storage and Use

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. The samples and data collected in accordance with the protocol will be used for biomarker detection and will not be used for any unrelated purposes.

15 PUBLICATION OF STUDY RESULTS

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

16 CLINICAL TRIAL PROGRESS

Anticipated enrollment of the first subject: Q1 of 2018

Anticipated enrollment of the last subject: Q4 of 2018

Anticipated time of last subject last visit: Q3 of 2019

Anticipated study completion: Q1 of 2020

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Appendix 1 ECOG PS Scoring Criteria

Score	ECOG Performance Status
0	Fully active, able to carry on normal activity without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature or office work
2	Ambulatory and capable of all self-care but unable to carry out any work; confined to bed < 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair of more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Death

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Appendix 2 Calculation of Creatinine Clearance

Creatinine Clearance Calculation Using the Cockcroft-Gault Formula

Please choose the appropriate formula corresponding to the unit of serum creatinine test:

If the unit of serum concentration of creatinine is mg/dL

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

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

If the unit of serum concentration of creatinine is μmol/L

$$\text{Creatinine Clearance in Males (mL/min)} = \frac{(140 - \text{Age}) \times (\text{Weight})}{0.81 \times \text{Serum creatinine}}$$

$$\text{Creatinine Clearance in Females (mL/min)} = \frac{0.85 \times (140 - \text{Age}) \times (\text{Weight})}{0.81 \times \text{Serum creatinine}}$$

Note: The unit of age is years old, and the unit of body weight is kilogram (kg).

Appendix 3 Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)

The following content is an excerpt from the RECIST v1.1 criteria.

1 MEASURABILITY OF TUMOR AT BASELINE

1.1 Definitions

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

1.1.1 Measurable

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

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

1.1.2 Non-measurable

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

1.1.3 Special considerations regarding lesion measurability

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

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions;

- Lytic lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by tomography techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above;
- Blastic lesions are non-measurable.

Cystic lesions:

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

Lesions with prior local treatment:

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

1.2 Specifications by Methods of Measurements

1.2.1 Measurement of lesions

All measurements should be recorded in metric notation if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 21 days (3 weeks) before the beginning of the treatment.

1.2.2 Method of assessment

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

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

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

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

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

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

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

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

2 TUMOR RESPONSE EVALUATION

2.1 Assessment of Overall Tumor Burden and Measurable Disease

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

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

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

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

Lymph nodes merit special mention since they are normal tissues which may be visible by imaging even if not involved by tumor metastasis. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15mm by CT scan. Only the short axis of these nodes needs to be measured at baseline. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by tumor metastasis. Nodule size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smallest of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm ×30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. Nodes with short axis ≥ 10 mm but < 15 mm should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

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

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

2.3 Response Criteria

2.3.1 Evaluation of target lesions

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

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

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

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

2.3.2 Special notes on the assessment of target lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. eCRFs or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become too small to measure: While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes

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

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

2.3.3 Evaluation of non-target lesions

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

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

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

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

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

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

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

2.3.5 New lesions

The appearance of new malignant lesions denotes PD; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of radiographically detected lesions; however, the finding of a new lesion should be unequivocal. For example, it should not be attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some new bone lesions that may be simply healing, or re-occurrence of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a new cystic lesion, which it is not.

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

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

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

Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

No FDG-PET at baseline and a positive FDG-PET at follow-up:

If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, PD is confirmed.

If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).

If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the imaging examination, this is not PD.

2.4 Evaluation of Best Overall Response

The best overall response evaluation is the best response recorded from the start of the trial until the end of study, while all necessary requirements shall be taken into account at the same time for confirmation. On occasion a response may not be documented until after the end of treatment, so protocols should be clear if post-treatment assessments are to be considered in the evaluation of best overall response. Protocols must specify how any new treatment introduced before progression will affect best response evaluation. The subject's best overall response evaluation will depend on the findings of both target and non-target lesions and will also take into consideration the characteristics of new lesions. Furthermore, it also depends on the nature of the study, the protocol requirements, and the judgment criteria of results. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to determine which one is the best overall response.

