Title: A single-arm, open-label, multi-center, phase II clinical study of anti-PD-1 antibody SHR-1210 in recurrent/metastatic nasopharyngeal carcinoma subjects who have received previous at least two lines of chemotherapy

Clinical trial registration number: NCT03558191

Date: 10 Aug., 2020

A SINGLE-ARM, OPEN-LABEL, MULTI-CENTER, PHASE II CLINICAL STUDY OF ANTI-PD-1 ANTIBODY SHR-1210 IN RECURRENT/METASTATIC NASOPHARYNGEAL CARCINOMA PATIENTS WHO HAVE RECEIVED PREVIOUS AT LEAST TWO LINES OF CHEMOTHERAPY

Protocol No.: SHR-1210-II-209
Study Phase: II
Compound Code: SHR-1210
Compound Name: Camrelizumab
Medical Director: Qing Yang
Leading Center of Clinical Study: Sun Yat-sen University Cancer Center
Principal Investigator: Prof. Li Zhang

Version No.: 3.0
Version Date: 10 Aug., 2020

Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.
No. 7 Kunlunshan Road, Lianyungang Economic and Technological Development Zone, Jiangsu 222047, China

Sponsor's Signature Page

I have read and confirmed this clinical study protocol (protocol no.: SHR-1210-II-209, version no.: 3.0, version date: 10 Aug., 2020). 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.

Qing Yang		
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 investigational drug; I have read the materials of preclinical studies of the investigational drug and the protocol for this clinical study (protocol no.: SHR-1210-II-209, version no.: 3.0, version date: 10 Aug., 2020). 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 investigational drug; I have read the materials of preclinical studies of the investigational drug and the protocol for this clinical study (protocol no.: SHR-1210-II-209, version no.: 3.0, version date: 10 Aug., 2020). 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 single-arm, open-label, multi-center, phase II clinical study of anti-PD-1 antibody SHR-1210 in recurrent/metastatic nasopharyngeal carcinoma subjects who have received previous at least two lines of chemotherapy
Protocol No.	SHR-1210-II-209
Version No.	3.0
Sponsor	Jiangsu Hengrui Pharmaceuticals Co., Ltd.
Principal Investigator	Prof. Li Zhang
Participating Study Centers	Sun Yat-Sen University Cancer Center and 7 other domestic centers
Study Objectives	Primary objective: To evaluate the objective response rate (ORR) of SHR-1210 in subjects with recurrent/metastatic nasopharyngeal carcinoma (NPC) who have failed at least two lines of chemotherapy by independent review committee (IRC). Secondary objective: To evaluate the efficacy and safety of SHR-1210 in subjects with recurrent/metastatic nasopharyngeal carcinoma who have failed at least two lines of chemotherapy. Exploratory objectives: (1) To evaluate the relationship between PD-L1 expression in tumor tissues and efficacy of SHR-1210. (2) To evaluate the relationship between immune-related cells (T lymphocytes, B lymphocytes, macrophages, dendritic cells, and bone marrow-derived suppressor cells) in tumor microenvironment and efficacy of SHR-1210. (3) To evaluate the immunogenicity of SHR-1210 in subjects with recurrent/metastatic nasopharyngeal carcinoma, and to investigate the correlation between immunogenicity and efficacy/safety.
Study Endpoints	Primary endpoint IRC-assessed ORR of SHR-1210 in subjects with recurrent/metastatic nasopharyngeal carcinoma who have failed at least two lines of chemotherapy Secondary endpoints Efficacy • Investigator-assessed ORR • Duration of response (DoR); • Disease control rate (DCR); • Time to response (TTR); • Progression-free survival (PFS) as per RECIST 1.1; • Overall survival (OS)

	Safety • Incidences and severity of adverse events (AEs) and serious adverse events (SAEs), laboratory abnormalities, as per NCI-CTCAE V4.03 • Incidence of treatment interruption and discontinuation due to AEs Exploratory endpoints • To evaluate the relationship between PD-L1 expression and efficacy of SHR-1210 • To evaluate the relationship between immune-related cells (T lymphocytes, B lymphocytes, macrophages, dendritic cells, and bone marrow-derived suppressor cells) in tumor microenvironment and efficacy of SHR-1210 • To investigate the anti-SHR-1210 antibodies (ADAs) in subjects after injection of SHR-1210
Study Population	Patients with recurrent/metastatic nasopharyngeal carcinoma who have failed at least two lines of chemotherapy
Study Design	This is a single-arm, open-label, multi-center phase II clinical study to investigate and evaluate the efficacy and safety of anti-PD-1 antibody SHR-1210 in subjects with recurrent/metastatic nasopharyngeal carcinoma who have failed at least two lines of chemotherapy.
Investigational Drug	Recombinant humanized anti-PD-1 monoclonal antibody for injection (SHR-1210) (Manufacturer: Suzhou Suncadia Biopharmaceuticals Co., Ltd.)
Method of Administration	SHR-1210: intravenous infusion (premedication not required) at a fixed dose of 200 mg over 30 min (no less than 20 min and no more than 60 min, including flushing), on D1 and D15 of each 4-week cycle. The treatment will continue until the occurrence of confirmed PD, intolerable toxicity, voluntary withdrawal by the subject, or treatment discontinuation determined by the investigator.
Inclusion Criteria	Patients must meet all of the following criteria to be eligible for this study: 1. Aged 18-75 years (inclusive), male or female; 2. Moderately differentiated or undifferentiated locally recurrent/metastatic nasopharyngeal carcinoma (WHO type II-III) in histopathology; 3. Patients in clinical stage IVb who have previously failed first-line platinum-based monotherapy or combined chemotherapy and second-line monotherapy or combined chemotherapy [the 2017 Chinese Staging of Nasopharyngeal Carcinoma (the 2008 Revised Expert Consensus on Staging of Nasopharyngeal Carcinoma)]. Definition of treatment failure: ongoing chemotherapy after recurrence/metastasis or progressive disease after treatment; concurrent chemoradiotherapy, with progression within 6 months, may be counted as first-line treatment; all modifications of dosing regimen due to drug intolerance are not considered treatment failure; 4. ECOG PS: 0-1; 5. Life expectancy ≥ 12 weeks;

	6. At least one measurable lesion per the Response Evaluation Criteria in Solid Tumors (RECIST 1.1), and the measurable lesions should not have been treated locally such as with radiotherapy; 7. Fresh tissues or tissue samples for biomarker (such as PD-L1) analysis must be provided. Fresh tissues are preferred. Archival samples of 5-8 paraffin embedded sections with a thickness of 3-5 μm are also acceptable when a fresh biopsy is not accessible; 8. Major organ functions must meet the following requirements (no blood components or cell growth factors are allowed to be used within 2 weeks before the start of study treatment): a. Absolute neutrophil count (ANC) ≥ 1.5×10^9/L b. Platelets ≥ 90×10^9/L; c. Hemoglobin ≥ 9 g/dL; d. Serum albumin ≥ 2.8 g/dL; e. Bilirubin ≤ 1.5 × ULN, ALT and AST ≤ 1.5 × ULN; for liver metastasis, ALT and AST ≤ 5 × ULN; f. Creatinine clearance ≥ 50 mL/min (Cockcroft-Gault); 9. Female patients of childbearing potential must have a negative pregnancy test result within 72 h prior to the start of study treatment, and be willing to take at least 2 highly effective contraceptive measures during the study and within 60 days after the last dose of the investigational drug (around 5 half-lives of the drug + menstrual cycle). Male patients with partners of childbearing potential must take at least two contraceptive measures during the study and within 120 days after the last dose of the investigational drug (around 5 half-lives of the drug + sperm production cycle); 10. Patients must participate voluntarily, sign the informed consent form, have good compliance, and cooperate with follow-up visits.
Exclusion Criteria	Patients meeting any of the following are ineligible to participate in this study 1. Patients with any active autoimmune disease or history of autoimmune disease (e.g., interstitial pneumonia, uveitis, enteritis, hepatitis, hypophysitis, vasculitis, myocarditis, nephritis, hyperthyroidism, and hypothyroidism (may be enrolled after effective hormone replacement therapy); patients with vitiligo or asthma in childhood that has completely relieved and requires no intervention in adulthood and patients requiring medical interventions with bronchodilators may be enrolled); 2. Patients with clinically symptomatic metastases to central nervous system (e.g., cerebral edema) requiring hormone interventions, or progression of brain metastasis. Patients who have received treatment for metastasis to brain or meninges may be enrolled if MRI and clinically stable (without the need of > 10 mg/day prednisone or equivalent); 3. Patients with other malignant tumors previously or currently (except for malignant tumors that have been cured with a cancer-free survival of more than 5 years, e.g., basal cell carcinoma, cervical carcinoma *in situ*, and papillary thyroid carcinoma); 4. Uncontrolled cardiac symptoms or disease, such as (1) > NYHA Class II cardiac failure, (2) unstable angina, (3) myocardial infarction within one year, and (4) clinically significant supraventricular or ventricular arrhythmias requiring clinical interventions;

	5. Patients requiring systemic treatment with corticosteroids (> 10 mg/day of prednisone or equivalent) or other immunosuppressive medications within 14 days prior to administration of the investigational drug. In the absence of active autoimmune disease, inhaled or topical use of corticosteroids and an equivalent dose to > 10 mg/day of prednisone for adrenal hormone replacement are permitted; 6. Patients who have received chemotherapy or targeted therapy less than 4 weeks prior to the start of study treatment; palliative radiotherapy for symptomatic control is permitted but must be completed at least 2 weeks prior to the start of study treatment, and no additional radiotherapy should be scheduled for the same lesion; patients with an AE induced by past treatment that has not recovered to CTCAE Grade ≤ 1 (except for alopecia and sequelae of relevant neurotoxicity of previous platinum therapy); 7. Patients with active infection or unexplained pyrexia > 38.5 ℃ at screening or prior to the first dose (those with tumor-induced pyrexia may be enrolled as per the judgment of the investigator); 8. Patients with congenital or acquired immune deficiency (such as HIV infection), active hepatitis B (HBV-DNA ≥ 10^4 copies/mL or 2000 IU/mL) or hepatitis C (positive anti-HCV antibodies, and HCV RNA titer higher than the lower limit of detection of the analytical method); 9. Patients who have participated in other clinical studies within 1 month before the start of study treatment or are participating in other clinical studies; 10. Patients who have received live vaccines within 4 weeks before the start of study treatment; 11. Patients who have used systemic antibiotics within 1 month before the start of study treatment; 12. Patients who have received previous treatment with other anti-PD-1 antibodies or other checkpoint monoclonal antibodies, including immunotherapy targeting CTLA-4 and PD-L1; 13. Patients with known history of psychotropic substance abuse, alcoholism, or drug abuse; 14. Pregnant or lactating women; 15. Other factors, as determined by the investigator, which may result in premature discontinuation of treatment. For example, other serious medical conditions (including mental illnesses) requiring concomitant treatment, serious laboratory abnormalities, family or social factors, and other conditions that may affect patients' safety or the collection of study data.
Immunogenicity Study	Collection time for immunogenicity blood samples: Once before the administration on C1D1, C2D1, C3D1, and C4D1, once every 3 cycles after Cycle 4, and once before withdrawal from study.

Study Withdrawal Criteria	A subject must withdraw from/discontinue the treatment when any one of the following conditions occurs: 1. The subjects withdraw informed consent and request to withdraw from the study; 2. Imaging examinations show progressive disease; As per RECIST v1.1, a confirmation is required 4-6 weeks after the first occurrence of progressive disease (except those with rapid progression or significant clinical progression); Subjects with re-confirmed progressive disease may continue the treatment if clinically stable (as assessed by the investigator) until further radiographic progression; Definition of stable clinical symptoms: a. no clinically significant symptoms or changes in laboratory tests; b. no changes in the performance status score (deterioration); and c. non-tumor rapid progression and tumor progression not involving major organs/sites (e.g., spinal cord compression); 3. Cumulative use of SHR-1210 for 2 years; 4. Subjects with intolerable toxicity; 5. Subjects with poor compliance; 6. Subjects lost to follow-up or becoming pregnant; 7. Other reasons for which the investigator considers a withdrawal necessary.
Study Treatment Discontinuation Criteria	The discontinuation criteria of this study include but are not limited to the following: 1. Discovery of unexpected, important, or unacceptable risks to the subjects; 2. Major errors in the protocol found during the implementation of the study; 3. Ineffective investigational drug/treatment, or meaninglessness to continue the study; 4. Discontinuation as determined by the sponsor due to reasons such as severe delay in enrollment or frequent protocol deviations.
Sample Size Determination	Efficacy hypothesis According to study SHR-1210-101, the ORR of all dose groups (n = 93) of NPC subjects was 29.0%, and the ORR of the 200 mg dose group (n = 68) was 36.8%. In the subgroup analysis, the ORR of all dose groups (n = 58) of subjects who had failed at least two lines of chemotherapy was 27.6%, and the ORR of the 200 mg dose group (n = 43) was 37.2%. Also, referring to the efficacy results of similar drugs, the intended study for registration will use a dose of 200 mg, and a conservative estimate of the upper limit of ORR is set at 26%. Pembrolizumab for the treatment of head and neck squamous cell carcinoma was approved by the FDA with an ORR of 16% in a single-arm study. Therefore, it is stipulated that the lower limit of the 95% confidence interval for the ORR for this study should not be less than 15%. Sample size calculation According to the above efficacy hypothesis (ORR = 26%), with a one-sided alpha = 0.025, enrolling 139 subjects can achieve a power of 90% that the lower limit of 95% confidence interval for ORR is not less than 15%. In order to ensure that the 139 subjects are included in the evaluation, assuming a dropout rate of 10%, 155 subjects should be enrolled.

Statistical Methods	Categorical data will be descriptively summarized using statistics including the frequency (n) and percentage (%), as well as the 95% confidence interval of the overall percentage when necessary. Continuous data will be descriptively summarized using statistics including the mean, standard deviation (SD), median, minimum, and maximum. For time to event data, the Kaplan-Meier method will be used to estimate the survival function, plot the survival curve, and estimate the median survival time, and its 95% confidence interval will be calculated. Safety analysis: For safety analysis, the following data (but not limited to) will be descriptively summarized based on the safety set. Summary of adverse events (of all causes and treatment-related); Incidence and severity of adverse events (of all causes and treatment-related); Summary of serious adverse events; Causality analysis of adverse events; Laboratory measurements, vital signs, ECG, and their changes from baseline; Number and rate of laboratory measurements, vital signs, and ECG data "changed from normal to abnormal" or "exacerbated abnormally" after the trial. Efficacy analysis: The objective response rate (ORR) and disease control rate (DCR) and their 95% confidence intervals (Clopper-Pearson method) will be estimated. The Kaplan-Meier method will be used to estimate the PFS, DoR, and OS and the corresponding 95% confidence intervals will be calculated (Brookmeyer-Crowley method based on log-log transformation, with the standard error calculated using the Greenwood formula). TTR will be described using mean, standard deviation, median, maximum, and minimum. Other analyses: Subject disposition and populations; Subjects' basic characteristics (including demographics, life history, medical history, and medication history); Discontinuations; Exploratory analysis, etc.
Study Time	Estimated enrollment of the first subject: Jun. 2018 Estimated enrollment of the last subject: Mar. 2019 Estimated study completion: one year after the last subject's first dose, the subjects undergoing treatment will enter the expansion study of SHR-1210 for continued treatment and observation.

