Supplement

Supplement to: Huiyan Luo, et al. Effect of Camrelizumab vs Placebo Added to Chemotherapy on Survival and Progression-Free Survival in Patients with Advanced or Metastatic Esophageal Squamous Cell Carcinoma: The ESCORT-1st Randomized Clinical Trial

The Supplement contains the following items:

1. Original protocol
2. Final protocol
3. Amendments made to the protocol
4. Statistical analysis plan

A RANDOMIZED, OPEN-LABEL, CONTROLLED, MULTI-CENTER PHASE III CLINICAL STUDY OF ANTI-PD-1 ANTIBODY SHR-1210 COMBINED WITH PACLITAXEL AND CISPLATIN VS. PACLITAXEL COMBINED WITH CISPLATIN AS FIRST-LINE TREATMENT OF ADVANCED ESOPHAGEAL CANCER

Protocol No.:	SHR-1210-III-306
Trial Phase:	III
Compound Code:	SHR-1210
Compound Name:	Camrelizumab
Medical Director:	Qing Yang
Coordinating Site:	Sun Yat-Sen University Cancer Center
Principal Investigator:	Ruihua Xu
Version No.:	1.0
Version Date:	12 Jun., 2018

Sponsor: Jiangsu Hengrui Medicine Co., Ltd.

No. 7 Kunlunshan Road, Lianyungang Economic and Technological Development Zone, Jiangsu 222047, China

Sponsor's Signature Page

I have read and confirmed this clinical trial protocol (protocol no.: SHR-1210-III-306, version no.: 1.0, version date: 12 Jun., 2018). I agree to fulfill my duties in accordance with Chinese laws, the Declaration of Helsinki, the Good Clinical Practice (GCP) in China, 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 Good Clinical Practice (GCP) in China, and personally participate in or directly lead this clinical study. I have received the Investigator's Brochure for the investigational product; I have read the materials of preclinical studies of the investigational product and the protocol for this clinical trial. 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 Good Clinical Practice (GCP) in China, and personally participate in or directly lead this clinical study. I have received the Investigator's Brochure for the investigational product; I have read the materials of preclinical studies of the investigational product and the protocol for this clinical trial. 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 Randomized, Open-Label, Controlled, Multi-Center Phase III Clinical Study of Anti-PD-1 Antibody SHR-1210 Combined with Paclitaxel and Cisplatin vs. Paclitaxel Combined with Cisplatin as First-Line Treatment of Advanced Esophageal Cancer
Protocol No.	SHR-1210-III-306
Version No.	1.0
Sponsor	Jiangsu Hengrui Medicine Co., Ltd.
Principal Investigator	Prof. Ruihua Xu
Participating Study Centers	Approximately 45 sites
Study Objectives	**Primary Objective** • To compare the progression-free survival (PFS) (IRC-assessed) and overall survival (OS) of SHR-1210 combined with paclitaxel and cisplatin vs. paclitaxel combined with cisplatin in the treatment of patients with advanced esophageal cancer. **Secondary Objectives** • To compare the PFS (investigator-assessed), OS rates, objective response rate (ORR), and disease control rate (DCR) of SHR-1210 combined with paclitaxel and cisplatin vs. paclitaxel combined with cisplatin in the treatment of patients with advanced esophageal cancer, and to evaluate the duration of response (DoR) of the two groups; • To evaluate the safety of SHR-1210 combined with paclitaxel and cisplatin vs. paclitaxel combined with cisplatin in the treatment of patients with advanced esophageal cancer. **Exploratory Objectives** • To determine the proportion of subjects showing anti-SHR-1210 antibodies; • To evaluate the relationship between PD-L1 expression in tumor tissues and efficacy.
Study Endpoints	**Primary Endpoints** • IRC-assessed PFS (RECIST v1.1 criteria); • OS. **Secondary Endpoints** • Investigator-assessed PFS (RECIST v1.1 criteria); • OS rates;

	• ORR (RECIST v1.1 criteria); • DCR (RECIST v1.1 criteria); • DoR; • Quality of life score (EORTC QLQ-C30, EORTC QLQ-OES18); • Safety: AEs, laboratory measurements, etc. **Exploratory Endpoints** • To determine the proportion of subjects showing anti-SHR-1210 antibodies; • To evaluate the relationship between PD-L1 expression in tumor tissues and efficacy.
Study Population	Patients with unresectable locally advanced/recurrent or distant metastatic esophageal squamous cell carcinoma who have not previously received systemic anti-tumor treatment
Study Design	A randomized, open-label, controlled, multi-center study design is adopted in this study. It is planned to enroll 548 subjects with unresectable locally advanced/recurrent or distant metastatic esophageal squamous cell carcinoma who have not previously received systemic anti-tumor treatment. Eligible subjects will be randomly assigned to the treatment group or the control group in a 1:1 ratio. The stratification factors include: liver metastasis (with vs. without), whether the subjects have received definitive chemoradiation (yes vs. no). The treatment group is given SHR-1210 (200 mg, D1) combined with paclitaxel (175 mg/m^2, D1) and cisplatin (75 mg/m^2, D1) in 3-week cycles, for up to 6 cycles, followed by SHR-1210 (200 mg, D1) monotherapy as maintenance treatment until progressive disease (PD), unacceptable toxicity, withdrawal of informed consent, or when the investigator judges that the subject should withdraw from the study treatment. The longest duration of administration with SHR-1210 is 2 years. The control group is given paclitaxel (175 mg/m^2, D1) combined with cisplatin (75 mg/m^2, D1) in 3-week cycles, for up to 6 cycles; no systemic anti-tumor treatment is allowed before PD, while best supportive care and local palliative treatment are allowed until PD. In this study, an interim analysis will be conducted when about 269 (66%) OS events (about 22.1 months) are collected. The screening period of the study is 28 days. After completing the screening examinations and evaluation, subjects who meet the inclusion/exclusion criteria will enter the treatment period and be treated according to the administration frequency specified in the protocol. Relevant examinations and assessments must be completed before each dose. In particular, tumor imaging assessment is conducted once every 6 weeks (± 7 days). All subjects must complete the safety examinations and tumor assessments at the withdrawal visit. Then, safety follow-up is conducted for 90 days in the treatment group and for 30 days in the control group. The survival follow-up will be carried out once every 30 days starting from the last dose; subjects who withdraw

	due to non-PD reasons should be followed up for tumor progression, and continue to undergo tumor assessments once every 6 weeks (± 7 days) until PD, start of a new anti-tumor treatment, withdrawal of informed consent, loss to follow-up, or death.
Study Drugs	Recombinant humanized anti-PD-1 monoclonal antibody for injection, SHR-1210 (Manufacturer: Suzhou Suncadia Biopharmaceuticals Co., Ltd.) Paclitaxel (Manufacturer: Beijing Union Pharmaceutical Factory) Cisplatin (Manufacturer: Jiangsu Hansoh Pharmaceutical Group Co., Ltd.)
Method of Administration	**Treatment group:** Intravenous drip infusion of study drugs on Day 1 of each cycle during the combined treatment. SHR-1210 200 mg/dose, paclitaxel 175 mg/m^2, and cisplatin 75 mg/m^2 are given sequentially, in 3-week cycles, for up to 6 cycles, followed by SHR-1210 (200 mg/dose) monotherapy as maintenance treatment on Day 1 of each cycle via intravenous drip infusion, in 3-week cycles, until meeting the criteria for withdrawal from the study treatment. **Control group:** Intravenous drip infusion on Day 1 of each cycle. Paclitaxel 175 mg/m^2 and cisplatin 75 mg/m^2 are given in 3-week cycles, for up to 6 cycles.
Inclusion Criteria	Subjects must meet all of the following inclusion criteria to be eligible for this study. 1. Aged 18–75 years, male or female; 2. Histologically or cytologically diagnosed with unresectable locally advanced/recurrent (unable to receive esophagectomy and definitive chemoradiation) or distant metastatic esophageal squamous cell carcinoma (patients with adenosquamous carcinoma with squamous cell carcinoma accounting for more than 50% may be screened); 3. Have not received any systemic anti-tumor treatment. A patient who has received neoadjuvant/adjuvant and definitive chemoradiation can be screened if his/her last chemotherapy is more than 6 months from recurrence or progression; 4. With at least one measurable lesion (cavity structures such as oesophagus may not serve as measurable lesions) according to RECIST v1.1 criteria, which has not received any local treatment including radiotherapy (a lesion located in an area subjected to a previous radiotherapy can be selected as the target lesion if PD is confirmed); 5. Tissue samples for biomarker (such as PD-L1) analysis must be provided. Fresh tissues are preferred. Archival samples of 5–8 paraffin embedded sections that are 3–5 μm thick are also acceptable if a fresh biopsy is not accessible; 6. ECOG: 0–1 (see Appendix I); 7. Expected survival ≥ 12 weeks; 8. Vital organ functions meet the following requirements (use of any blood components, cell growth factors, leukopoietic agents, thrombopoietic agents,

	or anti-anemic agents is not allowed within 14 days before the first dose of the study drug); a. Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L b. Platelets ≥ 100 × 10^9/L; c. Hemoglobin ≥ 9 g/dL; d. Serum albumin ≥ 2.8 g/dL; e. Total bilirubin ≤ 1.5 × ULN; ALT, AST, and/or AKP ≤ 2.5 × ULN; ALT and/or AST ≤ 5 × ULN in the presence of liver metastasis; AKP ≤ 5 × ULN in the presence of liver or bone metastases; f. Serum creatinine ≤ 1.5 × ULN or creatinine clearance > 60 mL/min (Cockcroft-Gault, see Appendix II); g. Activated partial thromboplastin time (APTT) and international normalized ratio (INR) ≤ 1.5 × ULN (those receiving stable doses of anticoagulant therapy, such as low molecular weight heparin or warfarin, whose INR is within the expected therapeutic range of anticoagulants can be screened); 9. Women of childbearing potential and males with female partners of childbearing potential are required to take a medically approved contraceptive measure (e.g., intra-uterine contraceptive device, contraceptive pills, or condoms) during the study treatment period, for at least 3 months after the last dose of SHR-1210, and for at least 6 months after the last dose of chemotherapy; 10. Subjects must participate voluntarily, sign the informed consent form, have good compliance, and cooperate with follow-up visits.
Exclusion Criteria	Subjects meeting any one of the following are not eligible to participate in this study. 1. BMI < 18.5 kg/m^2 or weight loss ≥ 10% within 2 months before screening (at the same time, the effect of a large amount of pleural effusions and ascites on body weight should be considered); 2. With a history of gastrointestinal perforation and/or fistula within 6 months prior to the first dose; 3. Significant tumor invasion into adjacent organs (aorta or trachea) of esophageal lesions leading to higher risk of bleeding or fistula; 4. Presence of uncontrollable pleural effusion, pericardial effusion, or ascites requiring repeated drainage; 5. With a history of allergy to any monoclonal antibody, any component of SHR-1210, paclitaxel, cisplatin, or any other platinum-based drug; 6. Have any of the following situations: a. Have received anti-PD-1 or anti-PD-L1 antibody therapy; b. Have received any investigational drug within 4 weeks prior to the first dose of the study drug;

	c. Simultaneously enrolled into another clinical study, except for an observational (non-interventional) clinical study or follow-up of an interventional clinical study; d. Received the last dose of anti-tumor treatment (including chemotherapy, radiotherapy, targeted therapy) within ≤ 4 weeks before the first dose of the study drug; e. Requiring systemic treatment with corticosteroids (> 10 mg/day of prednisone or equivalent) or other immunosuppressive medications within 2 weeks before the first dose of the study drug, except the use of corticosteroids for local inflammation of the esophagus and prevention of allergies, nausea, and vomiting. Other special circumstances must be communicated with the sponsor. In the absence of active autoimmune disease, inhaled or topical use of corticosteroids or an equivalent dose of > 10 mg/day of prednisone for adrenal hormone replacement are permitted; f. Have been inoculated with any anti-tumor vaccine, or have been inoculated with any live vaccine within 4 weeks prior to the first dose of the study drug; g. Have undergone major surgery or severe trauma within 4 weeks prior to the first dose of the study drug; 7. Suffering toxicity from prior anti-tumor therapy that has not recovered to CTCAE Grade ≤ 1 (except alopecia) or a level specified in inclusion/exclusion criteria; 8. With central nervous system metastases; 9. With any active autoimmune disease, or a history of autoimmune disease (including but not limited to interstitial pneumonia, colitis, hepatitis, hypophysitis, vasculitis, nephritis, hyperthyroidism, and hypothyroidism), except for: vitiligo, or cured childhood asthma/allergy that do not require any intervention in adulthood; autoimmune-mediated hypothyroidism treated with a stable dose of thyroid hormone replacement therapy; and type I diabetes mellitus treated with a stable dose of insulin; patients with asthma requiring medical intervention with bronchodilators cannot be enrolled; 10. With a history of immunodeficiency, including positive anti-HIV assay, or with any other acquired or congenital immunodeficiencies, or with a history of organ transplantation or allogeneic bone marrow transplantation; 11. Having any poorly-controlled cardiovascular clinical symptom or disease, including but not limited to: (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 arrhythmia without clinical intervention or is poorly controlled after clinical intervention; 12. Having any serious infection (CTCAE Grade > 2) within 4 weeks prior to the first dose of the study drug, such as serious pneumonia, bacteremia, or infection-related complication requiring hospitalization; baseline chest radiography suggesting presence of active lung inflammation, infection symptoms and signs present within 2 weeks prior to the first dose of the study drug or requiring

	treatment by oral or intravenous administration of any antibiotic, except prophylactic use of antibiotics; 13. With a history of interstitial lung disease (except radiation pneumonitis that has not received hormone treatment), or a history of non-infectious pneumonitis; 14. Having active tuberculosis infection found in medical history or through CT examination, or having a history of active tuberculosis infection within 1 year prior to enrollment, or having had a history of active tuberculosis infection more than 1 year prior to enrollment but being treatment-naive; 15. With active hepatitis B (HBV DNA ≥ 2000 IU/mL or 10^4 copies/mL), hepatitis C (positive for hepatitis C antibody, and HCV-RNA higher than the lower limit of detection of the analytical method); 16. Diagnosed with any other malignancy within 5 years prior to the first dose of the study drug, with the exception of malignancies with low risk of metastasis and death (5-year survival rate > 90%) such as adequately treated basal cell or squamous cell skin cancer or cervical carcinoma in situ; 17. Pregnant or lactating women; 18. 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.
ADA Study	For the treatment group only, blood samples are collected once before administration on C1D1, C2D1, C4D1, C6D1, and C9D1; thereafter, once every 4 cycles before administration; once upon withdrawal from study treatment; and once 30 days after the last dose (if applicable).
Study Withdrawal Criteria	Reasons for withdrawal may include: 1. Withdrawal of informed consent and refusal of further follow-ups; 2. Loss to follow-up; 3. Death; 4. Study termination by the sponsor.
Study Treatment Discontinuation Criteria	Criteria for treatment discontinuation are as follows: 1. Withdrawal of informed consent and refusal of further study treatment; 2. Deterioration of subject's clinical symptoms/performance status as per the investigator's judgment; 3. When judged as PD as per RECIST v1.1 criteria, administration shall be discontinued for the control group; subjects in the treatment group who meet the criteria of clinical stability (see section 7.1.5) may continue administration of SHR-1210 combined with chemotherapy or SHR-1210 monotherapy, until PD is

	confirmed or the subjects no longer clinically benefit from the treatment as per the investigator's judgment; 4. Unacceptable toxicity, including any clinical AE, laboratory abnormalities, or other medical conditions; if the toxicities of SHR-1210 or chemotherapy are unacceptable, the drug with unacceptable toxicities should be discontinued; 5. Major protocol deviations; 6. Other reasons for which the investigator considers that it is necessary to discontinue the study treatment; 7. Pregnancy; 8. Loss to follow-up; 9. Death; 10. Study termination by the sponsor.
Determination of Sample Size	A parallel design is adopted in this study. The sample size is calculated based on the comparison of the two primary efficacy endpoints, i.e., PFS and OS, of PD-1 antibody SHR-1210 combined with paclitaxel and cisplatin (treatment group) and paclitaxel combined with cisplatin (control group). The hypothesis for efficacy is as follows: The hazard ratio (HR) of PFS (treatment group/control group) is 0.67, the estimated median PFS of the control group is 5 months, the HR of OS (treatment group/control group) is 0.73, and the estimated median OS of the control group is 10 months. Assuming a one-sided $\alpha = 0.005$, a power of 90% can be obtained when 378 PFS events are collected, and the estimated final analysis time of PFS is approximately 22.0 months. An interim analysis is planned for the OS. The Lan-DeMets α spending function will be used to allocate the α, and the O'Brien & Fleming method will be used to preset the superiority boundary (EAST 6.4.1) to control the overall one-sided $\alpha = 0.02$. The interim analysis will be performed when 269 (66%) OS events (approximately 22.1 months) are collected. The final analysis of OS will be performed when 408 OS events are collected to obtain a power of 85% under the premise that the overall type I error does not exceed one-sided $\alpha = 0.02$. The enrollment period is approximately 18 months, and the follow-up period is approximately 18 months. With a randomization ratio of 1:1, a total of approximately 520 subjects are required. Considering a dropout rate of 5%, 548 subjects are intended to be enrolled.
Data Analysis/ Statistical Methods	The primary efficacy endpoints of this study are PFS and OS. An interim analysis of the efficacy is planned for the OS. The final analysis for the PFS will be performed when 378 PFS events are collected (about 22 months). It is expected that the interim analysis of OS will be performed when 269 (66%) events (about 22.1 months) are collected. The final analysis of OS will be performed when 408 events are collected. The survival functions of PFS and OS of the two groups will be compared using both stratified and non-stratified Log-Rank tests. The time-event indicators will be analyzed using the Kaplan-Meier method, so as to estimate the survival function of both groups and plot the survival curves. In addition,

	the Cox regression model will be used to estimate the HR between the two groups and its 95% confidence interval (95% CI). For binary variables, the Cochran-Mantel-Haenszel method considering the stratification factors for randomization will be used to estimate the intergroup difference and its 95% confidence interval (95% CI). The safety analysis will be summarized using descriptive statistics.
Study Dates	Anticipated enrollment of the first subject: August 2018 Anticipated enrollment of the last subject: February 2020 Anticipated study completion: August 2021

SCHEDULE OF ACTIVITIES

Study Procedures

	Screening Period		**Treatment Period**		**Withdrawal Visit[26] (+ 3 days)**	**Safety Follow-Up[27]**		**Survival Follow-Up (± 7 days)[28]**
			Combined Chemotherapy	**Maintenance Treatment[17]**				
Visit Window	**D-28 to D-1**	**D-7 to D-1**	**Every 3 weeks ± 3 days**	**Every 3 weeks ± 3 days**		**30 days (± 7 days) after the last dose**	**60 and 90 days (± 7 days) after the last dose**	
Signing of Informed Consent Form[1]	√							
Verification of Eligibility		√						
Demographics	√							
Medical History[2]	√							
ECOG PS Score[3]		√	√	√	√			
Vital Sign Measurement[4]		√	√	√	√			
Physical Examination[5]		√	√	√	√			
Hematology[6]		√	√	√	√	√		
Urinalysis[7]		√	√	√	√			
Fecal Occult Blood[8]		√	√	√				

	Screening Period		Treatment Period		Withdrawal Visit[26] (+ 3 days)	Safety Follow-Up[27]		Survival Follow-Up (± 7 days)[28]
			Combined Chemotherapy	Maintenance Treatment[17]				
Visit Window	**D-28 to D-1**	**D-7 to D-1**	**Every 3 weeks ± 3 days**	**Every 3 weeks ± 3 days**		**30 days (± 7 days) after the last dose**	**60 and 90 days (± 7 days) after the last dose**	
Blood Biochemistry[9]		√	√	√	√	√		
Thyroid Function[10]		√	√	√	√	√		
Coagulation Function[11]		√						
Virological Examination[12]	√							
ECG[13]		√	√	√	√			
Echocardiography[14]		√						
Pregnancy Test[15]		√			√			
Tumor Imaging Evaluation[16]	√		√					
Randomization		√						
SHR-1210 Administration[18]			√	√				
Administration of Paclitaxel[19]			√					
Administration of Cisplatin[20]			√					
AE[21]	√	√	√	√	√	√	√	

	Screening Period		Treatment Period		Withdrawal Visit[26] (+ 3 days)	Safety Follow-Up[27]		Survival Follow-Up (± 7 days)[28]
			Combined Chemotherapy	Maintenance Treatment[17]				
Visit Window	**D-28 to D-1**	**D-7 to D-1**	**Every 3 weeks ± 3 days**	**Every 3 weeks ± 3 days**		**30 days (± 7 days) after the last dose**	**60 and 90 days (± 7 days) after the last dose**	
Concomitant Medication[22]	√	√	√	√	√	√	√	
Quality of Life Score[23]			√	√	√	√		
ADA Blood Sampling[24]			√	√	√	√		
Tumor Tissues[25]	√							

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 Visits" section of the eCRF.

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

[2] Medical history: including tumor history (diagnosis, surgery, radiotherapy, and pharmacological treatment), history of other concurrent diseases, and history of drug allergy.

[3] ECOG PS score: within 7 days prior to the first dose, before administration on Day 1 of each cycle (not required for the first dose if completed within 7 days prior to the first dose at screening), and upon withdrawal from study treatment.

[4] Vital signs: blood pressure, pulse, body temperature, and respiratory rate; within 7 days prior to the first dose, before administration on Day 1 of each cycle (not required for the first dose if completed within 7 days prior to the first dose at screening), and upon withdrawal from study treatment.

[5] Physical examination: within 7 days prior to the first dose and upon withdrawal from study treatment, a comprehensive physical examination (including general conditions, head and face, neck, skin, lymph nodes, eyes, ear, nose, throat, mouth, respiratory system, cardiovascular system, abdomen, reproductive and urinary system, musculoskeletal system, nervous system, mental state, and others) is performed; before administration on Day 1 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 administration on Day 1 of each cycle (not required for the first dose if completed within 7 days prior to the first dose at screening), upon withdrawal from study treatment, 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 Day 1 of every 2 cycles, and upon withdrawal from study treatment. In case of a urine protein ≥ 2+, a 24-h urine protein quantitation should be added.

[8] Fecal occult blood: 7 days prior to the first dose, Day 1 of every 2 cycles.

[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 administration on Day 1 of each cycle (not required for the first dose if completed within 7 days prior to the first dose at screening), upon withdrawal from study treatment, and 30 days after the last dose.

[10] Thyroid function: TSH, FT3, FT4. Within 7 days prior to the first dose, before administration on Day 1 of every 2 cycles, upon withdrawal from study treatment, and 30 days after the last dose.

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

[12] 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.

[13] ECG: within 7 days prior to the first dose, before administration on Day 1 of each cycle (not required for the first dose if completed within 7 days prior to the first dose at screening), and upon withdrawal from study treatment.

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

[15] Pregnancy test: for women of childbearing potential only. Within 72 hours prior to the first dose, and upon withdrawal from study treatment.

[16] Tumor imaging evaluation: CT or MRI of the neck, chest, and abdomen (including pelvic cavity) (both are enhanced; plain scans may be used instead when contrast agents are contraindicated). Brain MRI (or CT if MRI is contraindicated, both are enhanced; plain scans may be used instead when contrast agents are contraindicated) is required for suspected or diagnosed brain metastasis. Bone scan is performed only when clinically indicated.

- ✓ At screening, tumor assessments up to 4 weeks before randomization and before informed consent may be used as long as they meet the RECIST v1.1 criteria. Bone scan is required for suspected or diagnosed bone metastases and must be performed within 42 days prior to the first dose.
- ✓ During the treatment period, baseline imaging examination is conducted once every 6 weeks. Unscheduled imaging examinations may be performed for suspected PD. Imaging examinations should be conducted timely upon the subject's withdrawal from study of any cause (± 4 weeks; the examination is not repeated if the time of previous examination is less than 4 weeks from the withdrawal visit). Imaging conditions should be the same as those at baseline (including slice thickness and contrast agent).
- ✓ A time window of ± 7 days is allowed for imaging examinations. Subjects who discontinue study treatment for reasons other than radiologically confirmed PD must also undergo a tumor assessment every 6 weeks until observation of PD, start of a new anti-tumor treatment, withdrawal of informed consent, loss to follow-up, or death.

[17] Maintenance treatment: After the end of combined medication for the treatment group, SHR-1210 monotherapy is used for maintenance treatment.

[18] SHR-1210 administration: on Day 1 of each 3-week cycle.

[19] Administration of paclitaxel: on Day 1 of each 3-week cycle during the combined treatment, for up to 6 cycles.

[20] Administration of cisplatin: on Day 1 of each 3-week cycle during the combined treatment, for up to 6 cycles.

[21] AE: collected from the signing of the informed consent form until 90 days after the last dose of SHR-1210 or 30 days after the last dose of paclitaxel and cisplatin (whichever occurs first). If the subject starts a new anti-tumor treatment during the AE collection period, only treatment-related AEs are collected after the start of the new anti-tumor treatment.

[22] Concomitant medication: concomitant medications from 30 days before signing informed consent form until the start of new anti-tumor treatment are documented; afterward, only concomitant medications for treatment-related AEs are documented.

[23] Quality of life score (EORTC QLQ-C30, EORTC QLQ-OES18): before the first dose, every 6 weeks, upon withdrawal from study treatment, and 30 days after the last dose (if applicable), with a time window of ± 7 days; recommended to be obtained prior to administration as well as adverse event and tumor assessments.

[24] ADA blood sampling: for treatment group only, collected once before administration on C1D1, C2D1, C3D1, C4D1, C6D1, and C9D1; thereafter, once every 4 cycles before administration; once upon withdrawal from study treatment; and once 30 days after the last dose (if applicable).

[25] Tumor tissue: obtained before randomization; fresh biopsy is preferred, otherwise use archival tumor tissue specimens.

[26] Withdrawal visit: completed when the subject must discontinue study treatment.

[27] Safety follow-up period: All subjects should return to the study site for a follow-up 30 days after the last dose (perform telephone follow-up if withdrawal visit is completed) and the follow-ups via telephone are required 60 days and 90 days after the last dose for subjects in the treatment group only. Safety information should be obtained via telephone follow-ups (including AE outcome, new SAE, and AE of special interest) with a time window of ± 7 days.

[28] Survival follow-up: once every 30 days after the last dose, with a time window of ± 7 days.

ABBREVIATIONS

Abbreviation	Full Name
ADA	Anti-drug antibody
ADL	Activities of daily living
AE	Adverse event
AKP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the curve
BUN	Blood urea nitrogen
CFDA	China food and drug administration
CR	Complete remission
Cr	Creatinine
CRF	Case report form
CRO	Contract research organization
D	Day
DoR	Duration of response
DLT	Dose-limiting toxicity
EC	Ethics committee
EC	Esophageal cancer
EDC	Electronic data collection
FAS	Full analysis set
FIB	Plasma fibrinogen
FT3	Free triiodothyronine
FT4	Free thyroxine
GC	Gastric carcinoma
GCP	Good Clinical Practice
GGT	Gamma glutamyl transpeptidase
h	Hour
HCC	Hepatocellular carcinoma
Hb	Hemoglobin
HR	Hazard ratio
IC_{50}	Half maximal inhibitory concentration
IDMC	Independent Data Monitoring Committee

Abbreviation	Full Name
iRECIST	Immune-related response evaluation criteria in solid tumors
IU	International unit
kg	Kilogram
LDH	Lactate dehydrogenase
mg	Milligram
min	Minimum
mL	Milliliter
mm	Millimeter
MRI	Magnetic resonance imaging
MTD	Maximal tolerable dose
NOAEL	No observed adverse effect levl
NPC	Nasopharyngeal cancer
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PR	Partial remission
PD	Progressive disease
PK	Pharmacokinetic
PFS	Progression free survival
PPS	Per-protocol analysis set
PT	ProthrombinTime
PLT	Blood platelet
RBC	Red blood cell count
RECIST	Response evaluation criteria in solid tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	stable disease
SS	Safety analysis set
T-BIL	Total bilirubin
TNBC	Triple negative breast cancer
TSH	Thyroid-stimulating hormone
UA	Uric acid
ULN	Upper limit of normal
WBC	White blood cell count

1. KEY FUNCTIONAL ROLES

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2. INTRODUCTION: BACKGROUND AND SCIENTIFIC RATIONALE

2.1. Background

2.1.1. Esophageal cancer

Esophageal cancer is a type of malignant tumor that occurs in the esophageal mucosa. Worldwide, esophageal cancer ranks the eighth in cancer incidence and the sixth in mortality. China accounts for more than 50% of all esophageal cancers[1]. In 2015, there were 477,900 new esophageal cancer patients in China. From 2001 to 2011, the incidence and mortality of esophageal cancer ranked the fifth and the fourth among male tumor patients, respectively, and the incidence and mortality of esophageal cancer among female patients showed a year-on-year decline[2]. More than 90% of esophageal cancers are squamous cell carcinoma, and there are obvious regional differences. The provinces with a high incidence of esophageal cancer are Hebei, Henan, Fujian, and Chongqing, followed by Xinjiang, Jiangsu, Shanxi, Gansu, and Anhui[3].