2.4.1 Time point response

Efficacy evaluations are assumed at each time point specified in protocol. Table 1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

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

2.4.2 Missing assessments and unevaluable designation

When no imaging/measurement is done at all at a particular time point, the subject is not evaluable at that time point. If only a subset of lesion measurements is made at an evaluation, usually the case is also considered not evaluable at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) has/have no effect on the assigned time point response. This would be most likely to happen in the case of PD. For example, if a subject had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions are assessed, but those gave a sum of 80 mm, the subject will have achieved PD status, regardless of the contribution of the missing lesion.

2.4.3 Best overall response: all time points

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

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

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

2.4.4 Special notes on response evaluation

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

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

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

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

In some circumstances it may be difficult to distinguish residual lesions from normal tissues. When the evaluation of complete response depends upon this definition, it is recommended that the local lesion be investigated via biopsy before assigning a status of complete response. FDG-PET may be used to confirm a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

Target Lesion	Non-Target Lesion	New Lesion	Overall Response
CR	CR	Non	CR
CR	Non-CR/Non-PD	Non	PR
CR	Not evaluable	Non	PR
PR	Non-PD or not all	Non	PR

Target Lesion	Non-Target Lesion	New Lesion	Overall Response
	evaluable		
SD	Non-PD or not all evaluable	Non	SD
Not all evaluable	Non-PD	Non	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
CR = Complete response	PR = Partial response	SD = Stable disease	PD = progressive disease NE = not evaluable

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

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

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

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

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

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

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

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

2.5 Frequency of Tumor Re-Evaluation

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

After the treatment, the need for tumor re-evaluations depends on whether the trial has made the response rate or the time to an event (progression/death) an endpoint. If time to an event (e.g. TTP/DFS[1]/PFS) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomized comparative studies in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6-8 weeks on treatment or every 3-4 months after treatment) and should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment group in the timing of disease assessment.

2.6 Confirmatory Evaluation/Duration of Response

2.6.1 Confirmation

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has

traditionally required confirmation in such trials. However, in all other circumstances, i.e., in randomized trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

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

2.6.2 Duration of overall response

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

2.6.3 Duration of stable disease

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

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

2.7 PFS/TTP

2.7.1 Phase II clinical study

This guideline is focused primarily on the use of objective response as study endpoints for phase II trials. In some circumstances, response rate may not be the optimal method to assess the potential anti-tumor activity of new agents/regimens. In such cases PFS/PPF at landmark time points, might

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

Appendix 4 List of Autoimmune Diseases That May Exist Before Enrollment

Carefully ask the subjects whether they have acquired or inherited immunodeficiency or autoimmune diseases. Such subjects must be excluded from this study, unless the possibility of the subject's history of allergies and childhood joint pain being suspected of an autoimmune disease is very low. In addition, subjects with transient autoimmune manifestations due to acute infectious diseases (such as Lyme arthritis) may be enrolled if they are cured with antibiotics. For indeterminate autoimmune diseases to be ruled out, contact the sponsor's medical department.

Autoimmune diseases include but are not limited to:

Acute sporadic encephalomyelitis	Autoimmune myocarditis	Rett syndrome
IgA nephropathy	Neuromyotonia	Type I diabetes mellitus
Addison's disease	Autoimmune oophoritis	Rheumatoid arthritis
Inflammatory bowel disease	Myoclonus syndrome	Autonomic dysfunction
Alopecia universalis	Autoimmune orchitis	Sarcoidosis
Interstitial cystitis	Optic neuritis	Eczema
Ankylosing spondylitis	Autoimmune thrombocytopenic purpura	Scleroderma
Myasthenia gravis syndrome	Ord's thyroiditis	Sjogren syndrome
Antiphospholipid antibody syndrome	Behcet's disease	Bullous skin lysis
Lupus erythematosus	Pemphigus	Stiff-man syndrome
Aplastic anemia	Bullous pemphigoid	Pemphigoid gestationis
Lyme disease (chronic)	Pernicious anemia	Multi-takayasu arteritis
Asthma	Gluten sensitivity	Giant cell arteritis
Meniere's syndrome	Polyarteritis	Ulcerative colitis
Autoimmune hemolysis	Chronic fatigue syndrome	Pulmonary hemorrhage-nephritic syndrome
Anemia	Polyarthritis	Vitiligo
Corneal ulcer	Chronic inflammatory demyelination	Graves' disease
Autoimmune hepatitis	Polyneuropathy	Vogt-Kovanagi-Harada disease
Localized autoimmune hypophysitis	Autoimmune syndrome	Guillain-Barre syndrome
Multiple sclerosis	Churg-Strauss syndrome	Vulva sore
Autoimmune hypoparathyroidism	Primary biliary cirrhosis	Hashimoto's disease
Myasthenia gravis	Crohn's disease	Wegener's granulomatosis
	Psoriasis dermatomyositis	Kawasaki disease