SCHEDULE OF ACTIVITIES

	Screening Period (-28 days)		Treatment Period				End of Treatment/ Withdrawal (+ 3 days)	After End of Treatment	
			C1		C2+				
Visit Window	**D-28 to D-1**	**D-7 to D-1**	**D1**	**D15 ±3**	**D1 ±3**	**D15 ±3**		**30 days (±7 days) after the last dose[23]**	**60 and 90 days (±7 days) after the last dose[23]**
Signing of Informed Consent Form[1]	√								
Verification of Eligibility		√							
Demographics	√								
Medical History[2]	√								
ECOG PS[3]		√			√		√		
Vital Signs[4]		√		√	√	√	√		
Physical Examination[5]		√		√	√	√	√		
Blood Routine[6]		√		√	√	√	√	√	
Urinalysis[7]		√			√		√		
Fecal Occult Blood[8]		√			√				
Blood Biochemistry[9]		√		√	√	√	√	√	
Thyroid Function[10]		√			√		√	√	
Coagulation Function[11]		√							

	Screening Period (-28 days)		Treatment Period				End of Treatment/ Withdrawal (+ 3 days)	After End of Treatment	
			C1		C2+				
Visit Window	**D-28 to D-1**	**D-7 to D-1**	**D1**	**D15 ±3**	**D1 ±3**	**D15 ±3**		**30 days (±7 days) after the last dose[23]**	**60 and 90 days (±7 days) after the last dose[23]**
EBV-DNA Test[12]	√				√		√		
Liver-Related Serology[13]	√								
ECG[14]		√		√	√	√	√		
Echocardiography[15]		√							
Pregnancy Test[16]		√					√		
Tumor Imaging Evaluation[17]	√		√						
Administration of SHR-1210[18]			√	√	√	√			
Adverse Events[19]	√	√	√	√	√	√	√	√	√
Concomitant Medication[20]	√	√	√	√	√	√	√	√	√
Immunogenicity[21]			√		√		√		
Tumor Tissue[22]	√								
Survival Follow-Up[24]								√	√

Note: Other than the examinations and time points listed in the table, the investigator may add visits and other investigations at any time when needed. Results should be documented in the "Unscheduled Examinations" section of eCRF.

[1] An informed consent form signed by the subject or legal representative must be first obtained before starting screening.

[2] Medical history: including tumor history (diagnosis, surgery, radiotherapy, chemotherapy history, as well as use of antibiotics within 3 months before enrollment) and history of other concurrent diseases.

[3] ECOG PS: within 7 days before the first dose, before each administration of each cycle (do not need to be tested for the first dose if completed within 7 days before the first dose at screening), and at the end of treatment/upon withdrawal.

[4] Vital signs: blood pressure, pulse, body temperature, and respiratory rate; within 7 days before the first dose, before each administration of each cycle (do not need to be tested for the first dose if completed within 7 days before the first dose at screening), and at the end of treatment/upon withdrawal.

[5] Physical examination: within 7 days before the first dose and at the end of treatment/upon withdrawal, a comprehensive physical examination (including head and face, skin, lymph nodes, neck, eyes, ears, nose and throat, mouth, respiratory system, cardiovascular system, abdomen, reproductive and urinary system, musculoskeletal system, nervous system and mental state) is performed; before each administration of each cycle (do not need to be tested for the first dose if completed within 7 days before the first dose at screening); symptom-directed physical examination can be performed if clinically indicated.

[6] Blood routine: RBC count, hemoglobin, platelet count, WBC count, neutrophil count, lymphocyte count; within 7 days before the first dose, before each administration of each cycle (do not need to be tested for the first dose if completed within 7 days before the first dose at screening), at the end of treatment/upon withdrawal, and 30 days after the last dose.

[7] Urinalysis: WBC, RBC, and urine protein. Within 7 days before the first dose, before administration on D1 of each cycle, and at the end of treatment/upon withdrawal. In case of a urine protein ≥ 2+, a 24-h urine protein test (quantitative) should be added.

[8] Fecal occult blood: within 7 days before the first dose, on D1 of each cycle.

[9] Blood biochemistry: ALT, AST, GGT, total bilirubin, direct bilirubin, AKP, blood urea nitrogen (preferred) or urea, total protein, albumin, creatinine, blood glucose, lactate dehydrogenase, K^+, Na^+, Ca^{2+}, Mg^{2+}, and Cl^-. Within 7 days before the first dose, before each administration of each cycle (do not need to be tested for the first dose if completed within 7 days before the first dose at screening), at the end of treatment/upon withdrawal, and 30 days after the last dose.

[10] Thyroid function: TSH, FT3, FT4. Within 7 days before the first dose, before administration on D1 of each cycle, at the end of treatment/upon withdrawal, and 30 days after the last dose.

[11] Coagulation function: APTT, PT, FIB, INR. Within 7 days before the first dose.

[12] EBV-DNA test: at screening, before administration on D1 of every 2 cycles, and at the end of treatment/upon withdrawal.

[13] Serology: HBsAg (if positive, HBV-DNA test required), HBsAb, HBeAg, HBeAb, HBcAb, HCV-Ab (if positive, HCV-RNA test required), and HIV-Ab. Within 14 days before the first dose.

[14] ECG: within 7 days before the first dose, before each administration of each cycle (do not need to be tested for the first dose if completed within 7 days before the first dose at screening), and at the end of treatment/upon withdrawal.

[15] Echocardiography: within 7 days before the first dose; performed when clinically indicated.

[16] Pregnancy test: for women of childbearing potential only. Within 72 h before the first dose, and at the end of treatment/upon withdrawal.

[17] Tumor imaging evaluation: CT or MRI of the nasopharynx, neck, chest and abdomen (including pelvic cavity); scanning with contrast is preferred if not contraindicated. Brain MRI is required when brain metastasis is suspected and confirmed (if MRI is contraindicated, CT can be used instead). Bone scan is performed only when clinically indicated and must be performed within 42 days before the first dose.

- ✓ At screening, tumor evaluations up to 4 weeks before administration and before informed consent may be used as long as they meet the RECIST 1.1.
- ✓ During the treatment period, imaging examinations should be performed every 8 weeks on the same sites as those of the baseline examinations. Examinations should also be performed as appropriate when new lesions are suspected. Tumor examinations should be performed in time when subjects withdraw from the study due to any reasons (±4 weeks, but not required to be repeated if the time from the previous examination is no more than 4 weeks). Imaging conditions should be the same as those at baseline (including slice thickness and contrast agent).
- ✓ The time window for imaging examination is ±7 days. Unscheduled imaging examination may be performed if PD is suspected (for example, worsening of symptoms). Subjects who discontinue treatment for reasons other than imaging-confirmed PD must also undergo a tumor evaluation every 8 weeks until documentation of confirmed PD, start of a new anti-tumor treatment, lost to follow-up, or death. Subjects showing CR or PR for the first time (whichever comes first) should undergo imaging evaluation for confirmation at least 4 weeks (28 days) later, with a time window of + 7 days.

[18] Administration of SHR-1210: once every 2 weeks. Administrations are given on D1 and D15 of each 4-week cycle.

[19] Adverse events: As per NCI CTCAE V4.03, any adverse event that occurs during the safety information collection period should be observed and documented. The safety information collection period is from the signing of the informed consent form to the start of a new anti-tumor treatment beyond or within 90 days after the last dose. After the safety information collection period, only treatment-related adverse events are collected. All investigational drug-related adverse events should be followed up until resolved, returning to baseline or ≤ Grade 1, reaching a steady state, obtaining a reasonable explanation, lost to follow-up, or death.

[20] Concomitant medications: Concomitant medications from 30 days before the first dose to 90 days after the last dose will be documented; only concomitant medications for treatment-related AEs will be documented from 30 days after the end of treatment. (The use of all antibiotics within 3 months before administration and during study treatment period will be documented)

[21] Immunogenicity blood sampling: once before the administration on C1D1, C2D1, C3D1, and C4D1; once every 3 cycles after Cycle 4; and once before withdrawal from study.

[22] Tumor tissue: collected before enrollment; fresh biopsy is preferred, otherwise collect archived tumor tissue specimens.

[23] 90 days after the last dose: Subjects must return to the study center for a follow-up 30 days after the last dose, and the safety information can be obtained via telephone calls on D60 and D90 after the last dose (including AE outcome, new SAEs and AEs of special interest); the time window is ±7 days.

[24] Survival follow-up: starting from the last dose, once per month, with a time window of ±7 days.

ABBREVIATIONS

Abbreviation	Full Name
12-Lead ECG	12-Lead electrocardiogram
Ab	Antibody
ADA	Anti-drug antibody
ADL	Activities of daily living
AE	Adverse event
AKP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
ASR	Age-standardized rate
AST	Aspartate aminotransferase
BOR	Best overall response
BUN	Blood urea nitrogen
Ca^{2+}	Calcium
CFDA	China Food and Drug Administration (now NMPA)
CI	Confidence interval
CIOMS	The Council for International Organizations of Medical Sciences
Cl^-	Blood chlorine
Cr	Creatinine
CR	Complete response
CRA	Clinical research associate
CRC	Clinical research coordinator
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T lymphocyte antigen 4
D	Day
DC	Dendritic cell
DCR	Disease control rate
DNA	Deoxyribonucleic acid
DoR	Duration of response
EBV	Epstein-Barr virus
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form

Abbreviation	Full Name
EDC	Electronic data capture system
FAS	Full analysis set
FT3	Free triiodothyronine
FT4	Free thyroxine
GCP	Good Clinical Practice
GGT	γ-Glutamyl transpeptidase
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
hr	Hour
Hb	Hemoglobin
HBV	Hepatitis B virus
HCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator's brochure
IEC	Independent ethics committee
INR	International normalized ratio
irAE	Immune-related adverse event
IRB	Institutional review board
IRC	Independent review committee
iRECIST	Modified RECIST 1.1 for immune based therapeutics
IV	Intravenously
IU	International unit
K^+	Serum potassium
kg	Kilogram
LSLV	Last subject last visit
Mg^{2+}	Magnesium
mg	Milligram
min	Minute
mL	Milliliter
mm	Millimeter
MRI	Magnetic resonance imaging
Na^+	Plasma sodium
NCI	National Cancer Institute
NPC	Nasopharyngeal carcinoma

Abbreviation	Full Name
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PI	Principal investigator
PLT	Blood platelet
PR	Partial response
PT	Prothrombin time
QA	Quality assurance
QC	Quality control
RBC	Red blood cell count
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
sec	Second
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation/stable disease
SDV	Source data verification
SOP	Standard operating procedure
T1DM	Type 1 diabetes mellitus
TSH	Thyroid-stimulating hormone
TTR	Time to response
ULN	Upper limit of normal
W	Week
WBC	White blood cell count
WHO	World Health Organization
μg	Microgram
μm	Micrometer

1 INTRODUCTION: BACKGROUND AND SCIENTIFIC RATIONALE

1.1 Background

Nasopharyngeal carcinoma is a relatively rare tumor worldwide, but has a higher incidence in Asian populations, with an age-standardized rate (ASR) of 2.3 in men and 0.9 in women. Especially in Southeast Asian populations, the ASR is 6.4 in men and 2.4 in women [(1)]. Nasopharyngeal carcinoma in China also shows a significant geographical pattern. It ranks first in the incidence of head and neck tumors and has a significant geographical pattern, mainly concentrated in southern China, with an annual incidence of up to 80/100,000 [(2)].

Radiotherapy is the primary treatment of early-stage nasopharyngeal carcinoma. The 5-year overall survival rates of stage I and IIA subjects are 90% and 84%, respectively. However, approximately 20-37% of subjects will have local recurrence or distant metastasis. Cisplatin-based combination chemotherapy is the first-line treatment regimen for such subjects. The response rate can reach 50-80%, the median time to progression is 5-11 months, and the median overall survival is around 12-20 months. For subjects who have failed first-line chemotherapy, there is no particularly effective treatment option. Although second-line chemotherapy drugs such as gemcitabine and capecitabine show some efficacy, the median survival of subjects has not been significantly improved, at only 7-11 months [(3)]. For distant metastases of nasopharyngeal carcinoma, on the one hand, it is difficult to achieve a durable response. Most subjects will have progressive disease within a short period of time after the initial response, and the recurrence site will generally be resistant to the second chemotherapy. On the other hand, it may result in mucositis, vomiting, myelosuppression, and other toxic side effects, which are intolerable for most subjects. Therefore, there is an urgent need to develop new drugs for the treatment of recurrent/metastatic nasopharyngeal carcinoma.

1.2 Scientific Rationale

1.2.1 Study rationale

Approximately 90% of nasopharyngeal carcinoma is histopathologically classified as undifferentiated or poorly differentiated squamous cell carcinoma, characterized by EBV virus infection and a large number of immune infiltration (mainly by T cells) in the primary tumor. Activated immune cells are very important in the removal of residual tumor foci. According to reports, local infiltration of T lymphocytes is a prognostic factor for nasopharyngeal carcinoma. However, there are many immunosuppressive mechanisms in the tumor microenvironment that can inactivate T cells, leading to an increased risk of recurrence [(4)].

The programmed cell death protein-1 (PD-1) pathway is one of the most critical checkpoint pathways responsible for regulating tumor-induced immunosuppression. PD-1 is a protein receptor expressed on the surface of T cells discovered in 1992 and is involved in the process of cell apoptosis. PD-1 is a member of the CD28 family and has a 23% consistency in amino acid sequence with cytotoxic T lymphocyte antigen 4 (CTLA-4). However, its expression is different from CTLA. It is primarily expressed by activated T cells, B cells, and myeloid cells. PD-1 has two ligands, PD-L1 and PD-L2. PD-L1 is primarily expressed on T cells, B cells, macrophages, and dendritic cells (DCs), and is up-regulated on activated cells. PD-L1 is expressed in approximately 89% of EBV-related nasopharyngeal carcinoma. The binding of PD-1 and PD-L1 can activate the PD-1 pathway and lead to T cell failure, ultimately resulting in a poor prognosis of this type of nasopharyngeal carcinoma [1]. Therefore, immune checkpoint inhibitors against PD-1/PD-L1 may be a new method of treating nasopharyngeal carcinoma.