Endoscopic treatment is preferred for early esophageal cancer (involving only the mucosa or submucosa). The 5-year survival rate is as high as 95%. However, as most patients are not treated in the early stage of the disease, the five-year survival rate for esophageal cancer is less than 20%[4]. First-line treatment for advanced unresectable, relapsed, metastatic esophageal cancer is platinum-based chemotherapy in combination with, for example, paclitaxel + cisplatin or 5-fluorouracil + cisplatin. The response rate is between 30–60% and the median OS is 5–10 months[3,5]. At present, treatment options for advanced esophageal cancer are very limited, and the survival of patients is relatively short.

2.1.2. SHR-1210

SHR-1210 is a humanized monoclonal antibody, whose heavy chain is immunoglobulin G4 (IgG4) and light chain is immunoglobulin κ (IgK). It is expressed in the supernatant of stable Chinese hamster ovary (CHO) cell lines. SHR-1210 can specifically bind to PD-1, blocking the interaction between PD-1 and its ligand (PD-L1), and restore T cell immune response to tumor cells.

2.1.2.1. Preclinical study results

In vitro pharmacodynamic studies showed that SHR-1210 had high affinity for PD-1 of humans, cynomolgus monkeys, and rhesus monkeys (2 nM, 8 nM, 4 nM, respectively), and effectively blocked PD-1/PD-L1 interaction (IC_{50} of 0.70 nM). In vivo pharmacodynamic studies showed that SHR-1210 had significant anti-tumor effects in mouse MC38 colorectal cancer model and xenograft mouse model of human malignant glioblastoma U87-MG.

Clinical pharmacokinetic studies in cynomolgus monkeys showed that the exposure (AUC and C_{max}) increased with dose, there was no gender difference in PK parameters, the clearance rate was dose-dependent, and the clearance rate was lower at higher doses. No drug accumulation was noted after repeated administration.

Toxicology studies showed that, for a single administration of SHR-1210 in cynomolgus monkeys, the MTD was ≥ 800 mg/kg; for repeated administrations, the MTD was ≥ 200 mg/kg. In the 4-week and 26-week toxicity studies, the NOAEL of SHR-1210 was 100 mg/kg.

Results of preclinical pharmacology studies showed that SHR-1210 had good anti-tumor activity, safety, and tolerability, supporting further clinical studies of SHR-1210. The detailed preclinical pharmacology data are presented in Investigator's Brochure.

2.1.2.2. Clinical study results

As of 28 Feb., 2018, 6 phase I, 9 phase II, and 2 phase III clinical studies of SHR-1210 have been conducted. The safety, efficacy, pharmacokinetics, and immunogenicity data summarized below are mainly from the following three phase I clinical studies (data cutoff date: 28 Feb., 2018).

SHR-1210-I-101 was an open-label, single-center, dose-escalation phase I clinical study evaluating the safety and tolerability of SHR-1210 in subjects with advanced solid tumors who had failed standard anti-tumor treatment. The study consisted of 3 stages: Stage 1 was the dose-escalation part. In the standard 3 + 3 dose-escalation design, SHR-1210 was intravenously infused at doses of 1 mg/kg, 3 mg/kg (approximately equivalent to a fixed dose of 200 mg), and 10 mg/kg, Q2W (except the first 4-week cycle, as subjects only received the study drug on Day 1

of this cycle for PK sampling and DLT observation). Stage 2 was the extension stage, during which the doses selected in Stage 1 were used, with up to 12 subjects in each group. Extension was conducted for indications of NPC and NSCLC in Stage 3. As of 28 Feb., 2018, a total of 123 subjects was enrolled in this study.

SHR-1210-I-102 was an open-label, single-center, dose-escalation phase I study evaluating the safety and tolerability of SHR-1210 in subjects with advanced malignant melanoma who had failed standard anti-tumor treatment. The study consisted of 2 stages: Stage 1 was the dose-escalation part. In the standard 3 + 3 dose-escalation design, SHR-1210 was intravenously infused at doses of 60 mg, 200 mg, and 400 mg, Q2W (except the first 4-week cycle, as subjects only received the study drug on Day 1 of this cycle for PK sampling and DLT observation). Stage 2 was the extension stage, during which the doses selected in Stage 1 were used, with up to 12 subjects in each group. As of 28 Feb., 2018, the enrollment of all 36 subjects of the study has been completed.

SHR-1210-I-103 was an open-label, single-center, dose-escalation phase I study evaluating the safety and tolerability of SHR-1210 in subjects with advanced solid tumors who had failed standard anti-tumor treatment. The study consisted of 3 stages: Stage 1 was the dose-escalation part. In the standard 3 + 3 dose-escalation design, SHR-1210 was intravenously infused at doses of 60 mg, 200 mg, and 400 mg, Q2W (except the first 4-week cycle, as subjects only received the study drug on Day 1 of this cycle for PK sampling and DLT observation). Stage 2 was the extension stage, during which the doses selected in Stage 1 were used, with up to 9–12 subjects in each group. Stage 3 would further explore the dosage for the Q2W regimen in subjects with EC, GC, HCC, and TNBC (60 subjects in total). As of 28 Feb., 2018, the enrollment of all 99 subjects of the study has been completed.

2.1.2.2.1. Safety results

A total of 258 subjects were enrolled in the three phase I clinical studies. No DLT was observed. All 258 (100.0%) subjects had at least one AE, 98 (38.0%) subjects had at least one Grade ≥ 3 AE, 256 (99.2%) subjects had at least one treatment-related AE, 82 (31.8%) subjects had at least one Grade ≥ 3 treatment-related AE, and 78 subjects had SAE, of which 61 had treatment-related SAE. AEs related to SHR-1210 were mostly of CTCAE Grade 1–2. Common treatment-related AEs 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%). Except for cutaneous capillary endothelial proliferation, other AEs were similar to those of similar drugs.

Overall, SHR-1210 had good safety and tolerability in patients with advanced solid tumors.

2.1.2.2.2. Efficacy results

In the SHR-1210-I-103 study, a total of 43 subjects with advanced esophageal squamous cell carcinoma who had failed the standard treatment were enrolled. The efficacy assessment showed an ORR of 25.6% and a disease control rate of 48.9%, demonstrating preliminary efficacy of SHR-1210 in patients with advanced esophageal squamous cell carcinoma.

2.1.2.2.3. Pharmacokinetics and immunogenicity

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, the median time to maximum concentration (T_{max}) of different dose groups (1 mg/kg, 3 mg/kg, 200 mg/dose, and 10 mg/kg) was in the range of 0.58–2.50 h; the in vivo exposure and elimination half-life ($t_{1/2}$) increased with the dose, the clearance rate (CL) slowly decreased with the increasing dose, and the volume of distribution (Vd) generally did not change with the increasing dose. After repeated administrations, the serum SHR-1210 concentration of each dose group generally reached a steady state after 3–5 treatment cycles. There was generally no accumulation at 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 administration frequency of Q2W.

A total of 117 subjects had immunogenicity results in the three phase I clinical studies. Twenty (17.1%) subjects were tested positive for anti-SHR-1210 antibodies at least once. Among them, 3 (2.6%) were tested positive for anti-SHR-1210 antibodies at baseline; 17 (14.5%) were tested negative at baseline and positive after baseline, of which 10 (8.5%) were transiently positive. Among the above-mentioned subjects tested positive for anti-SHR-1210 antibodies, only 1 (0.9%) showed neutralizing antibody activity (the subject's anti-SHR-1210 antibody was negative at baseline and persistently positive after baseline); the subject showed positive neutralizing activity only once before the administration of Cycle 2, and the neutralizing activity was negative in subsequent cycles. No significant effect of positive anti-SHR-1210 antibodies on the safety, efficacy, and drug clearance rate of subjects has been observed.

2.2. Scientific Rationale

2.2.1. Study rationale

Chemotherapeutic drugs were once thought to kill tumor cells directly through cytotoxicity. But with the deepening of research, it has been found that chemotherapeutic drugs also exert anti-tumor effects by regulating the body's immune system, cause immunogenic death of tumor cells, increase the antigen cross-presentation ability of dendritic cells, and activate the body's anti-tumor immune effect[6]; reduce myeloid-derived suppressor cells (MDSC), and relieve the immune suppression caused by them[7]; increase the ratio of cytotoxic lymphocytes to regulatory T cells, and reduce the inhibitory effect of regulatory T cells on immunity[8]; block the STAT6 pathway, down-regulate PD-L2 expressed by dendritic cells and tumor cells, and increase T cell activity and tumor cell recognition[9]. High expression of PD- L1 is related to tumor invasion and chemotherapy resistance[10]. Immune checkpoint inhibitors acting on the PD-1/PD-L1 pathway enhance tumor immune surveillance and anti-tumor immune responses by inhibiting the PD-1 signaling. Therefore, the combination of immune checkpoint inhibitors and chemotherapy may have a synergistic anti-tumor effect.

At present, clinical studies of immune checkpoint inhibitors nivolumab, pembrolizumab, and BGB-A317 in combination with chemotherapy as first-line treatment of advanced esophageal cancer are undergoing (as detailed in Table 1). The combination of chemotherapy with PD-1/PD-L1 immune checkpoint inhibitors may be a new first-line treatment for advanced esophageal cancer.

Table 1. Summary of clinical studies of immune checkpoint inhibitors combined with chemotherapy as first-line treatment for advanced esophageal cancer.

No.	Study Design	Sample Size	Administration Regimen	Primary Endpoints
1	Single-arm, non-randomized, open-label phase II clinical study	30	Esophageal squamous cell carcinoma group: Fluorouracil + cisplatin + BGB-A317	To evaluate the safety of the combination regimen by monitoring AEs and SAEs, laboratory assessments, physical examination, vital signs, and ECG.
2	Randomized, double-blind, placebo-controlled phase III clinical study	700	Treatment group: fluorouracil + cisplatin + pembrolizumab Control group: fluorouracil + cisplatin	PFS of all subjects; PFS of PD-L1 positive subjects; OS of all subjects; OS of PD-L1 positive subjects.
3	Randomized, open-label, active-controlled phase III clinical study	939	Treatment group: nivolumab + ipilimumab Nivolumab + fluorouracil + cisplatin	PFS of PD-L1 positive subjects; OS of PD-L1 positive subjects.

			Control group: fluorouracil + cisplatin	

Guidelines in China and abroad recommend paclitaxel and cisplatin as one of the first-line treatment regimens for advanced esophageal cancer. The ORR was 36–60%, the PFS was 5–8 months, and the OS was 7–17 months[11,12,13,14,15,16]. For patients with advanced esophageal cancer, the efficacy of existing first-line treatments has plateaued. In this study, SHR-1210 combined with paclitaxel and cisplatin is used as the first-line treatment for advanced esophageal cancer, so as to improve the survival benefits of subjects.

2.2.2. Basis of administration regimen

The design basis of the administration regimen in this study is as follows.

No DLT was observed for SHR-1210 at the calculated dose (1–10 mg/kg) and fixed dose (200 mg), and the type and frequency of AEs were similar. The results of the SHR-1210-101 study showed that the 200 mg dose group had a higher objective response rate (33%), and its pharmacokinetic behavior was generally consistent with that of the 3 mg/kg dose group. The PD-1 receptor occupancy rate remained around 75% 22 days after administration. Combined with the preliminary data on pharmacokinetics, pharmacodynamics, safety, and efficacy, and considering the convenience of clinical operation, SHR-1210 at a fixed dose of 200 mg is used in this study, in 3-week treatment cycles.

The recommended administration regimen of paclitaxel combined with cisplatin by NCCN Guidelines (2018) is paclitaxel 135–200 mg/m^2 (D1) plus cisplatin 75 mg/m^2 (D2), in 3-week treatment cycles. The recommend administration regimen of paclitaxel combined with cisplatin by China's Guidelines for Diagnosis and Treatment of Esophageal Cancer (2011) is paclitaxel 140–170 mg/m^2 (D1) plus cisplatin 80–100 mg/m^2 (D1 or divided into 2–5 days), in 3-week treatment cycles. There is currently no study with large sample size to clarify the fixed-dose regimen of paclitaxel and cisplatin. Paclitaxel combined with cisplatin is the first-line chemotherapy regimen commonly used in the treatment of advanced esophageal cancer in China. In a single-arm phase II clinical trial[13], 35 subjects with unresectable, recurrent or metastatic esophageal squamous cell carcinoma were enrolled and received paclitaxel 175 mg/m^2 on D1 plus cisplatin 75 mg/m^2 on D1, in 21-day treatment cycles. The ORR was 48.6% and the OS was 13 months. In another retrospective study[15] with the same administration regimen, the ORR was 42.5% and the OS was 13.46 months. With reference to the above results, the selected doses of paclitaxel and cisplatin in this study are 175 mg/m^2 (D1) and 75 mg/m^2 (D1), respectively, in 3-week treatment cycles.

2.3. Potential Risks and Benefits

2.3.1. Known potential risks

SHR-1210 is an immune checkpoint inhibitor. Subjects may develop a transient accelerated tumor growth, i.e., pseudoprogression, after receiving this type of drug. In this study, subjects in the treatment group who have radiographically confirmed progressive disease (PD) as per RECIST v1.1 criteria but are clinically stable are allowed to continue treatment with SHR-1210 combined with chemotherapy or SHR-1210 monotherapy. Since it is difficult to distinguish between pseudoprogression and true progression in imaging examinations, this operation may cause delay of other anti-tumor treatments in subjects with true progression. Therefore, the investigator should fully inform the subject of the risk, and comprehensively consider the subject's imaging examination, aspiration biopsy results, and clinical symptoms to determine whether the subject should continue medication.

Any drug or treatment may have unpredictable or even serious side effects. SHR-1210 is an immune checkpoint inhibitor that may cause immune-related AEs. The safety data from previous clinical studies suggested that the incidence of immune-related AEs of SHR-1210 was similar to that of similar drugs, mainly including immune-related thyroid dysfunction, pneumonia, hepatitis, and nephritis. In addition, the cutaneous capillary endothelial proliferation is a benign skin reaction and its incidence is relatively high. Cutaneous capillary endothelial proliferation occurring in areas prone to rubbing may cause damage and bleeding. Cutaneous capillary endothelial proliferation occurring in exposed areas such as the face may also affect the appearance of the subjects. Other treatment-related AEs are detailed in the Investigator's Brochure. Common treatment-related AEs of paclitaxel include myelosuppression, nausea, vomiting, and peripheral neuropathy. Common treatment-related AEs of cisplatin include nephrotoxicity, ototoxicity, neurotoxicity, myelosuppression, nausea, and vomiting, Other AEs related to paclitaxel and cisplatin are listed in their package inserts. The combination of SHR-1210 with paclitaxel and cisplatin may have a small possibility of toxicity but the probability of allergic reactions may increase. Safety risks exist during the study medication. Close follow-up is necessary during the course of the clinical study. Interventions and actions should be adopted in a timely manner.

2.3.2. Known potential benefits

Paclitaxel combined with cisplatin is a common first-line chemotherapy regimen for the treatment of advanced esophageal squamous cell carcinoma in the clinical practice. The combination of SHR-1210 with chemotherapy may have a synergistic anti-tumor effect, which will benefit patients with advanced esophageal squamous cell carcinoma.

3. OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary objective

- To compare the progression-free survival (PFS) (IRC-assessed) and overall survival (OS) of SHR-1210 combined with paclitaxel and cisplatin vs. paclitaxel combined with cisplatin in the treatment of patients with advanced esophageal cancer.

3.1.2. Secondary objectives

- To compare the PFS (investigator-assessed), OS rates, objective response rate (ORR), and disease control rate (DCR) of SHR-1210 combined with paclitaxel and cisplatin vs. paclitaxel combined with cisplatin in the treatment of patients with advanced esophageal cancer, and to evaluate the duration of response (DoR) of the two groups;
- To evaluate the safety of SHR-1210 combined with paclitaxel and cisplatin vs. paclitaxel combined with cisplatin in the treatment of patients with advanced esophageal cancer.

3.1.3. Exploratory objectives

- To determine the proportion of subjects showing anti-SHR-1210 antibodies;
- To evaluate the relationship between PD-L1 expression in tumor tissues and efficacy.

3.2. Study Endpoints

3.2.1. Primary endpoints

- IRC-assessed PFS (RECIST v1.1 criteria);
- OS.

3.2.2. Secondary endpoints

- Investigator-assessed PFS (RECIST v1.1 criteria);
- OS rates;
- ORR (RECIST v1.1 criteria);
- DCR (RECIST v1.1 criteria);
- DoR;

- Quality of life score (EORTC QLQ-C30, EORTC QLQ-OES18);
- Safety: AEs, laboratory measurements, etc.

3.2.3. Exploratory endpoints

- To determine the proportion of subjects showing anti-SHR-1210 antibodies;
- To evaluate the relationship between PD-L1 expression in tumor tissues and efficacy.

4. STUDY DESIGN

4.1. Overall Design

A randomized, open-label, controlled, multi-center study design is adopted in this study. It is planned to enroll 548 subjects with unresectable locally advanced/recurrent or distant metastatic esophageal squamous cell carcinoma who have not previously received systemic anti-tumor treatment. Eligible subjects will be randomly assigned to the treatment group or the control group in a 1:1 ratio (treatment allocation is presented in Table 2). The stratification factors include: liver metastasis (with vs. without), whether the subjects have received definitive chemoradiation (yes vs. no).

Table 2. Treatment groups.

Treatment Group	Combined Medication (in 3-week cycles, for up to 6 cycles)	Maintenance Treatment (in 3-week cycles)
Treatment Group	SHR-1210 + Paclitaxel + Cisplatin	SHR-1210
Control Group	Paclitaxel + Cisplatin	Best supportive care and local palliative treatment (see Section 7.3)

The treatment group and control group will receive combined medication for up to 6 cycles. After the completion of combined medication, subjects in the treatment group will continue to receive SHR-1210 monotherapy as maintenance treatment, until PD, unacceptable toxicity, withdrawal of informed consent, or when the investigator judges that the subject should withdraw from the study treatment. The longest duration of administration with SHR-1210 is 2 years. For subjects in the control group without PD, no systemic anti-tumor treatment is allowed, while best supportive care and local palliative treatment (see Section 7.3) are allowed until PD.

Subjects may experience pseudoprogression after receiving the immunotherapy drugs. Thus, if the subject in the treatment group is evaluated as PD for the first time as per RECIST v1.1 criteria, but the investigator judges that the subject is clinically stable and can clinically benefit, the subject may continue to receive SHR-1210 combined with chemotherapy or SHR-1210

monotherapy after approval by the sponsor. Imaging examination will be repeated after at least 4 weeks (± 7 days). If PD is confirmed in the subsequent imaging examination, the subject must discontinue SHR-1210 combined with chemotherapy or SHR-1210 monotherapy unless the investigator believes that the subject can continue to benefit clinically from the treatment. After discussing with the sponsor again and obtaining approval, the subject may continue treatment until the subject no longer benefits clinically as per the investigator's judgment.

In this study, an interim analysis will be conducted when about 269 (66%) OS events (about 22.1 months) are collected.

The screening period of the study is 28 days. After completing the screening examinations and evaluation, subjects who meet the inclusion/exclusion criteria will enter the treatment period and be treated according to the administration frequency specified in the protocol. Relevant examinations and assessments must be completed before each dose. In particular, tumor imaging assessment is conducted once every 6 weeks (± 7 days). All subjects must complete the safety examinations and tumor assessments at the withdrawal visit. Then, safety follow-up is conducted for 90 days in the treatment group and for 30 days in the control group. The survival follow-up will be carried out once every 30 days starting from the last dose; subjects who withdraw due to non-PD reasons should be followed up for tumor progression, and continue to undergo tumor assessments once every 6 weeks (± 7 days) until PD, start of a new anti-tumor treatment, withdrawal of informed consent, loss to follow-up, or death.

Refer to Figure 1 for study design.

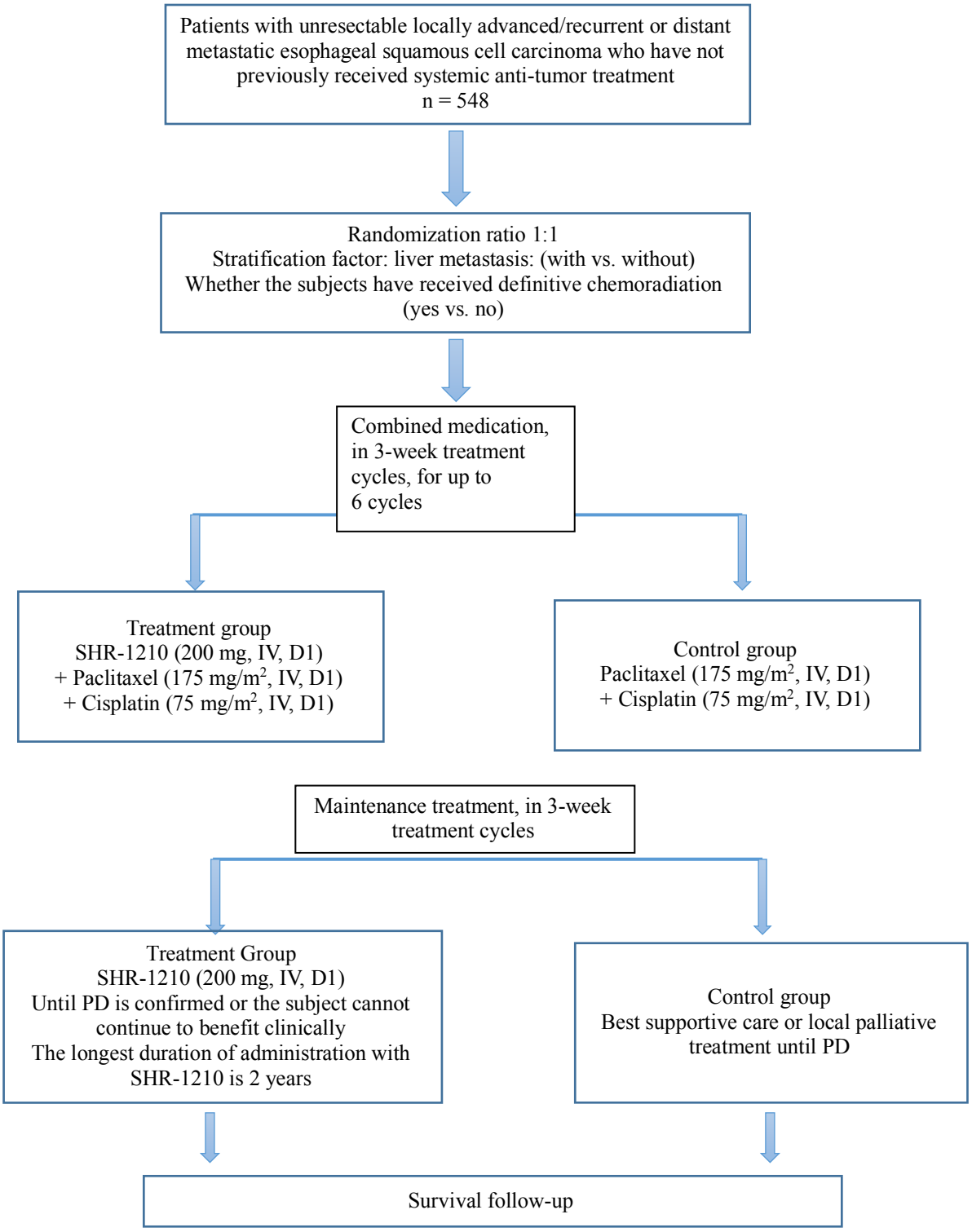

Figure 1. Study design schematic.

4.2. Methods to Reduce Bias

4.2.1. Enrollment/randomization/blinding

This study adopts a open-label design. The investigator will log in to the randomization system, enter the basic information of subjects who have signed the informed consent form and meet the inclusion criteria, and select the stratification factors for randomization to generate the randomization number and the allocated treatment group. The randomization ratio between the treatment group and the control group is 1:1. Stratified block randomization can ensure the balance of randomization.

No blinding is applied in this study. In order to reduce deviations, the frequency of imaging assessment of the treatment group and the control group remains the same. The imaging assessments of tumor lesions are performed according to RECIST v1.1 criteria. The primary efficacy endpoint, PFS, is assessed by the Independent Review Committee (IRC) under blinded state. The final analysis strategy will be determined before the primary efficacy endpoint analysis database is locked, including defining data censoring rules in advance. The efficacy analysis will only be carried out at the time point specified in the protocol.

4.2.2. Blinded assessment

Not applicable.

4.2.3. Unblinding

Not applicable.

5. SELECTION AND WITHDRAWAL OF SUBJECTS

5.1. Inclusion Criteria

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

1. Aged 18–75 years, male or female;
2. Histologically or cytologically diagnosed with unresectable locally advanced/recurrent (unable to receive esophagectomy and definitive chemoradiation) or distant metastatic esophageal squamous cell carcinoma (patients with adenosquamous carcinoma with squamous cell carcinoma accounting for more than 50% may be screened);
3. Have not received any systemic anti-tumor treatment. A patient who has received neoadjuvant/adjuvant and definitive chemoradiation can be screened if his/her last chemotherapy is more than 6 months from recurrence or progression;

4. With at least one measurable lesion (cavity structures such as oesophagus may not serve as measurable lesions) according to RECIST v1.1 criteria, which has not received any local treatment including radiotherapy (a lesion located in an area subjected to a previous radiotherapy can be selected as the target lesion if PD is confirmed);
5. Tissue samples for biomarker (such as PD-L1) analysis must be provided. Fresh tissues are preferred. Archival samples of 5–8 paraffin embedded sections that are 3–5 μm thick are also acceptable if a fresh biopsy is not accessible;
6. ECOG: 0–1 (see Appendix I);
7. Expected survival ≥ 12 weeks;
8. Vital organ functions meet the following requirements (use of any blood components, cell growth factors, leukopoietic agents, thrombopoietic agents, or anti-anemic agents is not allowed within 14 days before the first dose of the study drug);
    a. Absolute neutrophil count (ANC) ≥ 1.5×10^9/L
    b. Platelets ≥ 100×10^9/L;
    c. Hemoglobin ≥ 9 g/dL;
    d. Serum albumin ≥ 2.8 g/dL;
    e. Total bilirubin ≤ 1.5 × ULN; ALT, AST, and/or AKP ≤ 2.5 × ULN; ALT and/or AST ≤ 5 × ULN in the presence of liver metastasis; AKP ≤ 5 × ULN in the presence of liver or bone metastases;
    f. Serum creatinine ≤ 1.5 × ULN or creatinine clearance > 60 mL/min (Cockcroft-Gault, see Appendix II);
    g. Activated partial thromboplastin time (APTT) and international normalized ratio (INR) ≤ 1.5 × ULN (those receiving stable doses of anticoagulant therapy, such as low molecular weight heparin or warfarin, whose INR is within the expected therapeutic range of anticoagulants can be screened);

9. Women of childbearing potential and males with female partners of childbearing potential are required to take a medically approved contraceptive measure (e.g., intra-uterine contraceptive device, contraceptive pills, or condoms) during the study treatment period, for at least 3 months after the last dose of SHR-1210, and for at least 6 months after the last dose of chemotherapy;
10. Subjects must participate voluntarily, sign the informed consent form, have good compliance, and cooperate with follow-up visits.

