A SINGLE-ARM, OPEN-LABEL, MULTI-CENTER PHASE II CLINICAL STUDY OF AN PD-1 ANTIBODY SHR-1210 IN PATIENTS WITH RECURRENT OR METASTATIC NASOPHARYNGEAL CARCINOMA WHO FAILED SECOND-LINE OR ABOVE CHEMOTHERAPY

Protocol No.: SHR-1210-II-209
Trial Phase: Phase II
Compound Code: SHR-1210
Compound Name: Camrelizumab
Medical Director: Qing Yang
Coordinating Site: Sun Yat-Sen University Cancer Center
Principal Investigator: Prof. Li Zhang

Version No.: 1.0
Version Date: 20 Apr., 2018

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

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VERSION HISTORY/REVISION HISTORY

Version No.	Version Date	Summary of Major Changes
1.0	20 Apr., 2018	None
2.0	20 May, 2020	Exploratory objectives: • Added the following exploratory objectives: To evaluate the relationship between immune-related cells (T lymphocytes, B lymphocytes, macrophages, dendritic cells, and bone marrow-derived suppressor cells) in the tumor microenvironment and efficacy of SHR-1210 Exploratory endpoints: • Added the following exploratory endpoints: To evaluate the relationship between immune-related cells (T lymphocytes, B lymphocytes, macrophages, dendritic cells, and bone marrow-derived suppressor cells) in the tumor microenvironment and efficacy of SHR-1210 Biomarker testing: • Added the following biomarker testing: 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 testing is completed, the PD-L1 stained sections are saved until being destroyed by the end of the trial; the stained immune cell and remaining tissue sections are destroyed after the staining analysis is completed. Exploratory analysis: • Added the following exploratory analyses: To evaluate the relationship between immune-related cells (T lymphocytes, B lymphocytes, macrophages, dendritic cells, and bone marrow-derived suppressor cells) in the tumor microenvironment and efficacy of SHR-1210
3.0	7 Aug., 2020	Withdrawal criteria: • Updated withdrawal criterion 3 from "cumulative administration of SHR-1210 for 2 years (without radiographic progression)" to "cumulative administration of SHR-1210 for 2 years"; Definition of end of study:

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Version No.	Version Date	Summary of Major Changes
		• Updated from "one year after the last subject's first dose, the subjects undergoing treatment will be transferred to the extended project of SHR-1210 for continued treatment and observation" to "two years after the last subject's first dose"; SAE reporting: • Updated from "the investigator shall immediately report to relevant regulatory authorities as required by regulations within 24 h of acknowledgment, notify the sponsor, and report to the ethics committee in time" to "the investigator shall report to the sponsor within 24 h of acknowledgment, and report to relevant parties in time as required by local regulations"; • Updated the email for SAE reporting from "hengrui_drug_safety@shhrp.com" to "hengrui_drug_safety@hrglobe.cn"

SPONSOR'S SIGNATURE PAGE

I have read and confirmed this trial protocol (protocol no.: SHR-1210-II-209, version: 1.0, date: 20 Apr., 20) 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 Medicine Co., Ltd.

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

PRINCIPAL INVESTIGATOR'S SIGNATURE PAGE (COORDINATING 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 of the investigational product; I have read the materials of preclinical studies of the investigational product and the protocol for this clinical trial (protocol no.: SHR-1210-II-209, version: 1.0, date: 20 Apr., 20). 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 trial. 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 Site: _____

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 of the investigational product; I have read the materials of preclinical studies of the investigational product and the protocol for this clinical trial (protocol no.: SHR-1210-II-209, version: 1.0, date: 20 Apr., 20). 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 trial. 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 Site: _____

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

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SYNOPSIS

Study Title	A Single-Arm, Open-Label, Multi-Center Phase II Clinical Study of PD-1 Antibody SHR-1210 in Treatment of Patients with Recurrent or Metastatic Nasopharyngeal Carcinoma Who Failed Second-Line or Above Chemotherapy
Protocol No.	SHR-1210-II-209
Version No.	1.0
Sponsor	Jiangsu Hengrui Medicine Co., Ltd.
Principal Investigator	Prof. Li Zhang
Participating Study Centers	Sun Yat-Sen University Cancer Center and 7 other domestic sites
Study Objectives	Primary objective: To evaluate the objective response rate of SHR-1210 in the treatment of patients with recurrent or metastatic nasopharyngeal carcinoma (NPC) who have failed second-line or above chemotherapy through the independent review committee (IRC). Secondary objective: To evaluate the efficacy and safety of SHR-1210 in the treatment of patients with recurrent or metastatic nasopharyngeal carcinoma who have failed second-line or above chemotherapy. Exploratory objectives: (1) To evaluate the relationship between PD-L1 expression in tumor tissues and efficacy of SHR-1210.. (2) To evaluate the immunogenicity of SHR-1210 in the treatment of patients with recurrent or metastatic nasopharyngeal carcinoma, and to observe the correlation of immunogenicity with efficacy and safety.
Study Endpoints	Primary endpoint IRC-assessed objective response rate (ORR) of SHR-1210 in the treatment of patients with recurrent or metastatic nasopharyngeal carcinoma who have failed second-line or above chemotherapy Secondary endpoints Efficacy • Investigator-assessed objective response rate (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 severities of adverse events (AEs) and serious adverse events (SAEs), laboratory abnormalities, as per NCI-CTCAE v4.03 • Incidence of AEs resulting in dose interruption and discontinuation Exploratory endpoints • To evaluate the relationship between PD-L1 expression and efficacy of SHR-1210 • To investigate the anti-SHR-1210 antibodies (ADAs) in subjects after injection of SHR-1210
Study Population	Patients with relapsed or metastatic nasopharyngeal carcinoma who have failed second-line or above chemotherapy
Study Design	This study is a single-arm, open-label, multi-center phase II clinical trial to observe and evaluate the efficacy and safety of anti-PD-1 antibody SHR-1210 in the treatment of patients with recurrent or metastatic nasopharyngeal carcinoma who have failed second-line or above chemotherapy.
Investigational Product	Recombinant humanized anti-PD-1 monoclonal antibody for injection, SHR-1210 (Manufacturer: Suzhou Suncadia Biopharmaceuticals Co., Ltd.)
Method of Administration	SHR-1210 is administered through intravenous drip infusion (premedication not required) at a fixed dose of 200 mg. Each infusion takes 30 min (not less than 20 min and no more than 60 min, including flushing) (including final flushing). Administrations are given in D1 and D15 of each 4-week treatment cycle. The treatment will continue until confirmed PD, unacceptable toxicity, voluntary withdrawal by the subject, or discontinuation determined by the investigator.

Inclusion Criteria	Subjects must meet all of the following criteria to be eligible for this study: 1. Aged 18 to 75, male or female; 2. Moderately differentiated or undifferentiated locally recurrent/metastatic nasopharyngeal carcinoma (WHO class 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: 0-1; 5. Expected survival ≥ 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. Archived samples of 5-8 paraffin embedded sections with a thickness of 3-5 μm are also acceptable if a fresh biopsy is not accessible; 8. Major organ functions must meet the following requirements (No blood components or cell growth factors are allowed within 2 weeks prior to 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 (CrCl) ≥ 50 mL/min (Cockcroft-Gault); 9. Female subjects of childbearing age 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 course of the trial in 60 days after the last dose of the investigational product (around 5 half-lives of the drug + menstrual cycle). Male subjects with partners of childbearing potential must take at least two contraceptive measures during the course of the trial and in 120 days after the last dose of the investigational product (around 5 half-lives of the drug + sperm production cycle);

	10. Subject must participate voluntarily, sign the informed consent form, have good compliance, and cooperate with follow-up visits.
Exclusion Criteria	Subjects meeting any of the following are ineligible to participate in this study: 1. Patients with any active autoimmune disease or a 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 prednisone of more than 10 mg/day or equivalent hormone therapy) may be enrolled); 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. Patients with uncontrolled cardiac symptoms or disease, such as (1) NYHA Class II or higher 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 product. In the absence of active autoimmune disease, inhaled or topical use of corticosteroids and an equivalent dose to > 10mg/day of prednisone for adrenal hormone replacement are permitted; 6. Patients who have received chemotherapy and targeted therapy less than 4 weeks prior to the 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 resolved to CTCAE Grade ≤ 1 (except for alopecia and sequelae of relevant neurotoxicity of previous platinum therapy); 7. Patients with active infection or unexplained pyrexia of > 38.5 °C at screening or prior to the first dose (those with tumor-induced pyrexia may be enrolled as per the judgment of the investigator); 8. 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 subjects' safety or the collection of trial data.
Immunogenicity Study	Collection time for immunogenicity blood samples: Before the administration on C1D1, C2D1, C3D1, and C4D1, once every 3 cycles after C4, and once prior to withdrawal from study.
Withdrawal Criteria	A subject must withdraw from/discontinue the treatment when any one of the following conditions occurs: 1. A subject withdraws the informed consent and requests to withdraw from the study; 2. Radiographic progressive disease occurs; As per RECIST v1.1, a 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 stable clinical symptoms: a. no significant clinical symptoms or changes in laboratory measurements; b. no changes in the performance status score (deterioration); c. non-tumor rapid progression and tumor progression not involving important organs/sites (e.g., spinal cord compression); 3. Cumulative use of SHR-1210 for 2 years (without radiographic progression); 4. Subjects showing unacceptable toxicity; 5. Subjects with poor compliance; 6. Subjects lost to follow-up or becoming pregnant;