KEYNOTE-028 is a phase Ib clinical trial of Merck's pembrolizumab (MK-3475) conducted in subjects with advanced solid tumors with positive PD-L1 expression. Among the 27 evaluable subjects with nasopharyngeal carcinoma, 7 showed PR and 14 showed SD, with a best ORR of 25.9% (95% CI: 11.1-46.3) (5). Bristol Myers Squibb announced the results of the cohort of 24 subjects with advanced nasopharyngeal carcinoma in the study of nivolumab in the treatment of virus-related tumors (CheckMate-358) (6) at the 2017 ASCO. The ORR was 20.8% and the DCR was 45.8%. Currently, Bristol Myers Squibb's nivolumab (PD-1 inhibitor), Novartis' PDR001 (PD-1 inhibitor), Merck's pembrolizumab (MK-3475) (PD-1 inhibitor), and Merck/Pfizer's avelumab (anti-PD-L1 antibody) are currently under phase II clinical trials for the treatment of recurrent/metastatic nasopharyngeal carcinoma subjects who failed platinum-based treatments. The preliminary efficacy of PD-1/PD-L1 immune checkpoint inhibitors in the treatment of nasopharyngeal carcinoma further suggests that it may become a new generation of drugs for the treatment of nasopharyngeal carcinoma.

1.2.2 Rationale for drug development

Jiangsu Hengrui Pharmaceuticals Co., Ltd. used PD-1 as a target and recombinant PD-1 protein as an immunogen to obtain a series of PD-1 antibodies in mice. Through a large number of *in vitro* binding assays, *in vitro* ligand blocking assays, T cell proliferation assays, animal experiments, and antibody druggability assessments, an antibody prototype was selected. Then, a humanized design of the murine antibody prototype was carried out through computer simulations, resulting in several humanized anti-PD-1 monoclonal antibodies. Finally, SHR-1210, the one with the highest activity among those antibodies, was selected for further development. Phase I clinical trials have been conducted by Hengrui in Australia and China since 2015. Several clinical studies are currently underway.

1.2.2.1 Preclinical study results of SHR-1210

1.2.2.1.1 Drug name and physicochemical properties

[Generic Name]: SHR-1210 Injection

[English Name]: SHR-1210 Injection

[Molecular Weight]: approx. 146.3 kDa

1.2.2.1.2 Pharmacology and mechanism of action

Humanized anti-PD-1 monoclonal antibody can specifically bind to PD-1, blocking the interaction between PD-1 and its ligands, and restore T cell immune response to tumor cells.

1.2.2.1.3 Pharmacodynamic studies

(1) Antibody affinity

Results from affinity assays involving SHR-1210 and human, monkey, and murine PD-1 antigens showed that the affinity of SHR-1210 for human and monkey PD-1 antigens were 6.9 nM and 4.1 nM, respectively. No binding was detected with murine PD-1 antigens. See Table 1 for details.

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

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

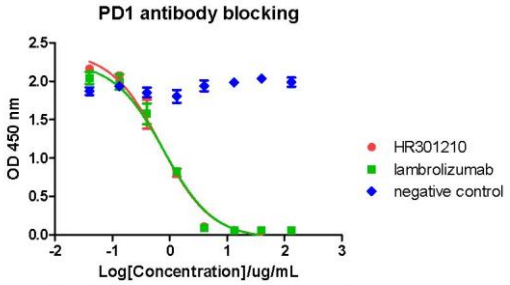
Results from the binding affinity assay showed that the binding affinity of SHR-1210 to human PD-1 antigen was 3.0 nM, similar to nivolumab and MK3475. See Table 2 for details.

Table 2. Binding affinity of SHR-1210, nivolumab, and MK3475 to PD-1 antigen

Antibody	Antigen	Affinity (nM)
SHR-1210	Human PD-1 antigen	3.0
Nivolumab	Human PD-1 antigen	4.0
MK3475	Human PD-1 antigen	3.2

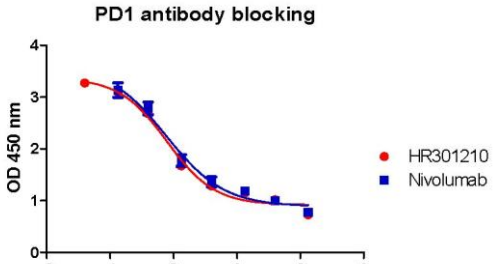
(2) Inhibition of PD-1/PD-L1 binding by SHR-1210

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



	HR301210	lambrolizumab
IC50	0.7007	0.7864

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



	HR301210	Nivolumab
IC50	0.7913	0.7745

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

1.2.2.1.4 Toxicology studies

In a pre-clinical single dose toxicity study in cynomolgus monkeys, 8 monkeys (half male and half female) were randomized to 2 groups. The animals in Group 2 were given an intravenous injection of SHR-1210 once every other day at doses of 200, 400, and 800 mg/kg, respectively, in a dose-escalation manner. No changes in clinical symptoms, body weight, food intake, and coagulation related to SHR-1210 were observed. Lymphocytes decreased for both sexes at doses ≥ 200 mg/kg. Serum globulin increased and albumin decreased at doses ≥ 400 mg/kg. Since the magnitude of these changes was small, they were not considered harmful effects. The maximum tolerated dose (MTD) of SHR-1210 was ≥ 800 mg/kg.

In a completed preclinical repeated dose toxicity study in cynomolgus monkeys, consecutively intravenous administration of SHR-1210 at 20, 50, and 100 mg/kg/dose once a week for 4 weeks (5 doses in total) was well-tolerated in animals of both sexes. Clinical symptoms, including injection site irritation, or changes in body weight, food intake, body temperature, ECG, blood pressure, heart rate, and respiratory measurements related to SHR-1210 were not observed. No changes in B and T cell differentiation, cytokines, immunoglobulins, and complements were seen. No changes in organ weight, gross lesions, or histopathological changes associated with SHR-1210 were found.

1.2.2.1.5 Pharmacokinetic study

The PK parameters obtained after a single intravenous infusion of SHR-1210 in cynomolgus monkeys are shown in Table 3.

Table 3. PK parameters of SHR-1210 after a single intravenous infusion at different doses in cynomolgus monkeys

Dose (mg/kg)	Gender	$T_{1/2}$ (hr)	T_{max} (hr)	C_{max} (μg/mL)	AUC_{last} (hr*μg/mL)	V_z (mL/kg)	Cl (mL/hr/kg)	MRT_{last} (hr)
1	Female	76.06 ±32.93	0.83 ±0.29	31.16 ±11.25	1716.12 ±453	54.09 ±14.85	0.57 ±0.17	80.95 ±18.58
	Male	91.72 ±25.26	0.83 ±0.29	35.96 ±13.09	2359.7 ±684.07	55.15 ±20.51	0.37 ±0.06	102.23 ±38.56
	Overall	83.89 ±27.62	0.83 ±0.26	33.56 ±11.23	2037.91 ±627.32	54.62 ±16.02	0.47 ±0.15	91.59 ±29.47
3	Female	92.95 ±22.60	0.83 ±0.29	81.09 ±12.66	6896.79 ±1673.36	40.75 ±12.66	0.44 ±0.11	120.92 ±49.96
	Male	113.54 ±8.26	1.67 ±0.58	71.65 ±10.85	6380.25 ±2062.85	47.05 ±27.05	0.47 ±0.12	127.10 ±59.25
	Overall	103.25 ±18.94	1.25 ±0.61	76.37 ±11.74	6638.51 ±1703.60	43.91 ±19.21	0.46 ±0.11	125.01 ±49.13
10	Female	169.70 ±38.96	2.17 ±1.76	217.46 ± 20.22	31357.28 ±9338.28	41.25 ±25.76	0.33 ±0.1	179.68 ±73.6
	Male	128.94 ±35.93	0.67 ±0.29	251.88 ±6.49	26779.98 ±7205.43	30.9 ±30.2	0.31 ±0.05	113.25 ±44.39
	Overall	149.32 ±40.28	1.42 ±1.39	234.67 ±23.15	29068.63 ±7869.83	36.07 ±25.34	0.32 ±0.07	146.46 ±65.42

1.2.2.2 Clinical study results

Camrelizumab for injection (Hengrui R&D code: SHR-1210) is a humanized PD-1 antibody independently developed and manufactured by Jiangsu Hengrui Pharmaceuticals Co., Ltd. On 26 Jan., 2016, it was approved for clinical studies (2016L01455). As of 15 Oct., 2017, a total of 14 clinical studies in the population with advanced malignant tumors have been carried out: including 4 on advanced solid tumors, 3 on non-small cell lung cancer (NSCLC), 1 on hepatocellular carcinoma (HCC), 1 on esophageal cancer (ESC), 1 on melanoma, 1 on nasopharyngeal carcinoma (NPC), 1 on primary liver cancer (PLC), 1 on classic Hodgkin's lymphoma (cHL), and 1 on extranodal NK/T cell lymphoma. In 2016, three phase I clinical trials, i.e., SHR-1210-101, SHR-1210-102, and SHR-1210-103, were carried out in China. As of 28 Feb., 2018, the three phase I clinical trials in China had enrolled 123, 36, and 98 subjects, respectively. All studies have not been completed and are still in progress.

Study SHR-1210-101 mainly included subjects with advanced solid tumors who have failed standard treatment or lack effective treatment methods. The study consisted of three stages, including bridge escalation, PK expansion, and clinical expansion. In Stage I, a "3 + 3" dose escalation mode was adopted, as well as three groups of calculated doses of SHR-1210 (1 mg/kg, 3 mg/kg, and 10 mg/kg) and one group of fixed-dose bridge escalation (200 mg/time, equivalent to the calculated dose of 3 mg/kg). In Stage II, dose expansion was carried out based on the preliminary safety data from Stage I, with 8-12 subjects with solid tumor enrolled in each dose group. Stage III was clinical expansion and set a fixed-dose group (200 mg/time). Subjects with nasopharyngeal carcinoma and lung cancer with brain metastases were included.

- Pharmacokinetic results from SHR-1210-101:

The pharmacokinetic results of the 49 subjects in the first two stages of study SHR-1210-101 showed that, after a single intravenous infusion of SHR-1210 in subjects with advanced solid tumors, most PK parameters of the dose groups (1 mg/kg, 3 mg/kg, 200 mg/time, and 10 mg/kg) showed a proportional dose-response relationship. Among them, C_{max} was linearly associated to dose administered, and the *in vivo* exposure ($AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$) increased with the increase of dose administered. Meanwhile, the half-life ($t_{1/2}$) of SHR-1210 also increased with the increase of dose, while the clearance rates (CLs) decreased slowly with the increase of dose. This may be due to the characteristic that endocytosis of macromolecular drugs after binding to the receptor results in receptor-mediated drug metabolism (TMDD). After repeated administrations, the serum SHR-1210 of each dose group generally reached a steady state after 3-5 treatment cycles. The maximum and minimum concentrations of SHR-1210 increased with the increase of dose. There was generally no accumulation at steady state. During repeated administrations, the overall receptor occupancy rate of each dose group of SHR-1210 maintained at approximately 75%. PD-1 receptor occupancy is the theoretical prerequisite for the anti-tumor effect of SHR-1210. This result suggested that SHR-1210 can fully occupy the PD-1 receptor and block the PD-1/PD-L1 signaling pathway at an administration frequency of Q2W.

- Efficacy results from study SHR-1210-101 in patients with advanced nasopharyngeal carcinoma

In study SHR-1210-101, a total of 31 subjects with nasopharyngeal carcinoma were enrolled in the first two stages. Stage III was clinical expansion and set a fixed-dose group (200 mg/time), with 62 subjects with nasopharyngeal carcinoma enrolled. A total of 93 subjects with advanced nasopharyngeal carcinoma were enrolled in the study. All subjects were in advanced stage, more than 90% of whom were in clinical stage IV; 55% of subjects had ≥ 3 organs with metastasis; more than 65% of subjects had received at least two lines of chemotherapy, of which 28% had received second-line chemotherapy and 34% had received third-line and above chemotherapy. The overall objective response rate was 29.0% (1 CR + 26 PR), and the disease control rate was 58.1% (1 CR + 26 PR + 27 SD). Especially in the 68 subjects of the 200 mg dose group, the objective response rate was 36.8% (1 CR + 24 PR), and the disease control rate was 64.7% (1 CR + 24 PR + 19 SD). In the subgroup analysis, 58 subjects had previously received at least two lines of chemotherapy, the objective response rate was 27.6% (1 CR + 15 PR), and the disease control rate was 51.7% (1 CR + 15 PR + 14 SD). A total of 43 subjects in the 200 mg dose group who had previously received at least two lines of chemotherapy had an objective response rate of 37.2% (1 CR + 15 PR) and a disease control rate of 58.1% (1 CR + 15 PR + 9 SD).

- Safety summary of the 3 phase I studies of SHR-1210

After camrelizumab was approved for clinical trials in 2016, 3 phase I clinical studies have been carried out in China, all of which are studies on the safety and tolerability in subjects with advanced solid tumors. As of 28 Feb., 2018, a total of 258 subjects with advanced solid tumors who failed standard treatment were included in the 3 phase I studies. The subjects included 190 males and 68 females, with an age of 51.2 ±11.22 year s old; height of 166.68 ±7.568 cm; weight of 61.00 ±11.130 kg; BMI of 21.92 ±3.461 kg/m ^{2}; 130 subjects (50.4%) had a baseline ECOG PS of 0 and 127 subjects (49.2%) had a baseline ECOG PS of 1; 257 subjects (99.6%) had a history of systemic chemotherapy; 155 subjects (60.1%) had a history of radiotherapy.

Among the 258 subjects, the adverse events related to camrelizumab for injection were mostly of CTCAE Grade 1-2, and the incidence of ≥ Grade 3 treatment-related adverse events was 31.8%; common treatment-related adverse events mainly included skin and subcutaneous tissue disorders: cutaneous capillary endothelial proliferation (81.8%), pruritis (22.1%), rash (16.3%); general disorders: asthenia (37.6%), fever (20.9%); blood and lymphatic system disorder: anemia (27.5%); investigations: aspartate aminotransferase increased (21.7%), alanine aminotransferase increased (18.6%), conjugated bilirubin increased (16.7%), white blood cell count decreased (14.7%), blood sodium decreased (14.3%), blood bilirubin increased (12.0%); renal and urinary disorder: proteinuria (22.1%); endocrine disorder: hypothyroidism (19.8%); metabolism and nutrition disorder: hypoproteinemia (19.4%); respiratory, thoracic, and mediastinal disorders: cough (19.0%); gastrointestinal disorders: diarrhea (11.2%), nausea (10.5%); infections and infestations: upper respiratory tract infection (10.1%). Common hematological adverse events included anemia. Common non-hematological adverse events included cutaneous capillary endothelial proliferation, ALT and AST increased, fever, rash, and blood bilirubin increased. Cutaneous capillary endothelial proliferation was a unique skin reaction of SHR-1210 with a high incidence. However, it was mild, clinically tolerable, and disappeared after dose discontinuation.