5.2. Exclusion Criteria

Subjects meeting any one of the following are not eligible to participate in this study.

1. BMI < 18.5 kg/m^2 or weight loss ≥ 10% within 2 months before screening (at the same time, the effect of a large amount of pleural effusions and ascites on body weight should be considered);
2. With a history of gastrointestinal perforation and/or fistula within 6 months prior to the first dose;
3. Significant tumor invasion into adjacent organs (aorta or trachea) of esophageal lesions leading to higher risk of bleeding or fistula;
4. Presence of uncontrollable pleural effusion, pericardial effusion, or ascites requiring repeated drainage;
5. With a history of allergy to any monoclonal antibody, any component of SHR-1210, paclitaxel, cisplatin, or any other platinum-based drug;
6. Have any of the following situations:
    a. Have received anti-PD-1 or anti-PD-L1 antibody therapy;
    b. Have received any investigational drug within 4 weeks prior to the first dose of the study drug;
    c. Simultaneously enrolled into another clinical study, except for an observational (non-interventional) clinical study or follow-up of an interventional clinical study;
    d. Received the last dose of anti-tumor treatment (including chemotherapy, radiotherapy, targeted therapy) within ≤ 4 weeks before the first dose of the study drug;

e. Requiring systemic treatment with corticosteroids (> 10 mg/day of prednisone or equivalent) or other immunosuppressive medications within 2 weeks before the first dose of the study drug, except the use of corticosteroids for local inflammation of the esophagus and prevention of allergies, nausea, and vomiting. Other special circumstances must be communicated with the sponsor. In the absence of active autoimmune disease, inhaled or topical use of corticosteroids or an equivalent dose of > 10 mg/day of prednisone for adrenal hormone replacement are permitted;

f. Have been inoculated with any anti-tumor vaccine, or have been inoculated with any live vaccine within 4 weeks prior to the first dose of the study drug;

g. Have undergone major surgery or severe trauma within 4 weeks prior to the first dose of the study drug;

7. Suffering toxicity from prior anti-tumor therapy that has not recovered to CTCAE Grade ≤ 1 (except alopecia) or a level specified in inclusion/exclusion criteria;

8. With central nervous system metastases;

9. With any active autoimmune disease, or a history of autoimmune disease (including but not limited to interstitial pneumonia, colitis, hepatitis, hypophysitis, vasculitis, nephritis, hyperthyroidism, and hypothyroidism), except for: vitiligo, or cured childhood asthma/allergy that do not require any intervention in adulthood; autoimmune-mediated hypothyroidism treated with a stable dose of thyroid hormone replacement therapy; and type I diabetes mellitus treated with a stable dose of insulin; patients with asthma requiring medical intervention with bronchodilators cannot be enrolled;

10. With a history of immunodeficiency, including positive anti-HIV assay, or with any other acquired or congenital immunodeficiencies, or with a history of organ transplantation or allogeneic bone marrow transplantation;

11. Having any poorly-controlled cardiovascular clinical symptom or disease, including but not limited to: (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 arrhythmia without clinical intervention or is poorly controlled after clinical intervention;

12. Having any serious infection (CTCAE Grade > 2) within 4 weeks prior to the first dose of the study drug, such as serious pneumonia, bacteremia, or infection-related complication requiring hospitalization; baseline chest radiography suggesting presence of active lung inflammation, infection symptoms and signs present within 2 weeks prior to the first dose of the study drug or requiring treatment by oral or intravenous administration of any antibiotic, except prophylactic use of antibiotics;
13. With a history of interstitial lung disease (except radiation pneumonitis that has not received hormone treatment), or a history of non-infectious pneumonitis;
14. Having active tuberculosis infection found in medical history or through CT examination, or having a history of active tuberculosis infection within 1 year prior to enrollment, or having had a history of active tuberculosis infection more than 1 year prior to enrollment but being treatment-naive;
15. With active hepatitis B (HBV DNA ≥ 2000 IU/mL or 10^4 copies/mL), hepatitis C (positive for hepatitis C antibody, and HCV-RNA higher than the lower limit of detection of the analytical method);
16. Diagnosed with any other malignancy within 5 years prior to the first dose of the study drug, with the exception of malignancies with low risk of metastasis and death (5-year survival rate > 90%) such as adequately treated basal cell or squamous cell skin cancer or cervical carcinoma in situ;
17. Pregnant or lactating women;
18. 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.

5.3. Randomization Criteria

Subjects who meet the inclusion and exclusion criteria will be randomized to the treatment group or control group in a 1:1 ratio using the randomization system. Randomization will be stratified by liver metastasis (with vs. without) and whether the subjects have received definitive chemoradiation (yes vs. no).

5.4. Lifestyle Requirements

5.4.1. Contraception

If the investigator believes that the female subject or the male subject's partner is at risk of pregnancy, the subject must take at least one highly effective contraceptive measure from the signing of the informed consent form until at least 3 months after the last dose of SHR-1210 for the treatment group and at least 6 months after the last dose of chemotherapy for the control group. After consulting with the subject, the investigator or designated personnel will select an appropriate contraceptive method from the following contraceptive methods, and confirm the subject's awareness of correct and consistent use the contraceptive method. At time points shown in SCHEDULE OF ACTIVITIES, the investigator shall notify the subject of the persistent and correct use of contraception (the subjects need to confirm that they use at least one of the selected contraceptive measures consistently and correctly). The subject should be aware that the investigator must be notified immediately once the selected method of contraception is stopped, or when the subject or the partner is suspected or confirmed of pregnancy.

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

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

5.5. Withdrawal from Study or Treatment Discontinuation

5.5.1. Study withdrawal criteria

Reasons for withdrawal may include:

1. Withdrawal of informed consent and refusal of further follow-ups;
2. Loss to follow-up;
3. Death;
4. Study termination by the sponsor.

5.5.2. Criteria for treatment discontinuation

Criteria for treatment discontinuation are as follows:

1. Withdrawal of informed consent and refusal of further study treatment;
2. Deterioration of subject's clinical symptoms/performance status as per the investigator's judgment;
3. When judged as PD as per RECIST v1.1 criteria, administration shall be discontinued for the control group; subjects in the treatment group who meet the criteria of clinical stability (see section 7.1.5) may continue administration of SHR-1210 combined with chemotherapy or SHR-1210 monotherapy, until PD is confirmed or the subjects no longer clinically benefit from the treatment as per the investigator's judgment;
4. Unacceptable toxicity, including any clinical AE, laboratory abnormalities, or other medical conditions; if the toxicities of SHR-1210 or chemotherapy are unacceptable, the drug with unacceptable toxicities should be discontinued;
5. Major protocol deviations;
6. Other reasons for which the investigator considers that it is necessary to discontinue the study treatment;
7. Pregnancy;
8. Loss to follow-up;
9. Death;
10. Study termination by the sponsor.

5.5.3. Procedures for withdrawal or discontinuation

Subjects should undergo efficacy and safety assessments as specified in the protocol at the withdrawal and safety follow-up visits. All AEs and their outcomes should be documented. 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 PD, start of a new anti-tumor treatment, withdrawal of informed consent form, loss to follow-up, or death.

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 can retain and continue to use all data collected before withdrawal of informed consent, unless the subject requests a retraction of collected data.

5.6. Early Termination or Suspension of Study

This study can be terminated early or suspended if there are sufficient reasons. This may result from the decision of the regulatory authorities, changes in comments by the Ethics Committee, efficacy or safety issues of the study medications, or the judgment of the sponsor. In addition, Hengrui reserves the right to terminate the research and development of SHR-1210. 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 provide relevant reasons.

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

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

5.7. Definition of Study Completion

Study completion is defined as follows: The number of events required for the primary efficacy endpoint, OS, has been observed.

6. IMMUNOGENICITY STUDY (FOR TREATMENT GROUP ONLY)

6.1. Collection and Processing of Blood Samples

6.1.1. Blood sampling time

Collected once before administration on C1D1, C2D1, C4D1, C6D1, and C9D1; thereafter, once every 4 cycles before administration; once upon withdrawal from study treatment; and once 30 days after the last dose (if applicable).

6.1.2. Processing and storage of blood samples

At each of the above time points, 4–6 mL of venous blood sample is 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). The cryotubes are stored in a low temperature freezer at -60 °C to -80 °C for 6 months or at -20 °C for 1 month, until they are transported to the central laboratory for testing. Please refer to the Laboratory Manual for specific operation details.

6.2. Shipping of Clinical Samples

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

7. STUDY MEDICATION

7.1. Description of the Study Drugs and Control Drug

7.1.1. Access to drugs

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

7.1.2. Dosage form, appearance, packaging, and label

Investigational product: SHR-1210 for injection (not marketed)

Manufacturer: Suzhou Suncadia Biopharmaceuticals Co., Ltd.

Dosage form: lyophilized powder

Strength: 200 mg in 20 mL vials

Batch No.: see Certificate of Analysis

Method of administration: intravenous 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

A Randomized, Open-Label, Controlled, Multi-Center Phase III Clinical Study of Anti-PD-1 Antibody SHR-1210 Combined with Paclitaxel and Cisplatin vs. Paclitaxel Combined with Cisplatin as First-Line Treatment of Advanced Esophageal Cancer

(Study No.: SHR-1210-III-306)

SHR-1210

For Clinical Study Use Only

Clinical study approval No.: 2016L01455

Indication: unresectable locally advanced/recurrent or distant metastatic esophageal squamous cell carcinoma

Dosage form: lyophilized powder for injection

Strength: 200 mg/vial

Method of administration: Prepare according to the product manual, for intravenous drip infusion only

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

Batch No.:

Expiry date: MM/DD/20YY

Manufacturer: Suzhou Suncadia Biopharmaceuticals Co., Ltd.

Investigational product: Paclitaxel

Manufacturer: Beijing Union Pharmaceutical Factory

Dosage form: Injection

Strength: 5 mL:30 mg

Batch No.: see package insert

Method of administration: intravenous infusion

Shelf life: 24 months

Storage conditions: stored below 25 °C, away from light, sealed

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

Paclitaxel

For Clinical Study Use Only

A Randomized, Open-Label, Controlled, Multi-Center Phase III Clinical Study of Anti-PD-1 Antibody SHR-1210 Combined with Paclitaxel and Cisplatin vs. Paclitaxel Combined with Cisplatin as First-Line Treatment of Advanced Esophageal Cancer

(Study No.: SHR-1210-III-306)

Sponsor: Jiangsu Hengrui Medicine Co., Ltd.

Note: Please return the remaining products to the pharmacist

Investigational product: Cisplatin

Manufacturer: Jiangsu Hansoh Pharmaceutical Group Co., Ltd.

Dosage form: Injection

Strength: 6 mL:30 mg

Batch No.: see package insert

Method of administration: intravenous infusion

Shelf life: 24 months (tentative)

Storage conditions: away from light, sealed

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

Cisplatin

For Clinical Study Use Only

A Randomized, Open-Label, Controlled, Multi-Center Phase III Clinical Study of Anti-PD-1 Antibody SHR-1210 Combined with Paclitaxel and Cisplatin vs. Paclitaxel Combined with Cisplatin as First-Line Treatment of Advanced Esophageal Cancer

(Study No.: SHR-1210-III-306)

Sponsor: Jiangsu Hengrui Medicine Co., Ltd.

Note: Please return the remaining products to the pharmacist

7.1.3. Storage and stability of drugs

The investigator or authorized personnel (such as a pharmacist) is responsible for ensuring all study drugs are stored in a secure, controlled access area that meets the storage conditions and complies with applicable regulatory requirements.

Study drugs should be stored under the storage conditions listed in Section 7.1.2. Where the protocol and other information differ, store according to the storage conditions listed on the SHR-1210 label. For paclitaxel and cisplatin, store according to the storage conditions outlined in the package insert.

Daily maximum and minimum temperatures of all storage zones must be measured and recorded by the study site (such as freezer, refrigerator or room temperature). Documentation should begin with the receipt of the drugs until the last subject of the study site completes the last study treatment. 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.

Report immediately if the storage conditions are found to deviate from the drug label, description on the storage condition, or package insert. The study site should actively adopt measures to ensure that the drugs are returned to the storage conditions described on the label or package insert, and the temperature deviations and measures adopted should be reported to the sponsor.

Study drugs affected by the temperature deviation should be isolated temporarily and may only be used after approval by the sponsor and if it is not a protocol deviation. Affected study drugs used 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.

7.1.4. Preparation of study drugs

Drugs used in this study are all administered via intravenous infusion. Therefore, the drugs should be prepared by a qualified or experienced study staff such as a study nurse. SHR-1210 does not contain preservatives, and must be prepared using aseptic technique. See Product Manual for details of drug preparation. Paclitaxel and cisplatin are approved drugs and should be prepared according to their package insert.

7.1.5. Administration of study drugs

Treatment group: The method of administration is shown in Table 3. SHR-1210 combined with paclitaxel and cisplatin may be given for up to 6 cycles. If SHR-1210, paclitaxel, or cisplatin has been discontinued due to toxicity, other study drugs may continue to be used for the rest of the cycle. Cycles without the use of chemotherapy are not counted toward combined medication cycles. After the completion of combined medication, SHR-1210 monotherapy will continue to be given as maintenance treatment until the withdrawal criteria are met.

Table 3. Method of administration in treatment group.

	SHR-1210	Paclitaxel	Cisplatin
Dose and Route of Administration	200 mg IV	175 mg/m^2 IV	75 mg/m^2 IV
Infusion Rate	Not less than 20 min, not more than 60 min, including flushing	More than 3 h or per the clinical practice of the study site	Approximately 60 min or per the clinical practice of the study site
Pretreatment before Administration	Not necessary	Pretreatment before administration should be given according to the clinical practice of the study site	Pretreatment before administration should be given according to the clinical practice of the study site
Time of Drug Administration	D1	D1	D1
Sequence of Combined Medication	After the end of SHR-1210 infusion, paclitaxel and cisplatin should be given sequentially at least 30 min later.		
Frequency of Combined Medication	Every cycle contains 3 weeks (for up to 6 cycles)		
Frequency of Monotherapy for Maintenance	Every cycle contains 3 weeks		
Total Administration Time of SHR-1210	Up to 2 years		

The time window of administration is ± 3 days from the scheduled date of administration (from the date of the first administration). Drugs administered outside the time window is considered a delayed dose, and subsequent doses shall be administered according to the actual date of last administration. During the combined medication, if the delay is expected to exceed 2 weeks due to the toxicity of chemotherapy, only SHR-1210 will be given until the toxicity returns to the acceptable level for chemotherapy administration, after which the combination of chemotherapy and SHR-1210 will be resumed. Chemotherapy may be suspended for up to 6 consecutive weeks; if longer than 6 weeks, the chemotherapy will be discontinued. If the delay is expected to exceed 2 weeks due to the toxicity of SHR-1210, only chemotherapy will be given until the toxicity returns to the standard of SHR-1210 administration, after which the combination of

chemotherapy and SHR-1210 will be resumed. SHR-1210 may be suspended for up to 12 consecutive weeks; if longer than 12 weeks, SHR-1210 will be discontinued. For dose delays due to toxicities with equivocal association that are expected to return to the standard of administration within 2 weeks, the three drugs shall be delayed simultaneously.

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 SHR-1210 combined with chemotherapy or SHR-1210 monotherapy after the first PD (per RECIST v1.1 criteria).

Accelerated tumor growth may include any of the following:

- Worsening of existing target lesions;
- Worsening of existing non-target lesions;
- New lesions.

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 at least 4 weeks (± 7 days) later. If unconfirmed PD is established using both iRECIST and RECIST v1.1 criteria, then treatment may be continued. Treatment should be discontinued if PD is confirmed, unless the investigator believes the subject may continue benefiting clinically so that 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).

Refer to the criteria listed in Table 4 for confirmation of PD.

Table 4. Confirmation criteria of PD.

	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 with the first episode of PD.	The absolute value of tumor load increases by < 5 mm when compared with the first episode of PD.
Non-Target Lesion	Clear and continuous progression of non-target lesions compared with the first episode of PD (qualitative).	No clear progression compared with the first episode of PD (qualitative).
New Lesion	(1) Onset of new lesion compared with 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 with 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.

Control group: The method of administration is shown in Table 5. Paclitaxel combined with cisplatin may be given for up to 6 cycles. If paclitaxel or cisplatin has been discontinued due to toxicity, another chemotherapy drug may continue to be used for the rest of the cycle. After the completion of combined medication, no systemic anti-tumor treatment is allowed, while best supportive care and local palliative treatment (see Section 7.3) are allowed until PD.

Table 5. Method of administration in control group.

	Paclitaxel	Cisplatin
Dose and Route of Administration	175 mg/m^2 IV	75 mg/m^2 IV
Infusion Rate	More than 3 h or per the clinical practice of the study site	Approximately 60 min or per the clinical practice of the study site
Pretreatment before Administration	Pretreatment before administration should be given according to the clinical practice of the study site	Pretreatment before administration should be given according to the clinical practice of the study site
Time of Drug Administration	D1	D1
Sequence of Combined Medication	First paclitaxel, followed by cisplatin	
Frequency of Combined Medication	Every cycle contains 21 days (for up to 6 cycles)	

The time window of administration is ± 3 days from the scheduled date of administration (from the date of the first administration). Drugs administered outside the time window is considered a delayed dose, and subsequent doses shall be administered according to the actual date of last administration. For dose delays due to toxicities, the two drugs should be delayed simultaneously and can be interrupted for up to 6 weeks; otherwise, the chemotherapy should be discontinued.

7.1.6. Dose modifications and delay

7.1.6.1. Dose modification

7.1.6.1.1. Dose modifications for SHR-1210

AEs related to SHR-1210 may be immune-related, and may develop shortly after the first dose or months after the last dose. SHR-1210 should be suspended if events listed in Table 6 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 suspended or resumed according to recommendations found in Table 6 or when the situation is not listed.

Table 6. Criteria for SHR-1210 dose modifications.

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

Immune-Related AE	Severity Grades for Treatment Interruption	Resumption	Discontinuation
Pneumonia	2	Recovered to Grade 0–1 and the dose of corticosteroids reduced to ≤ 10 mg of prednisone or equivalent	Do not resolve within 12 weeks from the last dose, or the dose of corticosteroids cannot be reduced to ≤ 10 mg of prednisone or equivalent within 12 weeks.
	3-4	Discontinuation	Discontinuation
Immune-Related Hypophysitis	2-3	Return to Grade 0-1; SHR-1210 treatment can be resumed 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 dose of corticosteroids reduced to ≤ 10 mg of prednisone or equivalent.	Do not resolve within 12 weeks from the last dose, or the dose of corticosteroids cannot be reduced to ≤ 10 mg of prednisone or equivalent within 12 weeks.
	3-4	Discontinuation	Discontinuation
Infusion Reactions	2	Symptoms disappear	Re-administer at 50% of the initial rate after symptoms resolve. Restore the original infusion rate (100%) if no complications occur within 30 minutes. Closely monitor. If symptoms return, the administration of the current SHR-1210 dose will be terminated.
	3-4	Discontinuation	Discontinuation
Others Treatment-Related AEs	3	Recovered to Grade 0–1 and the dose of corticosteroids reduced to ≤ 10 mg of prednisone or equivalent.	Do not resolve within 12 weeks from the last dose, or the dose of corticosteroids cannot be reduced to ≤ 10 mg of prednisone or equivalent within 12 weeks.
	4	Discontinuation	Discontinuation

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

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

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

7.1.6.1.2. Dose modification of paclitaxel and cisplatin

The criteria for dose modification and administration/resumption of paclitaxel and cisplatin are detailed in Table 7 and Table 8 or determined by the investigator according to routine clinical practices. The content of this section is for the reference of the investigator. If the toxicity is still not tolerated after dose reduction, the chemotherapy should be discontinued.

Table 7. Criteria for dose modification of paclitaxel and cisplatin.

AE	Paclitaxel	Cisplatin	Resumption
Febrile Neutropenia	Two dose reductions are permitted, 25% each	Two dose reductions are permitted, 25% each	Reduce dose after recovery
Grade 4 Neutropenia			Reduce dose after return to Grade ≤ 1
Grade 4 Platelet Count Decreased			
Grade 1 Nephrotoxicity	Dose reduction by 25%	Dose reduction by 25%	Dose reduction
Grade 2/3 Peripheral Neurotoxicity			Reduce dose after return to Grade ≤ 1
Grade ≥ 3 Non-Hematological Toxicity			
Grade ≥ 2 Nephrotoxicity	Not applicable	Not applicable	Discontinuation
Grade 4 Peripheral Neurotoxicity	Not applicable	Not applicable	Discontinuation

Table 8. Criteria for administration/resumption.

Absolute Neutrophil Count	≥ 1500/mm^3（1.5×10^9/L）
Platelet Count	≥ 100×10^9/L

7.2. Drug Management, Dispensation and Retrieval

Designated personnel are responsible for the management, dispensation, and retrieval of study drugs. The investigator must ensure that all study drugs are used by enrolled subjects only and the dose and route of administration comply with Section 7.1.5. Remaining or expired drugs should be returned to the sponsor and may not be used for non-participants.

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

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

7.2.1. Disposal of study drugs

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

7.3. Concomitant Treatment

Prohibited medications and vaccines specified in the exclusion criteria are prohibited during the entire course of the trial. If the subject develops a concurrent condition that requires the use of a prohibited drug, then study treatment may need to be stopped and the prohibited medication may need to be accepted. In this case, the investigator should consult with the sponsor. Whether the subject will continue the study treatment or accept a prohibited medication is ultimately decided together by the investigator, the sponsor, and the subject.

7.3.1. Permitted concomitant treatments

Topical use of corticosteroids such as ophthalmic, nasal, intra-articular, and inhaled is permitted. Premedication with corticosteroids before chemotherapy is allowed.

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 metastases and esophageal lesions. However, the following criteria must all be met and the sponsor must be consulted prior to starting palliative treatment.

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

All concomitant medications from 30 days before signing informed consent form until the start of new anti-tumor treatment should be documented in the eCRF; afterward, only concomitant medications for treatment-related AEs are documented.

7.3.2. Prohibited concomitant treatments

- Systemic anti-tumor treatment, including but not limited to chemotherapy and immunotherapy not specified in the protocol, targeted therapy, biological therapy, modern TCM preparation approved by the CFDA (now NMPA) for anti-tumor treatment (refer to Appendix III), and immunomodulator with auxiliary anti-tumor effect (e.g., 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;
- Applicable to treatment group only: In addition to alleviating symptoms due to immunological causes, long-term use of systemic corticosteroids for any other purpose shall be discussed with the sponsor. Short-term (< 3 weeks) and low-dose (≤ 10 mg of prednisone or equivalent) use of corticosteroids for non-autoimmune diseases and prophylactic use of corticosteroids (e.g., prevention of allergy to contrast agents) are permitted;
- Refer to the prescribing information for other prohibited medications for paclitaxel and cisplatin.

7.3.3. Supportive care

7.3.3.1. Guidance for SHR-1210 supportive care

Subjects should receive appropriate supportive treatment measures deemed necessary by the investigator. Supportive treatment measures for managing immune-related AEs 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 considers 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. Capillary endothelial proliferation

Subjects with capillary endothelial proliferation should undergo biopsy and pathological examination whenever possible. Endoscopic and MRI examinations are recommended for subjects with severe or long-lasting capillary endothelial proliferation to confirm whether the internal organs and mucosa are involved.

2. Diarrhea/colitis

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

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

The recommendations on treatment of infusion reactions are shown in Table 9.

Table 9. 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 minutes 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 can be considered based on clinical needs; The amount of study drug infused should be recorded in the original medical record; Pre-dose prophylactics are recommended for subsequent administrations: 50 mg of diphenhydramine or equivalent, and/or 325-1000 mg of acetaminophen can be given at least 30 minutes before the administration of SHR-1210. Use corticosteroids (equivalent to 25 mg 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 minutes. Closely monitor. If symptoms return, the administration of the current SHR-1210 dose will be terminated.
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;	Discontinuation

		• Based on the guidelines for anaphylaxis of the study site; Bedside observation and close monitoring should be given until recovery.	

7.3.3.2. Guidelines for supportive care of paclitaxel and cisplatin

Refer to the package inserts or per the clinical practice of the study site.

7.3.4. Hematopoietic growth factor

Granulocyte colony stimulating factor (G-CSF) is not allowed as primary prophylaxis. For retrospective assessments in the second or subsequent chemotherapy cycles, if subjects have experienced febrile neutropenia or dose-limiting neutropenia events in the previous chemotherapy cycle, prophylactic use of G-CSF may be considered, and dose delay or reduction may also be adopted to reduce the risk of recurrence. The investigator may make judgment based on clinical situations.

8. STUDY PROCEDURES

8.1. Screening

The screening period is the time from the signing of the informed consent form until randomization or screen failure. Subjects must sign the informed consent form before undergoing screening procedures for this study. Data from laboratory tests and radiographic assessments 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 informed consent form;
- Collection of demographics: gender, date of birth, ethnicity, height, weight, and BMI;
- Tumor diagnosis: date of first pathological diagnosis, pathological grade, site of metastasis, and clinical stage (locally advanced or distant metastatic);
- History of tumor treatment:
  - ✓ History of tumor surgery: name of surgery, date of surgery, and date of postoperative recurrence;
  - ✓ History of radiotherapy: site, dose, and start and end dates;

- ✓ Anti-tumor medication history: regimen, cycle, and start and end dates;

- History of concurrent disease, past medications, 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), and HIV-Ab;
- Fresh (preferred) or archival tumor tissue specimens.

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 hours 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, neck, skin, lymph nodes, eyes, ear, nose and throat, oral cavity, respiratory system, cardiovascular system, abdomen, reproductive-urinary system, musculoskeletal system, nervous system, mental state, and others;
- ✓ Hematology: 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, blood urea nitrogen (preferred)) or urea, total protein, albumin, creatinine, blood glucose, lactate dehydrogenase, K^+, Na^+, Ca^{2+}, Mg^{2+}, and Cl^-;
- ✓ Thyroid function: TSH, FT3, and FT4;
- ✓ Coagulation function: APTT, PT, FIB, INR;
- ✓ Echocardiography: including LVEF assessment. Perform if clinically indicated;
- ✓ 12-lead ECG: heart rate, PR interval, QT interval, and QTcF; the investigator may decide to add other investigations if results are abnormal;
- ✓ Pregnancy test (for women of childbearing potential);

- ✓ Imaging examination: CT or MRI of the neck, chest, and abdomen (including pelvic cavity) (both are enhanced; plain scans may be used instead when contrast agents are contraindicated). Brain MRI (or CT if MRI is contraindicated; both are enhanced; plain scans may be used instead when contrast agents are contraindicated) is required for suspected or confirmed brain metastasis. Tumor assessments up to 4 weeks before randomization and before informed consent may be used as long as they meet the RECIST v1.1 criteria. Bone scan is required for suspected or diagnosed bone metastases and must be performed within 42 days prior to the first dose;
- ✓ AEs: recorded starting from the signing of ICF;
- ✓ Concomitant medication: concomitant medications within 30 days prior to the signing of ICF shall be documented in detail.

8.2. Treatment Period

The treatment period starts from subject randomization. The first dose should be completed within 3 days after randomization.

- All examinations and assessments (except for quality of life score and tumor imaging evaluation) should be completed within 3 days prior to administration. The following assessments should be completed prior to administration in each cycle, but do not need 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;
  - ✓ Targeted physical examination: perform if clinically indicated;
  - ✓ Hematology: RBC count, hemoglobin, platelet count, WBC count, neutrophil count, and lymphocyte count;
  - ✓ Blood biochemistry: ALT, AST, GGT, total bilirubin, direct bilirubin, AKP, blood urea nitrogen (preferred)) or urea, total protein, albumin, creatinine, blood glucose, lactate dehydrogenase, K^+, Na^+, Ca^{2+}, Mg^{2+}, and Cl^-;
  - ✓ ECG; heart rate, PR interval, QT interval, and QTcF;
  - ✓ AE: recorded in details;
  - ✓ Concomitant medication: concomitant medication shall be documented in detail.