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	7. Other reasons for which the investigator consider a withdrawal necessary.
Criteria for Treatment Discontinuation	The termination criteria of this study include but are not limited to the following: 1. Discovery of unexpected, significant or unacceptable risks to the subjects; 2. Major errors in the protocol found during the implementation of the trial; 3. Ineffective investigational product/treatment, or meaninglessness to continue the trial; 4. Termination as determined by the sponsor due to reasons such as severe delay in enrollment or frequent protocol deviations.
Sample Size Determination	Efficacy assumptions According to study SHR-1210-101, the ORR of all dose groups (n = 93) of subjects with nasopharyngeal carcinoma 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 second-line and above 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%. The FDA-approved ORR in a single-arm study of pembrolizumab in the treatment of head and neck squamous cell carcinoma was 16%. Therefore, the lower limit of the 95% confidence interval for the ORR in this study should not be less than 15%. Sample size calculation According to the above efficacy assumptions (ORR = 26%), with a one-sided alpha = 0.025, 139 enrolled subjects could satisfy a 90% confidence that the lower limit of the 95% confidence interval of 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%, then 155 subjects shall 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-event data, the Kaplan-Meier method will be used to estimate the survival function, plot the survival curve, and estimate the median time and its 95% confidence interval. 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 AEs (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) are estimated. The Kaplan-Meier method is used to estimate the PFS, DoR, and OS and calculate the corresponding 95% confidence interval (based on the Brookmeyer-Crowley method with 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 distribution and populations; Subjects' basic characteristics (including demographics, habituation, past medical history, and medication history); Discontinuations; Exploratory analysis, etc.
Study Period	Anticipated enrollment of the first subject: Jun. 2018 Anticipated enrollment of the last subject: Mar. 2019 Expected study completion: one year after the last subject's first dose, the subjects undergoing treatment will be transferred to the extended project of SHR-1210 for continued treatment and observation;

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SCHEDULE OF ACTIVITIES

	Screening Period (-28 days)		**Treatment Period**				**End of Treatment/ Withdrawal (+3 days)**	**After 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 Scoring[3]		√			√		√		
Vital Sign Measurement [4]		√		√	√	√	√		
Physical Examination [5]		√		√	√	√	√		
Hematology [6]		√		√	√	√	√	√	
Urinalysis [7]		√			√		√		
Fecal Occult Blood [8]		√			√				
Blood Biochemistry [9]		√		√	√	√	√	√	
Thyroid Function [10]		√			√		√	√	

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	Screening Period (-28 days)		**Treatment Period**				**End of Treatment/ Withdrawal (+3 days)**	**After 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]
Coagulation Function [11]		√							
EBV-DNA Testing [12]	√				√		√		
Liver-Related Virological Examinations [13]	√								
ECG [14]		√		√	√	√	√		
Echocardiography [15]		√							
Pregnancy Test [16]		√					√		
Tumor Imaging Evaluation [17]	√		√						
SHR-1210 Administration [18]			√	√	√	√			
Adverse Events [19]	√	√	√	√	√	√	√	√	√
Concomitant Therapies [20]	√	√	√	√	√	√	√	√	√
Immunogenicity [21]			√		√		√		
Tumor Tissues [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 if needed. Results should be documented in the "Unscheduled Examinations" section of the 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 history, radiotherapy history, chemotherapy history, as well as use of antibiotics within 3 months before enrollment) and history of other concomitant diseases.

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

[5] Physical examination: within 7 days prior to 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, throat, mouth, respiratory system, cardiovascular system, abdomen, reproductive and urinary system, musculoskeletal system, nervous system, and mental state) is performed; before each dose of each cycle (not required for the first dose if completed within 7 days prior to the first dose at screening), symptom-directed physical examination can be performed if clinically indicated.

[6] Hematology: RBC count, hemoglobin, platelet count, WBC count, neutrophil count, lymphocyte count; within 7 days prior to the first dose, before each dose of each cycle (not required for the first dose if completed within 7 days prior to 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 prior to 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 quantitation should be added.

[8] Fecal occult blood: within 7 days prior to the first dose, 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 prior to the first dose, before each dose of each cycle (not required for the first dose if completed within 7 days prior to 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 prior to 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 prior to the first dose.

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

[13] Virological examinations: HBsAg (if positive, need to test HBV-DNA), HBsAb, HBeAg, HBeAb, HBcAb, HCV-Ab (if positive, need to test HCV-RNA) and HIV-Ab. Within 14 days prior to the first dose.

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

[15] Echocardiography: within 7 days prior to the first dose; performed if clinically indicated.

[16] Pregnancy test: for women of childbearing age only. Within 72 h prior to 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); enhanced scanning is preferred if not contraindicated. Brain MRI is required for suspected or confirmed cases of brain metastasis (or CT if MRI is contraindicated). Bone scan is performed only when clinically indicated and must be performed within 42 days prior to the first dose.

- ✓ At screening, tumor evaluations up to 4 weeks before the 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 evaluations should be performed in time when subjects withdraw due to any reasons (± 4 weeks, but not required to be repeated if the time from the withdrawal 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 tumor evaluation is ± 7 days. Additional tumor evaluations may be performed if PD is suspected (for example, worsening of symptoms). Except for radiologically confirmed PD, subjects who discontinue the study treatment for any other reasons must also undergo a tumor evaluation every 8 weeks until documentation of confirmed PD, start of a new anti-tumor treatment, loss to follow-up, or death.

Subjects with CR or PR for the first time (whichever comes first) shall be radiographically confirmed at least 4 weeks (28 days) later, with a time window of + 7 days.

[18] SHR-1210 administration: once every 2 weeks. Administrations are performed on D1 and D15 of each 4-week treatment 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 new anti-tumor treatment beyond or within 90 days after the last dose. After the safety information collection period, only investigational product-related adverse events are collected. All investigational product-related adverse events should be followed up until they return to baseline, are resolved, improved to Grade ≤ 1, or reasonably explained, or until the subjects are stable, lost to follow-up, or dead.

[20] Concomitant therapies: Concomitant therapies since 30 days before the first dose until 90 days after the last dose shall be documented. Only concomitant therapies for drug-related AEs shall be documented within 30 days after the end of treatment (The use of all antibiotics within 3 months before administration and during administration is documented)

[21] Immunogenicity blood sampling: Before the administration on C1D1, C2D1, C3D1, and C4D1, once every 3 cycles after C4, and once prior to withdrawal from study.

[22] Tumor tissue: Before enrollment; fresh biopsy is preferred, otherwise use archival tumor tissue specimens.

[23] Ninety days after the last dose: Subjects must return to the study site for a follow-up on D30 after the last dose, and the safety information are obtained via telephone calls on D60 and D90 after the last dose (including AE outcomes, new SAEs, and AEs of special interest); the time window is ± 7 days.

[24] Survival follow-up: 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
NMPA	National Medical Products Administration
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	Glutamyl transpeptidase
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
h	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

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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

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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)]. The occurrence of nasopharyngeal carcinoma in China also shows a significant geographical pattern. Nasopharyngeal carcinoma 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 patients are 90% and 84%, respectively. However, approximately 20–37% of patients will have local recurrence or distant metastasis. Cisplatin-based combination chemotherapy is the first-line treatment regimen for such patients. 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 patients 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 patients 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 sustained response. Most patients 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 unacceptable for most patients. Therefore, there is an urgent need to develop new drugs for the treatment of recurrent or 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 focus. 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.