1.2.3 Basis of administration regimen

Preliminary data analysis of the safety and efficacy of SHR-1210 at the calculated doses (1-10 mg/kg) and fixed dose (200 mg) showed no DLT in all dose groups in this study, but similar type and frequency of adverse events between groups. The proportions (the number of subjects with adverse events / the total number of subjects) of subjects who had at least one ≥ Grade 3 treatment-related adverse events in the 1 mg/kg, 3 mg/kg, 200 mg/time, and 10 mg/kg dose groups were 0/13, 2/12, 3/12, and 1/12, (0%, 16.7%, 25%, and 8.3% in percentage), respectively. There was no significant correlation between different doses and safety. The proportions (the number of subjects with response/the total number of subjects) of subjects who achieved disease response in the 1 mg/kg, 3 mg/kg, 200 mg/time, and 10 mg/kg dose groups were 0/13, 2/12, 4/12, and 4/12, respectively; the ORRs were 0%, 16.7%, 33.3%, and 33.3%, respectively. In this

study, the pharmacokinetic behavior of SHR-1210 in subjects with advanced solid tumors at the fixed dose of 200 mg/time and the calculated dose of 3 mg/kg after single and multiple administrations was generally the same. The serum concentration-time curves were similar, with the exposure distribution mostly overlapping and all within the exposure range of the study dose (1-10 mg/kg). The steady-state concentrations and accumulation ratios of SHR-1210 in serum after multiple administrations at the fixed dose of 200 mg/time and the calculated dose of 3 mg/kg were similar, and the levels of receptor occupancy at steady-state minimum concentration were close and maintained at a high level (with arithmetic averages of 77% and 75%, respectively). Combined with preliminary data on pharmacokinetics, pharmacodynamics, safety, and efficacy, doses of 200 mg or 3 mg/kg are recommended for later clinical studies. In addition, preliminary data analysis of the safety and efficacy of SHR-1210 showed that the range of acceptable therapeutic doses of SHR-1210 was large; the safety and efficacy of the fixed dose of 200 mg were both within the range of the calculated doses (1-10 mg/kg). It was inferred that the difference in subjects' weight did not have a significant impact on the coefficient of variation of the final *in vivo* drug exposure (PK). In summary, considering the convenience of clinical operations, a fixed dose of 200 mg can be used instead of the calculated dose of 3 mg/kg.

1.3 Potential Risks and Benefits

1.3.1 Known potential risks

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

As of 28 Feb., 2018, the summary results of the safety data of the 3 phase I clinical studies suggested that: the adverse events related to camrelizumab for injection were mostly of CTCAE Grade 1-2, and the incidence of ≥ Grade 3 treatment-related adverse events was 31.8%; common treatment-related adverse events mainly included skin and subcutaneous tissue disorders: cutaneous capillary endothelial proliferation (81.8%), pruritis (22.1%), rash (16.3%); general disorders: asthenia (37.6%), fever (20.9%); blood and lymphatic system disorder: anemia (27.5%); investigations: aspartate aminotransferase increased (21.7%), alanine aminotransferase increased (18.6%), conjugated bilirubin increased (16.7%), white blood cell count decreased (14.7%), blood sodium decreased (14.3%), blood bilirubin increased (12.0%); renal and urinary disorder: proteinuria (22.1%); endocrine disorder: hypothyroidism (19.8%); metabolism and nutrition disorder: hypoproteinemia (19.4%); respiratory, thoracic, and mediastinal disorders: cough (19.0%); gastrointestinal disorders: diarrhea (11.2%), nausea (10.5%); infections and infestations: upper respiratory tract infection (10.1%).

The above data showed that camrelizumab treatment may cause immune-related adverse events such as abnormal liver function and abnormal thyroid function. With the use of monotherapy of nivolumab, the incidence of hypothyroidism was 9%. The incidence of aspartate

aminotransferase increased or alanine aminotransferase increased varied across studies, with higher incidences in studies related to malignant melanoma, lung cancer, and Hodgkin's lymphoma, at 16-33%. With the use of pembrolizumab monotherapy, the incidence of hypothyroidism was 8.5% and the incidence in head and neck cancer was 15%. The incidence of aspartate aminotransferase increased or alanine aminotransferase increased varied as reported in different studies. In the studies in malignant melanoma and lung cancer, the incidence was approximately 21-26%. In KETNOTE 021, the incidence of alanine aminotransferase increased was as high as 40%. Thus, in addition to cutaneous capillary endothelial proliferation, common immune-related adverse events of SHR-1210 were similar to those reported of similar products.

Cutaneous capillary endothelial proliferation has been confirmed to be a benign skin reaction. The onset may be related to the inflammatory response of type 2 helper T cells (Th2) and type M2 macrophages in the epidermis and dermis of skin induced by camrelizumab, resulting in massive up-regulation of VEGF-A and excessive proliferation of capillaries. Cutaneous capillary endothelial proliferation in areas prone to rubbing may cause damage and bleeding. Cutaneous capillary endothelial proliferation in exposed areas such as the face also had some impact on the appearance of the subjects. Based on the mechanism of PD-1 monoclonal antibody, adverse reactions in various body systems may occur. Therefore, safety risks exist during the medication. Close follow-up is necessary during the course of the clinical study. Interventions and actions should be adopted in a timely manner.

1.3.2 Known potential benefits

There is currently no standard recommended second-line treatment for advanced recurrent/metastatic nasopharyngeal carcinoma. In study SHR-1210-101, the 93 subjects with advanced nasopharyngeal carcinoma showed gratifying preliminary results. Participating in this study and receiving investigational treatment may benefit subjects with advanced nasopharyngeal carcinoma.

2 OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary objective

- To evaluate the ORR of SHR-1210 in subjects with recurrent/metastatic nasopharyngeal carcinoma who have failed at least two lines of chemotherapy by IRC.

2.1.2 Secondary objective

- To evaluate the efficacy and safety of SHR-1210 in subjects with recurrent/metastatic nasopharyngeal carcinoma who have failed at least two lines of chemotherapy.

2.1.3 Exploratory objectives

- To evaluate the relationship between PD-L1 expression in tumor tissues and efficacy of SHR-1210.
- To evaluate the relationship between immune-related cells (T lymphocytes, B lymphocytes, macrophages, dendritic cells, and bone marrow-derived suppressor cells) in tumor microenvironment and efficacy of SHR-1210.
- To evaluate the immunogenicity of SHR-1210 in subjects with recurrent/metastatic nasopharyngeal carcinoma, and to investigate the correlation between immunogenicity and efficacy/safety.

2.2 Study Endpoints

2.2.1 Primary endpoint

- IRC-assessed ORR of SHR-1210 in subjects with recurrent/metastatic nasopharyngeal carcinoma who have failed at least two lines of chemotherapy

2.2.2 Secondary endpoints

Efficacy

- Investigator-assessed ORR
- Duration of response (DoR);
- Disease control rate (DCR);
- Time to response (TTR);
- Progression-free survival (PFS) as per RECIST 1.1;
- Overall survival (OS)

Safety

- Incidences and severity of adverse events (AEs) and serious adverse events (SAEs), laboratory abnormalities, as per NCI-CTCAE V4.03
- Incidence of treatment interruption and discontinuation due to AEs

2.2.3 Exploratory endpoints

- To evaluate the relationship between PD-L1 expression and efficacy of SHR-1210
- To evaluate the relationship between immune-related cells (T lymphocytes, B lymphocytes, macrophages, dendritic cells, and bone marrow-derived suppressor cells) in tumor microenvironment and efficacy of SHR-1210.
- To investigate the anti-SHR-1210 antibodies (ADAs) in subjects after injection of SHR-1210

3 STUDY DESIGN

3.1 Overview of Study Design

This is a single-arm, open-label, multi-center phase II clinical study to investigate and evaluate the efficacy and safety of anti-PD-1 antibody SHR-1210 in subjects with recurrent/metastatic nasopharyngeal carcinoma who have failed at least two lines of chemotherapy. A total of 155 subjects will be enrolled.

After being fully informed and providing a written informed consent form, eligible subjects will receive SHR-1210 200 mg, IV, q2W, in treatment cycles of 4 weeks. Treatment will continue until the criteria for treatment discontinuation as specified in the protocol are met. After the end of treatment, subjects will continue safety visits and survival follow-ups. Subjects who discontinue the treatment due to reasons other than progressive disease will also be followed for tumor progression after the end of treatment.

After subjects are enrolled in the study, safety follow-up will be conducted before administration of SHR-1210 on D1 and D15 of each treatment cycle. After treatment begins, response will be assessed once every 2 cycles until the end of treatment, withdrawal of informed consent, or death.

3.2 Methods to Reduce Bias

3.2.1 Enrollment/randomization/blinding

This is a single-arm study. Subjects will be allocated sequentially. There are no randomization and blinding processes.

3.2.2 Blinded assessment

Not applicable.

3.2.3 Unblinding

Not applicable.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

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

4.1 Inclusion Criteria

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

1. Aged 18-75 years (inclusive), male or female;
2. Moderately differentiated or undifferentiated locally recurrent/metastatic nasopharyngeal carcinoma (WHO type II-III) in histopathology;
3. Patients in clinical stage IVb who have previously failed first-line platinum-based monotherapy or combined chemotherapy and second-line monotherapy or combined chemotherapy [the 2017 Chinese Staging of Nasopharyngeal Carcinoma (the 2008 Revised Expert Consensus on Staging of Nasopharyngeal Carcinoma), Appendix V]. Definition of treatment failure: ongoing chemotherapy after recurrence/metastasis or progressive disease after treatment; concurrent chemoradiotherapy, with progression within 6 months, may be counted as first-line treatment; all modifications of dosing regimen due to drug intolerance are not considered treatment failure;
4. ECOG PS: 0-1 (refer to Appendix I for ECOG scoring criteria);
5. Life expectancy ≥ 12 weeks;
6. At least one measurable lesion per the Response Evaluation Criteria in Solid Tumors (RECIST 1.1), and the measurable lesions should not have been treated locally such as with radiotherapy;
7. Fresh tissues or tissue samples for biomarker (such as PD-L1) analysis must be provided. Fresh tissues are preferred. Archival samples of 5-8 paraffin embedded sections with a thickness of 3-5 μm are also acceptable when a fresh biopsy is not accessible;
8. Major organ functions must meet the following rules (no blood components or cell growth factors are allowed to be used within 2 weeks before the start of study treatment):
    g. Absolute neutrophil count (ANC) ≥ 1.5×10^9/L
    h. Platelets (PLT) ≥ 90×10^9/L;
    i. Hemoglobin (Hb) ≥ 9 g/dL;
    j. Serum albumin ≥ 2.8 g/dL;
    k. Bilirubin ≤ 1.5 × ULN, ALT and AST ≤ 1.5 ×ULN; for liver metastasis, ALT and AST ≤ 5 × ULN;
    l. Creatinine clearance ≥ 50 mL/min (Cockcroft-Gault, see Appendix II);

9. Female patients of childbearing potential must have a negative pregnancy test result within 72 h prior to the start of study treatment, and be willing to take at least 2 highly effective contraceptive measures during the study and within 60 days after the last dose of the investigational drug (around 5 half-lives of the drug + menstrual cycle). Male patients with partners of childbearing potential must take at least two contraceptive measures during the study and within 120 days after the last dose of the investigational drug (around 5 half-lives of the drug + sperm production cycle);
10. Patients must participate voluntarily, sign the informed consent form, have good compliance, and cooperate with follow-up visits.

4.2 Exclusion Criteria

Patients meeting any of the following criteria will be excluded:

1. Patients with any active autoimmune disease or history of autoimmune disease (e.g., interstitial pneumonia, uveitis, enteritis, hepatitis, hypophysitis, vasculitis, myocarditis, nephritis, hyperthyroidism, and hypothyroidism (may be enrolled after effective hormone replacement therapy); patients with vitiligo or asthma in childhood that has completely relieved and requires no intervention in adulthood and patients requiring medical interventions with bronchodilators may be enrolled);
2. Patients with clinically symptomatic metastases to central nervous system (e.g., cerebral edema) requiring hormone interventions, or progression of brain metastasis. Patients who have received treatment for metastasis to brain or meninges may be enrolled if MRI shows clinical stability (without the need of > 10 mg/day prednisone or equivalent);
3. Patients with other malignant tumors previously or currently (except for malignant tumors that have been cured with a cancer-free survival of more than 5 years, e.g., basal cell carcinoma, cervical carcinoma *in situ*, and papillary thyroid carcinoma);
4. Uncontrolled cardiac symptoms or disease, such as (1) > NYHA Class II cardiac failure, (2) unstable angina, (3) myocardial infarction within the past year, and (4) clinically significant supraventricular or ventricular arrhythmias requiring clinical interventions;
5. Patients requiring systemic treatment with corticosteroids (> 10 mg/day of prednisone or equivalent) or other immunosuppressive medications within 14 days prior to administration of the investigational drug. In the absence of active autoimmune disease, inhaled or topical use of corticosteroids and an equivalent dose to > 10 mg/day of prednisone for adrenal hormone replacement are permitted;

6. Patients who have received chemotherapy or targeted therapy less than 4 weeks prior to the start of study treatment; palliative radiotherapy for symptomatic control is permitted but must be completed at least 2 weeks prior to the start of study treatment, and no additional radiotherapy should be scheduled for the same lesion; patients with an AE induced by past treatment that has not recovered to CTCAE Grade ≤ 1 (except for alopecia and sequelae of relevant neurotoxicity of previous platinum therapy);
7. Patients with active infection or unexplained pyrexia > 38.5 ℃ at screening or prior to the first dose (those with tumor-induced pyrexia may be enrolled as per the judgment of the investigator);
8. Patients with congenital or acquired immune deficiency (such as HIV infection), active hepatitis B (HBV-DNA ≥ 10^4 copies/mL or 2000 IU/mL) or hepatitis C (positive anti-HCV antibodies, and HCV RNA titer higher than the lower limit of detection of the analytical method);
9. Patients who have participated in other clinical studies within 1 month before the start of study treatment or are participating in other clinical studies;
10. Patients who have received live vaccines within 4 weeks before the start of study treatment;
11. Patients who have used systemic antibiotics within 1 month before the start of study treatment;
12. Patients who have received previous treatment with other anti-PD-1 antibodies or other checkpoint monoclonal antibodies, including immunotherapy targeting CTLA-4 and PD-L1;
13. Patients with known history of psychotropic substance abuse, alcoholism, or drug abuse;
14. Pregnant or lactating women;
15. Other factors, as determined by the investigator, which may result in premature discontinuation of treatment. For example, other serious medical conditions (including mental illnesses) requiring concomitant treatment, serious laboratory abnormalities, family or social factors, and other conditions that may affect patients' safety or the collection of study data.