Appendix 5 Prohibited Traditional Chinese Medicines During the Study Period

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

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

Appendix 6 Guidelines on Dose Modifications and Handling of Toxicities of SHR-1210

<table>
<tr><th></th><th colspan="2">AE Grading/Dose Modification</th><th>Treatment of Toxicity</th></tr>
<tr><td rowspan="5">General Rules</td><td colspan="2">AEs are graded per the NCI CTCAE v4.03; if it is judged as an irAE, please refer to this guideline.</td><td rowspan="5">The guidelines described in this table are recommended for the treatment of irAEs.
– Subjects should be comprehensively evaluated to rule out any alternative causes (such as progressive disease, concomitant medication, infections, etc.)
– When there is no clear alternative cause and glucocorticoid therapy is needed, it should be judged as an irAE.
– For low-grade (Grade 1 or 2 unless otherwise specified) events, symptomatic and local treatment should be considered.
– For persistent low-grade events (Grade 1 or 2) or severe (Grade ≥ 3) events, systemic glucocorticoid therapy should be considered.
– If recurrence or deterioration occurs during the dose tapering of glucocorticoids, the dose of glucocorticoids should be increased until the symptoms are stable or improved, and then the dose of glucocorticoids should be tapered at a lower rate.
– Once sustained clinical improvement is observed, subjects receiving intravenous glucocorticoids can switch to an equivalent dose of oral glucocorticoid therapy at the beginning of the dose tapering or earlier (the low bioavailability of oral glucocorticoids should be considered).
– For events where systemic glucocorticoid therapy is ineffective, a stronger immunosuppressive agent, such as TNF antagonists (e.g., infliximab) or mycophenolate mofetil, should be considered after discussing with the study physician.
– For local inflammatory reactions of Grade 3/4 lesions (such as local pain, irritation, and rashes) caused by potential tumor response, SHR-1210 may not be discontinued at the judgment of the investigator.</td></tr>
<tr><td>Grade 1</td><td>Dose modification is not required.</td></tr>
<tr><td>Grade 2</td><td>Treatment interruption
• If aggravated, treat as Grade 3 or 4
• If improved to Grade 0-1 or baseline, continue the treatment on the next scheduled treatment date</td></tr>
<tr><td>Grade 3</td><td>Treatment interruption or permanent discontinuation</td></tr>
<tr><td>Grade 4</td><td>Permanent discontinuation</td></tr>
</table>

	AE Grading/Dose Modification		Treatment of Toxicity
Pneumonia	Any Grade		– Monitor the subject for symptoms and signs of pneumonia or interstitial lung disease (such as new onset of shortness of breath, cough, chest pain, or deterioration of existing symptoms and signs), and use imaging, lung function, and other examinations to evaluate the subject. – The initial examination may include clinical evaluation, arterial oxygen saturation, laboratory tests, and high-resolution CT scan.
	Grade 1	Dose modification is not required. However, dose interruption may be considered based on clinical needs and during the diagnostic examination for other causes.	For Grade 1: – Monitor symptoms and signs, arterial oxygen saturation for 2-4 days – Perform other laboratory tests as clinically indicated – Consider consultations of respiratory and infectious disease specialists
	Grade 2	Treatment interruption • If aggravated, treat as Grade 3 or 4 • If improved to Grade 0-1 or baseline, continue the treatment on the next scheduled treatment date	For Grade 2 – Monitor symptoms and signs daily and consider hospitalization – Discuss with the sponsor's medical department and consider giving systemic glucocorticoid therapy – Perform imaging examination again as clinically indicated – If no improvement is seen within 3-5 days, other examinations should be considered and the dose of glucocorticoid should be increased – If no improvement is seen within 3-5 days, a stronger immunosuppressant (such as infliximab) should be considered – Once improved, taper the dose of glucocorticoid within ≥ 4 weeks, and consider prophylactic antibiotics – Consider consultations of respiratory and infectious disease specialists