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 T cell surface protein receptor discovered in 1992, and is involved in the apoptosis process. PD-1 is a member of the CD28 family and has a 23% consistency in amino acid sequence with cytotoxic T lymphocyte antigen 4 (CTLA-4). However, 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 activates the PD-1 pathway and leads 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 patients with advanced solid tumors with positive PD-L1 expression. Among the 27 evaluable patients 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 a 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 in the treatment of recurrent or metastatic nasopharyngeal carcinoma that has 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 Medicine 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 antibody with the highest activity, was selected for further development. Phase I clinical studies 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 Product 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 mAb 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 Pharmacodynamics

(1) Affinity

Results from affinity assays involving SHR-1210 and human, monkey, and rat 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 rat PD-1 antigens. See **Table 1** for details.

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

Stationary Phase	Mobile phase	Affinity (nM)
SHR-1210	Human PD-1 antigen	6.9
SHR-1210	Rat 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, which was similar to the control antibodies 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

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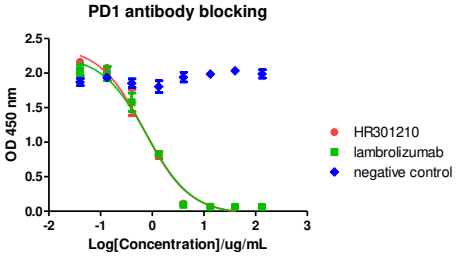
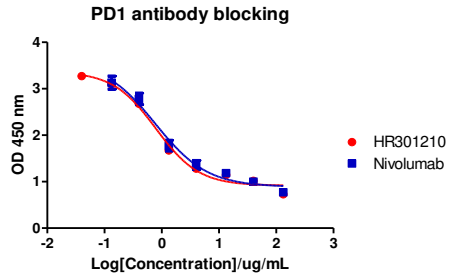
(2) Inhibition of PD-1/PD-L1 binding by SHR-1210

Experimental 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**). The IC_{50} was 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, 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 were small, they were not considered harmful effects. The maximum tolerated dose (MTD) of SHR-1210 was ≥ 800 mg/kg.

In a completed preclinical long term toxicity study in cynomolgus monkeys, continuous intravenous administration of SHR-1210 at 20, 50, and 100 mg/kg/dose for 4 weeks (5 total doses) were well-tolerated in 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 observed. No changes in organ weight, gross lesions, or histopathological changes associated with SHR-1210 were observed.

1.2.2.1.5 Pharmacokinetics

For SHR-1210 PK parameters after a single intravenous infusion in cynomolgus monkeys, see **Table 3**.

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

Dose (mg/kg)	Gender	$T_{1/2}$ (hr)	T_{max} (hr)	C_{max} (μg/mL)	AUC_{last} (hr·μg/mL)	Vz (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 Medicine Co., Ltd. On 26 Jan., 2016, it was approved for clinical trials (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, 3 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 3 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 patients with advanced solid tumors who failed standard treatment or lacked effective treatment methods. The study consists of three stages, including bridge escalation, PK extension, and clinical extension. Stage I adopts a "3 + 3" dose escalation mode, 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/dose, equivalent to the calculated dose of 3 mg/kg). In stage II, case extension is 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 is a clinical extension and sets a fixed-dose group (200 mg/dose). Subjects with nasopharyngeal carcinoma and lung cancer with brain metastases are 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/dose, 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 in dose administered. The half-life ($t_{1/2}$) of SHR-1210 also increased with the increase in dose, while the clearance rates (CLs) decreased slowly with the increase in 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 in dose. There was generally no accumulation in the steady state. During repeated administration, the overall receptor occupancy rate of each dose group of SHR-1210 maintained at approximately 75%. PD-1 receptor occupancy is the theoretical premise of SHR-1210's anti-tumor effect. This result suggested that SHR-1210 can fully occupy the PD-1 receptor and block the PD-1/PD-L1 signaling pathway at a dosing 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 included in the first two stages. Stage III was a clinical extension and set a fixed-dose group (200 mg/dose), and 62 subjects with nasopharyngeal carcinoma were 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 metastatic organs ≥ 3; more than 65% of subjects had received second-line or above chemotherapy, of which 28 % had received second-line chemotherapy and 34% had received third-line and above chemotherapy. The overall ORR was 29.0% (1 CR + 26 PR), and the DCR was 58.1% (1 CR + 26 PR + 27 SD). Especially in the 68 subjects of the 200 mg dose group, the ORR was 36.8% (1 CR +24 PR), and the DCR was 64.7% (1 CR +24 PR +19 SD). In the subgroup analysis, 58 subjects had previously received second-line or above chemotherapy, the ORR was 27.6% (1 CR + 15 PR), and the DCR was 51.7% (1 CR + 15 PR + 14 SD). A total of 43 subjects in the 200 mg dose group who had previously received second-line and above chemotherapy had an ORR of 37.2% (1 CR + 15 PR) and a DCR of 58.1% (1 CR + 15 PR + 9 SD).

- Safety summary of 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 patients with advanced solid tumors. As of 28 Feb., 2018, a total of 258 patients 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 years old, height of 166.68 ± 7.568 cm, weight 61.00 ± 11.130 kg, BMI of 21.92 ± 3.461 kg/m^2; 130 (50.4%) subjects had a baseline ECOG score of 0 and 127 (49.2%) had a score of 1; 257 (99.6%) subjects had a history of systemic chemotherapy; 155 (60.1%) subjects 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 drug-related adverse events was 31.8%; common drug-related adverse events mainly included cutaneous and subcutaneous tissue diseases: cutaneous capillary endothelial proliferation (81.8%), pruritis (22.1%), rash (16.3%); systemic diseases: asthenia (37.6%), fever (20.9%); blood and lymphatic diseases: 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 diseases: proteinuria (22.1%); endocrine disorder: hypothyroidism (19.8%); metabolism and nutrition disorders: 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, pyrexia, rash, and blood bilirubin increased. Cutaneous capillary endothelial proliferation is a unique skin reaction of SHR-1210 with a high incidence. However, it was mild, clinically tolerable, and disappeared after drug discontinuation.

1.2.3 Basis of dosing regimen

Preliminary data analysis of the safety and efficacy of SHR-1210 within the calculated doses (1-10 mg/kg) and fixed dose (200 mg) showed no DLT between the dose groups in this trial, similar in terms of the type and frequency of adverse events. The proportion of subjects who had at least one Grade ≥ 3 drug-related adverse event in the 1 mg/kg, 3 mg/kg, 200 mg/dose, and 10 mg/kg dose groups (the number of subjects with adverse events/the total number of subjects) 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 proportion of subjects who achieved disease response in the 1 mg/kg, 3 mg/kg, 200 mg/dose, and 10 mg/kg dose groups (the number of subjects with response/the total number of subjects) 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 trial, the pharmacokinetic behavior of SHR-1210 in patients with advanced solid tumors at the fixed dose of 200 mg/dose and the calculated dose of 3 mg/kg after single and multiple doses was generally the same. The drug concentration-time curve 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 concentration and accumulation ratio of SHR-1210 in serum after multiple doses at the fixed dose of 200 mg/dose and the calculated dose of 3 mg/kg were similar, and the level of steady-state minimum concentration of receptor occupancy was close to 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 patients' 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 product or treatment may have unpredictable or even serious side effects.

As of Feb. 28, 2018, the summary results of the safety data of the 3 phase I clinical studies suggested: the adverse events related to camrelizumab for injection were mostly of CTCAE Grade 1-2, and the incidence of Grade ≥ 3 drug-related adverse events was 31.8%; common drug-related adverse events mainly included skin and subcutaneous tissue diseases: cutaneous

capillary endothelial proliferation (81.8%), pruritis (22.1%), rash (16.3%); systemic diseases: asthenia (37.6%), fever (20.9%); blood and lymphatic diseases: 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 diseases: proteinuria (22.1%); endocrine disorder: hypothyroidism (19.8%); metabolism and nutrition disorders: 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. Among similar drugs, nivolumab monotherapy had an incidence of hypothyroidism of 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%. Pembrolizumab monotherapy had an incidence of hypothyroidism of 8.5% and an incidence in head and neck cancer of 15%. The incidence of aspartate aminotransferase increased or alanine aminotransferase increased varied as reported in different studies. In the study in malignant melanoma and lung cancer, the incidence was approximately 21-26%. In KETNOTE 021, the incidence of increased alanine aminotransferase 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. The proliferation of cutaneous capillaries in areas prone to rubbing may cause damage and bleeding. The proliferation of cutaneous capillaries 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 the treatment of advanced recurrent or 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 product treatment may benefit patients with advanced nasopharyngeal carcinoma.

2 OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary objective

- To evaluate through the independent review committee (IRC) the ORR of SHR-1210 in the treatment of patients with recurrent or metastatic nasopharyngeal carcinoma who have failed second-line or above chemotherapy.