- The following investigations should be completed every 2 cycles prior to administration:
  - ✓ 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 (treatment group: tested before and after administration; control group: tested if clinically indicated);
  - ✓ Thyroid function: TSH, FT3, FT4.
- Quality of life score (EORTC QLQ-C30, EORTC QLQ-OES18): Once every 6 weeks, with a window of ± 7 days. It is recommended to be performed prior to administration as well as AE and tumor assessments.
- Imaging examination: Baseline imaging examination should be performed every 6 weeks. Unscheduled imaging examinations may be performed for suspected PD. 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. A time window of ± 7 day is allowed for imaging examinations. Imaging conditions should be the same as those at baseline (including slice thickness and contrast agent). Time of radiographic assessment will not be adjusted due to dose delays.

  Subjects in the treatment group who develop PD for the first time but are clinically stable should be confirmed at least 4 weeks (± 7 days) later. If the confirmation is less than 4 weeks from the next scheduled imaging examination, the originally scheduled imaging examination will be skipped until the time for the next scheduled imaging examination.
- ADA blood sampling (for treatment group only): Collected once before administration on C1D1, C2D1, C4D1, C6D1, and C9D1; thereafter, once every 4 cycles before administration.

8.3. Withdrawal Visit

This visit will be completed when discontinuation of study treatment for a subject is confirmed. If the following assessments and examinations are not performed within 7 days before withdrawal from study treatment visit, they should be completed upon withdrawal from the study.

- ✓ ECOG PS score;
- ✓ Vital signs: pulse, respiratory rate, body temperature, and blood pressure;
- ✓ Comprehensive physical examination: general condition, head and face, neck, skin, lymph nodes, eyes, ear, nose and throat, oral cavity, respiratory system, cardiovascular system, abdomen, reproductive-urinary system, musculoskeletal system, nervous system, mental state, and others;
- ✓ Hematology: 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, blood urea nitrogen (preferred)) or urea, total protein, albumin, creatinine, blood glucose, lactate dehydrogenase, K^+, Na^+, Ca^{2+}, Mg^{2+}, and Cl^-;
- ✓ Thyroid function: TSH, FT3, and FT4;
- ✓ ECG: heart rate, PR interval, QT interval, and QTcF;
- ✓ Pregnancy test;
- ✓ Quality of life score;
- ✓ Imaging examination: An imaging examination should be performed at the withdrawal visit if it has not already been completed within 4 weeks prior to withdrawal from the study.
- ✓ ADA blood sampling (for treatment group only);
- ✓ AE: recorded in details;
- ✓ Concomitant medication: concomitant medication shall be documented in detail.

8.4. Safety Follow-Up

All subjects should return to the study site for a follow-up 30 days after the last dose or undergo telephone follow-up if withdrawal visit is completed; only subjects in the treatment group should undergo telephone follow-ups 60 days and 90 days after the last dose. Safety information should be obtained via telephone follow-ups (including AE outcome, new SAE, and AE of special interest).

- ✓ Hematology: RBC count, hemoglobin, platelet count, WBC count, neutrophil count, and lymphocyte count;
- ✓ Blood biochemistry: ALT, AST, GGT, total bilirubin, direct bilirubin, AKP, blood urea nitrogen (preferred)) or urea, total protein, albumin, creatinine, blood glucose, lactate dehydrogenase, K^+, Na^+, Ca^{2+}, Mg^{2+}, and Cl^-;
- ✓ Thyroid function: TSH, FT3, and FT4;
- ✓ ADA blood sampling (for treatment group only) (if applicable);
- ✓ Quality of life score (if applicable);
- ✓ Adverse events: recorded in details;
- ✓ Concomitant medication: concomitant medication shall be documented in detail.

8.5. Unscheduled Visits

The following should be documented during unscheduled visits if subjects develop AEs during the trial:

- ✓ Concomitant medications;
- ✓ AEs;
- ✓ All relevant examinations (including imaging assessment, if performed).

8.6. Survival follow-up

Survival follow-ups will be conducted once every 30 days 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.

8.7. Tumor Progression Follow-Up

For subjects who withdraw due to "non-PD" (such as unacceptable AEs), it is recommended to perform tumor assessments at the same frequency (every 6 weeks ± 7 days) as that of response assessments for this study, until PD, start of a new anti-tumor treatment, withdrawal of informed consent, loss to follow-up, or death. Follow-up information should be documented in the eCRF.

9. EVALUATIONS

9.1. Efficacy Evaluation

Progression-free survival (PFS): The time from the start of randomization to the date of first recording of objective tumor progression or death caused by any reasons, whichever occurs first. The independent review committee (IRC) will perform a central review on the primary endpoints. Refer to the IRC Charter for details. The secondary endpoints are based on investigator assessments. On the analysis cutoff date, if the PFS is not obtained, the data will be censored. The censoring rules are detailed in the Statistical Analysis Plan (SAP).

Overall survival (OS): The time from the start of randomization to the death of the subject caused by any reasons. On the analysis cutoff date, if the OS is not obtained, the data will be censored. The censoring rules are detailed in the SAP.

OS rates: Survival rates at 6 and 9 months after enrollment.

Objective response rate (ORR): Defined as the proportion of subjects whose best overall responses (BoR) are assessed as CR and PR among the subjects who have received at least one dose in each treatment group. BoR is defined as a parameter of best response starting from the date of randomization to the date of objective documentation of PD or subsequent anti-tumor treatment (whichever occurs first). For subjects with no record of PD or subsequent anti-tumor treatment, the BoR will be determined based on all results of response assessment.

Duration of response (DoR): The time from the first PR or CR to the first PD or death. On the analysis cutoff date, if the PD or death information is not obtained, the data will be censored. The censoring rules are detailed in the SAP.

Disease control rate (DCR): The proportion of subjects with CR, PR, and SD among subjects who have received at least one dose in each treatment group. DCR is defined as a parameter of best response starting from the date of randomization to the date of objective documentation of PD or subsequent anti-tumor treatment (whichever occurs first). For subjects with no record of PD or subsequent anti-tumor treatment, the DCR will be determined based on all results of response assessment.

Quality of life score (EORTC QLQ-C30, EORTC QLQ-OES18): As a core scale for all cancer patients, the EORTC QLQ-C30 scale comprises 30 items, 5 functional scales (physical, role, cognitive, emotional and social), 3 symptom scales (fatigue, pain and nausea/vomiting), 1 global health status/quality of life scale and 6 single-item scales (dyspnoea, insomnia, appetite loss, constipation, diarrhea and financial difficulties). The EORTC QLQ-OES18 scale is mainly used for patients with esophageal cancer and contains 18 symptom items.

Biomarker analysis is to evaluate the relationship between PD-L1 expression in tumor tissues and efficacy.

Immunogenicity analysis is to determine the proportion of subjects showing anti-SHR-1210 antibodies.

The reference criteria for imaging evaluation in this study is the RECIST v1.1 criteria. The requirements and frequency of imaging examinations are detailed in the Schedule of Activities.

9.2. Safety Evaluation

9.2.1. Pregnancy test

Female subjects of childbearing potential will receive a serum or urine pregnancy test within 72 hours before the first dose. Subjects with negative results should adopt appropriate contraceptive measures. Subjects with positive results will fail the screening. Enrolled subjects will undergo another serum or urine pregnancy test at the withdrawal visit.

9.2.2. Adverse events

Refer to NCI-CTCAE V4.03 for the severity of AEs.

9.2.3. Laboratory safety assessment

Please refer to the Schedule of Activities for details.

9.2.4. Vital signs and physical examination

Please refer to the Schedule of Activities for details.

9.2.5. 12-lead ECG

Please refer to the Schedule of Activities for details.

9.2.6. Independent Data Monitoring Committee

In this study, an Independent Data Monitoring Committee (IDMC) will be established to evaluate the safety and efficacy of the study drug at the data review meetings on a regular basis.
The safety data will be evaluated after the 60th subject enrolled has completed the Cycle 1 follow-up. An interim analysis will be performed when about 269 (66%) OS events are collected. The IDMC will make recommendations on whether to continue or terminate the study based on the safety and efficacy data and results.

The committee will include two independent oncologists and one independent statistician. The IDMC review meeting will be held at the time specified in the charter of the IDMC. The study enrollment will continue during IDMC meetings.

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

See details in IDMC charter.

10. ADVERSE EVENT REPORTING

10.1. Adverse Events (AEs)

10.1.1. Definition of AE

An adverse event (AE) refers to any untoward medical occurrence in a study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. In this study, AEs are collected from the signing of the informed consent form until 90 days after the last dose of SHR-1210 or 30 days after the last dose of paclitaxel and cisplatin (whichever occurs first). If the subject starts a new anti-tumor treatment during the AE collection period, only treatment-related AEs are collected after the start of the new anti-tumor treatment. AEs can include any unfavorable and unintended symptoms, signs, abnormal laboratory finding, or diseases, including the follows:

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

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

10.1.2. AE severity grading criteria

Please refer to NCI CTCAE 4.03 for grading criteria. Refer to Table 10 for the criteria for AEs not listed in NCI-CTCAE 4.03:

Table 10. Criteria for the severity of AEs.

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 are collected and documented regardless of whether the event is related to the study drug, whether the subject is assigned to the investigational treatment group, 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 study drug, such as whether there is a plausible temporal relationship with the study drug, the characteristics of the study drug, the toxicological and pharmacological effects of the study drug, whether there are concomitant medications, the subject's underlying diseases, medical history, family history, as well as dechallenge and rechallenge, etc. The causality assessment will be provided using the following five categories "definitely related, possibly related, unlikely related, definitely unrelated, and indeterminable".

10.2. Serious Adverse Events (SAEs)

10.2.1. Definition of SAE

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 that result in hospitalization (even if for less than 24 h) or prolonged hospitalization during the clinical study should be considered as SAEs.

Hospitalization does not include the following:

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

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

- Hospitalization due to pre-existing disease without the occurrence of new AEs or worsening of the pre-existing diseases (e.g., in order to examine the persistent laboratory abnormalities that started before the study);

- Hospitalization for management reasons (e.g., annual physical examination);
- Hospitalization during the study as specified in the study protocol (e.g., as required by the protocol);
- Elective hospitalization unrelated to worsening of AEs (e.g., elective surgery);
- Scheduled treatment or surgery that should be documented throughout the entire study protocol and/or subjects' individual baseline information;
- Hospitalization merely for use of blood products.

Diagnostic or therapeutic invasive (e.g., surgery) and non-invasive procedures should not be reported as AEs. However, when a condition resulting in such procedures meet 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 PD. Death, life-threatening events, hospitalization or prolonged hospitalization, permanent or severe disability/incapacity, congenital anomalies or birth defects resulting from signs and symptoms of progressive disease should not be reported as SAEs.

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 and reported as SAEs.

Potential drug-induced liver injury is defined in Table 11.

Table 11. Definition of potential drug-induced liver injury.

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

If the subject starts any other anti-tumor treatment, only study drug-related SAEs should be collected.

10.2.6. SAE reporting

SAEs should be collected from signing the ICF until 90 days after the last dose of SHR-1210 or 30 days after the last dose of paclitaxel and cisplatin (whichever occurs first). In the event of an SAE, whether it is the first report or a follow-up report, the investigator must complete the "Serious Adverse Event Report Form" immediately, with a signature and date, and notify the sponsor within 24 h of knowing of the event. Relevant authorities must be informed of such SAE in a timely manner according to regulatory requirements.

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

The symptoms, severity, relationship with the study drug, time of occurrence, treatment duration, measures taken, time and method of follow-up, and outcome should be documented in details in the SAE report. If the investigator believes that an SAE is unrelated to the study drug but potentially related to study conditions (such as the termination of the previous 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 study drug changes, a follow-up report should be submitted immediately. If an error is found in a previously reported SAE, such an SAE may be revised, revoked, or downgraded in follow-up reports and reported in accordance with the SAE reporting procedure.

10.2.7. Follow-up of AEs/SAEs

All the AEs/SAEs should be followed up until resolved, return to baseline levels or Grade ≤ 1, steady state, or reasonably explained (e.g., loss to follow-up, death).

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

10.3. Pregnancy

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

During the study, if the partner of a male subject becomes pregnant, the subject can continue in the study. The investigator must report to the sponsor within 24 hours 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.

Email the pregnancy report to: hengrui_drug_safety@hrglobe.cn.

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

If a subject experiences any SAE during pregnancy, then the "SAE Report Form" should be filled out and reported according to SAE reporting procedures.

10.4. AEs of Special Interest

For AEs of special interest listed below occurring in subjects of the treatment group, the investigator must fill out the "Report of Adverse Event of Special Interest for Hengrui Clinical Studies" and submit it to the sponsor within 24 hours of knowing of the event. If the AE of special interest is also an SAE, the "Serious Adverse Event Report Form" should also be filled out and submitted to relevant authorities according to SAE reporting procedures.

- Grade ≥ 3 infusion reactions;
- Grade ≥ 3 immune-related AEs;

11. CLINICAL MONITORING

The CRA 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 CRA actively. Specifically, the monitor is responsible for:

1. 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;
2. 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;
3. 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;
4. Confirming that all AEs have been documented, and that SAEs have been documented and reported within the specified time frame. Verifying that the study drugs are supplied, stored, dispensed, and returned in accordance with relevant regulations, and corresponding documentation should be made;
5. Recording clearly and faithfully visits, tests, and examinations that the investigator has failed to perform, and whether errors or omissions have been corrected;
6. Completing a written monitoring report after each visit, which should state the date and time of the monitoring visit, the name of the CRA, and the findings of the visit.

The Quality Assurance 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 at a reasonable time and in a reasonable way.

12. DATA ANALYSIS/STATISTICAL METHODS

The detailed statistical analysis of this study will be included in the Statistical Analysis Plan (SAP) and kept by the sponsor. The plan marked in the protocol can be appropriately modified in the SAP. However, any significant revisions to the definitions and analyses of primary study endpoints shall be reflected in the amendment versions of the protocol.

12.1. Sample Size

A parallel design is adopted in this study. The sample size is calculated based on the comparison of the two primary efficacy endpoints, i.e., PFS and OS, of PD-1 antibody SHR-1210 combined with paclitaxel and cisplatin (treatment group) and paclitaxel combined with cisplatin (control group).

The hypothesis for efficacy is as follows: The hazard ratio (HR) of PFS (treatment group/control group) is 0.67, the estimated median PFS of the control group is 5 months, the HR of OS (treatment group/control group) is 0.73, and the estimated median OS of the control group is 10 months. Assuming a one-sided $\alpha = 0.005$, a power of 90% can be obtained when 378 PFS events are collected, and the estimated final analysis time of PFS is approximately 22.0 months. An interim analysis is planned for the OS. The Lan-DeMets α spending function will be used to allocate the α, and the O'Brien & Fleming method will be used to preset the superiority boundary (EAST 6.4.1) to control the overall one-sided $\alpha = 0.02$. The interim analysis will be performed when 269 (66%) OS events (approximately 22.1 months) are collected. The final analysis of OS will be performed when 408 OS events are collected to obtain a power of 85% under the premise that the overall type I error does not exceed one-sided $\alpha = 0.02$. The enrollment period is approximately 18 months, and the follow-up period is approximately 18 months. With a randomization ratio of 1:1, a total of approximately 520 subjects are required. Considering a dropout rate of 5%, 548 subjects are intended to be enrolled.

12.2. Statistical Analysis Plan

In this study, SAS 9.4 or above is used for data processing and analysis.

The time-event indicators will be analyzed using the Kaplan-Meier method, so as to estimate the survival function of both groups and plot the survival curves. In addition, the Cox regression model will be used to estimate the HR between the two groups and its 95% confidence interval (95% CI).

For binary variables, the Cochran-Mantel-Haenszel method will be used to estimate the intergroup difference and its 95% CI.

The safety analysis will be summarized using descriptive statistics.

The detailed analysis plan and strategy will be described in the SAP.

12.3. Analysis Population

- Full analysis set (FAS): According to the ITT principle, all subjects who have passed the screening and received at least one dose of the study drugs are included in this set. 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 judged to have a significant impact on the study results.
- Safety analysis set (SS): Refers to enrolled and randomized subjects who have received at least one dose of the study drug.

The statistical analysis will be performed for the drug efficacy based on the FAS and PPS. Before database locking, the principal investigator, statistician, and sponsor should determine the final PPS during the data review meeting.

12.4. Statistical Methods

The following sections include the description of the planned statistical methods.

12.4.1. Basic methods

The primary efficacy endpoints of this study are PFS and OS. An interim analysis of the efficacy is planned for the OS. The final analysis for the PFS will be performed when 378 PFS events are collected (about 22 months). It is expected that the interim analysis of OS will be performed when 269 (66%) events (about 22.1 months) are collected. The final analysis of OS will be performed when 408 events are collected.

12.4.2. Primary efficacy endpoint analysis

The primary endpoints of the study are PFS and OS. The primary analysis will be based on the FAS. The survival functions of PFS and OS of the two groups will be compared using both stratified and non-stratified Log-Rank tests. Also, the Kaplan-Meier method will be used for estimating the PFS and OS and plotting the survival curve to estimate the median PFS and OS as well as their 95% CIs (Brookmeyer-Crowley method). The analysis with stratification factors is used as the primary analysis.

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

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

Table 12. Termination criteria and α spending in the primary analyses of PFS and OS.

Study Endpoint	Planned Analysis Time Point	Number of Events	Superiority Boundary Z (HR of superiority boundary) (treatment group/control group)	α Spending
			Effective (≤ Lower Limit)	
PFS	Final analysis (about 22 months)	378	-2.576 (HR = 0.65)	0.005
OS	Interim analysis (about 22.1 months)	About 269 (66%)	-2.638 (HR = 0.72)	0.004
OS	Final analysis (about 36 months)	408	-2.081 (HR = 0.81)	0.019

Note: The actual α spending value and margins for the interim analysis will be determined based on the proportion of the events at that time. The result is based on the Z value calculated using EAST 6.4.1, the Lan-DeMets α spending function is used to allocate α, and the O'Brien & Fleming method is used to preset the superiority boundary.

The final analysis will be performed when 378 PFS events are obtained. When the P-value (one-sided) based on the Log-Rank test in the final analysis of PFS is < 0.005, the comparison of PD-1 antibody SHR-1210 combined with paclitaxel and cisplatin (treatment group) vs. paclitaxel combined with cisplatin (control group) is statistically significant.

The final analysis will be performed when 408 OS events are obtained. When the P-value (one-sided) based on the Log-Rank test in the final analysis of OS is < 0.019 (see Table 12), the comparison of PD-1 antibody SHR-1210 combined with paclitaxel and cisplatin (treatment group) vs. paclitaxel combined with cisplatin (control group) is statistically significant. When the actual number of observed events does not reach or exceed 408 in the final analysis, automatic adjustments may be performed using EAST (e.g., "last look" item in the EAST IM tool) to control the overall type I errors. Refer to section 12.4.6 for the interim analysis of OS.

12.4.3. Secondary efficacy endpoint analysis

Based on the FAS, the secondary endpoints, ORR and DCR, and their two-sided 95% CIs (Clopper-Pearson method) will be estimated, the inter-group difference and their two-sided 95% CIs (normal approximation) will be calculated, and the inter-group P-value will be compared (Cochran-Mantel-Haenszel method).

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

12.4.4. Handling of missing data

In this trial, the missing data of the efficacy endpoints are not treated specially (see the SAP for detailed censoring rules), and the missing values are not estimated in the safety assessment.

12.4.5. Safety analysis

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

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

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

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

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

12.4.6. Interim analysis

In this study, an interim analysis will be conducted when 269 (66%) OS events (about 22.1 months) are collected. For PFS, interim analysis will not be conducted, and only final analysis will be conducted. In order to control the overall type I errors, the Lan-DeMets α spending function is used, and the O'Brien & Fleming method is used to preset the superiority boundary.

According to Table 12, when the P-value (one-sided) based on the Log-Rank test in the interim analysis of OS is < 0.004, and the Z value exceeds the efficacy boundary Z value of -2.638, with a corresponding HR (treatment group/control group) of 0.72, the comparison between the treatment group and the control group is determined to be statistically significant. If, in the interim analysis, the actual number of observed events does not reach or exceed 269, the boundary should be timely monitored and adjusted using EAST (e.g., using IM tool for monitoring). The final analysis will be performed when 408 OS events are obtained (see section 12.4.2).

The interim analysis will be completed by independent statisticians and their programming team. The results of interim analysis will be reviewed by the IDMC, which will recommend whether to continue the study

12.4.7. Subgroup analysis

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

Stratification factors:

Liver metastasis (with vs. without);

Whether the subjects have received definitive chemoradiation (yes vs. no)

12.4.8. Multiple comparison/multiplicity

This trial is a parallel design with two endpoints. An interim analysis is included for OS. To control the overall type I errors, the α is allocated as follows:

PFS: $\alpha = 0.005$ (one-sided)

OS: $\alpha = 0.02$ (one-sided)

The O'Brien-Fleming method is used for the α spending in the interim analysis and final analysis of OS. See section 12.4.6 for details.

12.4.9. Exploratory analysis

The following exploratory endpoints will be analyzed using descriptive statistics:

- Evaluation of the relationship between PD-L1 expression in tumor tissues and efficacy;
- Determination of the proportion of subjects showing anti-SHR-1210 antibodies.

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.

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 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

Implemented by: CRA.

Monitoring content: To confirm that whether the study protocol is adhered to; whether the records on eCRF are correct and complete, and consistent with the source documents such as study medical records and laboratory test reports, and whether there are errors or omissions in the data. According to the monitoring plan, the CRA will verify the completeness, consistency,

and accuracy of 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.

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 CRA, data manager, and medical personnel 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 mainly to determine the analysis data set (including FAS, PPS, and SS) for each case, the judgment of missing values, and the handling of outliers. All decisions made under data review must not be modified, and any decision must be documented.

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

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 shall 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 termination of the clinical trial.

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.

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

15. QUALITY ASSURANCE AND QUALITY CONTROL

To ensure data quality, the sponsor and investigator will discuss and formulate the clinical trial 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 study drugs, including receipt, storage, dispensing, return, and destruction (if applicable).

According to the GCP guidelines, necessary measures must be taken at the design and implementation phases of the study to ensure that all collected data are accurate, consistent, intact, and reliable. All observed results and abnormal findings in the clinical trial 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 trial must have stringent specifications and be operated under normal conditions.

The investigator will input data required by the protocol into the eCRF. The CRA will check whether the eCRF is completely and accurately filled and guide the study site personnel for 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 shall be conducted by persons 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 approval is obtained. The clinical approval number for SHR-1210 is 2016L01455.

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

- Provisions for Drug Registration;
- Good Clinical Practices;
- 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;
- Other applicable laws and regulations.

16.2. Ethical Standards

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

16.4.1. ICFs and other written information for subjects

The ICF describes the investigational product and study process in detail and fully explains the risks of the study to the subjects. Written documentation of informed consent must be obtained before starting any study-related procedures. The following informed consent materials will be submitted along with the protocol:

Informed consent form;

Recruitment advertisement.

16.4.2. Informed consent process and records

Informed consent begins before an individual decides to participate in the clinical trial and continues during the entire clinical trial. 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 a patient refuses to participate in this study, his or her rights will be fully protected, and the nursing quality will not be affected.

16.5. Confidentiality of Subject Information

The confidentiality of subject information will be strictly enforced by the investigator, participated 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 shall not to be disclosed to any unauthorized third-party without prior written approval from the sponsor.

Other authorized representatives of the sponsor, IRB, or regulatory authorities 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. When the study has ended, all the records will be kept in a secure place based on the time limit specified by local IRB and regulations.

The study data of 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.

16.5.1. Use of samples, specimens or data

- Planned use: The samples and data collected in accordance with this protocol will be used for exploratory studies to evaluate the relationship between PD-L1 expression and efficacy, and will not be used for any unrelated purposes.
- Storage: Samples and data will be numbered for storage in this study. The data in the computer will also be password protected. Only the investigator can have access to these samples and data.

16.5.2. Future use of archival specimens

In this study, archival specimens will not be used for purposes other than those specified in the protocol.

17. PUBLISHING OF STUDY RESULTS

The study outcomes belong to 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 study drug or not. However, the investigator should let the sponsor have the opportunity to review any proposed publication or other forms of publication before document submission or publication to prevent unintentional leakage of confidential information or unprotected inventions. The investigator should provide Hengrui with the manuscript, abstract, or full text of all planned publications (poster, invited lectures, or guest lectures) at least 30 days prior to submission for publication or other forms of release. To protect the intellectual property, 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 12 months after 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: August 2018

Anticipated enrollment of the last subject: February 2020

Anticipated study completion: August 2021

19. REFERENCES

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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

Appendix IV TNM Staging of Esophageal Cancer (8th Edition)

T Staging

Tx: Primary tumor cannot be assessed

T0: No evidence of primary tumor

Tis: High-grade dysplasia

T1: Tumor invades the lamina propria, muscularis mucosae, or submucosa

T1a: Tumor invades the lamina propria or muscularis mucosae

T1b: Tumor invades the submucosa

T2: Tumor invades the muscularis propria

T3: Tumor invades the fibrous membrane

T4: Tumor invades adjacent structures

T4a: Tumor invades the pleura, pericardium, azygos vein, diaphragm, or peritoneum

T4b: Tumor invades other adjacent structures such as aorta, vertebral body, or trachea

N Staging

Nx: Not assessable

N0: No regional lymph node metastasis

N1: Metastasis in 1-2 regional lymph nodes

N2: Metastasis in 3-6 regional lymph nodes

N3: Metastasis in 7 or more regional lymph nodes

M Staging

M0: No distant metastasis.

M1: With distant metastasis.

Tumor Differentiation (G)

Gx: Differentiation cannot be assessed;

G1: Well-differentiated, with prominent keratinization with pearl formation and a minor component of nonkeratinizing basal-like cells, tumor cells arranged in sheets, and mitotic counts low;

G2: Moderately differentiated, with variable histologic features ranging from parakeratotic to poorly keratinizing lesions and pearl formation generally absent;

G3*: Poorly differentiated, consisting predominantly of basal-like cells forming large and small nests with frequent central necrosis and with the nests consisting of sheets or pavement-like arrangements of tumor cells that are occasionally punctuated by small numbers of parakeratotic or keratinizing cells;

* If the "undifferentiated" cancer tissue is further tested as a squamous cell component, or if it is still undifferentiated after further testing, it is classified as G3 squamous cell carcinoma.