	AE Grading/Dose Modification		Treatment of Toxicity
	Grade 3 or Grade 4	Permanent discontinuation	For Grade 3-4 – Discuss with the sponsor's medical department – Consider consultations of respiratory and infectious disease specialists – Hospitalization – Supportive care (oxygen inhalation, etc.) – Systemic glucocorticoid therapy based on experience – If no improvement is seen within 3-5 days, other tests should be considered and other immunosuppressive agents (for example, infliximab) should be given – Once improved, taper the dose of glucocorticoid within ≥ 4 weeks, and consider prophylactic antibiotics
Diarrhea or enterocolitis	Any Grade		– Monitor for symptoms and signs that may be related to diarrhea/entercolitis (abdominal pain, intestinal cramps, change of bowel habit, melena, mucous stools, bloody stools, muscle resistance, etc.) – Subjects should be comprehensively evaluated to rule out any alternative causes (such as progressive disease, infections, etc.) – If no alternative cause is determined, glucocorticoid therapy should also be considered for low-grade events to prevent the event from progressing to higher grades – Use painkillers with caution (as they can mask the symptoms of perforation and peritonitis)
	Grade 1	Dose modification is not required.	For Grade 1 – Monitor the deterioration of symptoms closely – Consider symptomatic treatment, including rehydration, electrolyte replacement, diet adjustment, and administration of loperamide

	AE Grading/Dose Modification		Treatment of Toxicity
	Grade 2 or Grade 3	Treatment interruption • If aggravated, treat as Grade 3 or 4 • If improved to Grade 0-1 or baseline, continue the treatment on the next scheduled treatment date	For Grade 2-3 – Consider symptomatic treatment, including rehydration, electrolyte replacement, diet adjustments, and loperamide and/or budesonide – If the event persists (> 3-5 days) or worsens, consider systemic glucocorticoid therapy – If the event does not resolve or worsens within 3-5 days, other tests should be considered and the dose of glucocorticoid should be increased – If the event does not resolve or worsens within 3-5 days, other tests should be considered and other immunosuppressive agents (e.g., infliximab) should be given – Once improved, taper the dose of glucocorticoid within ≥ 4 weeks, and consider prophylactic antibiotics
	Grade 4	Permanent discontinuation	For Grade 4 – Monitor the frequency and volume of bowel movements and maintain hydration – If applicable, conduct emergency gastrointestinal consultation and lower gastrointestinal endoscopy and imaging examinations to confirm whether there is intestinal perforation – Systemic glucocorticoid therapy based on experience – If no improvement is seen within 3-5 days, consider increasing the dose of systemic glucocorticoid – If no improvement is seen within 3-5 days, other immunosuppressive agents should be considered (such as infliximab, but infliximab must not be used in cases of perforation or septicemia) – Once improved, taper the dose of glucocorticoid within ≥ 4 weeks, and consider prophylactic antibiotics