2.1.2 Secondary objectives

- To evaluate the efficacy and safety of SHR-1210 in the treatment of patients with recurrent or metastatic nasopharyngeal carcinoma who have failed second-line or above 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 immunogenicity of SHR-1210 in the treatment of patients with recurrent or metastatic nasopharyngeal carcinoma, and to observe the correlation of immunogenicity with efficacy and safety.

2.2 Study Endpoints

2.2.1 Primary endpoint

- IRC-assessed ORR of SHR-1210 in the treatment of patients with recurrent or metastatic nasopharyngeal carcinoma who have failed second-line or above chemotherapy

2.2.2 Secondary endpoints

Efficacy

- Investigator-assessed objective response rate (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 severities of adverse events (AEs) and serious adverse events (SAEs), laboratory abnormalities, as per NCI-CTCAE v4.03
- Incidence of AEs resulting in dose interruption and discontinuation

2.2.3 Exploratory endpoints

- To evaluate the relationship between PD-L1 expression 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 Overall Design

This study is a single-arm, open-label, multi-center phase II clinical trial to observe and evaluate the efficacy and safety of anti-PD-1 antibody SHR-1210 in the treatment of patients with recurrent or metastatic nasopharyngeal carcinoma who have failed second-line or above chemotherapy. A total of 155 subjects are expected to be enrolled.

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

Safety visits are conducted prior to SHR-1210 administration on D1 and D15 in 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 Reducing Bias

3.2.1 Enrollment/randomization/blinding

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

3.2.2 Blinding

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 trial. Subjects must meet the following criteria to be allowed to participate in this trial. Any medical or non-medical conditions of a subject are considered for his/her eligibility.

4.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for this trial.

1. Aged 18 to 75, male or female;
2. Moderately differentiated or undifferentiated locally recurrent/metastatic nasopharyngeal carcinoma (WHO class II-III) in histopathology;

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 Revised Expert Consensus on Staging of Nasopharyngeal Carcinoma),

Appendix I ECOG PS Scoring Criteria

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 Calculation of Creatinine Clearance

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 Age in years, weight in 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

3. Appendix 1]. Definition of treatment failure: Progression during or after chemotherapy following recurrence/metastasis; 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; (see Appendix I ECOG PS Score for evaluation criteria in details)
5. Expected survival ≥ 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. Archived samples of 5-8 paraffin embedded sections with a thickness of 3-5 μm are also acceptable if a fresh biopsy is not accessible;
8. Major organ functions must meet the following requirements (No blood components or cell growth factors are allowed within 2 weeks prior to 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/L;

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. CrCl ≥ 50 mL/min (Cockcroft-Gault); (see Appendix II)

9. Female subjects of childbearing age 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 course of the trial in 60 days after the last dose of the investigational product (around 5 half-lives of the drug + menstrual cycle). Male subjects with partners of childbearing potential must take at least two contraceptive measures during the course of the trial and in 120 days after the last dose of the investigational product (around 5 half-lives of the drug + sperm production cycle);

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

4.2 Exclusion Criteria

Subjects meeting any of the following criteria must be excluded:

1. Patients with any active autoimmune disease or a 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 prednisone of more than 10 mg/day or equivalent hormone therapy) may be enrolled);

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. Patients with uncontrolled cardiac symptoms or disease, such as (1) NYHA Class II or higher 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 product. In the absence of active autoimmune disease, inhaled or topical use of corticosteroids and an equivalent dose to > 10mg/day of prednisone for adrenal hormone replacement are permitted;
6. Patients who have received chemotherapy and targeted therapy less than 4 weeks prior to the 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 resolved to CTCAE Grade ≤ 1 (except for alopecia and sequelae of relevant neurotoxicity of previous platinum therapy);
7. Patients with active infection or unexplained pyrexia of > 38.5 °C at screening or prior to the first dose (those with tumor-induced pyrexia may be enrolled as per the judgment of the investigator);
8. 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 subjects' safety or the collection of trial data.

4.3 Withdrawal or Discontinuation

4.3.1 Withdrawal Criteria

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

1. A subject withdraws the informed consent and requests to withdraw from the study;
2. Radiographic progressive disease occurs;

As per RECIST v1.1, a 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 stable clinical symptoms: a. no significant clinical symptoms or changes in laboratory measurements; b. no changes in the performance status score (deterioration); c. non-tumor rapid progression and tumor progression not involving important organs/sites (e.g., spinal cord compression);

3. Cumulative use of SHR-1210 for 2 years (without radiographic progression);
4. Subjects showing unacceptable toxicity;
5. Subjects with poor compliance;
6. Subjects lost to follow-up or becoming pregnant;
7. Other reasons for which the investigator consider 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, significant or unacceptable risks to the subjects;
2. Major errors in the protocol found during the implementation of the trial;

3. Ineffective investigational product/treatment, or meaninglessness to continue the trial;
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 trial 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. Patients 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.

Survival status should still be followed even if the subject refuses to visit the study site, unless the subject withdraws consent to provide further information or consent to be further contacted. In that case, no further study assessments should be conducted and no further data should be collected. The sponsor may retain and continue to use all data collected prior to the withdrawal of consent, unless the subject requests that the collected information be withdrawn as well.

4.4 Early Termination or Suspension of Study

This study can be reasonably terminated or suspended. 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. 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 early 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 NMPA.

4.5 Definition of Study Completion

One year after the last subject's first dose, the subjects undergoing treatment will be transferred to the extended project of SHR-1210 for continued treatment and observation.

5 Study Medication

5.1 Overview of Investigational Product

5.1.1 Access to drugs

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

Concomitant therapies and premedications for adverse events are not study drugs and are not provided by the sponsor. Such drugs are all marketed products and are purchased and stored by the study site 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 the label

Route of administration: intravenous drip infusion

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

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

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

For Clinical Studies Only

SHR-1210 for Injection Strength: 200 mg/vial Dosage Form: Lyophilized Powder

Drug No.: ****

Subject No.: _____ Administration Date: DD/MM/YYYY

Study Title: A Single-Arm, Open-Label, Multi-Center Phase II Clinical Study of PD-1 Antibody SHR-1210 in Treatment of Patients with Recurrent or Metastatic Nasopharyngeal Carcinoma Who Failed Second-Line or Above Chemotherapy

Study No.: SHR-1210-II-209

Clinical study approval No.: 2016L01455

Method of Administration: intravenous drip injection

Note: Prepare according the requirements of the protocol

Storage: sealed, away from light, store at 2-8 °C

Batch No.: Expiration Date: DD/MM/20YY

Sponsor: Jiangsu Hengrui Medicine Co., Ltd.

Manufacturer: Suzhou Suncadia Biopharmaceuticals Co., Ltd.

5.1.3 Storage and stability of drugs

The investigator or his/her authorized representative (e.g., pharmacist) will ensure that all investigational products are stored in a safe zone conforming to storage conditions and the access is controlled. The storage must be in compliance with regulatory requirements.

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

Any deviations related to the labeled conditions on the product should be immediately reported upon discovery. The study site should actively adopt measures to ensure that the drugs are returned to the storage conditions described on the label, and the temperature deviations and measures adopted should be reported to the sponsor.

Investigational products that are affected by temperature deviations must be temporarily isolated until approved by the sponsor for further use, and such case is not considered a protocol deviation. The use of affected investigational products 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 site.

5.1.4 Preparation of investigational products

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

Refer to the SHR-1210 brochure for blending, concentration (preparation) and administration of the injection. Since this product 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 products

SHR-1210 is an intravenous injection. It must be used in the outpatient or ward of the study site by qualified or experienced investigators and must not be used outside of a study site.

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

SHR-1210 is administered through intravenous drip infusion at 200 mg/dose for 30 min (not less than 20 min and not more than 60 min, including flushing). Do not administer through intravenous bolus or rapid bolus injection. The intravenous drip infusions are 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. Administrations are performed on D1 and D15 of each 4-week treatment cycle. The treatment will continue of until

confirmed PD, unacceptable toxicity, voluntary withdrawal by the subject, or withdrawal 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 were 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 a 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;
- New lesions.