4.3 Withdrawal from Study or Treatment Discontinuation

4.3.1 Study withdrawal criteria

A subject must withdraw from/discontinue the treatment when any one of the following conditions occurs:

1. The subjects withdraw informed consent and request to withdraw from the study;
2. Imaging examinations show progressive disease;

As per RECIST v1.1, the confirmation is required 4-6 weeks after the first documentation of progressive disease (except those with rapid progression or significant clinical progression);

Subjects with re-confirmed progressive disease may continue the treatment if clinically stable (as assessed by the investigator) until further radiographic progression;

Definition of clinically stable: a. no clinically significant symptoms or changes in laboratory tests; b. no changes in the performance status score (deterioration); and c. non-tumor rapid progression and tumor progression not involving major organs/sites (e.g., spinal cord compression);

3. Cumulative use of SHR-1210 for 2 years;
4. Subjects with intolerable toxicity;
5. Subjects with poor compliance;
6. Subjects lost to follow-up or becoming pregnant;
7. Other reasons for which the investigator considers a withdrawal necessary.

4.3.2 Criteria for treatment discontinuation

The termination criteria of this study include but are not limited to the following:

1. Discovery of unexpected, important, or unacceptable risks to the subjects;
2. Major errors in the protocol found during the implementation of the study;
3. Ineffective investigational drug/treatment, or meaninglessness to continue the study;
4. Termination as determined by the sponsor due to reasons such as severe delay in enrollment or frequent protocol deviations.

4.3.3 Procedures for withdrawal or discontinuation

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

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 before withdrawal of informed consent, unless the subject requests a retraction of collected data.

4.4 Termination or Suspension of Study

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

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

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

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

4.5 Definition of End of Study

Two years after the last subject's first dose.

5 INVESTIGATIONAL DRUG

5.1 Overview of Investigational Drug

5.1.1 Access to investigational drug

The investigational drug is supplied by the sponsor, packaged uniformly and certified (see corresponding Certificate of Analysis).

Concomitant medications and preventive medications for adverse events are not investigational drug and are not provided by the sponsor. Such drugs are all marketed products and are purchased and stored by the study center based on the package insert or outlined product properties.

5.1.2 Dosage form, appearance, packaging, and label

SHR-1210 for injection

Manufacturer: Suzhou Suncadia Biopharmaceuticals Co., Ltd.

Dosage form: lyophilized powder

Strength: 200 mg in 20 mL vials.

Batch No.: see label

Route of administration: intravenous infusion

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

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

Label: For illustrative purposes only; refer to the actual product label

For Clinical Study Use Only

SHR-1210 for Injection Strength: 200 mg/vial Dosage Form: Lyophilized Powder Drug No.: ****
Subject ID: _____ Administration Date: DD/MM/YYYY
Study Title: A single-arm, open-label, multi-center, phase II clinical study of anti-PD-1 antibody SHR-1210 in recurrent/metastatic nasopharyngeal carcinoma subjects who have received previous at least two lines of chemotherapy
Study No.: SHR-1210-II-209
Clinical Study Approval No.: 2016L01455
Method of Administration: intravenous infusion Note: Prepare according the requirements of the protocol
Storage: sealed, protected from light, store at 2-8 ℃
Batch No.: Expiry Date: DD/MM/20YY
Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

5.1.3 Storage and stability of investigational drug

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

The investigational drugs should be stored in their original container and match with the labels. For inconsistence of the storage conditions on the label with those in other materials (such as IB), the label should be followed.

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

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

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

5.1.4 Drug preparation

SHR-1210 should be prepared by qualified or experienced study staff, such as physicians, pharmacists, and medical assistants (approved by national authorities or study center operating guidelines) according to the drug preparation manual (drug manual).

Refer to the drug manual of SHR-1210 for blending, concentration (preparation), and administration of the injection. Since this drug does not contain any antimicrobial preservatives or bacteriostatic agents, care must be taken to ensure that the preparations are sterile.

The total storage period (overall duration in the refrigerator and room temperature storage) from the preparation of SHR-1210 to administration should not exceed 24 h. Please refer to the pharmacy manual for details on storage of prepared medication at room temperature/under light and in the refrigerator.

Expired or remaining drug solutions must be disposed.

5.1.5 Administration of investigational drugs

SHR-1210 is an intravenous injection drug that must be administered by qualified or experienced study staff in the outpatient department or ward of the study center. Administration outside the study center is not permitted.

Subjects must complete all clinically required examinations except for tumor evaluations within 72 h before each dose to determine whether continuing the medication is appropriate.

SHR-1210 is administered through intravenous infusion at 200 mg/time over 30 min (no less than 20 min and no more than 60 min, including flushing). Do not administer through intravenous bolus or rapid bolus injection. The intravenous infusion should be performed through a medical infusion bag using an infusion set with an in-line filter (0.2 μM). Do not administer other medications with this infusion line before or after the infusion. Administration will be given on D1 and D15 of each 4-week cycle. The treatment will continue until the occurrence of confirmed PD, intolerable toxicity, voluntary withdrawal by the subject, or treatment discontinuation determined by the investigator.

The drug may be administered within 3 days before or after the scheduled administration day. Administration beyond 3 days after the scheduled administration day will be considered a dose delay. Subsequent administrations will be based on the actual date of the previous dose. All required examinations and evaluations must be completed prior to each dose. The interval between two doses must not be less than 12 days.

Some subjects may have temporary accelerated tumor growth in the first few months after starting immunotherapy, followed by response. Therefore, subjects are allowed to continue the treatment after the first PD.

Accelerated tumor growth may include any of the following:

- Worsening of existing target lesions;
- Worsening of existing non-target lesions;
- Appearance of new lesions.

If a subject develops PD as determined by RECIST v1.1, the investigator may decide whether treatment should be continued based on subject's overall clinical status, including performance status, clinical symptoms, and laboratory test results. Treatment can be continued when the subject is clinically stable, and a tumor evaluation should be performed again 4-6 weeks later. If non-PD is confirmed by both iRECIST and RECIST v1.1, the treatment will be continued, and otherwise, the treatment will be discontinued, unless the investigator believes the subject may continue benefiting from the study; the sponsor must be consulted to allow a subject with confirmed PD to continue the treatment. For subjects who are clinically unstable, treatment should be discontinued after the first PD, and the reevaluation is not required.

- ✓ Definition of clinically stable: No significant deterioration in subject's performance status, and no significant worsening of cancer-related symptoms;
- ✓ No rapid progressive disease;
- ✓ No progressive tumor requiring other urgent medical interventions at important anatomical sites (e.g., spinal cord compression);

In repeated imaging evaluation, PD can be confirmed by the criteria listed below.

	Conditions for Confirming PD (Any of the following conditions)	**Conditions Unable to Confirm PD (Meet all of the following conditions)**
Target Lesion	The absolute value of tumor burden increases by ≥ 5 mm compared to the first episode of PD.	The absolute value of tumor burden increases by < 5 mm compared to the first episode of PD.
Non-Target Lesion	Compared to the first episode of PD, non-target lesion shows clear and continued progression (qualitative).	Compared to the first episode of PD, there is no clear progression (qualitative).
New Lesion	(1) A new lesion occurs compared to the first episode of PD; (2) A new lesion that has appeared before increases in size or other new lesion occurs.	(1) Compared to the first episode of PD, no other new lesion occurs; (2) A new lesion that has appeared before is stable or decreases in size.

For subjects who receive the first PD evaluation, the date of the initial progression assessed by the investigator will be used in all progression-involved statistical analyses, regardless of post-progression treatment/discontinuation.

5.1.6 Dose modification and delay

5.1.6.1 Dose modification

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

Table 4. SHR-1210 dose modifications

Treatment-Related Immune-Related Adverse Events (irAEs)	Severity Grades for Treatment Interruption	Resumption	Discontinuation
Diarrhea/Colitis	2-3	Recovery to Grade 0-1 and corticosteroids reduction to ≤ 10 mg of prednisone or equivalent	Do not resolve within 12 weeks from the last dose, or the dose of corticosteroids cannot be reduced to ≤ 10 mg of prednisone or equivalent within 12 weeks.
	4	Discontinuation	Discontinuation
AST, ALT, or Bilirubin Increased	2	Recovery to Grade 0-1 and corticosteroids reduction to ≤ 10 mg of prednisone or equivalent	Do not resolve within 12 weeks from the last dose.
	3–4	Discontinuation	Discontinuation
Hyperthyroidism	3	Recovery to Grade 0-1 and corticosteroids reduction to ≤ 10 mg of prednisone or equivalent	Do not resolve within 12 weeks from the last dose, or the dose of corticosteroids cannot be reduced to ≤ 10 mg of prednisone or equivalent within 12 weeks.
	4	Discontinuation	Discontinuation
Hypothyroidism		Treatment can be continued after starting thyroxine replacement therapy	Treatment can be continued after starting thyroxine replacement therapy
Pneumonia	2	Recovery to Grade 0-1 and corticosteroids reduction to ≤ 10 mg of prednisone or equivalent	Do not resolve within 12 weeks from the last dose, or the dose of corticosteroids cannot be reduced to ≤ 10 mg of prednisone or equivalent within 12 weeks.
	3–4	Discontinuation	Discontinuation
Immune-Related Hypophysitis	2-3	Recovery to Grade 0-1; SHR-1210 treatment can be continued after starting endocrine replacement therapy	Do not resolve within 12 weeks from the last dose, or the dose of corticosteroids cannot be reduced to ≤ 10 mg of prednisone or equivalent within 12 weeks.
	4	Discontinuation	Discontinuation
Type I Diabetes Mellitus (New Onset) or Hyperglycemia	New type I diabetes mellitus or Grade 3-4 hyperglycemia with evidence of β-cell failure	After clinical and metabolic conditions are stable	Continue SHR-1210 treatment.

Treatment-Related Immune-Related Adverse Events (irAEs)	Severity Grades for Treatment Interruption	Resumption	Discontinuation
Renal Failure or Nephritis	2	Recovery to Grade 0-1 and corticosteroids reduction to ≤ 10 mg of prednisone or equivalent.	Do not resolve within 12 weeks from the last dose, or the dose of corticosteroids cannot be reduced to ≤ 10 mg of prednisone or equivalent within 12 weeks.
	3–4	Discontinuation	Discontinuation
Infusion Reactions	2	Symptoms disappear	Re-administer at 50% of the initial rate after symptoms resolve. Restore the original infusion rate (100%) if no complications occur within 30 minutes. Closely monitor. If the symptoms recur, the administration of the current SHR-1210 dose will be discontinued.
	3–4	Discontinuation	Discontinuation
Other Treatment-Related Adverse Events	3	Recovery to Grade 0-1 and corticosteroids reduction to ≤ 10 mg of prednisone or equivalent.	Do not resolve within 12 weeks from the last dose, or the dose of corticosteroids cannot be reduced to ≤ 10 mg of prednisone or equivalent within 12 weeks.
	4	Discontinuation	Discontinuation

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

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

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

5.1.7 Dose tracking

The study center should prepare the drugs and complete the documentation as per the Pharmacy Manual. The documentation system of the study center should include all relevant or required information with regards to preparation and administration.

5.1.8 Precautions for special drug delivery devices

Not applicable.

5.2 Dosing Regimen

SHR-1210: intravenous infusion (premedication not required) at a fixed dose of 200 mg over 30 min (no less than 20 min and no more than 60 min, including flushing), on D1 and D15 of each 4-week cycle. The treatment will continue until the occurrence of confirmed PD, intolerable toxicity, voluntary withdrawal by the subject, or treatment discontinuation determined by the investigator.

5.3 Drug Management, Dispensation and Retrieval

Designated personnel in GCP pharmacies of the study centers are responsible for the management, dispensation, and retrieval of investigational drugs. The investigator must ensure that all investigational drugs are used by enrolled subjects only and the dose and method of administration are in compliance with the study protocol. Remaining investigational drug SHR-1210 should be returned to the sponsor. Expired or remaining drugs must be disposed as per the standard for medical wastes. The investigational drugs must not be transferred to anyone who is not involved in this study.

The investigational drugs must be stored according to the label. Duplicate drug receipt forms should be signed upon arrival at the study center, one for the study center and one for the sponsor. If there is a need for retrieving remaining drugs and empty boxes at the end of the study, a retrieval form will also be signed by both parties. The dispensation and return of every drug should be immediately documented on designated forms.

The CRA is responsible for monitoring the supply, usage, and storage of the investigational drugs, and the management of remaining drugs.

Used investigational drugs should be disposed by the sponsor after retrieval, or by the study center upon authorization. Before disposal at authorized study centers, the CRA must verify the medication disposal procedures of the centers and ensure that a certificate of disposal can be provided after disposal.

5.3.1 Disposal of investigational drugs

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

5.4 Concomitant Treatment

Concomitant treatment refers to other treatment that is given for the benefit of subjects as determined by the investigator.

All concomitant medications and treatments within 30 days before the start of study treatment and during the study must be documented in the eCRF in strict accordance with the GCP. Antibiotic treatments within 3 months before medication and during the study period must be documented in detail.

Once the study treatment is interrupted, concomitant medications within 90 days after the last dose should be documented. Only concomitant medications for treatment-related AEs should be documented 30 days after the end of treatment.

5.4.1 Other anti-tumor/cancer or study drugs

5.4.1.1 Permitted concomitant medications

Topical use of corticosteroids such as ophthalmic, nasal, intra-articular, and inhaled is permitted.

Subjects should be given optimal supportive care during the treatment. The use of existing hormone replacement therapy and bisphosphonates for bone metastases are permitted.

Palliative treatment of local lesions that may cause significant symptoms is permitted. For example, local radiotherapy or surgery may be considered for bone lesions that cause pain. However, the following criteria must all be met. It is recommended to consult with the sponsor prior to starting palliative treatment.

1. The investigator must assess whether there is PD in subjects who require local treatment due to symptom exacerbations during the study;
2. Subjects with PD must meet the criteria for continuation of treatment beyond progression;
3. The locally treated lesions cannot be the target lesions.

All concomitant medications should be documented in the eCRF. Concomitant medications from 30 days before the first dose to 90 days after the last dose will be documented; only concomitant medications for treatment-related AEs will be documented from 30 days after the end of treatment. Antibiotic use within 3 months before medication and during the study period must be documented in detail.

5.4.1.2 Prohibited concomitant medications

- Anti-tumor systemic chemotherapy and biological therapy;
- Modern TCM preparations approved by CFDA (now NMPA) for anti-cancer treatment (refer to Appendix III);
- Immunotherapy not specified in the protocol;

- Immunomodulators with auxiliary anti-tumor effects, such as thymosin, lentinan, interleukin-12, etc.
- Vaccination of live vaccines within 4 weeks before the first dose and during the study. Live vaccines include, but not limited to, rubeola, epidemic parotitis, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid. Injections of inactivated influenza vaccine for seasonal influenza are permitted, but not live attenuated influenza vaccines for intranasal use;
- Physiological doses of systemic corticosteroids for purposes other than the relief of symptoms due to immunological causes may, after the consultation with the sponsor, be approved (inhaled steroids are permitted as a part of fixed treatment for asthma or chronic obstructive pulmonary disease). Corticosteroids may be used prophylactically to prevent allergic reactions (such as intravenous contrast agent);

5.4.2 Supportive care

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

1. Cutaneous capillary endothelial proliferation

Subjects with cutaneous capillary endothelial proliferation should undergo biopsy and pathological examination whenever possible. Endoscopic and MRI examinations are recommended for subjects with relatively severe or long-lasting cutaneous capillary endothelial proliferation to confirm the involvement of internal organs and/or mucosa. For cutaneous capillary endothelial proliferation that occurs in areas prone to rubbing, surgical resection, laser, freezing or ligation is recommended.