	AE Grading/Dose Modification		Treatment of Toxicity
Hepatitis (ALT, AST, or TBIL increased)	Any Grade		– Pay close attention to the symptoms and signs of hepatitis (such as jaundice, brown urine, nausea, vomiting, decreased appetite, pain in the liver area, bleeding tendency, etc.) – Monitor and evaluate hepatic function – Assess alternative causes (e.g., viral hepatitis, progressive disease, and combination medications) – The guidelines on dose modifications and handling of toxicities recommended in this table are applicable to subjects with normal baseline ALT, AST, and TBIL. For subjects with baseline ALT, AST, or TBIL > ULN, treatment should be interrupted when ALT, AST, or TBIL increases by ≥ 50% for < 7 days. For subjects with baseline ALT, AST, or TBIL > ULN, treatment should be permanently discontinued when ALT, AST, or TBIL increases by ≥ 50% for ≥ 7 days. The investigator shall handle the toxicities based on the actual situation.
	Grade 1	Dose modification is not required.	For Grade 1 – Continue hepatic function monitoring according to the protocol
	Grade 2	Treatment interruption • If aggravated, treat as Grade 3 or 4 • If improved to Grade 0-1 or baseline, continue the treatment on the next scheduled treatment date	For Grade 2 – If the event does not recover to Grade ≤ 1 within 3-4 days, discuss with the sponsor's medical department – In the case of ALT, AST, or TBIL increased, retest the hepatic function within 3-4 days and increase the monitoring frequency – If the event persists (> 3-5 days) or worsens, consider systemic glucocorticoid therapy – If no improvement is seen within 3-5 days, other examinations should be considered and the dose of glucocorticoid should be increased – If no improvement is seen within 3-5 days, a stronger immunosuppressant (e.g., mycophenolate mofetil) should be considered – Once improved, taper the dose of glucocorticoid within ≥ 4 weeks, and consider prophylactic antibiotics

	AE Grading/Dose Modification		Treatment of Toxicity
	Grade 3 or Grade 4	Permanent discontinuation	For Grade 3-4 – Discuss with the sponsor's medical department – Systemic glucocorticoid therapy based on experience – If no improvement is seen within 3-5 days, a stronger immunosuppressant (e.g., mycophenolate mofetil) should be considered – If no further improvement is seen within 3-5 days, consider other immunosuppressive therapies according to local guidelines – If applicable, perform gastroenterological consultations, abdominal examinations, and imaging examinations – Once improved, taper the dose of glucocorticoid within ≥ 4 weeks, and consider prophylactic antibiotics
Dermatitis	Any Grade		– Monitor the signs and symptoms of dermatitis, such as rash, effusion, hypopigmentation, solar sensitiveness, and pruritus – If there is any bulla formed, contact the sponsor's medical department – Consider consultation with the Department of Dermatology – Perform skin biopsy if necessary
	Grade 1	Dose modification is not required	For Grade 1 – Consider symptomatic treatment including oral antipruritics (such as diphenhydramine or hydroxyzine) and local treatment (such as urea cream or topical glucocorticoid cream)
	Grade 2	Dose modification is not required. • For refractory Grade 2 events (> 1-2 weeks), treatment should be interrupted until the event	For Grade 2: – Consider symptomatic treatment including oral antipruritics and topical treatment – Consider moderate-strength topical corticosteroids – If there is no improvement or deterioration within 3-5 days, discuss with the sponsor's medical department and consider systemic glucocorticoid therapy

	AE Grading/Dose Modification		Treatment of Toxicity
		recovers to Grade 0-1 or baseline, and continue the treatment on the next scheduled treatment date	– Consider consultation with the Department of Dermatology – If the event persists for > 1-2 weeks or recurs, consider skin biopsy – Once improved, taper the dose of glucocorticoid within ≥ 4 weeks, and consider prophylactic antibiotics
	Grade 3	Treatment interruption • If aggravated, treat it as Grade 4 • If the Grade 3 rash does not recover to Grade 0-1 or baseline within 30 days, the treatment will be permanently discontinued	For Grade 3-4: – Discuss with the sponsor's medical department – Consider hospitalization – Monitor the extent of the rash [Nine-Section method] – Consider consultation with the Department of Dermatology – If clinically feasible, consider skin biopsy (preferably more than once) – Systemic glucocorticoid therapy based on experience – If no improvement is seen within 3-5 days, other examinations should be considered and the dose of glucocorticoid should be increased – Once improved, taper the dose of glucocorticoid within ≥ 4 weeks, and consider prophylactic antibiotics
	Grade 4	Permanent discontinuation	
Hypopituitarism	All grades		– Monitor the subject's symptoms and signs of endocrine diseases, including faintness, fatigue, somnolence, nausea, vomiting, afraid of cold, abnormal defecation habits, behavior changes, mental status changes, hypotension, hypoglycemia, dizziness, headache, impaired vision, low libido in men, menstrual disorder, etc. – Subjects should be comprehensively evaluated to rule out any alternative causes (such as progressive disease, brain metastasis, infections, etc.) – Monitor and assess pituitary function tests: TSH, FT3, FT4, adrenocorticotropic hormone (ACTH), cortisol, luteinizing hormone, follicle stimulating hormone, growth hormone, prolactin, Na^+, blood glucose, estradiol, testosterone, and other laboratory tests suspected to be related to endocrine disorders, as well as functional tests if necessary (including ACTH stimulation test and hypoglycemia stimulation test)