If a subject develops PD as per RECIST 1.1, the investigator may decide whether treatment should be continued based on subject's overall clinical status, including performance status, clinical symptoms, as well as laboratory test results. Treatment can be continued if the subject is clinically stable, and a tumor evaluation should be performed again 4-6 weeks later. If non-PD is confirmed using both iRECIST and RECIST 1.1, then treatment may be continued. Treatment should be discontinued if PD is confirmed, unless the investigator believes the subject may continue benefiting clinically. The sponsor must be consulted before a subject with confirmed PD is allowed 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 examinations, the PD can be confirmed by referring to 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 load increases by ≥ 5 mm when compared to the first episode of PD.	The absolute value of tumor load increases by < 5 mm when compared to the first episode of PD.
Non-Target Lesion	Compared to the first episode of PD, clear and continuous progression of non-target lesions (qualitative).	No clear progression compared to the first episode of PD (qualitative).
New Lesion	(1) Onset of new lesion compared to the first episode of PD; (2) If a new lesion has appeared before, the new lesion has become larger or there are other new lesions.	(1) There are no other new lesions compared to the first episode of PD; (2) If a new lesion has appeared before, the new lesion is stable or becomes smaller.

The first date of PD will be used for all statistical analyses regardless of whether treatment is continued beyond progression.

5.1.6 Dose modifications and delay

5.1.6.1 Dose Modification

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

Table 4. SHR-1210 dose modifications.

Immune-Related Adverse Events (irAEs)	**Severity Grades for Treatment Interruption**	**Continuation**	**Discontinuation**
Diarrhea/colitis	2-3	Recovered to Grade 0-1 and the corticosteroids are reduced to 10 mg or less of prednisone or its equivalent dose	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	Recovered to Grade 0-1 and the corticosteroids are reduced to 10 mg or less of prednisone or its equivalent dose	Does not resolve within 12 weeks from the last dose.
	3-4	Discontinuation	Discontinuation

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<SHR-1210-II-209>
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Immune-Related Adverse Events (irAEs)	**Severity Grades for Treatment Interruption**	**Continuation**	**Discontinuation**
Hyperthyroidism	3	Recovered to Grade 0-1 and the corticosteroids are reduced to 10 mg or less of prednisone or its equivalent dose	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	Recovered to Grade 0-1 and the corticosteroids are reduced to 10 mg or less of prednisone or its equivalent dose	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	Return to Grade 0-1; SHR-1210 treatment can be continued after starting hormone 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-onset type I diabetes mellitus or Grade 3-4 hyperglycemia accompanied with evidence of β-cell depletion	After clinically and metabolically stabilized	Continue SHR-1210 treatment.
Renal failure or nephritis	2	Recovered to Grade 0-1 and the corticosteroids are reduced to 10 mg or less of prednisone or its equivalent dose.	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 Reaction	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 min. Closely monitor. If the symptoms return, the administration of the current SHR-1210 dose will be discontinued.
	3-4	Discontinuation	Discontinuation

Immune-Related Adverse Events (irAEs)	Severity Grades for Treatment Interruption	Continuation	Discontinuation
Other Drug-Related Adverse Events	3	Recovered to Grade 0-1 and the corticosteroids are reduced to 10 mg or less of prednisone or its equivalent dose.	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 drug-related AE recurs or any life-threatening event occurs.

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

the treatment shall be discontinued permanently.

The investigator may consider interrupting SHR-1210 in subjects who develop unacceptable or persistent Grade 2 drug-related AEs.

The treatment should be discontinued if a persistent Grade 2 adverse drug reaction does not resolve to Grade 0-1 within 12 weeks from the last dose.

5.1.7 Dose tracking

The study site shall prepare the drugs and complete the documentation as per the product brochure. The documentation system of the trial site 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 is administered through intravenous drip infusion (premedication not required) at a fixed dose of 200 mg. Each infusion takes 30 min (not less than 20 min, no more than 60 min) (including final flushing). Administrations are performed on D1 and D15 of each 4-week treatment cycle. The treatment will continue until confirmed PD, unacceptable toxicity, voluntary withdrawal by the subject, or discontinuation determined by the investigator.

5.3 Drug Management, Dispensation, and Retrieval

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

The investigational products must be stored according to the label. Duplicate drug receipt forms should be signed upon arrival at the study site, one for the study site 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 monitor is responsible for monitoring the supply, usage and storage of the investigational products, and the management of remaining products.

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

5.3.1 Disposal of investigational products

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

5.4 Concomitant Treatment

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

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

Once the study treatment is interrupted, concomitant therapies within 90 days after the last dose are documented. Only concomitant therapies for drug-related AEs are recorded within 30 days after the end of treatment

5.4.1 Other anti-tumor/cancer or investigational products

5.4.1.1 Permitted concomitant therapies

Topical use of corticosteroids such as ophthalmic, nasal, intra-articular, and inhaled are 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 progressive disease in subjects who require local treatment due to symptom exacerbations during the study;
2. Subjects with progressive disease must meet the criteria for continuation of treatment beyond progression;
3. The locally treated lesions can not be the target lesions.

All concomitant therapies should be documented in the eCRF since 30 days before the first dose until 90 days after the last dose. Only concomitant therapies for drug-related AEs are recorded within 30 days after the last dose. Antibiotic use within the 3 months before medication and during the study period must be documented in detail.

5.4.1.2 Prohibited Concomitant Therapies

- Anti-tumor systemic chemotherapy and biological therapy;
- Modern TCM preparations approved by the NMPA for anti-tumor treatment (refer to Appendix III);
- Immunotherapy not specified in the protocol;
- Immunomodulators with auxiliary anti-tumor effects, such as thymosin, lentinan, interleukin-12, etc.
- Inoculation of live vaccines within 4 weeks prior to 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. Seasonal inactivated flu vaccines for injection are permitted, but intranasal live attenuated flu vaccines are not permitted;
- Physiological doses of systemic corticosteroids for any purpose other than the relief of symptoms due to immunological causes may, after consulting with the sponsor, be approved (inhaled steroids are permitted as part of a fixed treatment for asthma or chronic obstructive pneumopathy). 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, as well as other anti-inflammatory medications if symptoms do not improve 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. If the investigator is sure that the AE is related to SHR-1210, supportive treatments listed below should be followed. If the AE is not related to SHR-1210, then the supportive treatments listed below do not need to be followed.

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 severe or long-lasting cutaneous capillary endothelial proliferation to confirm whether the internal organs and mucosa are involved. 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, haematochezia or mucus stools, with or without pyrexia) and intestinal perforations (such as peritonitis and obstruction intestinal).

- 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. Consider consulting GI and endoscopy 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.
- Begin tapering corticosteroids after symptoms improve to Grade 1 or lower. Taper for no less than 4 weeks.

3. AST, ALT, or bilirubin increased

- Subjects should receive IV or oral corticosteroids for Grade 2 events. Liver function should be monitored more frequently until returned to baseline (consider testing once per week).
- Subjects should receive 24-48 h of IV corticosteroids for Grade 3-4 events.
- Begin tapering corticosteroids after symptoms improve to Grade 1 or lower. Taper 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 disease.

- For subjects with Grade 2 hyperthyroidism, it is recommended to use non-selective beta-blockers (such as propranolol) as initial treatment.
- Subjects with Grade 3-4 hyperthyroidism should receive IV corticosteroids followed by oral corticosteroids. Begin tapering corticosteroids after symptoms improve to Grade 1 or lower. Taper 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 pneumonitis should receive systemic corticosteroids. Begin tapering corticosteroids after symptoms improve to Grade 1 or lower. Taper for no less than 4 weeks.
- If chronic use of corticosteroids is acceptable, antibiotic prophylaxis should be used.

6. Immune-Related Hypophysitis

- Persistent corticosteroid treatment should be used for Grade 2 hypophysitis. Begin tapering corticosteroids after symptoms improve to Grade 1 or lower. Taper for no less than 4 weeks. During the tapering process, appropriate hormone replacement therapy may be required.

- Subjects with Grade 3-4 hypophysitis should receive IV corticosteroids followed by oral corticosteroids. Begin tapering corticosteroids after symptoms improve to Grade 1 or lower. Taper 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. Evaluate the subjects' blood glucose, and full metabolic panel, urinary ketones, HbA1C, and C-peptide.

8. Renal failure or nephritis

- Subjects with Grade 2 events should receive corticosteroids.
- Subjects with Grade 3-4 events should receive systemic corticosteroids.
- Begin tapering corticosteroids after symptoms improve to Grade 1 or lower. Taper for no less than 4 weeks.