Esophageal segments are divided according to the center of the tumor into:

Esophageal Segment	**Site of Primary Lesion**
Unknown	Tumor site cannot be assessed
Upper segment	From the cervical esophagus to the lower edge of arch of azygos vein
Middle segment	From the lower edge of arch of azygos vein to the lower edge of inferior pulmonary vein
Lower segment	From the inferior pulmonary vein to the stomach, including the esophagogastric junction

*When the midpoint of the tumor is within 2 cm from the cardia, it will be staged based on the staging of esophageal cancer; when the midpoint of the tumor is 2 cm away from the cardia, it will be staged based on the staging of gastric cancer.

cTNM Staging

	cT	**cN**	**M**
0	Tis	N0	M0
I	T1	N0-1	M0
II	T2	N0-1	M0
	T3	N0	M0
III	T3	N1	M0
	T1-3	N2	M0
IVA	T4	N0-2	M0
	Any T	N3	M0
IVB	Any T	Any N	M1

pTNM Staging

	pT	**pN**	**M**	**G**	**Segment**
0	Tis	N0	M0	N/A	Any
IA	T1a	N0	M0	G1	Any
	T1a	N0	M0	GX	Any
IB	T1a	N0	M0	G2-3	Any
	T1b	N0	M0	G1-3	Any
	T1b	N0	M0	GX	Any
	T2	N0	M0	G1	Any
IIA	T2	N0	M0	G2-3	Any
	T2	N0	M0	GX	Any
	T3	N0	M0	Any	Lower segment
	T3	N0	M0	G1	Upper segment/ middle segment
IIB	T3	N0	M0	G2-3	Upper segment/ middle segment
	T3	N0	M0	GX	Any
	T3	N0	M0	Any	Unknown
	T1	N1	M0	Any	Any
IIIA	T1	N2	M0	Any	Any
	T2	N1	M0	Any	Any
IIIB	T2	N2	M0	Any	Any
	T3	N1-2	M0	Any	Any
	T4a	N0-1	M0	Any	Any
IVA	T4a	N2	M0	Any	Any
	T4b	N0-2	M0	Any	Any
	Any T	N3	M0	Any	Any
IVB	Any T	Any N	M1	Any	Any

pTNM Staging

	ypT	**ypN**	**M**
I	T0-2	N0	M0
II	T3	N0	M0
IIIA	T0-2	N1	M0
IIIB	T3	N1	M0
	T0-3	N2	M0
	T4a	N0	M0
IVA	T4a	N1-2	M0
	T4a	Nx	M0
	T4b	N0-2	M0
	Any T	N3	M0
IVB	Any T	Any N	M1

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTI-CENTER PHASE III CLINICAL STUDY OF ANTI-PD-1 ANTIBODY SHR-1210 COMBINED WITH PACLITAXEL AND CISPLATIN VS. PLACEBO COMBINED WITH PACLITAXEL AND CISPLATIN AS FIRST-LINE TREATMENT OF ADVANCED ESOPHAGEAL CANCER

Protocol No.:	SHR-1210-III-306
Trial Phase:	III
Compound Code:	SHR-1210
Compound Name:	Camrelizumab
Medical Director:	Qing Yang
Coordinating Site:	Sun Yat-Sen University Cancer Center
Principal Investigator:	Ruihua Xu
Version No.:	6.0
Version Date:	28 Sep., 2020

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

Sponsor's Signature Page

I have read and confirmed this clinical trial protocol (protocol no.: SHR-1210-III-306, version no.: 6.0, version date: 28 Sep., 2020). I agree to fulfill my duties in accordance with Chinese laws, the Declaration of Helsinki, the Good Clinical Practice (GCP) in China, 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 Good Clinical Practice (GCP) in China, and personally participate in or directly lead this clinical study. I have received the Investigator's Brochure for the investigational product; I have read the materials of preclinical studies of the investigational product and the protocol for this clinical trial. 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 Good Clinical Practice (GCP) in China, and personally participate in or directly lead this clinical study. I have received the Investigator's Brochure for the investigational product; I have read the materials of preclinical studies of the investigational product and the protocol for this clinical trial. 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 Randomized, Double-Blind, Placebo-Controlled, Multi-Center Phase III Clinical Study of Anti-PD-1 Antibody SHR-1210 Combined with Paclitaxel and Cisplatin vs. Placebo Combined with Paclitaxel and Cisplatin as First-line Treatment of Advanced Esophageal Cancer
Protocol No.	SHR-1210-III-306
Version No.	6.0
Sponsor	Jiangsu Hengrui Medicine Co., Ltd.
Principal Investigator	Prof. Ruihua Xu
Participating Study Centers	Approximately 50 sites
Study Objectives	**Primary Objective** • To compare the progression-free survival (PFS) (IRC-assessed) and overall survival (OS) of SHR-1210 combined with paclitaxel and cisplatin vs. placebo combined with paclitaxel and cisplatin in the treatment of patients with advanced esophageal cancer. **Secondary Objectives** • To compare the PFS (investigator-assessed), OS rates, objective response rate (ORR), and disease control rate (DCR) of SHR-1210 combined with paclitaxel and cisplatin vs. placebo combined with paclitaxel and cisplatin in the treatment of patients with advanced esophageal cancer, and to evaluate the duration of response (DoR) of the two groups; • To evaluate the safety of SHR-1210 combined with paclitaxel and cisplatin vs. placebo combined with paclitaxel and cisplatin in the treatment of patients with advanced esophageal cancer. **Exploratory Objectives** • To determine the proportion of subjects showing anti-SHR-1210 antibodies; • To evaluate the relationship between PD-L1 expression in tumor tissues and efficacy.
Study Endpoints	**Primary Endpoints** • IRC-assessed PFS (RECIST v1.1 criteria); • OS. **Secondary Endpoints** • Investigator-assessed PFS (RECIST v1.1 criteria); • OS rates; • ORR (RECIST v1.1 criteria);

	• DCR (RECIST v1.1 criteria); • DoR; • Quality of life score (EORTC QLQ-C30, EORTC QLQ-OES18); • Safety: AEs, laboratory measurements, etc. **Exploratory Endpoints** • To determine the proportion of subjects showing anti-SHR-1210 antibodies; • To evaluate the relationship between PD-L1 expression in tumor tissues and efficacy.
Study Population	Patients with unresectable locally advanced/recurrent or distant metastatic esophageal squamous cell carcinoma who have not previously received systemic anti-tumor treatment
Study Design	A randomized, double-blind, placebo-controlled, multi-center study design is adopted in this study. It is planned to enroll 548 subjects with unresectable locally advanced/recurrent or distant metastatic esophageal squamous cell carcinoma who have not previously received systemic anti-tumor treatment. Eligible subjects will be randomly assigned to the treatment group or the control group in a 1:1 ratio. The stratification factors include: liver metastasis (with vs. without), whether the subjects have received definitive chemoradiation (yes vs. no). The treatment group is given SHR-1210 (200 mg, D1) combined with paclitaxel (175 mg/m^2, D1) and cisplatin (75 mg/m^2, D1) in 3-week cycles, for up to 6 cycles of chemotherapy. The control group is given placebo (D1) combined with paclitaxel (175 mg/m^2, D1) and cisplatin (75 mg/m^2, D1) in 3-week cycles, for up to 6 cycles of chemotherapy. After the end of 6 cycles of chemotherapy, SHR-1210 (200 mg, D1)/placebo (D1) monotherapy is given as maintenance treatment, until progressive disease (PD), unacceptable toxicity, start of new anti-tumor treatment, withdrawal of informed consent, or when the investigator judges that the subject should withdraw from the study treatment. The longest duration of administration with SHR-1210/placebo is 2 years. In this study, an interim analysis will be conducted when about 269 (66%) OS events (about 22.1 months) and about 347 (85%) OS events (about 28.4 months) are collected, respectively. The screening period of the study is 28 days. After completing the screening examinations and evaluation, subjects who meet the inclusion/exclusion criteria will enter the treatment period and be treated according to the administration frequency specified in the protocol. Relevant examinations and assessments must be completed before each dose. In particular, tumor imaging assessment is conducted once every 6 weeks (± 7 days). All subjects must complete the safety examinations and tumor assessments at the withdrawal visit. Then, the subjects will enter a 90-day safety follow-up period. The survival follow-up will be carried out once every 30 days starting from the last dose; subjects who withdraw due to non-PD reasons should be followed up for tumor progression, and continue to undergo tumor assessments once every 6 weeks (± 7 days) until PD, start of a new anti-tumor treatment, withdrawal of informed consent, loss to follow-up, or death.

Study Drugs	Recombinant humanized anti-PD-1 monoclonal antibody for injection, SHR-1210 (Manufacturer: Suzhou Suncadia Biopharmaceuticals Co., Ltd.) Placebo (Manufacturer: Suzhou Suncadia Biopharmaceuticals Co., Ltd.) Paclitaxel (Manufacturer: Beijing Union Pharmaceutical Factory) Cisplatin (Manufacturer: Jiangsu Hansoh Pharmaceutical Group Co., Ltd.)
Method of Administration	**Treatment group:** Intravenous drip infusion of study drugs. SHR-1210 200 mg, paclitaxel 175 mg/m^2, and cisplatin 75 mg/m^2 are given sequentially on Day 1 of each 3-week cycle, for up to 6 cycles of chemotherapy. **Control group:** Intravenous drip infusion of study drugs. Placebo, paclitaxel 175 mg/m^2, and cisplatin 75 mg/m^2 are given sequentially on Day 1 of each 3-week cycle, for up to 6 cycles of chemotherapy. After the end of 6 cycles of chemotherapy, SHR-1210 (200 mg, D1)/placebo (D1) monotherapy is given as maintenance treatment, until PD, unacceptable toxicity, start of new anti-tumor treatment, withdrawal of informed consent, or when the investigator judges that the subject should withdraw from the study treatment. The longest duration of administration with SHR-1210/placebo is 2 years.
Inclusion Criteria	Subjects must meet all of the following inclusion criteria to be eligible for this study. 1. Aged 18–75 years, male or female; 2. Histologically or cytologically diagnosed with unresectable locally advanced/recurrent (unable to receive esophagectomy and definitive chemoradiation) or distant metastatic esophageal squamous cell carcinoma; 3. Have not received any systemic anti-tumor treatment. A patient who has received neoadjuvant/adjuvant and definitive chemoradiation can be screened if his/her last treatment is more than 6 months from recurrence or progression; 4. With at least one measurable lesion (cavity structures such as oesophagus may not serve as measurable lesions) according to RECIST v1.1 criteria, which has not received any local treatment including radiotherapy (a lesion located in an area subjected to a previous radiotherapy can be selected as the target lesion if PD is confirmed); 5. Tissue samples for biomarker (such as PD-L1) analysis must be provided. Fresh tissues are preferred. Archival samples of 5–8 paraffin embedded sections that are 3–5 μm thick are also acceptable if a fresh biopsy is not accessible; 6. ECOG: 0–1 (see Appendix I);

	7. Expected survival ≥ 12 weeks; 8. Vital organ functions meet the following requirements (use of any blood components and cell growth factors is not allowed within 14 days before the screening examinations); a. Absolute neutrophil count (ANC) ≥ 1.5×10^9/L b. Platelets ≥ 100×10^9/L; c. Hemoglobin ≥ 9 g/dL; d. Serum albumin ≥ 2.8 g/dL; e. Total bilirubin ≤ 1.5 × ULN; ALT, AST, and/or AKP ≤ 2.5 × ULN; ALT and/or AST ≤ 5 × ULN in the presence of liver metastasis; AKP ≤ 5 × ULN in the presence of liver or bone metastases; f. Serum creatinine ≤ 1.5 × ULN or creatinine clearance > 60 mL/min (Cockcroft-Gault, see Appendix II); g. Activated partial thromboplastin time (APTT) and international normalized ratio (INR) ≤ 1.5 × ULN (those receiving stable doses of anticoagulant therapy, such as low molecular weight heparin or warfarin, whose INR is within the expected therapeutic range of anticoagulants can be screened); 9. Women of childbearing potential and males with female partners of childbearing potential are required to take a medically approved contraceptive measure (e.g., intra-uterine contraceptive device, contraceptive pills, or condoms) during the study treatment period, for at least 3 months after the last dose of SHR-1210/placebo, and for at least 6 months after the last dose of chemotherapy; 10. Subjects must participate voluntarily, sign the informed consent form, have good compliance, and cooperate with follow-up visits.
Exclusion Criteria	Subjects meeting any one of the following are not eligible to participate in this study. 1. BMI < 18.5 kg/m^2 or weight loss ≥ 10% within 2 months before screening (at the same time, the effect of a large amount of pleural effusions and ascites on body weight should be considered); 2. With a history of gastrointestinal perforation and/or fistula within 6 months prior to the first dose; 3. Significant tumor invasion into adjacent organs (aorta or trachea) of esophageal lesions leading to higher risk of hemorrhage or fistula; 4. Presence of uncontrollable pleural effusion, pericardial effusion, or ascites requiring repeated drainage; 5. With a history of allergy to any monoclonal antibody, any component of SHR-1210, paclitaxel, cisplatin, or any other platinum-based drug; 6. Have any of the following situations:

	a. Have received anti-PD-1 or anti-PD-L1 antibody therapy; b. Have received any investigational drug within 4 weeks prior to the first dose of the study drug; c. Simultaneously enrolled into another clinical study, except for an observational (non-interventional) clinical study or follow-up of an interventional clinical study; d. Received the last dose of anti-tumor treatment (including radiotherapy) within ≤ 4 weeks before the first dose of the study drug; e. Requiring systemic treatment with corticosteroids (> 10 mg/day of prednisone or equivalent) or other immunosuppressive medications within 2 weeks before the first dose of the study drug, except the use of corticosteroids for local inflammation of the esophagus and prevention of allergies, nausea, and vomiting. Other special circumstances must be communicated with the sponsor. In the absence of active autoimmune disease, inhaled or topical use of corticosteroids or an equivalent dose of > 10 mg/day of prednisone for adrenal hormone replacement are permitted; f. Have been inoculated with any anti-tumor vaccine, or have been inoculated with any live vaccine within 4 weeks prior to the first dose of the study drug; g. Have undergone major surgery or severe trauma within 4 weeks prior to the first dose of the study drug; 7. Suffering toxicity from prior anti-tumor therapy that has not recovered to CTCAE Grade ≤ 1 (except alopecia) or a level specified in inclusion/exclusion criteria; 8. With central nervous system metastases; 9. With any active autoimmune disease, or a history of autoimmune disease (including but not limited to interstitial pneumonia, colitis, hepatitis, hypophysitis, vasculitis, nephritis, hyperthyroidism, and hypothyroidism), except for: vitiligo, or cured childhood asthma/allergy that do not require any intervention in adulthood; autoimmune-mediated hypothyroidism treated with a stable dose of thyroid hormone replacement therapy; and type I diabetes mellitus treated with a stable dose of insulin; 10. With a history of immunodeficiency, including positive anti-HIV assay, or with any other acquired or congenital immunodeficiencies, or with a history of organ transplantation or allogeneic bone marrow transplantation; 11. Having any poorly-controlled cardiovascular clinical symptom or disease, including but not limited to: (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 arrhythmia without clinical intervention or is poorly controlled after clinical intervention; 12. Having any serious infection (CTCAE Grade > 2) within 4 weeks prior to the first dose of the study drug, such as serious pneumonia, bacteremia, or infection-related complication requiring hospitalization; baseline chest radiography suggesting presence of active lung inflammation, infection symptoms and signs present within 2

	weeks prior to the first dose of the study drug requiring treatment by oral or intravenous administration of any antibiotic, except prophylactic use of antibiotics; 13. With a history of interstitial lung disease (except radiation pneumonitis that has not received hormone treatment), or a history of non-infectious pneumonitis; 14. Having active tuberculosis infection found in medical history or through CT examination, or having a history of active tuberculosis infection within 1 year prior to enrollment, or having had a history of active tuberculosis infection more than 1 year prior to enrollment but being treatment-naive; 15. With active hepatitis B (HBV DNA ≥ 2000 IU/mL or 10^4 copies/mL), hepatitis C (positive for hepatitis C antibody, and HCV-RNA higher than the lower limit of detection of the analytical method); 16. Diagnosed with any other malignancy prior to the first dose of the study drug, with the exception of malignancies with low risk of metastasis and death (5-year survival rate > 90%) such as adequately treated basal cell or squamous cell skin cancer or cervical carcinoma in situ; 17. Pregnant or lactating women; 18. 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.
ADA Study	Blood sampling time points: Collected once before the 1st, 2nd, 4th, 6th, and 9th administration of SHR-1210/placebo; thereafter, once every 4 doses of SHR-1210/placebo before administration; once upon withdrawal from study treatment; and once 30 days after the last dose (if applicable).
Study Withdrawal Criteria	Reasons for withdrawal may include: 1. Withdrawal of informed consent and refusal of further follow-ups; 2. Loss to follow-up; 3. Death; 4. Study termination by the sponsor.
Study Treatment Discontinuation Criteria	Criteria for treatment discontinuation are as follows: 1. Withdrawal of informed consent and refusal of further study treatment; 2. Deterioration of subject's clinical symptoms/performance status as per the investigator's judgment; 3. When judged as PD as per RECIST v1.1 criteria, subjects who meet the criteria of clinical stability (see Section 7.1.5 Use of drug) may continue the treatment, until PD

	is confirmed or the subject no longer benefits clinically from the treatment as per the investigator's judgment; 4. Unacceptable toxicity, including any clinical AE, laboratory abnormalities, or other medical conditions; if the toxicities of SHR-1210 or chemotherapy are unacceptable, the drug with unacceptable toxicities should be discontinued; 5. Significant protocol deviations; 6. Other reasons for which the investigator considers that it is necessary to discontinue the study treatment; 7. Pregnancy; 8. Loss to follow-up; 9. Death; 10. Study termination by the sponsor.
Determination of Sample Size	A parallel design is adopted in this study. The sample size is calculated based on the comparison of the two primary efficacy endpoints, i.e., PFS and OS, of PD-1 antibody SHR-1210 combined with paclitaxel and cisplatin (treatment group) and placebo combined with paclitaxel and cisplatin (control group). The hypothesis for efficacy is as follows: The hazard ratio (HR) of PFS (treatment group/control group) is 0.67, the estimated median PFS of the control group is 5 months, the HR of OS (treatment group/control group) is 0.73, and the estimated median OS of the control group is 10 months. Assuming a one-sided $\alpha = 0.005$, a power of 90% can be obtained when 378 PFS events are collected, and the estimated final analysis time of PFS is approximately 22.0 months. Two interim analyses are planned for the OS. The Lan-DeMets α spending function will be used to allocate the α, and the O'Brien & Fleming method will be used to preset the superiority boundary (EAST 6.4.1) to control the overall one-sided $\alpha = 0.02$. The first interim analysis will be performed when about 269 (66%) OS events (approximately 22.1 months) are collected, and the second interim analysis will be performed when 347 (85%) OS events (approximately 28.4 months) are collected. The final analysis of OS will be performed when 408 OS events are collected to obtain a power of 85% under the premise that the overall type I error does not exceed one-sided $\alpha = 0.02$. The enrollment period is approximately 18 months, and the follow-up period is approximately 18 months. With a randomization ratio of 1:1, a total of approximately 520 subjects are required. Considering a dropout rate of 5%, 548 subjects are intended to be enrolled.
Data Analysis/ Statistical Methods	The primary efficacy endpoints of this study are PFS and OS. Two interim analyses of the efficacy are planned for the OS. The final analysis of PFS will be performed when 378 PFS events (about 22 months) are collected; at the same time, the first interim analysis of OS will be performed, when about 269 (66%) events (about 22.1 months) are collected. The second interim analysis of OS will be performed when about 347 (85%) events (about 28.4 months) are collected. The final analysis of OS will be performed when 408 events are collected. The time-event indicators will be analyzed using the Kaplan-Meier method, so as to

	estimate the survival function of both groups and plot the survival curves. In addition, the Cox regression model will be used to estimate the HR between the two groups and its 95% confidence interval (95% CI). For binary variables, the Cochran-Mantel-Haenszel method considering the stratification factors for randomization will be used to estimate the intergroup difference and its 95% confidence interval (95% CI). The safety analysis will be summarized using descriptive statistics.
Study Dates	Anticipated enrollment of the first subject: October 2018 Anticipated enrollment of the last subject: April 2020 Anticipated study completion: October 2021

SCHEDULE OF ACTIVITIES

Study Procedures

	Screening Period		Treatment Period		Withdrawal Visit [26] (+ 3 days)	Safety Follow-Up [27]		Survival Follow-Up (± 7 days) [28]
			Combined Chemotherapy	Maintenance Treatment [17]				
Visit Window	**D-28 to D-1**	**D-7 to D-1**	**Every 3 weeks ± 3 days**	**Every 3 weeks ± 3 days**		**30 days (± 7 days) after the last dose**	**60 and 90 days (± 7 days) after the last dose**	
Signing of Informed Consent Form [1]	√							
Verification of Eligibility		√						
Demographics	√							
Medical History [2]	√							
ECOG PS Score [3]		√	√	√	√			
Vital Sign Measurement [4]		√	√	√	√			
Physical Examination [5]		√	√	√	√			
Hematology [6]		√	√	√	√	√		
Urinalysis [7]		√	√	√	√			
Fecal Occult Blood [8]		√	√	√				

	Screening Period		Treatment Period		Withdrawal Visit [26] (+ 3 days)	Safety Follow-Up [27]		Survival Follow-Up (± 7 days) [28]
			Combined Chemotherapy	Maintenance Treatment [17]				
Visit Window	**D-28 to D-1**	**D-7 to D-1**	**Every 3 weeks ± 3 days**	**Every 3 weeks ± 3 days**		**30 days (± 7 days) after the last dose**	**60 and 90 days (± 7 days) after the last dose**	
Blood Biochemistry [9]		√	√	√	√	√		
Thyroid Function [10]		√	√	√	√	√		
Coagulation Function [11]		√						
Virological Examination [12]	√							
ECG [13]		√	√	√	√			
Echocardiography [14]		√						
Pregnancy Test [15]		√			√			
Tumor Imaging Evaluation [16]	√		√					
Randomization		√						
Administration of SHR-1210/Placebo [18]			√	√				
Administration of Paclitaxel [19]			√					

	Screening Period		Treatment Period		Withdrawal Visit [26] (+ 3 days)	Safety Follow-Up [27]		Survival Follow-Up (± 7 days) [28]
			Combined Chemotherapy	Maintenance Treatment [17]				
Visit Window	**D-28 to D-1**	**D-7 to D-1**	**Every 3 weeks ± 3 days**	**Every 3 weeks ± 3 days**		**30 days (± 7 days) after the last dose**	**60 and 90 days (± 7 days) after the last dose**	
Administration of Cisplatin [20]			√					
AE[21]	√	√	√	√	√	√	√	

	Screening Period		Treatment Period		Withdrawal Visit [26] (+ 3 days)	Safety Follow-Up [27]		Survival Follow-Up (± 7 days) [28]
			Combined Chemotherapy	Maintenance Treatment [17]				
Visit Window	**D-28 to D-1**	**D-7 to D-1**	**Every 3 weeks ± 3 days**	**Every 3 weeks ± 3 days**		**30 days (± 7 days) after the last dose**	**60 and 90 days (± 7 days) after the last dose**	
Concomitant Medication [22]	√	√	√	√	√	√	√	
Quality of Life Score [23]			√	√	√	√		
ADA Blood Sampling [24]			√	√	√	√		
Tumor Tissues [25]	√							

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 Visits" section of the eCRF.

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

[2] Medical history: including tumor history (diagnosis, surgery, radiotherapy, and pharmacological treatment), history of other concurrent diseases, and history of drug allergy.

[3] ECOG PS score: within 7 days prior to the first dose, before administration on Day 1 of each cycle (not required for the first dose if completed within 7 days prior to the first dose at screening), and upon withdrawal from study treatment.

[4] Vital signs: blood pressure, pulse, body temperature, and respiratory rate; within 7 days prior to the first dose, before administration on Day 1 of each cycle (not required for the first dose if completed within 7 days prior to the first dose at screening), and upon withdrawal from study treatment.

[5] Physical examination: within 7 days prior to the first dose and upon withdrawal from study treatment, a comprehensive physical examination (including general conditions, head and face, neck, skin, lymph nodes, eyes, ear, nose, throat, mouth, respiratory system, cardiovascular system, abdomen, reproductive and urinary system, musculoskeletal system, nervous system, mental state, and others) is performed; before administration on Day 1 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 administration on Day 1 of each cycle (not required for the first dose if completed within 7 days prior to the first dose at screening), upon withdrawal from study treatment, 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 Day 1 of every 2 cycles, and upon withdrawal from study treatment. In case of a urine protein ≥ 2+, a 24-h urine protein quantitation should be added.

[8] Fecal occult blood: 7 days prior to the first dose, Day 1 of every 2 cycles.

[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 administration on Day 1 of each cycle (not required for the first dose if completed within 7 days prior to the first dose at screening), upon withdrawal from study treatment, and 30 days after the last dose.

[10] Thyroid function: TSH, FT3, FT4. Within 7 days prior to the first dose, before administration on Day 1 of every 2 cycles, upon withdrawal from study treatment, and 30 days after the last dose.

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

[12] 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.

[13] ECG: within 7 days prior to the first dose, before administration on Day 1 of each cycle (not required for the first dose if completed within 7 days prior to the first dose at screening), and upon withdrawal from study treatment.

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

[15] Pregnancy test: for women of childbearing potential only. Within 72 hours prior to the first dose, and upon withdrawal from study treatment.

[16] Tumor imaging evaluation: CT or MRI of the neck, chest, and abdomen (including pelvic cavity) (both are enhanced; plain scans may be used instead when contrast agents are contraindicated). Brain MRI (or CT if MRI is contraindicated, both are enhanced; plain scans may be used instead when contrast agents are contraindicated) is required for suspected or diagnosed brain metastasis. Bone scan is performed only when clinically indicated.

- ✓ At screening, tumor assessments up to 4 weeks before randomization and before informed consent may be used as long as they meet the RECIST v1.1 criteria. Bone scan is required for suspected or diagnosed bone metastases and must be performed within 42 days prior to the first dose.

- ✓ During the treatment period, baseline imaging examination is conducted once every 6 weeks. Unscheduled imaging examinations may be performed for suspected PD. Imaging examinations should be conducted timely upon the subject's withdrawal from study of any cause (± 4 weeks; the examination is not repeated if the time of previous examination is less than 4 weeks from the withdrawal visit). Imaging conditions should be the same as those at baseline (including slice thickness and contrast agent).
- ✓ A time window of ± 7 days is allowed for imaging examinations. Subjects who discontinue study treatment for reasons other than radiologically confirmed PD must also undergo a tumor assessment every 6 weeks until observation of PD, start of a new anti-tumor treatment, withdrawal of informed consent, loss to follow-up, or death.

[17] Maintenance treatment: After the end of combined medication, SHR-1210/placebo monotherapy is used for maintenance treatment.

[18] Administration of SHR-1210/placebo: on Day 1 of each cycle during the combined treatment, and on Day 1 of each cycle during the maintenance treatment period, with every cycle containing 3 weeks.

[19] Administration of paclitaxel: on Day 1 of each 3-week cycle during the combined treatment, for up to 6 cycles.

[20] Administration of cisplatin: on Day 1 of each 3-week cycle during the combined treatment, for up to 6 cycles.

[21] AE: collected from the signing of the informed consent form until 90 days after the last dose. If the subject starts a new anti-tumor treatment during the AE collection period, only treatment-related AEs are collected after the start of the new anti-tumor treatment.

[22] Concomitant medication: concomitant medications from 30 days before signing informed consent form until the start of new anti-tumor treatment are documented; afterward, only concomitant medications for treatment-related AEs are documented.

[23] Quality of life score (EORTC QLQ-C30, EORTC QLQ-OES18): before the first dose, every 6 weeks, upon withdrawal from study treatment, and 30 days after the last dose (if applicable), with a time window of ± 7 days; recommended to be obtained prior to administration as well as adverse event and tumor assessments.

[24] ADA blood sampling: Collected once before the 1st, 2nd, 4th, 6th, and 9th administration of SHR-1210/placebo; thereafter, once every 4 doses of SHR-1210/placebo before administration; once upon withdrawal from study treatment; and once 30 days after the last dose (if applicable).

[25] Tumor tissue: obtained before randomization; fresh biopsy is preferred, otherwise use archival tumor tissue specimens.

[26] Withdrawal visit: completed when the subject must discontinue study treatment.

[27] Safety follow-up period: All subjects should return to the study site for a follow-up 30 days after the last dose (perform telephone follow-up if withdrawal visit is completed) and the follow-ups via telephone are required 60 days and 90 days after the last dose. Safety information should be obtained via telephone follow-ups (including AE outcome, new SAE, and AE of special interest) with a time window of ± 7 days.

[28] Survival follow-up: once every 30 days after the last dose, with a time window of ± 7 days.