2. Diarrhea/colitis

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

- Subjects with diarrhea/colitis should drink an adequate amount of fluids. Fluids and electrolytes should be administered intravenously if adequate oral intake is not possible. GI consultation and endoscopy should be considered to confirm or rule out colitis for subjects with Grade 2 or greater diarrhea.
- Oral corticosteroids should be prescribed for Grade 2 diarrhea/colitis.
- Subjects with Grade 3 or 4 diarrhea/colitis should be treated with intravenous corticosteroids followed by oral high-dose corticosteroids.
- Corticosteroids should begin to taper after symptoms improve to Grade 1 or lower. Taper will last for no less than 4 weeks.

3. AST, ALT, or bilirubin increased

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

4. Hyperthyroidism/hypothyroidism

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

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

5. Pneumonia

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

6. Immune-related hypophysitis

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

7. Type I diabetes mellitus

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

8. Renal failure or nephritis

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

9. Infusion reactions

Table 5. Classification and clinical treatment recommendations for infusion reactions

CTCAE Grade	Clinical Symptoms	Clinical Management	SHR-1210 Treatment
Grade 1	Mild and transient reactions	Bedside observation and close monitoring until recovery. Pre-administration prophylactics are recommended for subsequent infusions: 50 mg of diphenhydramine or equivalent and/or 325-1000 mg of acetaminophen at least 30 min before SHR-1210 being given.	Continue

CTCAE Grade	Clinical Symptoms	Clinical Management	SHR-1210 Treatment
Grade 2	Moderate reactions requiring treatment or interruption; rapidly resolve after symptomatic treatment (such as antihistamines, non-steroidal antiphlogistics, anesthetics, bronchodilators, intravenous fluids)	Intravenous administration of normal saline, 50 mg of diphenhydramine IV or equivalent and/or 325-1000 mg of acetaminophen; bedside observation and close monitoring until recovery. Corticosteroids or bronchodilators can be considered based on clinical needs; the amount of investigational drug infused should be recorded in the original medical record; pre-administration prophylactics are recommended for subsequent infusions: 50 mg of diphenhydramine or equivalent and/or 325-1000 mg of acetaminophen at least 30 min before SHR-1210 is given. Corticosteroids (equivalent to 25 mg of hydrocortisone) can be used when necessary.	Interruption. Re-administer at 50% of the initial rate after symptoms resolve. Restore the original infusion rate (100%) if no complications occur within 30 minutes. Closely monitor. If the symptoms recur, the administration of the current SHR-1210 dose will be discontinued.
≥ Grade 3	Grade 3: Severe reactions with no rapid resolution after intervention and/or treatment interruption; symptom recurrence after resolution; sequelae requiring hospitalization. Grade 4: life-threatening	Immediately discontinue SHR-1210 infusion; Administer normal saline by intravenous drip. • Bronchodilators are recommended: subcutaneous injection of 0.2-1 mg of 1:1000 adrenaline solution or slow intravenous infusion of 0.1-0.25 mg of 1:10,000 adrenaline solution, and/or 50 mg of diphenhydramine + 100 mg of methylprednisolone or equivalent by intravenous injection when necessary; • Based on the guidelines for anaphylaxis of the study center; Bedside observation and close monitoring until recovery.	Discontinuation

6 STUDY PROCEDURES

Before the study commences, the subjects must read and sign the current informed consent form approved by the ethics committee (EC). All examinations and study procedures will be carried out according to the schedule of activities, and will not be affected by the duration of drug interruption. However, it is allowed to change within the window period of test items due to holidays, weekends or other administrative reasons.

6.1 Screening

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

Unless otherwise stated, the following screening procedures should be completed within 28 days before the start of study treatment.

- Signing the informed consent form;
- Collecting demographics: gender, date of birth, ethnicity, height, and weight.
- Tumor diagnosis: site of primary tumor, the date of pathological diagnosis, pathological staging, and the location of the metastatic lesion.
- History of cancer treatment
  - ✓ Cancer surgery history: name of surgery, date of surgery, postoperative TNM staging, and date of postoperative recurrence;
  - ✓ History of radiotherapy: site, dose, and start and end dates.
  - ✓ History of neoadjuvant chemotherapy: chemotherapy regimen, cycles, and start and end dates;
  - ✓ History of adjuvant chemotherapy: chemotherapy regimen, cycles, and start and end dates;
  - ✓ Rescue treatment: regimen, cycles, start and end dates, best overall response, time to tumor progression, and presence of changes in treatment due to tumor progression;
  - ✓ History of concurrent diseases, past medications, and medication allergies;
  - ✓ Serology (completed within 14 days before the first dose): HbsAg (if positive, HBV-DNA test required), HBsAb, HBeAg, HBeAb, HBcAb, HCV-Ab (if positive, HCV-RNA test required), HIV-Ab, and EBV-DNA;
  - ✓ Fresh (preferred) or archived tumor tissue specimens for PD-L1 testing. The following screening procedures should be completed within 7 days before the start of study treatment. A pregnancy test should be completed within 72 h before the start of study treatment.
  - ✓ ECOG PS;

- ✓ Vital signs: pulse, respiratory rate, body temperature, and blood pressure;
- ✓ Comprehensive physical examination: general condition, head and face, skin, lymph nodes, neck, eyes, ears, nose and throat, mouth, respiratory system, cardiovascular system, abdomen, reproductive and urinary system, musculoskeletal system, nervous system, mental state, and others;
- ✓ Blood routine: RBC count, hemoglobin, platelet count, WBC count, neutrophil count, and lymphocyte count;
- ✓ Urinalysis: WBC, RBC, and urine protein. In case of a urine protein ≥ 2+, a 24-h urine protein test (quantitative) should be added;
- ✓ Fecal occult blood;
- ✓ Blood biochemistry: ALT, AST, GGT, total bilirubin, direct bilirubin, AKP, blood urea nitrogen (preferred) or urea, total protein, albumin, creatinine, blood glucose, lactate dehydrogenase, K^+, Na^+, Ca^{2+}, Mg^{2+}, and Cl^-;
- ✓ Thyroid function: TSH, FT3, and FT4;
- ✓ Coagulation function: APTT, PT, FIB, INR;
- ✓ Echocardiography: including LVEF assessment. Perform when clinically indicated.
- ✓ 12-Lead ECG: additional necessary investigations required when an abnormality is seen as determined by the investigator;
- ✓ Pregnancy test: serum or urine (for women of childbearing potential);
- ✓ Imaging examination: CT or MRI of nasopharynx, neck, chest, upper and lower abdomen (including pelvis). Brain MRI is required when brain metastasis is suspected and confirmed (if MRI is contraindicated, CT can be used instead). Bone scan is performed only when clinically indicated and must be performed within 42 days before the first dose. At screening, tumor evaluations up to 4 weeks before administration and before informed consent may be used as long as they meet the RECIST 1.1.
- ✓ Adverse events: Documented from the signing of ICF.

- Concomitant medications: Concomitant medications within 30 days before the first dose will be documented in detail; antibiotic use within 3 months before enrollment will be documented.

6.2 Enrollment

- Confirmation of inclusion/exclusion criteria.
- Administration to subjects.

6.3 Treatment Period

- All examinations and evaluations (except imaging evaluations) should be completed within 3 days before administration. The following items should be examined/assessed before each administration in each cycle; items are not required for examination/assessment in the first cycle when they have been examined/assessed at screening within 7 days before the first administration.
  - ✓ ECOG PS;
  - ✓ Vital signs: pulse, respiratory rate, body temperature, and blood pressure;
  - ✓ Physical examination: general condition, head and face, skin, lymph nodes, neck, eyes, ears, nose and throat, mouth, respiratory system, cardiovascular system, abdomen, reproductive and urinary system, musculoskeletal system, nervous system, mental state, and others;
  - ✓ Blood routine: complete blood count with differential (white blood cells, red blood cells, lymphocytes, monocytes, neutrophils, basophils, eosinophils, and hemoglobin), platelet counts;
  - ✓ Blood biochemistry: ALT, AST, GGT, total bilirubin, direct bilirubin, AKP, blood urea nitrogen (preferred) or urea, total protein, albumin, creatinine, blood glucose, lactate dehydrogenase, K^+, Na^+, Ca^{2+}, Mg^{2+}, and Cl^-;
  - ✓ 12-Lead ECG: additional necessary investigations required when an abnormality is seen as determined by the investigator;
  - ✓ Concomitant medications: Concomitant medications will be documented;
  - ✓ Adverse events: document AEs in detail;
- The following investigations should be completed before the administration on D1 of each cycle:
  - ✓ Urinalysis: WBC, RBC, and urine protein. In case of a urine protein ≥ 2+, a 24-h urine protein test (quantitative) should be added;
  - ✓ Fecal occult blood (before or after administration);

- ✓ Thyroid function: TSH, FT3, and FT4 (T3 and T4 can be used instead if FT3 and FT4 are unavailable);
- ✓ Concomitant medications: Concomitant medications will be documented;
- ✓ Adverse events: document AEs in detail;
- The following investigations should be completed every 2 cycles before administration
- ✓ EBV-DNA testing;

- Imaging evaluation: CT or MRI of the nasopharynx, neck, chest, and abdomen (including pelvic cavity); enhanced scanning with contrast is preferred if not contraindicated. Imaging examinations are performed every 8 weeks. For lesions of bone metastases, bone scans are only required when the evaluation result of other lesions is CR and it is necessary to confirm the presence of lesions of bone metastases or when clinically indicated. For subjects exiting the group for any reason, a tumor imaging evaluation should be performed at the time of exiting when an evaluation has not been carried out within 4 weeks before exiting. Imaging conditions should be the same as those at baseline (including slice thickness and contrast agent). The time window for imaging examination is ±7 days. Unscheduled imaging examination may be performed if PD is suspected (for example, worsening of symptoms). Subjects who discontinue treatment for reasons other than imaging-confirmed PD must also undergo a tumor evaluation every 8 weeks until documentation of confirmed PD, start of a new anti-tumor treatment, lost to follow-up, or death. Time of imaging evaluation will not be adjusted due to dose delays. Subjects showing CR or PR for the first time (whichever comes first) should undergo imaging evaluation for confirmation at least 4 weeks (28 days) later, with a time window of + 7 days.

Subjects who are clinically stable should have a confirmation scan 4-6 weeks after the first occurrence of PD based on iRECIST and RECIST (v1.1). The subsequent tumor evaluations will be performed at the pre-specified time point.

- Immunogenicity blood sampling: once before the C1D1, C2D1, C3D1, and C4D1 administrations; once every 3 cycles after Cycle 4; and once before withdrawal from study.

6.4 Follow-Up

Subjects should return to the study center for a follow-up 30 days after the last dose, and safety information can be obtained via telephone calls on D60 and D90 after the last dose (including AE outcome, new SAEs and AEs of special interest), with a time window of ±7 days.

When a subject starts a new anti-tumor treatment within 30 days after the last treatment, the visit should be completed before the new treatment is started.

- ✓ Blood routine: RBC count, hemoglobin, platelet count, WBC count, neutrophil count, and lymphocyte count;
- ✓ Blood biochemistry: ALT, AST, GGT, total bilirubin, direct bilirubin, AKP, blood urea nitrogen (preferred) or urea, total protein, albumin, creatinine, blood glucose, lactate dehydrogenase, K^+, Na^+, Ca^{2+}, Mg^{2+}, and Cl^-;
- ✓ Thyroid function: TSH, FT3, and FT4;
- ✓ Immunogenicity: collect once before withdrawal from study.
- ✓ Adverse events: document AEs in detail;

Concomitant medications: Concomitant medications within 90 days after the last treatment will be documented. Only concomitant medications for treatment-related AEs will be documented 30 days after the last treatment.

Survival follow-up visits will be conducted once a month after the last treatment via effective methods such as telephone. It is necessary to record whether the subjects have subsequently received a new anti-tumor treatment. When there is any new anti-tumor treatment, record the treatment regimen and start/end time of the treatment while completing the survival follow-up visit records.

For subjects who withdraw from the group due to "non-PD" (such as intolerable AEs) reasons, it is recommended to conduct tumor progression follow-up visit in the frequency identical to that for response evaluation (every 8 weeks ±7 days) until PD, death, or start of a new anti-tumor treatment. Follow-up information should be documented in eCRF.

6.5 Visit for Early Discontinuation of Treatment

If relevant evaluations and examinations have not been performed within 7 days before the subject withdrawal, the following procedures should be followed:

- ✓ ECOG PS;
- ✓ Vital signs: pulse, respiratory rate, body temperature, and blood pressure;
- ✓ Comprehensive physical examination: general condition, head and face, skin, lymph nodes, neck, eyes, ears, nose and throat, mouth, respiratory system, cardiovascular system, abdomen, reproductive and urinary system, musculoskeletal system, nervous system, mental state, and others;
- ✓ Blood routine: RBC count, hemoglobin, platelet count, WBC count, neutrophil count, and lymphocyte count;

- ✓ Urinalysis: WBC, RBC, and urine protein. In case of urine protein ≥ 2+, an additional 24-h urine protein test (quantitative) is required. Blood biochemistry: ALT, AST, GGT, total bilirubin, direct bilirubin, AKP, BUN (preferred) or urea, total protein, albumin, creatinine, blood glucose, lactate dehydrogenase, K^+, Na^+, Ca^{2+}, Mg^{2+}, and Cl^-;
- ✓ Thyroid function: TSH, FT3, and FT4;
- ✓ EBV-DNA testing.
- ✓ ECG;
- ✓ Imaging evaluation: An imaging evaluation should be performed at the end of treatment/upon withdrawal when it has not been done within 4 weeks before withdrawal. Subjects who discontinue treatment for reasons other than imaging-confirmed PD must also undergo a tumor evaluation every 8 weeks until documentation of confirmed PD, start of new anti-tumor treatment, or death.
- ✓ Adverse events: document AEs in detail;
- ✓ Concomitant medications: Concomitant medications will be documented;

6.6 Unscheduled Visits

The following items should be documented during unscheduled visits if subjects develop AEs during the study and within 90 days after the last dose or within 90 days until the start of a new anti-tumor treatment:

- ✓ Concomitant medications;
- ✓ Adverse events;
- ✓ All relevant examinations (including imaging evaluations, if any).

7 IMMUNOGENICITY STUDIES

7.1 Immunogenicity and Drug Trough Concentration Blood Sampling and Processing

7.1.1 Blood sampling time

Once before the administration on C1D1, C2D1, C3D1, and C4D1, once every 3 cycles after Cycle 4, and once before withdrawal from study.