9. Infusion Reaction

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 should be given until recovery. Pre-dose prophylactics are recommended for subsequent administrations: 50 mg of diphenhydramine or equivalent, and/or 325-1000 mg of acetaminophen, at least 30 min before the administration of SHR-1210.	Continuation
Grade 2	Moderate reactions requiring treatment or interruption; rapidly resolve after symptomatic treatment (such as antihistamines, non-steroidal antiphlogistics, anesthetics, bronchodilators, intravenous fluids, etc.)	Intravenous administration of normal saline: 50 mg of diphenhydramine IV or equivalent and/or 325-1000 mg of acetaminophen; Bedside observation and close monitoring should be given until recovery. Corticosteroids or bronchodilators may be considered based on clinical needs; The amount of investigational product infused should be recorded in the source medical record; Pre-dose prophylactics are recommended for subsequent administrations: 50 mg of diphenhydramine or equivalent, and/or 325-1000 mg of acetaminophen can be given at least 30 min before the administration of SHR-1210. Use corticosteroids (equivalent to 25mg of hydrocortisone) when necessary.	Interrupt. Re-administer at 50% of the initial rate after symptoms resolve. Restore the original infusion rate (100%) if no complications occur within 30 min. Closely monitor. If the symptoms return, the administration of the current SHR-1210 dose will be discontinued.

CTCAE Grade	Clinical Symptoms	Clinical Management	SHR-1210 Treatment
Grade ≥ 3	Grade 3: Severe reaction without rapid recovery with treatment and/or interruption; or symptoms recur after alleviation; or the subject develops sequelae that requires hospitalization. Grade 4 (Life-threatening)	Immediately discontinue SHR-1210; Administer normal saline by intravenous drip infusion. • Bronchodilators are recommended. Subcutaneous injection of 0.2-1 mg of 1:1000 adrenaline solution or slow intravenous infusion of 0.1-0.25 mg of 1:10000 adrenaline solution, and/or 50 mg of diphenhydramine plus 100 mg methylprednisolone or equivalent by intravenous injection if necessary; • Based on the guidelines for anaphylaxis of the study site; Bedside observation and close monitoring should be given 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 trial procedures will be carried out according to the time schedule of the study procedures, 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 radiographic evaluations 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 prior to the start of study treatment.

- Signing of 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 surgical history: name of surgery, date of surgery, postoperative TNM staging, and date of postoperative recurrence;

- ✓ Radiotherapy history: site, dose, and start and end dates.
- ✓ Neoadjuvant chemotherapy history: chemotherapy regimen, cycles, and start and end dates;
- ✓ Adjuvant chemotherapy history: chemotherapy regimen, cycles, and start and end dates;
- ✓ Rescue treatment: regimen, cycles, start and end date, best overall response, time to tumor progression, and presence of changes in treatment due to tumor progression;
- ✓ History of concurrent disease, past medications, and medication allergies;
- ✓ Virological examinations (completed within 14 days prior to the first dose): HBsAg (if positive, need to test HBV-DNA), HBsAb, HBeAg, HBeAb, HBcAb, HCV-Ab (if positive, need to test HCV-RNA), HIV-Ab, and EBV-DNA;
- ✓ Fresh (preferred) or archival tumor tissue specimens for PD-L1 testing;

The following screening procedures should be completed within 7 days prior to the start of study treatment. A pregnancy test should be completed within 72 h prior to the start of study treatment.

- ✓ ECOG PS score;
- ✓ Vital signs: pulse, respiratory rate, body temperature, and blood pressure;
- ✓ Comprehensive physical examination: general condition, head and face, skin, lymph nodes, neck, eyes, ear, nose, and throat, oral cavity, respiratory system, cardiovascular system, abdomen, reproductive-urinary system, musculoskeletal system, nervous system, mental state, and others;
- ✓ Routine blood test: 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 should be added;
- ✓ Fecal occult blood;
- ✓ Blood biochemistry: ALT, AST, GGT, total bilirubin, direct bilirubin, AKP, BUN or urea (BUN preferred), 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, and INR;
- ✓ Echocardiography: including LVEF assessment. Perform if clinically indicated.
- ✓ 12-lead ECG: The investigator may decide to add other investigations if results are abnormal;
- ✓ 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 for suspected or confirmed cases of brain metastasis (or CT if MRI is contraindicated). Bone scan is performed only when clinically indicated and must be performed within 42 days prior to the first dose. At screening, tumor evaluations up to 4 weeks before the administration and before informed consent may be used as long as they meet the RECIST 1.1.
- ✓ Adverse events: Document adverse events starting from the signing of ICF.

- Concomitant therapies: Concomitant therapies within 30 days prior to the first dose shall be documented in detail; antibiotic use within the 3 months before enrollment shall be documented in detail.

6.2 Enrollment

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

6.3 Treatment Period

- All examinations and evaluations (except for imaging evaluations) should be completed within 3 days prior to administration. The following assessments should be completed prior to each dose in each cycle, but are not required to be repeated if they have been completed at screening within 7 days prior to the first dose;
  - ✓ ECOG PS score;
  - ✓ Vital signs: pulse, respiratory rate, body temperature, and blood pressure;
  - ✓ Physical examination: general condition, head and face, skin, lymph nodes, neck, eyes, ear, nose, and throat, oral cavity, respiratory system, cardiovascular system, abdomen, reproductive-urinary system, musculoskeletal system, nervous system, mental state, and others;

- ✓ Hematology: complete blood count with differential (white blood cells, red blood cells, lymphocytes, monocytes, neutrophils, basophils, eosinophils, and hemoglobin), and platelet 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+, Ca2+, Mg2+, and Cl-.
- ✓ 12-lead ECG: The investigator may decide to add other investigations if results are abnormal;
- ✓ Combined therapies: Combined therapies shall be documented in detail;
- ✓ Adverse events: document AEs in detail;

- The following investigations should be completed prior to 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 should be added;
  - ✓ Fecal occult blood (either before or after drug administration);
  - ✓ Thyroid function: TSH, FT3, and FT4 (if FT3 and FT4 are not available, use T3 and T4 instead);
  - ✓ Combined therapies: Combined therapies shall be documented in detail;
  - ✓ Adverse events: Document AEs in detail;
- The following investigations should be completed every 2 cycles prior to administration
  - ✓ EBV-DNA testing;
- Imaging evaluation: CT or MRI of the nasopharynx, neck, chest, and abdomen (including pelvic cavity); enhanced scanning is preferred if not contraindicated. Imaging examinations are performed every 8 weeks. For lesions of bone metastases, bone scans are only required if the evaluation of other lesions is CR and it is necessary to confirm whether the lesions of bone metastases have all disappeared, or if there are clinical indications. For subjects exiting the group for any reasons, tumor imaging evaluation should be performed at the time of withdrawal if an evaluation has not been done within 4 weeks prior to exiting. Imaging conditions should be the same as those at baseline (including slice thickness and contrast agent). The time window for tumor evaluation is ± 7 days. Additional tumor evaluations may be performed if PD is

suspected (for example, worsening of symptoms). Except for radiologically confirmed PD, subjects who discontinue the study treatment for any other reasons must also undergo a tumor evaluation every 8 weeks until documentation of confirmed PD, start of a new anti-tumor treatment, loss to follow-up, or death. Time of radiographic evaluation will not be adjusted due to dose delays. Subjects with CR or PR for the first time (whichever comes first) shall be radiographically confirmed at least 4 weeks (28 days) later, with a time window of + 7 days. Subjects who show PD for the first time but are clinically stable should have a confirmation scan 4-6 weeks thereafter as per the iRECIST and RECIST 1.1. The subsequent tumor evaluations will be performed at the pre-specified time points.

- Immunogenicity: Before the administration on C1D1, C2D1, C3D1, and C4D1, once every 3 cycles after C4, and once prior to withdrawal from study.

6.4 Follow-Up

Subjects should return to the study site for a follow-up 30 days after the last dose. Safety information is obtained via telephone follow-ups on D60 and D90 after the last dose (including AE outcomes, new SAE,s and AEs of special interest) with a time window of ± 7 days.

If subject starts a new anti-tumor treatment within 30 days after the last dose, then the visit should be completed before starting the new anti-tumor treatment.

- ✓ Routine blood test: RBC count, hemoglobin, platelet count, WBC count, neutrophil count, and lymphocyte count;
- ✓ Blood biochemistry: ALT, AST, GGT, total bilirubin, direct bilirubin, AKP, BUN or urea (BUN preferred), 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 therapies: Concomitant therapies within 90 days since the last dose should be documented. Only concomitant therapies for drug-related AEs are documented within 30 days after the last dose.