ABBREVIATIONS

Abbreviation	Full Name
ADA	Anti-drug antibody
ADL	Activities of daily living
AE	Adverse event
AKP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the curve
BUN	Blood urea nitrogen
CFDA	China food and drug administration
CR	Complete remission
Cr	Creatinine
CRF	Case report form
CRO	Contract research organization
D	Day
DoR	Duration of response
DLT	Dose-limiting toxicity
EC	Ethics committee
EC	Esophageal cancer
EDC	Electronic data collection
ITT	Intent-To-Treat Set
FIB	Plasma fibrinogen
FT3	Free triiodothyronine
FT4	Free thyroxine
GC	Gastric carcinoma
GCP	Good Clinical Practice
GGT	Gamma glutamyl transpeptidase
h	Hour
HCC	Hepatocellular carcinoma
Hb	Hemoglobin
HR	Hazard ratio
IC_{50}	Half maximal inhibitory concentration

Abbreviation	Full Name
IDMC	Independent Data Monitoring Committee
iRECIST	Immune-related response evaluation criteria in solid tumors
IU	International unit
kg	Kilogram
LDH	Lactate dehydrogenase
mg	Milligram
min	Minimum
mL	Milliliter
mm	Millimeter
MRI	Magnetic resonance imaging
MTD	Maximal tolerable dose
NOAEL	No observed adverse effect levl
NPC	Nasopharyngeal cancer
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PR	Partial remission
PD	Progressive disease
PK	Pharmacokinetic
PFS	Progression free survival
PPS	Per-protocol analysis set
PT	ProthrombinTime
PLT	Blood platelet
RBC	Red blood cell count
RECIST	Response evaluation criteria in solid tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SS	Safety analysis set
T-BIL	Total bilirubin
TNBC	Triple negative breast cancer
TSH	Thyroid-stimulating hormone
UA	Uric acid
ULN	Upper limit of normal
WBC	White blood cell count

1. KEY FUNCTIONAL ROLES

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2. INTRODUCTION: BACKGROUND AND SCIENTIFIC RATIONALE

2.1. Background

2.1.1. Esophageal cancer

Esophageal cancer is a type of malignant tumor that occurs in the esophageal mucosa. Worldwide, esophageal cancer ranks the eighth in cancer incidence and the sixth in mortality. China accounts for more than 50% of all esophageal cancers [1]. In 2015, there were 477,900 new esophageal cancer patients in China. From 2001 to 2011, the incidence and mortality of esophageal cancer ranked the fifth and the fourth among male tumor patients, respectively, and the incidence and mortality of esophageal cancer among female patients showed a year-on-year decline [2]. More than 90% of esophageal cancers are squamous cell carcinoma, and there are obvious regional differences. The provinces with a high incidence of esophageal cancer are Hebei, Henan, Fujian, and Chongqing, followed by Xinjiang, Jiangsu, Shanxi, Gansu, and Anhui [3].

Endoscopic treatment is preferred for early esophageal cancer (involving only the mucosa or submucosa). The 5-year survival rate is as high as 95%. However, as most patients are not treated in the early stage of the disease, the five-year survival rate for esophageal cancer is less than 20% [4]. First-line treatment for advanced unresectable, relapsed, metastatic esophageal cancer is platinum-based chemotherapy in combination with, for example, paclitaxel + cisplatin or 5-fluorouracil + cisplatin. The response rate is between 30–60% and the median OS is 5–10

months [3,5]. At present, treatment options for advanced esophageal cancer are very limited, and the survival of patients is relatively short.

2.1.2. SHR-1210

SHR-1210 is a humanized monoclonal antibody, whose heavy chain is immunoglobulin G4 (IgG4) and light chain is immunoglobulin κ (IgK). It is expressed in the supernatant of stable Chinese hamster ovary (CHO) cell lines. SHR-1210 can specifically bind to PD-1, blocking the interaction between PD-1 and its ligand (PD-L1), and restore T cell immune response to tumor cells.

2.1.2.1. Preclinical study results

In vitro pharmacodynamic studies showed that SHR-1210 had high affinity for PD-1 of humans, cynomolgus monkeys, and rhesus monkeys (2 nM, 8 nM, 4 nM, respectively), and effectively blocked PD-1/PD-L1 interaction (IC_{50} of 0.70 nM). *In vivo* pharmacodynamic studies showed that SHR-1210 had significant anti-tumor effects in mouse MC38 colorectal cancer model and xenograft mouse model of human malignant glioblastoma U87-MG.

Clinical pharmacokinetic studies in cynomolgus monkeys showed that the exposure (AUC and C_{max}) increased with dose, there was no gender difference in PK parameters, the clearance rate was dose-dependent, and the clearance rate was lower at higher doses. No drug accumulation was noted after repeated administration.

Toxicology studies showed that, for a single administration of SHR-1210 in cynomolgus monkeys, the MTD was ≥ 800 mg/kg; for repeated administrations, the MTD was ≥ 200 mg/kg. In the 4-week and 26-week toxicity studies, the NOAEL of SHR-1210 was 100 mg/kg.

Results of preclinical pharmacology studies showed that SHR-1210 had good anti-tumor activity, safety, and tolerability, supporting further clinical studies of SHR-1210. The detailed preclinical pharmacology data are presented in Investigator's Brochure.

2.1.2.2. Clinical study results

As of 28 Feb., 2018, 6 phase I, 9 phase II, and 2 phase III clinical studies of SHR-1210 have been conducted. The safety, efficacy, pharmacokinetics, and immunogenicity data summarized below are mainly from the following three phase I clinical studies (data cutoff date: 28 Feb., 2018).

SHR-1210-I-101 was an open-label, single-center, dose-escalation phase I clinical study evaluating the safety and tolerability of SHR-1210 in subjects with advanced solid tumors who had failed standard anti-tumor treatment. The study consisted of 3 stages: Stage 1 was the dose-

escalation part. In the standard 3 + 3 dose-escalation design, SHR-1210 was intravenously infused at doses of 1 mg/kg, 3 mg/kg (approximately equivalent to a fixed dose of 200 mg), and 10 mg/kg, Q2W (except the first 4-week cycle, as subjects only received the study drug on Day 1 of this cycle for PK sampling and DLT observation). Stage 2 was the extension stage, during which the doses selected in Stage 1 were used, with up to 12 subjects in each group. Extension was conducted for indications of NPC and NSCLC in Stage 3. As of 28 Feb., 2018, a total of 123 subjects was enrolled in this study.

SHR-1210-I-102 was an open-label, single-center, dose-escalation phase I study evaluating the safety and tolerability of SHR-1210 in subjects with advanced malignant melanoma who had failed standard anti-tumor treatment. The study consisted of 2 stages: Stage 1 was the dose-escalation part. In the standard 3 + 3 dose-escalation design, SHR-1210 was intravenously infused at doses of 60 mg, 200 mg, and 400 mg, Q2W (except the first 4-week cycle, as subjects only received the study drug on Day 1 of this cycle for PK sampling and DLT observation). Stage 2 was the extension stage, during which the doses selected in Stage 1 were used, with up to 12 subjects in each group. As of 28 Feb., 2018, the enrollment of all 36 subjects of the study has been completed.

SHR-1210-I-103 was an open-label, single-center, dose-escalation phase I study evaluating the safety and tolerability of SHR-1210 in subjects with advanced solid tumors who had failed standard anti-tumor treatment. The study consisted of 3 stages: Stage 1 was the dose-escalation part. In the standard 3 + 3 dose-escalation design, SHR-1210 was intravenously infused at doses of 60 mg, 200 mg, and 400 mg, Q2W (except the first 4-week cycle, as subjects only received the study drug on Day 1 of this cycle for PK sampling and DLT observation). Stage 2 was the extension stage, during which the doses selected in Stage 1 were used, with up to 9–12 subjects in each group. Stage 3 would further explore the dosage for the Q2W regimen in subjects with EC, GC, HCC, and TNBC (60 subjects in total). As of 28 Feb., 2018, the enrollment of all 99 subjects of the study has been completed.

2.1.2.2.1. Safety results

A total of 258 subjects were enrolled in the three phase I clinical studies. No DLT was observed. All 258 (100.0%) subjects had at least one AE, 98 (38.0%) subjects had at least one Grade ≥ 3 AE, 256 (99.2%) subjects had at least one treatment-related AE, 82 (31.8%) subjects had at least one Grade ≥ 3 treatment-related AE, and 78 subjects had SAE, of which 61 had treatment-related SAE. AEs related to SHR-1210 were mostly of CTCAE Grade 1–2. Common treatment-related AEs 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%). Except for cutaneous capillary endothelial proliferation, other AEs were similar to those of similar drugs.

Overall, SHR-1210 had good safety and tolerability in patients with advanced solid tumors.

2.1.2.2.2. Efficacy results

In the SHR-1210-I-103 study, a total of 43 subjects with advanced esophageal squamous cell carcinoma who had failed the standard treatment were enrolled. The efficacy assessment showed an ORR of 25.6% and a disease control rate of 48.9%, demonstrating preliminary efficacy of SHR-1210 in patients with advanced esophageal squamous cell carcinoma.

2.1.2.2.3. Pharmacokinetics and immunogenicity

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, the median time to maximum concentration (T_{max}) of different dose groups (1 mg/kg, 3 mg/kg, 200 mg/dose, and 10 mg/kg) was in the range of 0.58–2.50 h; the *in vivo* exposure and elimination half-life ($t_{1/2}$) increased with the dose, the clearance rate (CL) slowly decreased with the increasing dose, and the volume of distribution (Vd) generally did not change with the increasing dose. After repeated administrations, the serum SHR-1210 concentration of each dose group generally reached a steady state after 3–5 treatment cycles. There was generally no accumulation at 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 administration frequency of Q2W.

A total of 117 subjects had immunogenicity results in the three phase I clinical studies. Twenty (17.1%) subjects were tested positive for anti-SHR-1210 antibodies at least once. Among them, 3 (2.6%) were tested positive for anti-SHR-1210 antibodies at baseline; 17 (14.5%) were tested negative at baseline and positive after baseline, of which 10 (8.5%) were transiently positive. Among the above-mentioned subjects tested positive for anti-SHR-1210 antibodies, only 1

(0.9%) showed neutralizing antibody activity (the subject's anti-SHR-1210 antibody was negative at baseline and persistently positive after baseline); the subject showed positive neutralizing activity only once before the administration of Cycle 2, and the neutralizing activity was negative in subsequent cycles. No significant effect of positive anti-SHR-1210 antibodies on the safety, efficacy, and drug clearance rate of subjects has been observed.

2.2. Scientific Rationale

2.2.1. Study rationale

Chemotherapeutic drugs were once thought to kill tumor cells directly through cytotoxicity. But with the deepening of research, it has been found that chemotherapeutic drugs also exert anti-tumor effects by regulating the body's immune system, cause immunogenic death of tumor cells, increase the antigen cross-presentation ability of dendritic cells, and activate the body's anti-tumor immune effect [6]; reduce myeloid-derived suppressor cells (MDSC), and relieve the immune suppression caused by them [7]; increase the ratio of cytotoxic lymphocytes to regulatory T cells, and reduce the inhibitory effect of regulatory T cells on immunity [8]; block the STAT6 pathway, down-regulate PD-L2 expressed by dendritic cells and tumor cells, and increase T cell activity and tumor cell recognition [9]. High expression of PD- L1 is related to tumor invasion and chemotherapy resistance [10]. Immune checkpoint inhibitors acting on the PD-1/PD-L1 pathway enhance tumor immune surveillance and anti-tumor immune responses by inhibiting the PD-1 signaling. Therefore, the combination of immune checkpoint inhibitors and chemotherapy may have a synergistic anti-tumor effect.

At present, clinical studies of immune checkpoint inhibitors nivolumab, pembrolizumab, and BGB-A317 in combination with chemotherapy as first-line treatment of advanced esophageal cancer are undergoing (as detailed in Table 1). The combination of chemotherapy with PD-1/PD-L1 immune checkpoint inhibitors may be a new first-line treatment for advanced esophageal cancer.

Table 1. Summary of clinical studies of immune checkpoint inhibitors combined with chemotherapy as first-line treatment for advanced esophageal cancer.

No.	Study Design	Sample Size	Administration Regimen	Primary Endpoints
1	Single-arm, non-randomized, open-label phase II clinical study	30	Esophageal squamous cell carcinoma group: Fluorouracil + cisplatin + BGB-A317	To evaluate the safety of the combination regimen by monitoring AEs and SAEs, laboratory assessments, physical examination, vital signs, and ECG.

No.	Study Design	Sample Size	Administration Regimen	Primary Endpoints
2	Randomized, double-blind, placebo-controlled phase III clinical study	700	Treatment group: fluorouracil + cisplatin + pembrolizumab Control group: fluorouracil + cisplatin	PFS of all subjects; PFS of PD-L1 positive subjects; OS of all subjects; OS of PD-L1 positive subjects.
3	Randomized, open-label, active-controlled phase III clinical study	939	Treatment group: nivolumab + ipilimumab Nivolumab + fluorouracil + cisplatin Control group: fluorouracil + cisplatin	PFS of PD-L1 positive subjects; OS of PD-L1 positive subjects.

Guidelines in China and abroad recommend paclitaxel and cisplatin as one of the first-line treatment regimens for advanced esophageal cancer. The ORR was 36–60%, the PFS was 5–8 months, and the OS was 7–17 months [11,12,13,14,15,16]. For patients with advanced esophageal cancer, the efficacy of existing first-line treatments has plateaued. In this study, SHR-1210 combined with paclitaxel and cisplatin is used as the first-line treatment for advanced esophageal cancer, so as to improve the survival benefits of subjects.

2.2.2. Basis of administration regimen

The design basis of the administration regimen in this study is as follows.

No DLT was observed for SHR-1210 at the calculated dose (1–10 mg/kg) and fixed dose (200 mg), and the type and frequency of AEs were similar. The results of the SHR-1210-101 study showed that the 200 mg dose group had a higher objective response rate (33%), and its pharmacokinetic behavior was generally consistent with that of the 3 mg/kg dose group. The PD-1 receptor occupancy rate remained around 75% 22 days after administration. Combined with the preliminary data on pharmacokinetics, pharmacodynamics, safety, and efficacy, and considering the convenience of clinical operation, SHR-1210 at a fixed dose of 200 mg is used in this study, in 3-week treatment cycles.

The recommended administration regimen of paclitaxel combined with cisplatin by NCCN Guidelines (2018) is paclitaxel 135–200 mg/m^2 (D1) plus cisplatin 75 mg/m^2 (D2), in 3-week treatment cycles. The recommend administration regimen of paclitaxel combined with cisplatin by China's Guidelines for Diagnosis and Treatment of Esophageal Cancer (2011) is paclitaxel 140–170 mg/m^2 (D1) plus cisplatin 80–100 mg/m^2 (D1 or divided into 2–5 days), in 3-week treatment cycles. There is currently no study with large sample size to clarify the fixed-dose regimen of paclitaxel and cisplatin. Paclitaxel combined with cisplatin is the first-line chemotherapy regimen commonly used in the treatment of advanced esophageal cancer in China. In a single-arm phase II clinical trial [13], 35 subjects with unresectable, recurrent or metastatic

esophageal squamous cell carcinoma were enrolled and received paclitaxel 175 mg/m^2 on D1 plus cisplatin 75 mg/m^2 on D1, in 21-day treatment cycles. The ORR was 48.6% and the OS was 13 months. In another retrospective study [15] with the same administration regimen, the ORR was 42.5% and the OS was 13.46 months. With reference to the above results, the selected doses of paclitaxel and cisplatin in this study are 175 mg/m^2 (D1) and 75 mg/m^2 (D1), respectively, in 3-week treatment cycles.

2.3. Potential Risks and Benefits

2.3.1. Known potential risks

SHR-1210 is an immune checkpoint inhibitor. Subjects may develop a transient accelerated tumor growth, i.e., pseudoprogression, after receiving this type of drug. In this study, subjects in the treatment group who have radiographically confirmed progressive disease (PD) as per RECIST v1.1 criteria but are clinically stable are allowed to continue treatment with SHR-1210 combined with chemotherapy or SHR-1210 monotherapy. Since it is difficult to distinguish between pseudoprogression and true progression in imaging examinations, this operation may cause delay of other anti-tumor treatments in subjects with true progression. Therefore, the investigator should fully inform the subject of the risk, and comprehensively consider the subject's imaging examination, aspiration biopsy results, and clinical symptoms to determine whether the subject should continue medication.

Any drug or treatment may have unpredictable or even serious side effects. SHR-1210 is an immune checkpoint inhibitor that may cause immune-related AEs. The safety data from previous clinical studies suggested that the incidence of immune-related AEs of SHR-1210 was similar to that of similar drugs, mainly including immune-related thyroid dysfunction, pneumonia, hepatitis, and nephritis. In addition, the cutaneous capillary endothelial proliferation is a benign skin reaction and its incidence is relatively high. Cutaneous capillary endothelial proliferation occurring in areas prone to rubbing may cause damage and bleeding. Cutaneous capillary endothelial proliferation occurring in exposed areas such as the face may also affect the appearance of the subjects. Other treatment-related AEs are detailed in the Investigator's Brochure. Common treatment-related AEs of paclitaxel include myelosuppression, nausea, vomiting, and peripheral neuropathy. Common treatment-related AEs of cisplatin include nephrotoxicity, ototoxicity, neurotoxicity, myelosuppression, nausea, and vomiting, Other AEs related to paclitaxel and cisplatin are listed in their package inserts. The combination of SHR-1210 with paclitaxel and cisplatin may have a small possibility of toxicity but the probability of allergic reactions may increase. Safety risks exist during the study medication. Close follow-up is necessary during the course of the clinical study. Interventions and actions should be adopted in a timely manner.

2.3.2. Known potential benefits

Paclitaxel combined with cisplatin is a common first-line chemotherapy regimen for the treatment of advanced esophageal squamous cell carcinoma in the clinical practice. The combination of SHR-1210 with chemotherapy may have a synergistic anti-tumor effect, which will benefit patients with advanced esophageal squamous cell carcinoma.

3. OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary objective

To compare the progression-free survival (PFS) (IRC-assessed) and overall survival (OS) of SHR-1210 combined with paclitaxel and cisplatin vs. placebo combined with paclitaxel and cisplatin in the treatment of patients with advanced esophageal cancer.

3.1.2. Secondary objectives

- To compare the PFS (investigator-assessed), OS rates, objective response rate (ORR), and disease control rate (DCR) of SHR-1210 combined with paclitaxel and cisplatin vs. placebo combined with paclitaxel and cisplatin in the treatment of patients with advanced esophageal cancer, and to evaluate the duration of response (DoR) of the two groups;
- To evaluate the safety of SHR-1210 combined with paclitaxel and cisplatin vs. placebo combined with paclitaxel and cisplatin in the treatment of patients with advanced esophageal cancer.

3.1.3. Exploratory objectives

- To determine the proportion of subjects showing anti-SHR-1210 antibodies;
- To evaluate the relationship between PD-L1 expression in tumor tissues and efficacy.

3.2. Study Endpoints

3.2.1. Primary endpoints

- IRC-assessed PFS (RECIST v1.1 criteria);
- OS.

3.2.2. Secondary endpoints

- Investigator-assessed PFS (RECIST v1.1 criteria);
- OS rates;
- ORR (RECIST v1.1 criteria);
- DCR (RECIST v1.1 criteria);
- DoR;
- Quality of life score (EORTC QLQ-C30, EORTC QLQ-OES18);
- Safety: AEs, laboratory measurements, etc.

3.2.3. Exploratory endpoints

- To determine the proportion of subjects showing anti-SHR-1210 antibodies;
- To evaluate the relationship between PD-L1 expression in tumor tissues and efficacy.

4. STUDY DESIGN

4.1. Overall Design

A randomized, double-blind, placebo-controlled, multi-center study design is adopted in this study. It is planned to enroll 548 subjects with unresectable locally advanced/recurrent or distant metastatic esophageal squamous cell carcinoma who have not previously received systemic anti-tumor treatment. Eligible subjects will be randomly assigned to the treatment group or the control group in a 1:1 ratio (treatment allocation is presented in Table 2). The stratification factors include: liver metastasis (with vs. without), whether the subjects have received definitive chemoradiation (yes vs. no).

Table 2. Treatment groups.

Treatment Group	Combined Medication (in 3-week cycles, for up to 6 cycles)	Maintenance Treatment (in 3-week cycles)
Treatment Group	SHR-1210 + Paclitaxel + Cisplatin	SHR-1210
Control Group	Placebo + Paclitaxel + Cisplatin	Placebo

Subjects in the two groups will receive the study treatment until PD, unacceptable toxicity, start of a new anti-tumor treatment, withdrawal of informed consent, when the investigator judges that the subject should withdraw from the study treatment, or the subject has been receiving SHR-1210/placebo treatment for up to 2 years.

Subjects may experience pseudoprogression after receiving the immunotherapy drugs. Thus, if the subject is evaluated as PD for the first time as per RECIST v1.1 criteria, but the investigator judges that the subject is clinically stable and can clinically benefit, the subject may continue treatment after approval by the sponsor. Imaging examination will be repeated after at least 4 weeks (± 7 days). If PD is confirmed in the subsequent imaging examination, the subject must discontinue treatment unless the investigator believes that the subject can continue to benefit clinically from the treatment. After discussing with the sponsor again and obtaining approval, the subject may continue treatment after re-signing an informed consent form for continuing treatment beyond PD, until the subject no longer benefits clinically as per the investigator's judgment.

In this study, an interim analysis will be conducted when about 269 (66%) OS events (about 22.1 months) and about 347 (85%) OS events (about 28.4 months) are collected, respectively.

The screening period of the study is 28 days. After completing the screening examinations and evaluation, subjects who meet the inclusion/exclusion criteria will enter the treatment period and be treated according to the administration frequency specified in the protocol. Relevant examinations and assessments must be completed before each dose. In particular, tumor imaging assessment is conducted once every 6 weeks (± 7 days). All subjects must complete the safety examinations and tumor assessments at the withdrawal visit. Then, the subjects will enter a 90-day safety follow-up period. The survival follow-up will be carried out once every 30 days starting from the last dose; subjects who withdraw due to non-PD reasons should be followed up for tumor progression, and continue to undergo tumor assessments once every 6 weeks (± 7 days) until PD, start of a new anti-tumor treatment, withdrawal of informed consent, loss to follow-up, or death.

Refer to Figure 1 for study design.

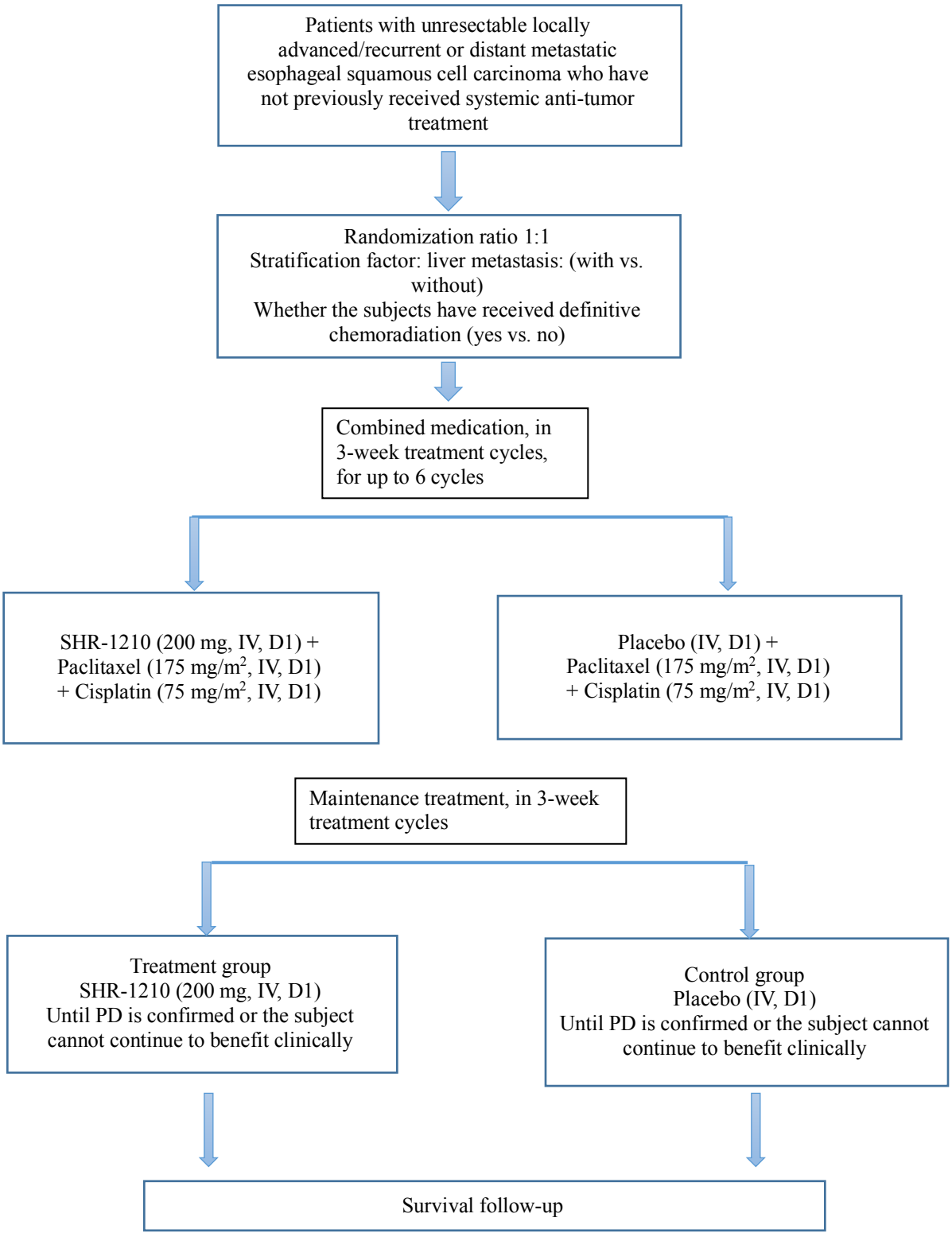

Figure 1. Study design schematic.

4.2. Methods to Reduce Bias

4.2.1. Enrollment/randomization/blinding

This study adopts a double-blind, placebo-controlled design. The investigator will log in to the randomization system, enter the basic information of subjects who have signed the informed consent form and meet the inclusion criteria, and select the stratification factors for randomization to generate the randomization number. The randomization ratio between the treatment group and the control group is 1:1. Stratified block randomization can ensure the balance of randomization.

The same packaging will be adopted for SHR-1210 and placebo to maintain the blind. Double-blind technique will be used. Designated study nurses will prepare SHR-1210 and placebo, and nurses for preparing drugs do not participate in the operation on subjects as much as possible during the trial; other study nurses are responsible for the administration. Subjects, investigators, and staff of the sponsor or designated personnel who participate in the treatment or clinical evaluation of the subjects are not aware of the grouping status.

4.2.2. Blinded assessment

In order to reduce deviations, the frequency of imaging assessment of the treatment group and the control group remains the same. The imaging assessments of tumor lesions are performed according to RECIST v1.1 criteria. The primary efficacy endpoint, PFS, is assessed by the Independent Review Committee (IRC) under blinded state. The final analysis strategy will be determined before the primary efficacy endpoint analysis database is locked, including defining data censoring rules in advance. The efficacy analysis will only be carried out at the time specified in the protocol.

4.2.3. Unblinding

This study will remain blinded to the subjects, investigators or designated personnel, study sites, and the sponsor until the study is terminated. To minimize the possibility of bias, treatment randomization information will be kept confidential during the course of the study and will not be disclosed to the blinded team before the study database is locked.

Treatment randomization information will be stored in a third-party IWRS, and access permissions will be strictly controlled.

The established database will be locked and unblinded after being confirmed correct per the blinded review, with the issuance of a blinded review report. After the database is locked, the data must be properly stored for future reviews. The blind code and the database should be statistically analyzed by the statistician.

Treatment identification information will be unblinded only when necessary in consideration of the subject's interests. Unless necessary, the subject should be kept blinded as much as possible.