7.1.2 Processing and storage of blood samples

At each of the above time points, 4-6 mL of venous blood samples will be collected into serum separation tubes to collect the serum, which will be then transferred to 4 cryotubes (aliquoted equally into 3 test tubes, 1 for ADA, 1 for drug trough concentration, and 1 for antibody neutralizing activity, and 1 backup tube). Refer to the "Laboratory Manual" for operation details and sample storage and transportation conditions.

7.1.3 Shipping of clinical samples

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

8 BIOMARKER TESTING

- Tissue PD-L1 testing: Tissue samples should be collected before enrollment. Fresh tissues are preferred. Archived samples of 5-8 paraffin embedded sections are also acceptable for PD-L1 testing when fresh tissue samples are not available.
- Testing of immune-related cells in the tumor microenvironment: T lymphocytes, B lymphocytes, macrophages, dendrites, and bone marrow-derived suppressor cells are analyzed using the remaining tissue samples after PD-L1 testing with multiple staining method.

After the above tests are completed, the PD-L1 stained sections will be saved until being destroyed at the end of the study; the stained immune cells and remaining tissue sections will be destroyed after the staining analysis is completed.

9 EVALUATION

9.1 Efficacy Evaluation

The primary efficacy endpoint for this study is the ORR assessed by IRC as per RECIST v1.1.

The ORR will be evaluated using the RECIST v1.1, including the CR and PR cases.

CR or PR must be confirmed at least 4 weeks (28 days) after the first evaluation. The objective response rate refers to the result obtained by dividing the number of subjects whose best overall response (BOR) is complete response (CR) or partial response (PR) by the total number of subjects.

Assessments of tumor response include all known or suspected lesions. Imaging includes CT or MRI scans of the chest, abdomen, or pelvis. Brain CT or MRI is performed for subjects with known or suspected brain metastasis, while bone scan and/or bone x-ray scan is performed for subjects with known or suspected bone metastasis.

The same imaging technique should be used in subsequent tumor evaluations for the same type of lesions as at screening. Anti-tumor activity evaluation will be carried out during the screening period and treatment process through radiography according to the schedule of activities; the evaluation will also be performed when progressive disease is suspected (such as exacerbation of symptoms) and upon withdrawal (if evaluation is not performed within the past 4 weeks).

Evaluation will be performed in accordance with the RECIST version 1.1 (Appendix IV).

Documentation and radiographic data of all subjects must be accessible for source validation and peer review.

9.2 Safety Evaluation

9.2.1 Pregnancy test

Female subjects of childbearing potential will receive a serum or urine pregnancy test within 72 hours before the start of administration. When the pregnancy test shows negative during the screening period, appropriate contraceptive measures shall be taken. If the hCG test shows positive result, the subject should withdraw from the study.

9.2.2 Adverse events

The incidence and severity of adverse events (AE) and serious adverse events (SAEs) will be assessed according to NCI-CTCAE V4.03.

Incidence of treatment interruption and discontinuation due to AEs.

AEs that occur during the study, including signs and symptoms at screening period, will be recorded in the eCRF. Treatment interruption and dose reduction as well as other modifications will be documented in the eCRF.

9.2.3 Laboratory safety evaluation

All laboratory abnormalities that are clinically significant or meet the definition of AE/SAE should be recorded in the eCRF:

Investigators are recommended to use clinical terms rather than laboratory terms (such as anemia instead of hemoglobin reduced) in reports.

9.2.4 Vital signs and physical examinations

Vital sign measurement, physical examination, and body weight measurements will be performed according to the schedule of activities.

A comprehensive physical examination is required during the screening period, and all test results should be recorded in the eCRF. A comprehensive physical examination is required during the treatment period, but only abnormal findings need to be documented in the eCRF. Repeated documentation is not required if there is no change from baseline.

9.2.5 12-Lead ECG

All abnormal ECG results that are clinically significant or meet the definition of AE/SAE should be recorded in the eCRF.

10 ADVERSE EVENT REPORTING

10.1 Adverse Event (AE)

10.1.1 Definition of adverse event

An adverse event (AE) refers to any untoward medical condition in a clinical trial subject who receives a pharmaceutical product, and the condition does not necessarily have a causality with the treatment. Safety information should be collected from the subject's signing of the informed consent form to 90 days after the last dose or the start of new anti-tumor treatment (if the anti-tumor treatment starts within 30 days after the last dose, the subject should be followed up until at least 30 days after the last dose; if the tumor treatment starts beyond 30 days after the last dose, the subjects should be followed up until the start of the new anti-tumor treatment). An AE may be any untoward and unexpected symptom, vital sign, laboratory test abnormality, or disease, including the following:

1) Worsening of pre-existing (prior to entering clinical study) medical conditions/diseases (including worsening symptoms, signs, or laboratory abnormalities);
2) Any new AE: Any new adverse medical conditions (including symptoms, signs, and newly diagnosed diseases);
3) Clinically significant abnormal laboratory values or results that are not caused by concomitant diseases.

Any AEs should be recorded in detail, including name of events and description of all relevant symptoms, time of occurrence, severity, causes, correlation with investigational drug, duration, measures taken, and final results and outcomes.

10.1.2 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.

Grade	Clinical Description of Severity
3	Severe or medically significant symptoms but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. Self-care ADL: Refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden
4	Life-threatening consequences; urgent intervention indicated
5	Resulting in death

10.1.3 Causality assessment

AEs will be collected and documented from signing the informed consent form until 90 days after the last study dose or the start of new anti-tumor treatments, regardless of whether the event is related to the investigational drug or whether the medication is administered. All subject complaints and abnormal changes in laboratory tests during the treatment period should be documented truthfully. The severity, duration, measures taken, and outcome of the AE shall be noted. The investigator should assess the relationship between the AE and the investigational drug, such as whether there is a plausible temporal relationship with the investigational drug, the characteristics of the investigational drug, the toxicological and pharmacological effects of the investigational drug, whether there are concomitant medications, the subject's underlying diseases, medical history, family history, as well as dechallenge and rechallenge, etc. The causality assessment will be provided using the following five categories "definitely related, possibly related, unlikely related, definitely unrelated, and indeterminable". Events that are assessed to be "definitely related", "possibly related", "unlikely related", and "indeterminable" will be listed as adverse drug reactions. When calculating the incidence of adverse events, the total of these four categories will be used as the numerator and the total number of subjects for safety evaluation will be used as the denominator.

10.2 Serious Adverse Event (SAE)

10.2.1 Definition of serious adverse event

SAE refers to a medical occurrence during the clinical study that results in hospitalization, prolonged hospitalization, disability, incapacity, life-threatening or death, or congenital malformation. The following medical events are included:

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

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

10.2.2 Hospitalization

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

Hospitalization does not include the following:

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

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

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

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

10.2.3 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 is reported as an SAE.

10.2.4 Potential drug-induced liver injury

Drug-induced liver injury is 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 values ≥ 3 ×ULN

After being notified of the abnormal results, the subjects should return to the study center for an assessment where 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 subjects, 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 the etiological tests of liver function. Potential drug-induced liver injury should be reported as an SAE.

10.2.5 Other anti-tumor treatments

SAEs should be recorded from the signing of the informed consent form until 90 days after the last dose of the investigational drug. SAEs must be reported regardless of whether the patient starts a new anti-tumor treatment.

10.2.6 SAE reporting

The collection period for SAEs begins with the signing of the informed consent form until 90 calendar days (inclusive) after the last study dose. In 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 local regulatory requirements.

The sponsor's email address for SAE reporting is: hengrui_drug_safety@hrglobe.cn

SAEs that occur 90 days after the last study dose are generally not reported unless they are suspected to be related to the investigational drug. The symptoms, severity, relationship with the investigational drug, time of occurrence, treatment duration, measures taken, time and method of follow-up, and outcome should be documented in details in the SAE report. If the investigator believes that an SAE is unrelated to the investigational drug but potentially related to study conditions (such as the termination of the previous treatment, or comorbidities during the study), their relationship should be explained in the description section of the SAE report form. If the severity of an ongoing SAE or its relationship to the investigational drug changes, a follow-up report should be submitted immediately. If an error is found in a previously reported SAE, such an SAE may be revised, revoked, or downgraded in follow-up reports and reported in accordance with the SAE reporting procedure.

10.2.7 Follow-up of AEs/SAEs

All SAEs and treatment-related AEs should be followed up until recovery, returning to baseline or $\leq$ Grade 1, reaching a steady state, or obtaining a reasonable explanation (e.g., lost to follow-up, death).

During each visit, the investigator should ask about the AEs/SAEs that occur after the last visit and whether there are new AE/SAEs, document relevant updated information including the outcome, and provide follow-up information in a timely manner based on the sponsor's query request.

10.3 Pregnancy

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

During the study, if the partner of a male subject becomes pregnant, he may continue the study. The investigator will report it to the sponsor within 24 h 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 a subject experiences any SAE during pregnancy, then "SAE Report Form" should be filled out and reported according to SAE reporting procedure.

10.4 Adverse Events of Special Interest

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

- ≥ Grade 3 infusion reactions;
- ≥ Grade 2 diarrhea/colitis, uveitis, interstitial pneumonitis;
- Other ≥ Grade 3 immune-related adverse events (irAEs);
- Any events that meet Hy's Law (ALT/AST > 3 ×ULN accompanied with total bilirubin > 2 ×ULN and without other causes);

11 CLINICAL MONITORING

The CRA must follow the GCP and SOP, make visits to the study center for clinical monitoring on a regular basis or according to the actual conditions, supervise the implementation and progress of the clinical study, check and confirm that all data recorded and entered into CRF are correct and intact and are consistent with source data, and ensure that the clinical study is implemented following the study protocol. The investigator should cooperate with the CRA actively. Specifically, the CRA is responsible for:

i. Confirming that the study center is qualified prior to starting the study, including personnel and training, a well-equipped and functional laboratory with various study-related test conditions, sufficient number of subjects, and study personnel's familiarity with the protocol requirements;

ii. Monitoring how the investigator is implementing the study protocol during the course of the study, confirming that informed consent forms are obtained from all subjects before the study, the enrollment rate and progress of the study, as well as the eligibility of enrolled subjects;

iii. Confirming the accuracy and integrity of documentations and reports, and ensuring accurate data entry of all case report forms and consistency with source data. All errors or omissions have been corrected or noted, signed and dated by the investigator. Dose modifications, treatment changes, concomitant medications, intercurrent diseases, lost to follow-up, and missing investigations should be confirmed and documented for each subject. Verifying that withdrawal and lost to follow-up of enrolled subjects are explained in the case report forms;

iv. Confirming that all AEs have been recorded, and that SAEs have been recorded and reported within the specified time frame; verifying that the investigational drugs are supplied, stored, dispensed, and returned in accordance with relevant regulations, and corresponding documentation are made;

v. Recording clearly and faithfully visits, tests, and examinations that the investigator has failed to perform, and whether errors or omissions have been corrected;

vi. Completing a written monitoring report after each visit, which should state the date and time of the monitoring visit, the name of the CRA, and the findings of the visit.

The Quality Assurance Unit of the sponsor may conduct audit on the study in the clinical research institution. The audit covers the supply of drugs, required study documents, documentation of the informed consent process, and consistency between case report forms and original documents. The content and scope of the audit may also be expanded according to the situation. The investigator agrees to participate at a reasonable time and in a reasonable way.

12 DATA ANALYSIS/STATISTICAL METHOD

12.1 Sample Size

Efficacy hypothesis

According to study SHR-1210-101, the ORR of all dose groups (n = 93) of NPC subjects was 29.0%, and the ORR of the 200 mg dose group (n = 68) was 36.8%. In the subgroup analysis, the ORR of all dose groups (n = 58) of subjects who had failed at least two lines of chemotherapy was 27.6%, and the ORR of the 200 mg dose group (n = 43) was 37.2%. Also, referring to the efficacy results of similar drugs, the intended study for registration will use a dose of 200 mg, and a conservative estimate of the upper limit of ORR is set at 26%.

Pembrolizumab for the treatment of head and neck squamous cell carcinoma was approved by the FDA with an ORR of 16% in a single-arm study. Therefore, it is stipulated that the lower limit of the 95% confidence interval for the ORR for this study should not be less than 15%.

Sample size calculation

According to the above efficacy hypothesis (ORR = 26%), with a one-sided alpha = 0.025, enrolling 139 subjects can achieve a power of 90% that the lower limit of 95% confidence interval for ORR is not less than 15%. In order to ensure that the 139 subjects are included in the evaluation, assuming a dropout rate of 10%, 155 subjects should be enrolled.

12.2 Statistical Analysis Plan

In this study, SAS 9.4 or later will be used for data processing and analysis.

Categorical data will be descriptively summarized using statistics including the frequency (n) and percentage (%), as well as the 95% confidence interval of the overall percentage when necessary. Continuous data will be descriptively summarized using statistics including the mean, standard deviation (SD), median, minimum, and maximum.

For the analysis of the primary endpoint, the IRC-assessed ORR and its 95% confidence interval (Clopper-Pearson method) will be estimated.

The detailed analysis plan and strategy will be described in the Statistical Analysis Plan (SAP).

12.3 Statistical Hypothesis and Decision Rule

The primary endpoint of this study is the ORR. The ORR of the investigational drug is compared with the ORR of 15% for the monotherapy (refer to the ORR in the single-arm study of pembrolizumab in the treatment of head and neck squamous cell carcinoma for which the drug is approved by the FDA).

Hypotheses

*H*0: The ORR of the investigational drug = 15%

*H*1: The ORR of the investigational drug ≠ 15%

α level: 0.05 (two-sided).

12.4 Analysis Population

- Full analysis set (FAS): all eligible subjects who have used the investigational drug after enrollment. The FAS is the primary analysis set for the efficacy analysis of this study.
- Per-protocol set (PPS): a subset of the FAS, excluding subjects with important protocol deviations which significantly impact study results.
- Safety analysis set (SS): enrolled subjects who have received at least one dose of investigational drug and have at least one safety assessment.
- Slice-testing biomarker analysis set: all enrolled subjects who have received at least one dose of investigational drug and have at least one slice-testing biomarker data for PD-L1.
- ADA analysis set: all enrolled subjects who have received at least one dose of investigational drug and have at least one ADA assessment data.

12.5 Statistical Methods

12.5.1 Basic methods

This is a single-arm, open-label, multi-center phase II clinical study. Six months after the last subject in, the primary endpoints, secondary endpoints, and safety will be statistically analyzed.

12.5.2 Primary efficacy endpoint analysis

Primary endpoint will be analyzed based on the FAS. For the analysis of the primary endpoint, the IRC-assessed ORR and its 95% confidence interval (Clopper-Pearson method) will be estimated.

Objective response rate (ORR): refers to the objective tumor response as per the RECIST1.1 criteria and is obtained by dividing the number of subjects whose best overall response (BOR) is complete response (CR) or partial response (PR) by the number of subjects.

The analysis on the PPS is similar to the analysis on the FAS in terms of detailed analytical methods.

12.5.3 Secondary efficacy endpoints analysis

The investigator-assessed ORR, disease control rate (DCR), and their 95% confidence intervals (Clopper-Pearson method) will be estimated.