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

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

6.5 Visit for Early Discontinuation of Treatment

If relevant assessments and examinations have not been performed within 7 days before the subjects withdraw from the group, the following procedures should be followed:

- ✓ ECOG PS score;
- ✓ Vital signs: pulse, respiratory rate, body temperature, and blood pressure;
- ✓ Comprehensive physical examination: general condition, head and face, skin, lymph nodes, neck, eyes, ear, nose, and throat, oral cavity, respiratory system, cardiovascular system, abdomen, reproductive-urinary system, musculoskeletal system, nervous system, mental state, and others;
- ✓ Routine blood test: 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 should be added; Blood biochemistry: ALT, AST, GGT, total bilirubin, direct bilirubin, AKP, BUN or urea (BUN preferred), 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 examination: An imaging examination should be performed at the end of treatment/upon withdrawal if it has not already been done within 4 weeks prior to withdrawal. Subjects who discontinue treatment for reasons other than confirmed

PD must also undergo a tumor evaluation every 8 weeks until documentation of confirmed PD, start of a new anti-tumor treatment, or death.

- ✓ Adverse events: Document AEs in detail;
- ✓ Concomitant therapies: Concomitant therapies shall be documented in detail.

6.6 Unscheduled Visits

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

- ✓ Recording of concomitant medications;
- ✓ Adverse events;
- ✓ All relevant examinations (including imaging evaluations, if performed).

7 IMMUNOGENICITY STUDY

7.1 Sampling and Processing of Immunogenicity and Drug Trough Concentration Blood Samples

7.1.1 Blood sampling time

Before the administration on C1D1, C2D1, C3D1, and C4D1, once every 3 cycles after C4, and once prior to 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 are collected into a serum separation tube to collect the serum, which is then transferred to 4 cryotubes (aliquoted equally into 3 test tubes, 1 for ADA test, 1 for drug trough concentration test, 1 for the detection of 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 are 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 shipping information are described in the Laboratory Manual.

8 BIOMARKER TESTING

- Tissue PD-L1 testing: Tissue samples are collected before enrollment, preferentially newly acquired tissues. Patients who are unable to provide newly acquired tissues may instead provide 5-8 archival paraffin sections for PD-L1 testing.

9 EVALUATIONS

9.1 Efficacy Evaluation

The primary efficacy endpoint for this study is the ORR as assessed by IRC as per the RECIST 1.1.

The RECIST 1.1 are used to evaluate the ORR, 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 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 assessment shall be carried out during the screening period and treatment process through radiography according to the study procedure; tumor evaluation should also be performed when progressive disease is suspected (such as exacerbation of symptoms) and upon withdrawal (if no evaluation is not performed within the past 4 weeks).

Evaluations shall be conducted in accordance with the RECIST 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 h before the start of administration. After a negative result is obtained from the pregnancy test during the screening period, appropriate contraceptive measures should be taken. If an hCG test

is positive, the subject shall withdraw from the trial.

9.2.2 Adverse events

The incidence and severity of adverse events (AEs) 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, will be recorded in the eCRF. Treatment interruption and reduction as well as other modifications will be documented in the eCRF.

9.2.3 Laboratory safety assessment

All laboratory abnormalities that are clinically significant or meet the definition of an 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 examination

Vital signs, physical examinations, and body weight measurements will be performed according to the "Schedule of Study Procedures".

A comprehensive physical examination is required during the screening period, and all test results should be recorded in the eCRF.

A comprehensive physical examinations is required during the treatment period, and only abnormalities need to be recorded in the eCRF. If there is no change from the screening period, repeated records are not required.

9.2.5 12-lead ECG

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

10 ADVERSE EVENT REPORTING

10.1 Adverse Events (AEs)

10.1.1 Definition of AEs

An adverse event is any untoward medical occurrence in a study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. Safety

information is 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 treatments (if the 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 tumor treatment). An adverse event can be any unfavorable and unintended symptom, sign, abnormal laboratory finding, or disease, including the following:

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

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

3) Clinically significant laboratory abnormal values or results that are not caused by concomitant diseases.

All AEs that occurred in the subjects were documented in detail by the investigator, including: description of the AE and all related symptoms, onset time, severity, causes, relevance to the investigational product, 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 symptoms; clinical or diagnostic observations 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, etc.
3	Severe or medically significant symptoms but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. Self-care ADL: refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden
4	Life-threatening consequences; urgent intervention indicated
5	Resulting in death

10.1.3 Causality assessment

AEs will be collected and documented from the signing of the informed consent form to 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 product 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 product, such as whether there is a plausible temporal relationship with the investigational product, the characteristics of the investigational product, the toxicological and pharmacological effects of the investigational product, whether there are concomitant medications, the subject's underlying diseases, medical history, family history, 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 deemed "definitely related", "possibly related", "possibly unrelated", and "indeterminable" shall be listed as adverse drug reactions. When calculating the incidence of AEs, the total of these four categories shall be used as the numerator and the total number of subjects for safety assessments shall be used as the denominator.

10.2 Serious Adverse Events (SAEs)

10.2.1 Definition of SAEs

SAE refers to a medical occurrence during the clinical trial 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 leading to hospitalization or prolonged hospitalization;
- Events leading to permanent or serious disability/incapacity/impairment of work ability;
- Congenital anomalies or birth defects;
- Other important medical events (defined as events that may jeopardize the subject or require interventions to prevent any of the above).

10.2.2 Hospitalization

AEs resulting in hospitalization (even if for less than 24 h) or prolongation of 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 prolongation of 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 from before the trial 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 surgical procedures, which should be documented in the individual subject's baseline information;
- Hospitalization merely due to the 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 an AE, it should be reported as so. 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 progressive disease. 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	• Abnormal baseline: AST or ALT ≥ 2 × baseline level, and values ≥ 3 × ULN; or AST or ALT ≥ 8 × ULN • with TBIL increase ≥ 1 × ULN or ≥ 3 × ULN

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

Except for reexaminations of AST and ALT, albumin, creatine kinase, TBIL, direct and indirect bilirubin, γ-glutamyltransferase, prothrombin time (PT)/international normalized ratio (INR), and ALP shall also be tested. Detailed medical history should include history of alcohol, acetaminophen, soft drugs, various supplements, family diseases, occupational exposure, sexual behavior, travel, contact with patients with jaundice, surgery, blood transfusion, hepatic diseases or 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, and the possibility of potential drug-induced liver injury should be considered in the absence of any other causes of abnormal liver function, without waiting for all liver function test results. Potential drug-induced liver injury should be reported as an SAE.

10.2.5 Other anti-tumor treatments

SAEs should be recorded from the signing of the informed consent form until 90 days after the last dose of the investigational product. 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 shall immediately report to relevant regulatory

authorities as required by regulations within 24 h of acknowledgment, notify the sponsor, and report to the ethics committee in time.

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 product. The symptoms, severity, relationship with the investigational product, 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 believed that an SAE is not related to the investigational product but potentially related to the study conditions (such as the termination of past treatment, or comorbidities during the trial), their relationship should be explained in the description section of the SAE report form. If the severity of an SAE or its relationship to the investigational product 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 drug-related AEs should be followed up until resolved, return to baseline levels or Grade ≤ 1, steady state, or reasonably explained (e.g., loss to follow-up and death).

During each visit, the investigator should ask about the AEs/SAEs that occurred 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 clinical trial, if a female subject becomes pregnant, she must immediately discontinue the investigational product treatment. The investigator must report to the sponsor within 24 h after becoming aware of the event and fill out the "Pregnancy Report/Follow-Up Form for Hengrui Clinical Trials".

During the study, if the partner of a male subject becomes pregnant, the subject can continue in the study. The investigator must report 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.

If the outcome of the pregnancy is stillbirth, spontaneous abortion, or fetal malformation, it is

considered a SAE and should be reported accordingly within the time limit.

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 AEs of Special Interest

When an AE of special interest specified in the trial protocol occurs, the investigator must fill out the "Report of Adverse Event of Special Interest for Hengrui's Clinical Trials" and report 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;
- Grade ≥ 3 other immune-related adverse events (irAE);
- Any events that meet Hy's Law (ALT/AST > 3 × ULN accompanied with total bilirubin > 2 × ULN, with a lack of other causes);

11 CLINICAL MONITORING

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

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

ii. Monitoring how the investigator is implementing the trial protocol during the course of the trial, confirming that informed consent forms are obtained from all subjects before the trial, the enrollment rate and progress of the trial, 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 therapies, intercurrent diseases, loss to follow-up, and missing investigations should be confirmed and documented for each subject; Verifying that withdrawal and loss to follow-up of enrolled subjects are explained in the case report forms;

iv. Confirming that all adverse events have been recorded, and that SAEs have been recorded and reported within the specified time frame. Verifying that the investigational products are supplied, stored, dispensed, and returned in accordance with relevant regulations, and corresponding documentation should be 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 after each visit a written monitoring report, which should state the date and time of the monitoring visit, the name of the monitor, and the findings of the visit.