	AE Grading/Dose Modification		Treatment of Toxicity
			– Consider a pituitary MRI scan – Consider endocrinology consultation – Consider sending a blood sample for appropriate autoimmune antibody testing
	Grade 1	Dose modification is not required.	For Grade 1: – Appropriately monitor the subject's pituitary function tests – Comprehensively evaluate the subject to rule out any alternative causes – Consider endocrinology consultation as clinically indicated
	Grade 2	Treatment interruption • If it aggravates to Grade 3-4, the treatment is permanently discontinued • If it recovers to Grade 0-1 or baseline, continue the treatment on the next scheduled treatment date	For Grade 2-4: – Discuss with the sponsor's medical department – Consider endocrinology consultation – Consider hospitalization when necessary – Assess the endocrine function and consider a pituitary MRI scan as clinically indicated – Start hormone replacement therapy as needed (cortisone replacement therapy should start one week before levothyroxine treatment) – Start immunosuppressive therapy based on experience, and consider systemic glucocorticoid therapy – Once improved, taper the dose of glucocorticoid within ≥ 4 weeks (cortisone used for replacement therapy is adjusted according to the recovery of endocrine function, and subjects who cannot recover must receive long-term medication), and consider prophylactic antibiotics during the dose tapering to prevent opportunistic infections
	Grade 3 or Grade 4	Permanent discontinuation	

	AE Grading/Dose Modification		Treatment of Toxicity
Adrenal cortical hypofunction	Any Grade		– Monitor the subject's symptoms and signs of endocrine diseases, including fatigue, pigmentation, appetite absent, hypotension, and faintness – Comprehensively evaluate the subject to rule out any alternative causes – Monitor and evaluate adrenal cortex function: cortisol, ACTH, serum natrium, blood potassium, blood glucose, and other endocrine laboratory indicators suspected to be related to adrenocortical function, and perform ACTH stimulation test if necessary – Provide immunosuppressive therapy if necessary – Provide hormone replacement therapy (cortisone) if necessary – Consider endocrinology consultation – Consider sending a blood sample for appropriate autoimmune antibody testing
	Grade 1	Dose modification is not required.	For Grade 1 – Appropriately monitor the subject's adrenal gland function tests – Consider endocrinology consultation as clinically indicated
	Grade 2	Treatment interruption • If it worsens to Grade 3 or 4, the treatment is permanently discontinued • If it recovers to Grade 0-1 or baseline, continue the treatment on the next scheduled treatment date	For Grade 2 – Discuss with the sponsor's medical department – Assess adrenal cortex function and start hormone replacement therapy as needed