When the investigator needs to confirm the drug and dosage for the subject in cases of emergencies, the responsible investigator at the study site shall submit the application, and the medical director of the sponsor and the principal investigator shall make a joint decision on whether to unblind. The investigator will use the IWRS to unblind the subject and report the unblinding to the sponsor. Before unblinding, the investigator must enter the toxicity level of the observed adverse event, the correlation with the study drug, and the causes in the medical record and other documents.

Subjects whose treatment allocation is unblinded by the investigator and/or non-study physician must discontinue the study treatment, but should continue to be monitored during the trial.

Upon unblinding, the circumstances of the unblinding (e.g., the date, causes, and the person responsible for unblinding) must be documented immediately, and the sponsor's CRA must be notified as soon as possible.

5. SELECTION AND WITHDRAWAL OF SUBJECTS

5.1. Inclusion Criteria

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

1. Aged 18–75 years, male or female;
2. Histologically or cytologically diagnosed with unresectable locally advanced/recurrent (unable to receive esophagectomy and definitive chemoradiation) or distant metastatic esophageal squamous cell carcinoma;
3. Have not received any systemic anti-tumor treatment. A patient who has received neoadjuvant/adjuvant and definitive chemoradiation can be screened if his/her last treatment is more than 6 months from recurrence or progression;
4. With at least one measurable lesion (cavity structures such as oesophagus may not serve as measurable lesions) according to RECIST v1.1 criteria, which has not received any local treatment including radiotherapy (a lesion located in an area subjected to a previous radiotherapy can be selected as the target lesion if PD is confirmed);
5. Tissue samples for biomarker (such as PD-L1) analysis must be provided. Fresh tissues are preferred. Archival samples of 5–8 paraffin embedded sections that are 3–5 μm thick are also acceptable if a fresh biopsy is not accessible;

6. ECOG: 0–1 (see Appendix I);
7. Expected survival ≥ 12 weeks;
8. Vital organ functions meet the following requirements (use of any blood components and cell growth factors is not allowed within 14 days before the screening examinations);
    a. Absolute neutrophil count (ANC) ≥ 1.5×10^9/L
    b. Platelets ≥ 100×10^9/L;
    c. Hemoglobin ≥ 9 g/dL;
    d. Serum albumin ≥ 2.8 g/dL;
    e. Total bilirubin ≤ 1.5 × ULN; ALT, AST, and/or AKP ≤ 2.5 × ULN; ALT and/or AST ≤ 5 × ULN in the presence of liver metastasis; AKP ≤ 5 × ULN in the presence of liver or bone metastases;
    f. Serum creatinine ≤ 1.5 × ULN or creatinine clearance > 60 mL/min (Cockcroft-Gault, see Appendix II);
    g. Activated partial thromboplastin time (APTT) and international normalized ratio (INR) ≤ 1.5 × ULN (those receiving stable doses of anticoagulant therapy, such as low molecular weight heparin or warfarin, whose INR is within the expected therapeutic range of anticoagulants can be screened);
9. Women of childbearing potential and males with female partners of childbearing potential are required to take a medically approved contraceptive measure (e.g., intra-uterine contraceptive device, contraceptive pills, or condoms) during the study treatment period, for at least 3 months after the last dose of SHR-1210/placebo, and for at least 6 months after the last dose of chemotherapy;
10. Subjects must participate voluntarily, sign the informed consent form, have good compliance, and cooperate with follow-up visits.

5.2. Exclusion Criteria

Subjects meeting any one of the following are not eligible to participate in this study.

1. BMI < 18.5 kg/m^2 or weight loss ≥ 10% within 2 months before screening (at the same time, the effect of a large amount of pleural effusions and ascites on body weight should be considered);

2. With a history of gastrointestinal perforation and/or fistula within 6 months prior to the first dose;
3. Significant tumor invasion into adjacent organs (aorta or trachea) of esophageal lesions leading to higher risk of hemorrhage or fistula;
4. Presence of uncontrollable pleural effusion, pericardial effusion, or ascites requiring repeated drainage;
5. With a history of allergy to any monoclonal antibody, any component of SHR-1210, paclitaxel, cisplatin, or any other platinum-based drug;
6. Have any of the following situations:
    a. Have received anti-PD-1 or anti-PD-L1 antibody therapy;
    b. Have received any investigational drug within 4 weeks prior to the first dose of the study drug;
    c. Simultaneously enrolled into another clinical study, except for an observational (non-interventional) clinical study or follow-up of an interventional clinical study;
    d. Received the last dose of anti-tumor treatment (including radiotherapy) within ≤ 4 weeks before the first dose of the study drug;
    e. Requiring systemic treatment with corticosteroids (> 10 mg/day of prednisone or equivalent) or other immunosuppressive medications within 2 weeks before the first dose of the study drug, except the use of corticosteroids for local inflammation of the esophagus and prevention of allergies, nausea, and vomiting. Other special circumstances must be communicated with the sponsor. In the absence of active autoimmune disease, inhaled or topical use of corticosteroids or an equivalent dose of > 10 mg/day of prednisone for adrenal hormone replacement are permitted;
    f. Have been inoculated with any anti-tumor vaccine, or have been inoculated with any live vaccine within 4 weeks prior to the first dose of the study drug;
    g. Have undergone major surgery or severe trauma within 4 weeks prior to the first dose of the study drug;
7. Suffering toxicity from prior anti-tumor therapy that has not recovered to CTCAE Grade ≤ 1 (except alopecia) or a level specified in inclusion/exclusion criteria;
8. With central nervous system metastases;

9. With any active autoimmune disease, or a history of autoimmune disease (including but not limited to interstitial pneumonia, colitis, hepatitis, hypophysitis, vasculitis, nephritis, hyperthyroidism, and hypothyroidism), except for: vitiligo, or cured childhood asthma/allergy that do not require any intervention in adulthood; autoimmune-mediated hypothyroidism treated with a stable dose of thyroid hormone replacement therapy; and type I diabetes mellitus treated with a stable dose of insulin;
10. With a history of immunodeficiency, including positive anti-HIV assay, or with any other acquired or congenital immunodeficiencies, or with a history of organ transplantation or allogeneic bone marrow transplantation;
11. Having any poorly-controlled cardiovascular clinical symptom or disease, including but not limited to: (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 arrhythmia without clinical intervention or is poorly controlled after clinical intervention;
12. Having any serious infection (CTCAE Grade > 2) within 4 weeks prior to the first dose of the study drug, such as serious pneumonia, bacteremia, or infection-related complication requiring hospitalization; baseline chest radiography suggesting presence of active lung inflammation, infection symptoms and signs present within 2 weeks prior to the first dose of the study drug requiring treatment by oral or intravenous administration of any antibiotic, except prophylactic use of antibiotics;
13. With a history of interstitial lung disease (except radiation pneumonitis that has not received hormone treatment), or a history of non-infectious pneumonitis;
14. Having active tuberculosis infection found in medical history or through CT examination, or having a history of active tuberculosis infection within 1 year prior to enrollment, or having had a history of active tuberculosis infection more than 1 year prior to enrollment but being treatment-naive;
15. With active hepatitis B (HBV DNA $\geq$ 2000 IU/mL or 10^4 copies/mL), hepatitis C (positive for hepatitis C antibody, and HCV-RNA higher than the lower limit of detection of the analytical method);
16. Diagnosed with any other malignancy prior to the first dose of the study drug, with the exception of malignancies with low risk of metastasis and death (5-year survival rate > 90%) such as adequately treated basal cell or squamous cell skin cancer or cervical carcinoma in situ;

17. Pregnant or lactating women;

18. 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.

5.3. Randomization Criteria

Subjects who meet the inclusion and exclusion criteria will be randomized to the treatment group or control group in a 1:1 ratio using the randomization system. Randomization will be stratified by liver metastasis (with vs. without) and whether the subjects have received definitive chemoradiation (yes vs. no).

5.4. Lifestyle Requirements

5.4.1. Contraception

If the investigator believes that the female subject or the male subject's partner is at risk of pregnancy, the subject must take at least one highly effective contraceptive measure from the signing of the informed consent form until at least 3 months after the last dose of SHR-1210/placebo and at least 6 months after the last dose of chemotherapy. After consulting with the subject, the investigator or designated personnel will select an appropriate contraceptive method from the following contraceptive methods, and confirm the subject's awareness of correct and consistent use the contraceptive method. At time points shown in SCHEDULE OF ACTIVITIES, the investigator shall notify the subject of the persistent and correct use of contraception (the subjects need to confirm that they use at least one of the selected contraceptive measures consistently and correctly). The subject should be aware that the investigator must be notified immediately once the selected method of contraception is stopped, or when the subject or the partner is suspected or confirmed of pregnancy.

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

1. Commonly used hormonal contraceptive methods associated with the suppression of ovulation (e.g., oral, inserted, injectable, implants, subcutaneous) should meet the requirement that the female subject or partner of male subject has been using this method for a period of time with proven effectiveness, and plans to continue using it correctly throughout the study;

2. Correctly inserted intrauterine devices;

3. Male/female condom combined with topical spermicides (i.e., foams, gels, films, creams, or suppositories);
4. Male sterilization by vasectomy;
5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusion (the occlusion should be proven effective by relevant instruments).

5.5. Withdrawal from Study or Treatment Discontinuation

5.5.1. Study withdrawal criteria

Reasons for withdrawal may include:

1. Withdrawal of informed consent and refusal of further follow-ups;
2. Loss to follow-up;
3. Death;
4. Study termination by the sponsor.

5.5.2. Criteria for treatment discontinuation

Criteria for treatment discontinuation are as follows:

1. Withdrawal of informed consent and refusal of further study treatment;
2. Deterioration of subject's clinical symptoms/performance status as per the investigator's judgment;
3. When judged as PD as per RECIST v1.1 criteria, subjects who meet the criteria of clinical stability (see Section 7.1.5 Use of drug) may continue the treatment, until PD is confirmed or the subject no longer benefits clinically from the treatment as per the investigator's judgment;
4. Unacceptable toxicity, including any clinical AE, laboratory abnormalities, or other medical conditions; if the toxicities of SHR-1210/placebo or chemotherapy are unacceptable, the drug with unacceptable toxicities should be discontinued;
5. Major protocol deviations;
6. Other reasons for which the investigator considers that it is necessary to discontinue the study treatment;
7. Pregnancy;

8. Loss to follow-up;
9. Death;
10. Study termination by the sponsor.

5.5.3. Procedures for withdrawal or discontinuation

Subjects should undergo efficacy and safety assessments as specified in the protocol at the withdrawal and safety follow-up visits. All AEs and their outcomes should be documented. 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 PD, start of a new anti-tumor treatment, withdrawal of informed consent form, loss to follow-up, or death.

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 can retain and continue to use all data collected before withdrawal of informed consent, unless the subject requests a retraction of collected data.

5.6. Early Termination or Suspension of Study

This study can be terminated early or suspended if there are sufficient reasons. This may result from the decision of the regulatory authorities, changes in comments by the Ethics Committee, efficacy or safety issues of the study medications, or the judgment of the sponsor. In addition, Hengrui reserves the right to terminate the research and development of SHR-1210. 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 provide relevant reasons.

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

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

5.7. Definition of Study Completion

Study completion is defined as follows: The number of events required for the primary efficacy endpoint, OS, has been observed.

6. IMMUNOGENICITY STUDY

6.1. Collection and Processing of Blood Samples

6.1.1. Blood sampling time

Collected once before the 1st, 2nd, 4th, 6th, and 9th administration of SHR-1210/placebo; thereafter, once every 4 doses of SHR-1210/placebo before administration; once upon withdrawal from study treatment; and once 30 days after the last dose (if applicable).

6.1.2. Processing and storage of blood samples

At each of the above time points, 4–6 mL of venous blood sample is 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). The cryotubes are stored in a low temperature freezer at -60 °C to -80 °C for 6 months or at -20 °C for 1 month, until they are transported to the central laboratory for testing. Please refer to the Laboratory Manual for specific operation details.

6.2. Shipping of Clinical Samples

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

7. STUDY MEDICATION

7.1. Description of the Study Drugs and Control Drug

7.1.1. Access to drugs

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

7.1.2. Dosage form, appearance, packaging, and label

Investigational product: SHR-1210 for injection (not marketed)

Manufacturer: Suzhou Suncadia Biopharmaceuticals Co., Ltd.

Dosage form: lyophilized powder

Strength: 200 mg in 20 mL vials

Batch No.: see Certificate of Analysis

Method of administration: intravenous 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

A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Phase III Clinical Study of Anti-PD-1 Antibody SHR-1210 Combined with Paclitaxel and Cisplatin vs. Placebo Combined with Paclitaxel and Cisplatin as First-line Treatment of Advanced Esophageal Cancer

For Clinical Study Use Only

Clinical Study Approval No.: 2016L01455	Drug No.: _____
Study No.: SHR-1210-III-306	Indication: Esophageal squamous cell carcinoma
Drug Name: SHR-1210 for injection/placebo	Dosage Form: Lyophilized powder for injection Strength: 200 mg/vial

Method of Administration: Prepare according to the product manual, for intravenous injection only
Subject No.: _____

Storage Conditions: Sealed, away from light, stored at 2–8 °C

Batch No.:

Expiry Date: DD/MM/20YY

Manufacturer: Suzhou Suncadia Biopharmaceuticals Co., Ltd. Sponsor: Jiangsu Hengrui Medicine Co., Ltd.

Investigational product: Placebo

Manufacturer: Suzhou Suncadia Biopharmaceuticals Co., Ltd.

Dosage form: lyophilized powder

Strength: In 20 mL vials

Batch No.: see Certificate of Analysis

Method of administration: intravenous 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

A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Phase III Clinical Study of Anti-PD-1 Antibody SHR-1210 Combined with Paclitaxel and Cisplatin vs. Placebo Combined with Paclitaxel and Cisplatin as First-line Treatment of Advanced Esophageal Cancer

For Clinical Study Use Only

Clinical Study Approval No.: 2016L01455	Drug No.: _____
Study No.: SHR-1210-III-306	Indication: Esophageal squamous cell carcinoma
Drug Name: SHR-1210 for injection/placebo	Dosage Form: Lyophilized powder for injection Strength: 200 mg/vial

Method of Administration: Prepare according to the product manual, for intravenous injection only
Subject No.: _____

Storage Conditions: Sealed, away from light, stored at 2–8 °C

Batch No.:

Expiry Date: DD/MM/20YY

Manufacturer: Suzhou Suncadia Biopharmaceuticals Co., Ltd. Sponsor: Jiangsu Hengrui Medicine Co., Ltd.

Investigational product: Paclitaxel

Manufacturer: Beijing Union Pharmaceutical Factory

Dosage form: Injection

Strength: 5 mL:30 mg

Batch No.: see package insert

Method of administration: intravenous infusion

Shelf life: 24 months

Storage conditions: stored below 25 °C, away from light, sealed

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

Paclitaxel

For Clinical Study Use Only

A Randomized, Open-Label, Controlled, Multi-Center Phase III Clinical Study of Anti-PD-1 Antibody SHR-1210 Combined with Paclitaxel and Cisplatin vs. Paclitaxel Combined with Cisplatin as First-Line Treatment of Advanced Esophageal Cancer

(Study No.: SHR-1210-III-306)

Sponsor: Jiangsu Hengrui Medicine Co., Ltd.

Note: Please return the remaining products to the pharmacist

Investigational product: Cisplatin

Manufacturer: Jiangsu Hansoh Pharmaceutical Group Co., Ltd.

Dosage form: Injection

Strength: 6 mL:30 mg

Batch No.: see package insert

Method of administration: intravenous infusion

Shelf life: 24 months (tentative)

Storage conditions: away from light, sealed

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

Cisplatin

For Clinical Study Use Only

A Randomized, Open-Label, Controlled, Multi-Center Phase III Clinical Study of Anti-PD-1 Antibody SHR-1210 Combined with Paclitaxel and Cisplatin vs. Paclitaxel Combined with Cisplatin as First-Line Treatment of Advanced Esophageal Cancer

(Study No.: SHR-1210-III-306)

Sponsor: Jiangsu Hengrui Medicine Co., Ltd.

Note: Please return the remaining products to the pharmacist

7.1.3. Storage and stability of drugs

The investigator or authorized personnel (such as a pharmacist) is responsible for ensuring all study drugs are stored in a secure, controlled access area that meets the storage conditions and complies with applicable regulatory requirements.

Study drugs should be stored under the storage conditions listed in Section 7.1.2. Where the protocol and other information differ, store according to the storage conditions listed on the SHR-1210/placebo label. For paclitaxel and cisplatin, store according to the storage conditions outlined in the package insert.

Daily maximum and minimum temperatures of all storage zones must be measured and recorded by the study site (such as freezer, refrigerator or room temperature). Documentation should begin with the receipt of the drugs until the last subject of the study site completes the last study treatment. 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.

Report immediately if the storage conditions are found to deviate from the drug label, description on the storage condition, or package insert. The study site should actively adopt measures to ensure that the drugs are returned to the storage conditions described on the label or package insert, and the temperature deviations and measures adopted should be reported to the sponsor.

Study drugs affected by the temperature deviation should be isolated temporarily and may only be used after approval by the sponsor and if it is not a protocol deviation. Affected study drugs used 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.

7.1.4. Preparation of study drugs

Drugs used in this study are all administered via intravenous infusion. Therefore, the drugs should be prepared by a qualified or experienced study staff such as a study nurse. SHR-1210 does not contain preservatives, and must be prepared using aseptic technique. See Product Manual for details of drug preparation. Paclitaxel and cisplatin are approved drugs and should be prepared according to their package insert.

7.1.5. Use of drug

The preparation of drug in this study is blinded. Nurses for preparing drugs should prepare drugs in a separate treatment room to prevent unblinding. Drugs should be kept the same in the appearance, packaging, label, and other characteristics. Nurses for preparing drugs do not

participate in the operation on subjects as much as possible during the trial; other study nurses are responsible for the administration.

The method of administration is shown in Table 3. For SHR-1210/placebo combined with paclitaxel and cisplatin, chemotherapy may be given for up to 6 cycles. If SHR-1210/placebo, paclitaxel, or cisplatin has been discontinued due to toxicity, other study drugs may continue to be used for the rest of the cycle until the withdrawal criteria are met. Cycles without the use of chemotherapy are not counted toward combined medication cycles. After the completion of combined medication, SHR-1210/placebo monotherapy will continue to be given as maintenance treatment until the withdrawal criteria are met.

For the pretreatment of paclitaxel chemotherapy, the requirements on the package insert and local clinical practice may be referenced. The following is a pretreatment recommendation for chemotherapy: dexamethasone, 20 mg, divided into 2 doses, orally administered 12 h and 6 h before chemotherapy; diphenhydramine, 50 mg, intravenously injected 30–60 min before chemotherapy (or equivalent dose of other similar drugs); cimetidine (300 mg) or ranitidine (50 mg), intravenously injected 30–60 min before chemotherapy.

To prevent renal toxicity, cisplatin needs to be fully hydrated. When used, cisplatin needs to be hydrated for 3 days, i.e., D0–D2. The recommended dosage is 1500 mL/m^2. Also, potassium chloride, mannitol, and furosemide should be used to maintain a daily urine output of 2000–3000 mL. Cisplatin is a highly emetic chemotherapeutic drug. NK-1 receptor antagonists (aprepitant) combined with 5-HT3 receptor antagonists are recommended for antiemetic treatment when cisplatin is first used; also, antiemetics such as dopamine receptor blockers (metoclopramide) and antihistamines (e.g., phenergan and diphenhydramine) are recommended in combination. While, long-term, continuous use of glucocorticoid is not recommended for chemotherapy-related nausea and vomiting.

Table 3. Method of administration.

	SHR-1210/Placebo	**Paclitaxel [1]**	**Cisplatin [1]**
Dose and Route of Administration	200 mg IV	175 mg/m^2 IV	75 mg/m^2 IV
Infusion Rate	Not less than 20 min, not more than 60 min, including flushing	More than 3 h or per the clinical practice of the study site	Approximately 60 min or per the clinical practice of the study site
Pretreatment before Administration	Not necessary	Pretreatment before administration should be given according to the clinical practice of the study site	Pretreatment before administration should be given according to the clinical practice of the study site

	SHR-1210/Placebo	Paclitaxel [1]	Cisplatin [1]
Time of Drug Administration	D1	D1	D1
Sequence of Combined Medication	Administration in the order of SHR-1210/placebo, paclitaxel, and cisplatin on Day 1.		
Frequency of Combined Medication	Every cycle contains 3 weeks (for up to 6 cycles)		
Frequency of Monotherapy for Maintenance	Every cycle contains 3 weeks		
Total Administration Time of SHR-1210/Placebo	Up to 2 years		

[1] If the subject's weight fluctuates less than 10% from baseline (the day of the first administration), the baseline weight is used to calculate the body surface area, based on which the dosage of chemotherapy is calculated. Otherwise, the dosage of chemotherapy is calculated based on the actual body weight on the day of scheduled administration. For the convenience of administration, a deviation of ± 5% for the calculated total dosage per infusion is allowed as per the protocol.

The time window of administration is ± 3 days from the scheduled date of administration (from the date of the first administration). Drugs administered outside the time window is considered a delayed dose, and subsequent doses shall be administered according to the actual date of last administration. During the combined medication, if the delay is expected to exceed 2 weeks due to the toxicity of chemotherapy, only SHR-1210/placebo will be given until the toxicity returns to the acceptable level for chemotherapy administration, after which the combination of chemotherapy and SHR-1210/placebo will be resumed. Chemotherapy may be suspended for up to 6 consecutive weeks; if longer than 6 weeks, the chemotherapy will be discontinued. If the delay is expected to exceed 2 weeks due to the toxicity of SHR-1210/placebo, only chemotherapy will be given until the toxicity returns to the standard of SHR-1210/placebo administration, after which the combination of chemotherapy and SHR-1210/placebo will be resumed. SHR-1210/placebo may be suspended for up to 12 consecutive weeks; if longer than 12 weeks, SHR-1210/placebo will be discontinued. For dose delays due to toxicities with equivocal association that are expected to return to the standard of administration within 2 weeks, the three drugs shall be delayed simultaneously. 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 medication after the first PD (per RECIST v1.1 criteria).

Accelerated tumor growth may include any of the following:

- Worsening of existing target lesions;
- Worsening of existing non-target lesions;

- New lesions.

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 can clinically benefit as per the investigator's judgment after discussing with the sponsor and obtaining the approval; a tumor assessment should be performed again at least 4 weeks (± 7 days) later. If unconfirmed PD is established using both iRECIST and RECIST v1.1 criteria, then treatment may be continued. Treatment should be discontinued if PD is confirmed, unless the subject can clinically benefit as per the investigator's judgment after discussing with the sponsor and obtaining the approval followed by the signing of another informed consent form for continued treatment beyond PD, until the subject cannot clinically benefit as per the investigator's judgment. 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).

Refer to the criteria listed in Table 4 for confirmation of PD.

Table 4. Confirmation criteria of PD.

	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 with the first episode of PD.	The absolute value of tumor load increases by < 5 mm when compared with the first episode of PD.
Non-Target Lesion	Clear and continuous progression of non-target lesions compared with the first episode of PD (qualitative).	No clear progression compared with the first episode of PD (qualitative).
New Lesion	(1) Onset of new lesion compared with 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 with 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.

7.1.6. Dose modifications and delay

7.1.6.1. Dose modification

7.1.6.1.1. Dose modification for SHR-1210/placebo

AEs related to SHR-1210/placebo may be immune-related, and may develop shortly after the first dose or months after the last dose. SHR-1210/placebo should be interrupted if events listed in Table 5 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 5 or when the situation is not listed.

Table 5. Criteria for SHR-1210/placebo dose modifications.

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

Immune-Related AE	Severity Grades for Treatment Interruption	Resumption	Discontinuation
Immune-Related Hypophysitis	2-3	Return to Grade 0–1; SHR-1210/placebo treatment can be resumed 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/placebo treatment.
Renal Failure or Nephritis	2	Recovered to Grade 0–1 and the dose of corticosteroids reduced to ≤ 10 mg of prednisone or equivalent.	Do not resolve within 12 weeks from the last dose, or the dose of corticosteroids cannot be reduced to ≤ 10 mg of prednisone or equivalent within 12 weeks.
	3-4	Discontinuation	Discontinuation
Infusion Reactions	2	Symptoms disappear	Re-administer at 50% of the initial rate after symptoms resolve. Restore the original infusion rate (100%) if no complications occur within 30 minutes. Closely monitor. If the symptoms return, the administration of the current SHR-1210/placebo dose will be discontinued.
	3-4	Discontinuation	Discontinuation
Others Treatment-Related AEs	3	Recovered to Grade 0–1 and the dose of corticosteroids reduced to ≤ 10 mg of prednisone or equivalent.	Do not resolve within 12 weeks from the last dose, or the dose of corticosteroids cannot be reduced to ≤ 10 mg of prednisone or equivalent within 12 weeks.
	4	Discontinuation	Discontinuation

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

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

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

7.1.6.1.2. Dose modification of paclitaxel and cisplatin

The criteria for dose modification and administration/resumption of paclitaxel and cisplatin are detailed in Table 6 and Table 7 or determined by the investigator according to routine clinical practices. The content of this section is for the reference of the investigator. If the toxicity is still not tolerated after dose reduction, the chemotherapy should be discontinued.

Table 6. Criteria for dose modification of paclitaxel and cisplatin.

AE	Paclitaxel	Cisplatin	Resumption
Febrile Neutropenia	Two dose reductions are permitted, 25% each	Two dose reductions are permitted, 25% each	Reduce dose after recovery
Grade 4 Neutropenia			Reduce dose after return to Grade ≤ 1
Grade 4 Platelet Count Decreased			
Grade 1 Nephrotoxicity	Dose reduction by 25%	Dose reduction by 25%	Dose reduction
Grade 2/3 Peripheral Neurotoxicity			Reduce dose after return to Grade ≤ 1
Grade ≥ 3 Non-Hematological Toxicity			
Grade ≥ 2 Nephrotoxicity	Not applicable	Not applicable	Discontinuation
Grade 4 Peripheral Neurotoxicity	Not applicable	Not applicable	Discontinuation

Table 7. Criteria for administration/resumption.

Absolute Neutrophil Count	≥ 1500/mm^3（1.5×10^9/L）
Platelet Count	≥ 100×10^9/L

7.2. Drug Management, Dispensation and Retrieval

Designated personnel are responsible for the management, dispensation, and retrieval of study drugs. The investigator must ensure that all study drugs are used by enrolled subjects only and the dose and route of administration comply with Section 7.1.5 Use of drug. Remaining or expired drugs should be returned to the sponsor and may not be used for non-participants.

When transporting the drugs to the study site, drug receipt forms should be signed in duplicate by both parties, one for the study site and one for the sponsor. When returning remaining drugs and empty packaging, both parties must sign the drug retrieval form. The dispensation and return of every drug should be immediately documented on designated forms.

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

7.2.1. Disposal of study drugs

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

7.3. Concomitant Treatment

Prohibited medications and vaccines specified in the exclusion criteria are prohibited during the entire course of the trial. If the subject develops a concurrent condition that requires the use of a prohibited drug, then study treatment may need to be stopped and the prohibited medication may need to be accepted. In this case, the investigator should consult with the sponsor. Whether the subject will continue the study treatment or accept a prohibited medication is ultimately decided together by the investigator, the sponsor, and the subject.

7.3.1. Permitted concomitant treatments

Topical use of corticosteroids such as ophthalmic, nasal, intra-articular, and inhaled is permitted. Premedication with corticosteroids before chemotherapy is allowed.

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 metastases and esophageal lesions. However, the following criteria must all be met and the sponsor must be consulted prior to starting palliative treatment.

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

All concomitant medications from 30 days before signing informed consent form until the start of new anti-tumor treatment should be documented in the eCRF; afterward, only concomitant medications for treatment-related AEs are documented.