The Kaplan-Meier method will be used to estimate the PFS, DoR, and OS and the corresponding 95% confidence intervals will be calculated (Brookmeyer-Crowley method based on log-log transformation, with the standard error calculated using the Greenwood formula).

TTR will be descriptively summarized using the mean, standard deviation, median, maximum, and minimum.

Disease control rate (DCR): refers to the result obtained by dividing the number of subjects whose BOR is CR, PR, or stable disease (SD ≥ 8 weeks) by the number of subjects.

Progression-free survival (PFS): refers to the time from the date of first dose to progressive disease or death, whichever occurs first.

Duration of response (DoR): refers to the time from measurement criteria are first met for CR/PR (whichever is first recorded) to the first documentation of disease recurrence/progression or death (whichever comes first).

Overall survival (OS): refers to the time from first study dose to death of any cause.

Time to response (TTR): refers to the time from the date of the first dose to meeting the CR or PR criteria for the first time (whichever is measured first).

The secondary endpoints will be analyzed based on the FAS and PPS.

12.5.4 Handling of missing data

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

12.5.5 Safety analysis

The analysis will be performed based on SS.

AEs that occur during the study will be coded according to MedDRA v21.0. The frequency and incidence of AEs will be summarized by system organ class and preferred term. The causality and severity of AEs will be further tabulated for description. Descriptive statistics will be used to summarize other safety endpoints. The incidences of AEs, adverse reactions, AEs resulting in withdrawal from study, AEs resulting in death, and the incidence of SAEs will be summarized. Severity of AEs and adverse reactions: For the same AE occurring multiple times in the same subject, the highest severity will be included in the analysis; for different AEs occurring in the same subject, the most severe AE will be included in the analysis.

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

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

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

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

12.5.6 Exploratory analysis

The relationship between PD-L1 expression and efficacy of SHR-1210 will be evaluated.

The relationship between immune-related cells (T lymphocytes, B lymphocytes, macrophages, dendritic cells, and bone marrow-derived suppressor cells) in tumor microenvironment and efficacy of SHR-1210 will be evaluated.

The generation of anti-SHR-1210 antibodies (ADAs) vs. time of measurement will be statistically described.

13 DATA MANAGEMENT

13.1 Data Recording

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

13.1.1 eCRF entry

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

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

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

13.1.2 eCRF review

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

13.2 Data Monitoring

Implemented by: CRA.

Monitoring content: To confirm that the study protocol is adhered to; the records on CRF 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. Ensure that the data in the eCRF are consistent with source data. This process is also known as source data verification (SDV).

13.3 Data Management

13.3.1 EDC database establishment

The data manager will establish a study data collection system and database according to the study protocol, which will be available for online usage before the first subject is enrolled. Before using the system, 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.)

13.3.2 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 guideline. After submitting the eCRF, the CRA, data manager, and medical reviewer should review the data. Questions during the review are 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.

13.3.3 Data review and database locking

After the clinical 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 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 as confirmed by the data review meeting. The data manager will export the data to the statistics department for data analysis.

13.3.4 Data archiving

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

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

14 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.

15 QUALITY ASSURANCE AND QUALITY CONTROL

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

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

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

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

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

16 REGULATIONS, ETHICS, INFORMED CONSENT, AND SUBJECT PROTECTION

16.1 Regulatory Considerations

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

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

1) Provisions for Drug Registration
2) Good Clinical Practice
3) 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 Ethical Guidelines
4) Other applicable laws and regulations

16.2 Ethical Standards

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", CFDA's (now NMPA) "Good Clinical Practice (GCP)", and relevant regulations. Before the study is initiated, approval must be obtained from the IEC/IRB of the hospital.

The study protocol must not be unilaterally modified without approvals from both the sponsor and investigator. The investigator can modify or deviate from the study protocol before obtaining an approval from the IRB/IEC 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 IRB/IEC 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 IEC/IRB. After the end of the study, the completion should be informed to the IEC/IRB.

16.3 Independent Ethics Committee

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

16.4 Informed Consent

The ICF describes the investigational drug and study process in detail and fully explains the risks of the study to the subjects. Written ICFs must be obtained prior to screening.

16.4.1 ICFs and other written information for subjects

The following informed consent materials will be submitted along with the protocol:

Informed consent form;

Subject contact card;

Recruitment advertisement.

16.4.2 Informed consent process and records

Informed consent will begin before an individual decides to participate in the clinical study and continues during the entire clinical study. The risks and potential benefits of participating in the study should be discussed fully and in detail with the subjects or their legal representatives. Subjects will be asked to read and review the ICF that has been approved by the IEC/IRB. The investigator will explain the clinical study to the subjects and answer any questions posed by the

subjects. Subjects can only participate in the study after they have signed the ICFs. During the clinical study, subjects can withdraw the informed consents at any time. One copy of the signed ICF will be kept by the subjects. Even if a patient refuses to participate in this study, his or her rights will be fully protected, and the nursing quality will not be affected.

16.5 Confidentiality of Subject Information

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

Other authorized representatives of the sponsor, IRB or regulatory authorities, and the representatives of the pharmaceutical company that provides the investigational drugs can examine all 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. At the end of the study, all the records will be kept in a secure place based on the time limit specified by local IRB and regulations.

The study data of subjects collected for statistical analysis and scientific reports will be uploaded and stored in Sun Yat-Sen University Cancer Center. 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 and Sun Yat-Sen University Cancer Center are all confidential and password-protected. At the end of the study, all identification information in the study database will be erased and archived in Sun Yat-Sen University Cancer Center.

17 PUBLISHING OF STUDY RESULTS

The study results belong to Jiangsu Hengrui Pharmaceuticals Co., Ltd. Hengrui does not restrict the publication of any collected or research information by investigators, regardless of whether the results are beneficial to the investigational drug or not. However, the investigator should let the sponsor have the opportunity to review any proposed publication or other forms of publication before document submission or publication to prevent unintentional leakage of confidential information or unprotected inventions. The investigator should provide Hengrui

with the manuscript, abstract, or full text of all planned publications (poster, invited lectures, or guest lectures) at least 30 days prior to submission for publication or other forms of release. To protect the intellectual property rights that need to be patented, the investigator should agree to delay publications, and the delay period should not exceed 60 days. Before open publication, Hengrui can require the investigator to delete any previously unpublished confidential information (except for study results). If this study is part of a multicenter study, the investigator must agree that the first publication is an integrated result from all study centers. However, if a manuscript of the integrated analysis is not submitted 12 months after the study is completed or terminated in all study centers, the investigator can independently publish results based on other requirements in this section.

18 CLINICAL STUDY PROGRESS

Estimated enrollment of the first subject: Jun. 2018

Estimated enrollment of the last subject: Mar. 2019

Estimated study completion: one year after the last subject's first dose, the subjects undergoing treatment will enter the expansion study of SHR-1210 for continued treatment and observation.

19 REFERENCES

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Appendix I. ECOG PS

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

Appendix II. Creatinine Clearance Calculation

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

Serum Creatinine (mg/dL):

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

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

Serum Creatinine (μmol/L):

$$\text{Creatinine Clearance in Males (mL/min)} = \frac{(140 - \text{Age}) \times (\text{Weight})^{a}}{0.818 \times \text{Serum Creatinine}}$$

$$\text{Creatinine Clearance in Females (mL/min)} = \frac{0.85 \times (140 - \text{Age}) \times (\text{Weight})^{a}}{0.818 \times \text{Serum Creatinine}}$$

[a]: The unit for age is year and for weight is kg.

Appendix III. Prohibited Traditional Chinese Medicine

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

Appendix IV. Response Evaluation Criteria in Solid Tumors

Response Evaluation Criteria in Solid Tumors Version 1.1 (Excerpt)

(New Response Evaluation Criteria in Solid Tumors: Revised RECIST Version 1.1)

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

1 BACKGROUND

Omitted

2 PURPOSE

Omitted

3 MEASURABILITY OF TUMOR AT BASELINE

3.1 Definitions

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

3.1.1 Measurable

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

- 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 nodule: pathologically enlarged and measurable, single lymph nodule must be ≥ 15 mm in short axis by CT scan (CT scan slice thickness no greater than 5 mm). At baseline and during follow-up, only the short axis will be measured and followed.

3.1.2 Non-measurable

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodule with ≥ 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.

3.1.3 Special considerations regarding lesion measurability

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

Bone lesions:

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

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts;
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions. Lesions with prior local treatment:
- Tumor lesions situated in a previously irradiated area, or in an area subjected to other locoregional therapy, are usually considered non-measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

3.2 Specifications by Methods of Measurements

3.2.1 Measurement of lesions

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

3.2.2 Method of assessment

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

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

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

CT, MRI: CT is currently the best available and reproducible method for efficacy 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 trials in ovarian cancer.

Cytology/Histology: These techniques can be used to differentiate between PR and CR in certain cases specified in the protocol (e.g., residual benign tumor tissue is often present in the lesions of germ cell tumors). When effusions are known to be a potential adverse effect of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the

neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met the criteria for response or stable disease in order to differentiate between response (or stable disease) and PD.

4 TUMOR RESPONSE EVALUATION

4.1 Assessment of Overall Tumor Burden and Measurable Disease

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

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

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

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

Lymph nodes merit special mention since they are normal tissues which may be visible by imaging even if not involved by tumor metastasis. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes needs to be measured at baseline. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by tumor metastasis. Nodule size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smallest of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm ×30 mm 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 should be recorded as "present", "absent", or in rare cases "unequivocal progression". It is possible to record multiple target lesions involving the same organ as a single item on the case record form (e.g. "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

4.3 Response Criteria

4.3.1 Evaluation of target lesions

Complete response (CR): Disappearance of all target lesions. Any pathological lymph nodes (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.

4.3.2 Special notes on the assessment of target lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. CRFs or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must 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 CRF. 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 could 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 could be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false evaluation based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

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

4.3.3 Evaluation of non-target lesions

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

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

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

The concept of progression of non-target disease requires additional explanation as follows: When the patient also has measurable disease, to achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that the overall tumor load has increased sufficiently to the point where treatment must be discontinued. A modest increase in the size of one or more non-target lesions is usually not sufficient to quality 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 subjects for unequivocal progression is to consider if the increase in overall disease load based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease. For example, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large", an increase in lymphangitic disease from localized to widespread, or may be described in protocols as "sufficient to require a change in treatment". Examples include an increase in a pleural effusion from trace to large, an increase in lymphangitic disease from localized to widespread, or may be described in protocols as "sufficient to require a change in therapy". If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

4.3.5 New lesions

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

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

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

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

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

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

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

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

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

4.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the trial until the end of trial taking into account any necessary requirement for confirmation. On occasion a response may not be documented until after the end of treatment, so protocols should be clear if post-treatment assessments are to be considered in the evaluation of best overall response. Protocols must specify how any new treatment introduced before progression will affect best response evaluation. The patient's best overall response evaluation will depend on the findings of both target and non-target diseases and will also take into consideration the characteristics of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to determine either one is the best overall response.

4.4.1 Time point response

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

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

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

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

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

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

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

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

4.4.2 Missing assessments and inevaluable designation

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

4.4.3 Best overall response: all time points

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

Best response determination in trials where confirmation of complete or partial response is not required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD in evaluation at Cycle 1, PR at Cycle 2, and PD at the last cycle has a best overall response 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 best overall response, the patient's best overall response depends on the subsequent assessments. For example, a patient who has SD at cycle 1, PD at cycle 2 and does not meet minimum duration for SD, will have a best overall response of PD. The same patient lost to follow-up after the first SD assessment would be considered not evaluable.

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

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

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

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

[a]: If a CR is truly met at first time point, then 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 overall response will depend on whether minimum duration for SD is met. However, sometimes CR may be claimed when subsequent scans suggest small lesions are likely still present and in fact the subject has PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

4.4.4 Special notes on response assessment

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 "zero" recorded on the case report form (CRF).

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

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

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

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

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

4.5 Frequency of Tumor Re-Evaluation

Frequency of tumor re-evaluation during treatment should be protocol-specific and consistent with the type and schedule of treatment. However, in the phase II studies where the beneficial effect of treatment is not known, follow-ups for every 6-8 weeks (timed to coincide with the end of a cycle) is reasonable. Interval adjustments 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/PFS) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomized comparative trials 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 arm in the timing of disease assessment.

4.6 Confirmatory Measurement/Duration of Response

4.6.1 Confirmation

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

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

4.6.2 Duration of overall response

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

4.6.3 Duration of stable disease

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

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

4.7 PFS/TTP

4.7.1 Phase II trials

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-cancer activity of new agents/regimens. In such cases, PFS/PPF at landmark time points might be considered appropriate alternatives to provide an initial signal of biologic effect of new agents. It is clear, however, that in an uncontrolled trial, these measures are subject to criticism since an apparently promising observation may be related to biological factors such as patient selection and not the impact of the intervention. Thus, phase II screening trials 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 V. The 2017 Chinese Staging of Nasopharyngeal Carcinoma (the 2008 Revised Expert Consensus on Staging of Nasopharyngeal Carcinoma)

T Staging

T_x: The primary tumor cannot be evaluated

T_0: The tumor is not found, but with positive EBV and metastasis to lymph nodes on the neck

T_1: The tumor is in the nasopharynx, or has invaded the oropharynx and/or nasal cavity, but does not involve parapharyngeal space

T_2: The tumor has invaded the parapharyngeal space, and/or involved the adjacent soft tissues (internal pterygoid muscle, external pterygoid muscle, anterior vertebral muscle)

T_3: The tumor has invaded the bone structure of the skull base, cervical vertebrae, pterygoid structure, and/or paranasal sinuses

T_4: The tumor has invaded the skull, with involvement of cranial nerves, hypopharynx, orbits, and parotid glands, and/or extensive soft tissue invasion beyond the lateral edge of the pterygoid muscle

N Staging

N_x: Regional lymph nodes cannot be evaluated

N_0: No regional lymph node metastasis

N_1: Metastasis to lymph nodes of the neck of one side and/or postpharyngeal lymph nodes (regardless of the number of sides): maximum diameter ≤ 6 cm, and located above the lower edge of the cricoid cartilage

N_2: Metastasis to lymph nodes on both sides of the neck: maximum diameter ≤ 6 cm, and located above the lower edge of the cricoid cartilage

N_3: Metastasis to postpharyngeal lymph nodes (regardless of the number of sides): the largest diameter > 6 cm and/or located below the lower edge of the cricoid cartilage

Clinical Stage

Stage 0: $T_{is}N_0M_0$

Stage I: $T_iN_0M_0$

Stage II: $T_{0\text{-}1}N_1M_0$, $T_2N_{0\text{-}1}M_0$

Stage III: $T_{0\text{-}2}N_2M_0$, $T_3N_{0\text{-}2}M_0$

Stage IV_A: $T_{0\text{-}3}N_3M_0$ or $T_4N_{0\text{-}3}M_0$

Stage IV_B: Any T and N plus M_1