	AE Grading/Dose Modification		Treatment of Toxicity
	Grade 3 or Grade 4	Permanent discontinuation	For Grade 3-4: – Discuss with the sponsor's medical department – Consider endocrinology consultation – Consider systemic glucocorticoid therapy – For adrenal crisis, severe dehydration, hypotension, or shock, intravenous corticosteroids with mineralocorticoid activity should be started immediately – Once improved, taper the dose of glucocorticoid within ≥ 4 weeks (cortisone used for replacement therapy is adjusted according to the recovery of endocrine function, and subjects who cannot recover must receive long-term medication), and consider prophylactic antibiotics during the dose tapering to prevent opportunistic infections
Hyperthyroidism/hypothyroidism	Any Grade		– Monitor the subject's symptoms and signs related to abnormal thyroid function, such as hyperthyroidism related (palpitations, sweating, increased food intake and bowel movements, weight loss, etc.) and hypothyroidism related (weakness generalized, fatigue, afraid of cold, decreased memory, constipation etc.) – Comprehensively evaluate the subject to rule out any alternative causes – Monitor and evaluate thyroid function – Consider endocrinology consultation – Consider sending a blood sample for thyroid autoantibody test (anti-thyroglobulin antibody, anti-thyroid peroxidase antibody, and thyroid stimulating hormone receptor antibody)
	Grade 1 or Grade 2	Dose modification is not required	For Grade 1-2: – Regularly monitor thyroid function and thyroid autoantibodies – Provide levothyroxine replacement therapy or hyperthyroidism drug therapy if necessary

	AE Grading/Dose Modification		Treatment of Toxicity
	Grade 3 or Grade 4	Hyperthyroidism • Permanent discontinuation Hypothyroidism • Dose modification is not required.	For Grade 3-4: – Discuss with the sponsor's medical department – Monitor thyroid function and thyroid autoantibodies – Consider endocrinology consultation *Hyperthyroidism* – Hyperthyroidism drug therapy – For tachycardia, consider beta blockers *Hypothyroidism* – Consider levothyroxine replacement therapy
Type 1 diabetes	Any Grade		– Pay close attention to relevant symptoms and signs, such as polyuria, polydipsia, polyphagia, fatigue, faintness, weight loss, etc. – Comprehensively evaluate the subject to rule out any alternative causes – Monitor and evaluate pancreatic islet function: blood glucose, insulin, C-peptide, pancreatic β-cell autoantibodies, blood ketones, and other endocrine laboratory indicators suspected to be related to type 1 diabetes
	Grade 1 or Grade 2	Dose modification is not required	For Grade 1-2 – Monitor and evaluate pancreatic islet function – Provide insulin treatment if necessary
	Grade 3	Treatment interruption – Resume after blood glucose is controlled	For Grade 3-4 – Contact the sponsor's medical department – Monitor and evaluate pancreatic islet function – Consider endocrinology consultation – Prescribe insulin for blood glucose control, and adjust the dose of insulin based on the control of blood glucose
	Grade 4	Permanent discontinuation	

	AE Grading/Dose Modification		Treatment of Toxicity
			– Subjects who develop ketoacidosis must be admitted to the hospital for insulin, fluid replacement, and alkali supplement
Renal insufficiency (blood creatinine increased)	Any Grade		– Pay close attention to relevant symptoms and signs (such as decreased urine output, darkened urine, anemia, fatigue and weakness, weight loss, etc.) – Comprehensively evaluate the subject to rule out any alternative causes – Monitor and evaluate renal function tests – Consider nephrology consultation – Consider a kidney biopsy to differentiate the cause of inflammation from non-inflammation when necessary
	Grade 1	Dose modification is not required	For Grade 1 – Monitor the creatinine level once a week – If it recovers to the baseline level, resume routine creatinine monitoring according to the study protocol
	Grade 2 or Grade 3	Treatment interruption • If it improves to Grade 0-1, continue the treatment on the next scheduled treatment date • If it lasts > 7 days or aggravates, treat it as Grade 4	For Grade 2-3 – Discuss with the sponsor's medical department – Monitor the creatinine level every 2-3 days – Systemic glucocorticoid therapy based on experience – If it improves to Grade 1, taper the dose of glucocorticoid for ≥ 4 weeks, and consider prophylactic antibiotics to prevent opportunistic infections – Consider kidney biopsy – Conduct nephrology consultation
	Grade 4	Permanent discontinuation	For Grade 4 – Discuss with the sponsor's medical department – Monitor the creatinine level once a day