The Quality Assurance Department of the sponsor may conduct audit on the trial in the clinical research institution. The audit covers the supply of drugs, required trial 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 in a reasonable time and in a reasonable way.

12 DATA ANALYSIS/STATISTICAL METHODS

12.1 Sample Size

Efficacy assumptions

According to study SHR-1210-101, the ORR of all dose groups (n = 93) of subjects with nasopharyngeal carcinoma 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 second-line and above 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%.

The FDA-approved ORR in a single-arm study of pembrolizumab in the treatment of head and neck squamous cell carcinoma was 16%. Therefore, the lower limit of the 95% confidence interval for the ORR in this study should not be less than 15%.

Sample size calculation

According to the above efficacy assumptions (ORR = 26%), with a one-sided alpha = 0.025, 139 enrolled subjects could satisfy a 90% confidence that the lower limit of the 95% confidence interval of 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%, then 155 subjects shall be enrolled.

12.2 Statistical Analysis Plan

In this study, SAS 9.4 or above is 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 Discriminatory Rules

The primary endpoint of this trial is the ORR. The ORR of the investigational product was 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 was approved by the FDA).

Assumptions

$H0$: The ORR of the investigational product = 15%

$H1$: The ORR of the investigational product ≠ 15%

α level: 0.05 (two-sided).

12.4 Analysis Population

- Full analysis set (FAS): all eligible subjects who have used the investigational product after the screening. 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 major protocol deviations which significantly impact study results.

- Safety analysis set (SS): subjects who have taken the investigational product at least once and have at least one safety assessment after enrollment.
- Slice-testing biomarker analysis set: all enrolled subjects who have taken the investigational product at least once and have at least one slice-testing biomarker data for PD-L1.
- ADA analysis set: all enrolled subjects who have taken the investigational product at least once 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 patient is enrolled, the primary endpoints, secondary endpoints, and safety will be statistically analyzed.

12.5.2 Primary efficacy endpoint analysis

Primary endpoints will be analyzed based on the FAS. For the analysis of the primary endpoints, 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 RECIST 1.1 and is obtained by dividing the number of subjects whose BOR is CR or 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 endpoint analysis

The investigator-assessed ORR and DCR and their 95% confidence intervals (Clopper-Pearson method) are estimated.

The Kaplan-Meier method is used to estimate the progression-free survival (PFS), duration of remission (DoR), and overall survival (OS) and calculate the corresponding 95% confidence intervals (based on the Brookmeyer-Crowley method with log-log transformation, with the standard error calculated using the Greenwood formula).

The time to response (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 the measurement of the first CR or PR (whichever is measured first) to the time of first record 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 trial, the missing data of the efficacy endpoints are not treated specially, and the missing values are not estimated in the safety assessment.

12.5.5 Safety analysis

The safety is analyzed based on the 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 relevance and severity of AEs will be further tabulated for description. Descriptive statistics are used to summarize other safety endpoints. Summarize the incidence of AEs, adverse reactions, AEs resulting in withdrawal from the trial, AEs resulting in death, and SAEs. Severity of adverse events 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

Evaluate the relationship between PD-L1 expression and the efficacy of SHR-1210.

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 trial data are collected using the HRTAU EDC system.

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

Modifications: The system instructions must be followed when correcting the eCRF data as needed, and the reason for data correction must be recorded. The logic verification program in the system will verify the integrity and logic of the clinical trial data entered into the EDC system and generate an error message prompt for questionable data. The PI or data entry personnel (CRC) is permitted to modify or explain the problematic data. If necessary, multiple inquiries 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 the eCRF in a timely manner. The PI or CRC should promptly respond to queries raised by the monitor, data manager, and medical reviewer. After data cleaning is completed, the investigator will sign the completed eCRF for verification.

13.2 Data Monitoring

Implementer: CRA.

Monitoring content: To confirm that the study protocol is adhered to; the records on CRF is correct and complete, and consistent with the original medical records and laboratory test results, and whether there are errors or omissions in the data. According to the monitoring plan, the CRA will verify the completeness, consistency, and accuracy of trial data in the database. The CRA will discuss any queries with study personnel and direct them to add or correct the data whenever

necessary. Ensure that the data in the eCRF are consistent with source data. This process is also known as source data verification (SDV).

13.3 Data Management

13.3.1 EDC database establishment

The data manager will establish a study data collection system and database according to the study protocol, which will be available for online usage before the first subject is enrolled. Before use, all EDC users should receive adequate training and get the corresponding account to log into the system. (Access to EDC system will only be granted to the study site 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 guide. After submitting the eCRF, the monitor, 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 trial is completed, the study director, sponsor, statistician, and data manager will conduct a joint data review before statistical analysis. The important content is to determine the analysis data set (including the 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 trial, 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 shall be preserved until 2 years after the investigational

product is approved for marketing or 5 years after the clinical trial is terminated.

14 SOURCE DATA AND DOCUMENTS

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

The source data are the whole information that is required to reconstruct and evaluate the clinical study and the original records of clinical findings, observations, and other activities. These source documents and data records include but are not limited to: hospital record, laboratory records, memos, patient 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 subjects' 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

In order to ensure the data quality, the sponsor and investigator will jointly discuss and formulate the clinical study plan before the official commencement of the study All study personnel will receive GCP training.

All the study sites must comply with the SOPs for the management of the investigational product, including receipt, storage, dispensing, recovery, and destruction (if applicable).

According to the GCP guidelines, necessary steps 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 clinical study must have stringent specifications and be operated under normal conditions.

The investigator will input data required by the protocol into the eCRF. The monitor will check whether the eCRF is completely and accurately filled in and guide the study site personnel to carry out necessary correction and addition.

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

16 REGULATORY ETHICS, INFORMED CONSENT, AND SUBJECT PROTECTION

16.1 Regulatory Considerations

According to the corresponding regulatory requirements in China, an application should be submitted to the NMPA before starting a new drug trial and the clinical trial can only be carried out after an approval is obtained. The clinical trial 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 Ethics 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 trial must comply with the Declaration of Helsinki, Good Clinical Practice (GCP) enacted by the NMPA, and other relevant regulations. Before the trial is initiated, approval must be obtained from the ethics committee of the hospital.

The study protocol must not be unilaterally modified without approvals from both the sponsor and investigator. The investigator can modify or deviate from the study protocol before obtaining an approval from the 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 deviations.

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 ethics committee. After the end of the trial, the completion should be informed to the ethics committee.

16.3 Independent Ethics Committee

The protocol, informed consent form, recruitment material, and all subject materials must be reviewed and approved by the ethics committee. 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 ethics committee prior to being implemented. All revisions to the ICF must be approved by the ethics committee, 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 product 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;

Subjects contact card;

Recruitment advertisement.

16.4.2 Informed consent process and records

Informed consent begins 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 ethics committee. The investigator will explain the clinical trial to the subject and answer any questions posed by the subject. 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 subject. Even if the subject refuses to participate in this study, their rights will be fully protected. It will also be emphasized to the subjects that the nursing quality they can obtain will not be affected.

16.5 Confidentiality of Subject Information

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

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

The contact information of the subjects will be safely kept in each study site and only used internally during the study. After the end of the study, all the records would 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 research personnel at the study sites 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 are the property of Jiangsu Hengrui Medicine Co., Ltd. Hengrui does not limit the publication of any collected or research information by investigators, regardless of whether the results are beneficial to the investigational product 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, especially before the acquisition of patent, the investigator should agree to delay the publication, and the delay period should not exceed 60 days. Before open publication, Hengrui can require investigators to remove any previously unpublished confidential information (except for study results). If this study is part of a multi-center study, the investigator must agree that the first publication is an integrated result from all study sites. However, if a manuscript of the integrated analysis is not submitted after 12 months when the study is completed or terminated in all study sites, the investigator can independently publish results based on other requirements in this section.

18 CLINICAL TRIAL PROGRESS

Anticipated enrollment of the first subject: Jun. 2018

Anticipated enrollment of the last subject: Mar. 2019

Expected study completion: One year after the last subject's first dose, the subjects undergoing treatment will be transferred to the extended project of SHR-1210 for continued treatment and observation

19 REFERENCES

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Appendix IV ECOG PS Scoring Criteria

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 V Calculation of Creatinine Clearance

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 Age in years, weight in kg.

Appendix VI 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

<Camrelizumab for Injection>
<SHR-1210-II-209>
<Final Version V 1.0>, <(Version Date) 20 Apr., 20>

Appendix VIIAppendix 1. 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 metastasis to regional lymph nodes

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 Staging

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