	AE Grading/Dose Modification		Treatment of Toxicity
			– Systemic glucocorticoid therapy based on experience – If it improves to Grade 1, taper the dose of glucocorticoid for ≥ 4 weeks, and consider prophylactic antibiotics to prevent opportunistic infections – Consult the nephrologists – Consider kidney biopsy
Immune-related neurotoxicity (except for myasthenia gravis and Guillain-Barre syndrome)	Any Grade		– Monitor the subject's systemic symptoms (headache, nausea, dizziness, behavior changes, or faintness) – Subjects should be comprehensively evaluated to rule out any alternative causes (such as progressive disease, infections, metabolic syndrome, medications, etc.) – Consider appropriate diagnostic tests (e.g., electromyography and nerve conduction studies) – If applicable, conduct symptomatic treatment and neurology consultation
	Grade 1	Dose modification is not required.	– Closely follow up the symptoms and signs
	Grade 2	Treatment interruption • If it improves to Grade 0-1, continue the treatment on the next scheduled treatment date • If it aggravates, treat it as Grade 3	For Grade 2-4 – Discuss with the sponsor's medical department – Consider neurology consultation – Consider hospitalization when necessary – Appropriate drugs (e.g., gabapentin, duloxetine, etc.) may be used to treat sensory neuropathy and neuropathic pain – Consider systemic glucocorticoid therapy – If no improvement is seen within 3-5 days, other tests should be considered and other immunosuppressive agents should be given (e.g., intravenous immunoglobulin G (IVIgG)) – Once stable, taper the dose of glucocorticoid within ≥ 4 weeks
	Grade 3	Permanent discontinuation	
	Grade 4		

	AE Grading/Dose Modification		Treatment of Toxicity
Immune-related peripheral nerve syndromes, such as Guillain-Barre syndrome and myasthenia gravis	Any Grade		– Pay close attention to relevant symptoms and signs (myasthenia gravis: sore and discomfort of the eyes or limbs, blurred vision, fatigue, etc., characterized as milder in the morning and severer in the evening; Guillain-Barre syndrome: sudden severe radicular pain, flaccid paralysis of the limbs, abnormalities in limbs such as numbness, tingling, burning, etc.) – Subjects may experience unpredictable acute decompensation, leading to severe illness or death, and thus timely diagnosis of immune-related peripheral nerve syndrome is very important. Pay special attention to certain symptoms or signs that may indicate serious consequences, such as evident dysphagia, rapidly progressing faintness, respiratory insufficiency, or autonomic instability – Neural and electrophysiological examinations should be performed to rule out any alternative causes (such as progressive disease, infection, metabolic syndrome, and drug effects). It is worth noting that the disease itself and treatment of cancer subjects can affect neurological function. Diagnosis of immune-related peripheral nerve syndrome is difficult, and neurology consultation should be actively carried out. – For Guillain-Barre syndrome, plasma exchange or IVIgG therapy should be considered (glucocorticoid therapy is usually ineffective)
	Grade 1	Dose modification is not required.	For Grade 1 – Discuss with the study physician – Monitor the symptoms and signs – Consider neurology consultation
	Grade 2	Treatment interruption • If it improves to Grade 0-1, continue the treatment on the next scheduled treatment date • If it aggravates, treat it as Grade 3-4	For Grade 2-4 – Discuss with the sponsor's medical department – Monitor the symptoms and signs – Perform neurology consultation – Consider hospitalization when necessary

	AE Grading/Dose Modification		Treatment of Toxicity
	Grade 3 or Grade 4	Permanent discontinuation	– Appropriate drugs (e.g., gabapentin, duloxetine, etc.) may be used to treat sensory neuropathy/neuropathic pain *Myasthenia gravis* – Glucocorticoids may be used to treat myasthenia gravis (glucocorticoid therapy (especially at high doses) may cause short-term deterioration of myasthenia and thus should be used under the supervision of a neurologist) – Subjects who cannot tolerate glucocorticoids may be treated with plasma exchange or IVIgG
			– In the case of myasthenia gravis-like neurotoxicity, consider giving acetylcholinesterase inhibitors in addition to glucocorticoids *Guillain-Barre syndrome* – For Guillain-Barre syndrome, plasma exchange or IVIgG therapy should be considered (glucocorticoid therapy is usually ineffective)