7.3.2. Prohibited concomitant treatments

- Systemic anti-tumor treatment, including but not limited to chemotherapy and immunotherapy not specified in the protocol, targeted therapy, biological therapy, modern TCM preparation approved by the CFDA (now NMPA) for anti-tumor treatment (refer to Appendix III), and immunomodulator with auxiliary anti-tumor effect (e.g., 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;
- In addition to alleviating symptoms due to immunological causes, long-term use of systemic corticosteroids for any other purpose shall be discussed with the sponsor. Short-term (< 3 weeks) and low-dose (≤ 10 mg of prednisone or equivalent) use of corticosteroids for non-autoimmune diseases and prophylactic use of corticosteroids (e.g., prevention of allergy to contrast agents) are permitted;
- Refer to the prescribing information for other prohibited medications for paclitaxel and cisplatin.

7.3.3. Supportive care

7.3.3.1. Guidelines for supportive care of SHR-1210/placebo

Subjects should receive appropriate supportive treatment measures deemed necessary by the investigator. Supportive treatment measures for managing immune-related AEs 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 considers that the AE is related to SHR-1210/placebo, supportive treatments listed below should be followed. If the AE is not related to SHR-1210/placebo, then the supportive treatments listed below do not need to be followed.

1. Capillary endothelial proliferation

Subjects with capillary endothelial proliferation should undergo biopsy and pathological examination whenever possible. Endoscopic and MRI examinations are recommended for subjects with severe or long-lasting capillary endothelial proliferation to confirm whether the internal organs and mucosa are involved.

2. Diarrhea/colitis

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

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

The recommendations on treatment of infusion reactions are shown in Table 8.

Table 8. Recommendations for infusion reactions.

CTCAE Grade	Clinical Symptoms	Clinical Management	SHR-1210/Placebo 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 can be given at least 30 minutes before the administration of SHR-1210/placebo.	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 can be considered based on clinical needs; The amount of study drug infused should be recorded in the original medical record; Pre-dose prophylactics are recommended for subsequent 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/placebo. Use corticosteroids (equivalent to 25 mg 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 minutes. Closely monitor. If the symptoms return, the administration of the current SHR-1210/placebo dose will be discontinued.
Grade ≥ 3	Grade 3: Severe reaction without rapid recovery with treatment and/or interruption; or symptoms recur after alleviation; or the subject develops	Immediately discontinue SHR-1210/placebo; 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	Discontinuation

CTCAE Grade	Clinical Symptoms	Clinical Management	SHR-1210/Placebo Treatment
	sequelae that requires hospitalization. Grade 4: Life-threatening	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.	

7.3.3.2. Guidelines for supportive care of paclitaxel and cisplatin

Refer to the package inserts or per the clinical practice of the study site.

7.3.4. Hematopoietic growth factor

For patients with high or medium risk factors for febrile neutropenia or myelosuppression (including but not limited to: aged > 65 years old, have previously received radiotherapy/ chemotherapy, with persistent neutropenia, recent surgery or open trauma, hepatic insufficiency, renal insufficiency, tumors involving bone marrow, febrile neutropenia in the past) as judged by the investigator, preventive use of G-CSF is allowed in the first cycle. The investigator may determine the use of G-CSF based on clinical situations.

8. STUDY PROCEDURES

8.1. Screening

The screening period is the time from the signing of the informed consent form until randomization or screen failure. Subjects must sign the informed consent form before undergoing screening procedures for this study. Data from laboratory tests and radiographic assessments 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 informed consent form;
- Collection of demographics: gender, date of birth, ethnicity, height, weight, and BMI;
- Tumor diagnosis: date of first pathological diagnosis, pathological grade, site of metastasis, and clinical stage (locally advanced or distant metastatic);

- History of tumor treatment:
  - ✓ History of tumor surgery: name of surgery, date of surgery, and date of postoperative recurrence;
  - ✓ History of radiotherapy: site, dose, and start and end dates;
  - ✓ Anti-tumor medication history: regimen, cycle, and start and end dates;
- History of concurrent disease, past medications, medication allergies, smoking and alcohol drinking;
- 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), and HIV-Ab;
- Fresh (preferred) or archival tumor tissue specimens.

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 hours 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, neck, skin, lymph nodes, eyes, ear, nose and throat, oral cavity, respiratory system, cardiovascular system, abdomen, reproductive-urinary system, musculoskeletal system, nervous system, mental state, and others;
- ✓ Hematology: 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, blood urea nitrogen (preferred)) or urea, total protein, albumin, creatinine, blood glucose, lactate dehydrogenase, K^+, Na^+, Ca^{2+}, Mg^{2+}, and Cl^-;
- ✓ Thyroid function: TSH, FT3, and FT4;

- ✓ Coagulation function: APTT, PT, FIB, INR;
- ✓ Echocardiography: including LVEF assessment. Perform if clinically indicated;
- ✓ 12-lead ECG: heart rate, PR interval, QT interval, and QTcF; the investigator may decide to add other investigations if results are abnormal;
- ✓ Pregnancy test (for women of childbearing potential);
- ✓ Imaging examination: CT or MRI of the neck, chest, and abdomen (including pelvic cavity) (both are enhanced; plain scans may be used instead when contrast agents are contraindicated). Brain MRI (or CT if MRI is contraindicated; both are enhanced; plain scans may be used instead when contrast agents are contraindicated) is required for suspected or confirmed brain metastasis. Tumor assessments up to 4 weeks before randomization and before informed consent may be used as long as they meet the RECIST v1.1 criteria. Bone scan is required for suspected or diagnosed bone metastases and must be performed within 42 days prior to the first dose;
- ✓ AEs: recorded starting from the signing of ICF;
- ✓ Concomitant medication: concomitant medications within 30 days prior to the signing of ICF shall be documented in detail.

8.2. Treatment Period

The treatment period starts from subject randomization. The first dose should be completed within 3 days after randomization.

- All examinations and assessments (except for quality of life score and tumor imaging evaluation) should be completed within 3 days prior to administration. The following assessments should be completed prior to administration in each cycle, but do not need 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;
  - ✓ Targeted physical examination: perform if clinically indicated;
  - ✓ Hematology: RBC count, hemoglobin, platelet count, WBC count, neutrophil count, and lymphocyte count;

- ✓ Blood biochemistry: ALT, AST, GGT, total bilirubin, direct bilirubin, AKP, blood urea nitrogen (preferred)) or urea, total protein, albumin, creatinine, blood glucose, lactate dehydrogenase, K^+, Na^+, Ca^{2+}, Mg^{2+}, and Cl^-;
- ✓ ECG; heart rate, PR interval, QT interval, and QTcF;
- ✓ AE: recorded in details;
- ✓ Concomitant medication: concomitant medication shall be documented in detail.

- The following investigations should be completed every 2 cycles prior to administration:
  - ✓ 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;
  - ✓ Thyroid function: TSH, FT3, FT4.
- Quality of life score (EORTC QLQ-C30, EORTC QLQ-OES18): Once every 6 weeks, with a window of ± 7 days. It is recommended to be performed prior to administration as well as AE and tumor assessments.
- Imaging examination: Baseline imaging examination should be performed every 6 weeks. Unscheduled imaging examinations may be performed for suspected PD. 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. A time window of ± 7 day is allowed for imaging examinations. Imaging conditions should be the same as those at baseline (including slice thickness and contrast agent). Time of radiographic assessment will not be adjusted due to dose delays.

  Subjects who develop PD for the first time but are clinically stable should be confirmed at least 4 weeks (± 7 days) later. If the confirmation is less than 4 weeks from the next scheduled imaging examination, the originally scheduled imaging examination will be skipped until the time for the next scheduled imaging examination.
- ADA blood sampling: Collected once before the 1st, 2nd, 4th, 6th, and 9th administration of SHR-1210/placebo; thereafter, once every 4 doses of SHR-1210/placebo before administration.

8.3. Withdrawal Visit

This visit will be completed when discontinuation of study treatment for a subject is confirmed. If the following assessments and examinations are not performed within 7 days before withdrawal from study treatment visit, they should be completed upon withdrawal from the study.

- ✓ ECOG PS score;
- ✓ Vital signs: pulse, respiratory rate, body temperature, and blood pressure;
- ✓ Comprehensive physical examination: general condition, head and face, neck, skin, lymph nodes, eyes, ear, nose and throat, oral cavity, respiratory system, cardiovascular system, abdomen, reproductive-urinary system, musculoskeletal system, nervous system, mental state, and others;
- ✓ Hematology: 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, blood urea nitrogen (preferred)) or urea, total protein, albumin, creatinine, blood glucose, lactate dehydrogenase, K^+, Na^+, Ca^{2+}, Mg^{2+}, and Cl^-;
- ✓ Thyroid function: TSH, FT3, and FT4;
- ✓ ECG: heart rate, PR interval, QT interval, and QTcF;
- ✓ Pregnancy test;
- ✓ Quality of life score;
- ✓ Imaging examination: An imaging examination should be performed at the withdrawal visit if it has not already been completed within 4 weeks prior to withdrawal from the study.
- ✓ ADA blood sampling;
- ✓ AE: recorded in details;
- ✓ Concomitant medication: concomitant medication shall be documented in detail.

8.4. Safety Follow-Up

All subjects should return to the study site for a follow-up 30 days after the last dose or undergo telephone follow-up if withdrawal visit is completed, and undergo telephone follow-ups 60 days and 90 days after the last dose. Safety information should be obtained via telephone follow-ups (including AE outcome, new SAE, and AE of special interest).

- ✓ Hematology: RBC count, hemoglobin, platelet count, WBC count, neutrophil count, and lymphocyte count;
- ✓ Blood biochemistry: ALT, AST, GGT, total bilirubin, direct bilirubin, AKP, blood urea nitrogen (preferred)) or urea, total protein, albumin, creatinine, blood glucose, lactate dehydrogenase, K^+, Na^+, Ca^{2+}, Mg^{2+}, and Cl^-;
- ✓ Thyroid function: TSH, FT3, and FT4;
- ✓ ADA blood sampling (if applicable);
- ✓ Quality of life score (if applicable);
- ✓ Adverse events: recorded in details;
- ✓ Concomitant medication: concomitant medication shall be documented in detail.

8.5. Unscheduled Visits

The following should be documented during unscheduled visits if subjects develop AEs during the trial:

- ✓ Concomitant medications;
- ✓ AEs;
- ✓ All relevant examinations (including imaging assessment, if performed).

8.6. Survival Follow-Up

Survival follow-ups will be conducted once every 30 days 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.

8.7. Tumor Progression Follow-Up

For subjects who withdraw due to "non-PD" (such as unacceptable AEs), it is recommended to perform tumor assessments at the same frequency (every 6 weeks ± 7 days) as that of response assessments for this study, until PD, start of a new anti-tumor treatment, withdrawal of informed consent, loss to follow-up, or death. Follow-up information should be documented in the eCRF.

9. EVALUATIONS

9.1. Efficacy Evaluation

Progression-free survival (PFS): The time from the start of randomization to the date of first recording of objective tumor progression or death caused by any reasons, whichever occurs first. The independent review committee (IRC) will perform a central review on the primary endpoints. Refer to the IRC Charter for details. The secondary endpoints are based on investigator assessments. On the analysis cutoff date, if the PFS is not obtained, the data will be censored. The censoring rules are detailed in the Statistical Analysis Plan (SAP).

Overall survival (OS): The time from the start of randomization to the death of the subject caused by any reasons. On the analysis cutoff date, if the OS is not obtained, the data will be censored. The censoring rules are detailed in the SAP.

OS rates: Survival rates at 6 and 9 months after enrollment.

Objective response rate (ORR): Defined as the proportion of subjects whose best overall responses (BoR) are assessed as CR and PR among the subjects who have received at least one dose in each treatment group. BoR is defined as a parameter of best response starting from the date of randomization to the date of objective documentation of PD or subsequent anti-tumor treatment (whichever occurs first). For subjects with no record of PD or subsequent anti-tumor treatment, the BoR will be determined based on all results of response assessment.

Duration of response (DoR): The time from the first PR or CR to the first PD or death. On the analysis cutoff date, if the PD or death information is not obtained, the data will be censored. The censoring rules are detailed in the SAP.

Disease control rate (DCR): The proportion of subjects with CR, PR, and SD among subjects who have received at least one dose in each treatment group. DCR is defined as a parameter of best response starting from the date of randomization to the date of objective documentation of PD or subsequent anti-tumor treatment (whichever occurs first). For subjects with no record of PD or subsequent anti-tumor treatment, the DCR will be determined based on all results of response assessment.

Quality of life score (EORTC QLQ-C30, EORTC QLQ-OES18): As a core scale for all cancer patients, the EORTC QLQ-C30 scale comprises 30 items, 5 functional scales (physical, role, cognitive, emotional and social), 3 symptom scales (fatigue, pain and nausea/vomiting), 1 global health status/quality of life scale and 6 single-item scales (dyspnoea, insomnia, appetite loss, constipation, diarrhea and financial difficulties). The EORTC QLQ-OES18 scale is mainly used for patients with esophageal cancer and contains 18 symptom items.

Biomarker analysis is to evaluate the relationship between PD-L1 expression in tumor tissues and efficacy.

Immunogenicity analysis is to determine the proportion of subjects showing anti-SHR-1210 antibodies.

The reference criteria for imaging evaluation in this study is the RECIST v1.1 criteria. The requirements and frequency of imaging examinations are detailed in the Schedule of Activities.

9.2. Safety Evaluation

9.2.1. Pregnancy test

Female subjects of childbearing potential will receive a serum or urine pregnancy test within 72 hours before the first dose. Subjects with negative results should adopt appropriate contraceptive measures. Subjects with positive results will fail the screening. Enrolled subjects will undergo another serum or urine pregnancy test at the withdrawal visit.

9.2.2. Adverse events

Refer to NCI-CTCAE V4.03 for the severity of AEs.

9.2.3. Laboratory safety assessment

Please refer to the Schedule of Activities for details.

9.2.4. Vital signs and physical examination

Please refer to the Schedule of Activities for details.

9.2.5. 12-lead ECG

Please refer to the Schedule of Activities for details.

9.2.6. Independent Data Monitoring Committee

In this study, an Independent Data Monitoring Committee (IDMC) will be established to evaluate the safety and efficacy of the study drug at the data review meetings on a regular basis. The safety data will be evaluated after the 60th subject enrolled has completed the Cycle 1 follow-up. Interim analyses will be performed when about 269 (66%) OS events and 347 (85%) OS events are collected. The IDMC will make recommendations on whether to continue or terminate the study based on the safety and efficacy data and results.

The committee will include two independent oncologists and one independent statistician. The IDMC review meeting will be held at the time specified in the charter of the IDMC. The study enrollment will continue during IDMC meetings.

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

An unblinded independent statistician will provide the results of the interim analysis to the IDMC. As the principal reviewer of the safety and primary efficacy analysis results, IDMC will advise the sponsor whether to terminate the study. If the IDMC recommends to terminate the study, the safety and efficacy results may be unblinded to the sponsor, such that the sponsor can take action on these recommendations. The unblinded independent statistician will record the degree of unblinding for the interim analysis results by relevant personnel. See details in IDMC charter.

10. ADVERSE EVENT REPORTING

10.1. Adverse Events (AEs)

10.1.1. Definition of AE

An adverse event (AE) refers to any untoward medical occurrence in a study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. In this study, AEs are collected from the signing of the informed consent form until 90 days after the last dose. If the subject starts a new anti-tumor treatment during the AE collection period, only treatment-related AEs are collected after the start of the new anti-tumor treatment. AEs can include any unfavorable and unintended symptoms, signs, abnormal laboratory finding, or diseases, including the follows:

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

- Any new AE: Any new adverse medical condition (including symptoms, signs, and newly diagnosed diseases);
- Clinically significant abnormal laboratory findings.

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

10.1.2. AE severity grading criteria

Please refer to NCI CTCAE 4.03 for grading criteria. Refer to Table 9 for the criteria for AEs not listed in NCI-CTCAE 4.03:

Table 9. Criteria for the severity of AEs.

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 are collected and documented regardless of whether the event is related to the study drug, whether the subject is assigned to the investigational treatment group, 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 study drug, such as whether there is a plausible temporal relationship with the study drug, the characteristics of the study drug, the toxicological and pharmacological effects of the study drug, whether there are concomitant medications, the subject's underlying diseases, medical history, family history, as well as dechallenge and rechallenge, etc. The causality assessment will be provided using the following five categories "definitely related, possibly related, unlikely related, definitely unrelated, and indeterminable".

10.2. Serious Adverse Events (SAEs)

10.2.1. Definition of SAE

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 that result in hospitalization (even if for less than 24 h) or prolonged hospitalization during the clinical study should be considered as SAEs.

Hospitalization does not include the following:

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

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

- Hospitalization due to pre-existing disease without the occurrence of new AEs or worsening of the pre-existing diseases (e.g., in order to examine the persistent laboratory abnormalities that started before the study);

- Hospitalization for management reasons (e.g., annual physical examination);
- Hospitalization during the study as specified in the study protocol (e.g., as required by the protocol);
- Elective hospitalization unrelated to worsening of AEs (e.g., elective surgery);
- Scheduled treatment or surgery that should be documented throughout the entire study protocol and/or subjects' individual baseline information;
- Hospitalization merely for use of blood products.

Diagnostic or therapeutic invasive (e.g., surgery) and non-invasive procedures should not be reported as AEs. However, when a condition resulting in such procedures meet 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 PD. Death, life-threatening events, hospitalization or prolonged hospitalization, permanent or severe disability/incapacity, congenital anomalies or birth defects resulting from signs and symptoms of progressive disease should not be reported as SAEs.

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 and reported as SAEs.

Potential drug-induced liver injury is defined in Table 10.

Table 10. Definition of potential drug-induced liver injury.

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

If the subject starts any other anti-tumor treatment, only study drug-related SAEs should be collected.

10.2.6. SAE reporting

SAEs should be collected from signing the ICF until 90 days after the last dose. In the event of an SAE, whether it is the first report or a follow-up report, the investigator must complete the "Serious Adverse Event Report Form" immediately, with a signature and date, and notify the sponsor within 24 h of knowing of the event. Relevant authorities must be informed of such SAE in a timely manner according to regulatory requirements.

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

The symptoms, severity, relationship with the study drug, time of occurrence, treatment duration, measures taken, time and method of follow-up, and outcome should be documented in details in the SAE report. If the investigator believes that an SAE is unrelated to the study drug but potentially related to study conditions (such as the termination of the previous 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 study drug changes, a follow-up report should be submitted immediately. If an error is found in a previously reported SAE, such an SAE may be revised, revoked, or downgraded in follow-up reports and reported in accordance with the SAE reporting procedure.

10.2.7. Follow-up of AEs/SAEs

All the AEs/SAEs should be followed up until resolved, return to baseline levels or Grade ≤ 1, steady state, or reasonably explained (e.g., loss to follow-up, death).

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

10.3. Pregnancy

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

During the study, if the partner of a male subject becomes pregnant, the subject can continue in the study. The investigator must report to the sponsor and the ethics committee within 24 hours 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 and the ethics committee.

Email the pregnancy report to: hengrui_drug_safety@hrglobe.cn.

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

If a subject experiences any SAE during pregnancy, then the "SAE Report Form" should be filled out and reported according to SAE reporting procedures.

10.4. AEs of Special Interest

For AEs of special interest listed below, the investigator must fill out the "Report of Adverse Event of Special Interest for Hengrui Clinical Studies" and submit it to the sponsor within 24 hours of knowing of the event. If the AE of special interest is also an SAE, the "Serious Adverse Event Report Form" should also be filled out and submitted to relevant authorities according to SAE reporting procedures.

- Grade ≥ 3 infusion reactions (related to SHR-1210/placebo);
- Grade ≥ 3 immune-related AEs;

11. CLINICAL MONITORING

The CRA 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 CRA is responsible for:

1. 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;
2. 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;
3. 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;
4. Confirming that all AEs have been documented, and that SAEs have been documented and reported within the specified time frame. Verifying that the study drugs are supplied, stored, dispensed, and returned in accordance with relevant regulations, and corresponding documentation should be made;
5. Recording clearly and faithfully visits, tests, and examinations that the investigator has failed to perform, and whether errors or omissions have been corrected;
6. Completing a written monitoring report after each visit, which should state the date and time of the monitoring visit, the name of the CRA, and the findings of the visit.

The Quality Assurance 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 at a reasonable time and in a reasonable way.

12. DATA ANALYSIS/STATISTICAL METHODS

The detailed statistical analysis of this study will be included in the Statistical Analysis Plan (SAP) and kept by the sponsor. The plan marked in the protocol can be appropriately modified in the SAP. However, any significant revisions to the definitions and analyses of primary study endpoints shall be reflected in the amendment versions of the protocol.

12.1. Sample Size

A parallel design is adopted in this study. The sample size is calculated based on the comparison of the two primary efficacy endpoints, i.e., PFS and OS, of PD-1 antibody SHR-1210 combined with paclitaxel and cisplatin (treatment group) and placebo combined with paclitaxel and cisplatin (control group).

The hypothesis for efficacy is as follows: The hazard ratio (HR) of PFS (treatment group/control group) is 0.67, the estimated median PFS of the control group is 5 months, the HR of OS (treatment group/control group) is 0.73, and the estimated median OS of the control group is 10 months. Assuming a one-sided $\alpha = 0.005$, a power of 90% can be obtained when 378 PFS events are collected, and the estimated final analysis time of PFS is approximately 22.0 months. Two interim analyses are planned for the OS. The Lan-DeMets α spending function will be used to allocate the α, and the O'Brien & Fleming method will be used to preset the superiority boundary (EAST 6.4.1) to control the overall one-sided $\alpha = 0.02$. The first interim analysis will be performed when about 269 (66%) OS events (approximately 22.1 months) are collected, and the second interim analysis will be performed when 347 (85%) OS events (approximately 28.4 months) are collected. The final analysis of OS will be performed when 408 OS events are collected to obtain a power of 85% under the premise that the overall type I error does not exceed one-sided $\alpha = 0.02$. The enrollment period is approximately 18 months, and the follow-up period is approximately 18 months. With a randomization ratio of 1:1, a total of approximately 520 subjects are required. Considering a dropout rate of 5%, 548 subjects are intended to be enrolled.

12.2. Statistical Analysis Plan

In this study, SAS 9.4 or above is used for data processing and analysis.

The time-event indicators will be analyzed using the Kaplan-Meier method, so as to estimate the survival function of both groups and plot the survival curves. In addition, the Cox regression model will be used to estimate the HR between the two groups and its 95% confidence interval (95% CI).

For binary variables, the Cochran-Mantel-Haenszel method will be used to estimate the intergroup difference and its 95% CI.

The safety analysis will be summarized using descriptive statistics.

The detailed analysis plan and strategy will be described in the SAP.

12.3. Analysis Population

- Intent-to-treat (ITT) set: According to the ITT principle, all subjects who have passed the screening and have been enrolled and randomized. The ITT set is the primary analysis set for the efficacy analysis of this study.
- Per-protocol set (PPS): A subset of the ITT set, excluding subjects with major protocol deviations judged to have a significant impact on the study results.
- Safety analysis set (SS): Refers to enrolled and randomized subjects who have received at least one dose of the study drug.

The statistical analysis will be performed for the drug efficacy based on the ITT set and PPS. Before database locking, the principal investigator, statistician, and sponsor should determine the final PPS during the data review meeting.

12.4. Statistical Methods

The following sections include the description of the planned statistical methods.

12.4.1. Basic methods

The primary efficacy endpoints of this study are PFS and OS. Two interim analyses of the efficacy are planned for the OS. The final analysis of PFS will be performed when 378 PFS events (about 22 months) are collected; at the same time, the first interim analysis of OS will be performed, when about 269 (66%) events (about 22.1 months) are collected. The second interim analysis of OS will be performed when about 347 (85%) events (about 28.4 months) are collected. The final analysis of OS will be performed when 408 events are collected.

12.4.2. Primary efficacy endpoint analysis

The primary endpoints of the study are PFS and OS. The primary analysis will be based on the ITT set. The survival functions of PFS and OS of the two groups will be compared using both stratified and non-stratified Log-Rank tests. Also, the Kaplan-Meier method will be used for estimating the PFS and OS and plotting the survival curve to estimate the median PFS and OS as well as their 95% CIs (Brookmeyer-Crowley method). The analysis with stratification factors is used as the primary analysis.

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

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

Table 11. Boundary value and α spending in the analyses of PFS and OS.

Study Endpoints	**Planned Analysis Time Point**	**Number of Events**	**Superiority Boundary Z (HR of superiority boundary) (treatment group/control group)**	**α Spending** (one-sided)
			Effective (≤ Lower Limit)	
PFS	Final analysis (about 22 months)	378	-2.576 (HR = 0.767)	0.005
OS	First interim analysis (about 22.1 months)	About 269 (66%)	-2.638 (HR = 0.725)	0.004
	Second interim analysis (about 28.4 months)	About 347 (85%)	-2.312 (HR = 0.780)	0.010
	Final analysis (about 36 months)	408 (100%)	-2.137 (HR = 0.809)	0.016

Note: The actual α spending value and margins for the interim analysis will be determined based on the proportion of the events at that time. The result is based on the Z value calculated using EAST 6.4.1, the Lan-DeMets α spending function is used to allocate α, and the O'Brien & Fleming method is used to preset the superiority boundary.

The final analysis will be performed when 378 PFS events are obtained. When the P-value (one-sided) based on the stratified Log-Rank test in the final analysis of PFS is < 0.005, and the Z value exceeds the efficacy boundary Z value of -2.576, the comparison of PD-1 antibody SHR-1210 combined with paclitaxel and cisplatin (treatment group) vs. placebo combined with paclitaxel and cisplatin (control group) is statistically significant.

The final analysis will be performed when 408 OS events are obtained. When the P-value (one-sided) based on the stratified Log-Rank test in the final analysis of OS is < 0.016, and the Z value exceeds the efficacy boundary Z value of -2.137, the comparison of PD-1 antibody SHR-1210 combined with paclitaxel and cisplatin vs. placebo combined with paclitaxel and cisplatin is statistically significant. When the actual number of observed events does not reach or exceed 408 in the final analysis, automatic adjustments may be performed using EAST to control the overall type I errors. Refer to section 12.4.6 for the interim analysis of OS.

12.4.3. Secondary efficacy endpoint analysis

Based on the FAS, the secondary endpoints, ORR and DCR, and their two-sided 95% CIs (Clopper-Pearson method) will be estimated, the inter-group difference and their two-sided 95% CIs (normal approximation) will be calculated, and the inter-group P-value will be compared (Cochran-Mantel-Haenszel method).

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

12.4.4. Handling of missing data

In this trial, the missing data of the efficacy endpoints are not treated specially (see the SAP for detailed censoring rules), and the missing values are not estimated in the safety assessment.

12.4.5. Safety analysis

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

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

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

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

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

12.4.6. Interim analysis

In this study, an interim analysis will be conducted when about 269 (66%) OS events (about 22.1 months) and about 347 (85%) OS events (about 28.4 months) are collected, respectively. For PFS, interim analysis will not be conducted, and only final analysis will be conducted. In order to control the overall type I errors, the Lan-DeMets α spending function is used, and the O'Brien & Fleming method is used to preset the superiority boundary.

According to Table 11, when the P-value (one-sided) based on the stratified Log-Rank test in the first interim analysis of OS is < 0.004, and the Z value exceeds the efficacy boundary Z value of -2.638, the comparison between the treatment group and the control group is determined to be statistically significant and the trial is discontinued. If, in the first interim analysis, the actual number of observed events does not reach or exceed 269, the boundary should be timely monitored and adjusted using EAST.

According to Table 11, when the P-value (one-sided) based on the stratified Log-Rank test in the second interim analysis of OS is < 0.010, and the Z value exceeds the efficacy boundary Z value of -2.312, the comparison between the treatment group and the control group is determined to be statistically significant and the trial is discontinued. If, in the second interim analysis, the actual number of observed events does not reach or exceed 347, the boundary should be timely monitored and adjusted using EAST.

The final analysis will be performed when 408 OS events are obtained (see section 12.4.2).

The interim analysis will be completed by independent statisticians and their programming team. The results of interim analysis will be reviewed by the IDMC, which will recommend whether to continue the study.

12.4.7. Subgroup analysis

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

Stratification factors:

Liver metastasis (with vs. without);

Whether the subjects have received definitive chemoradiation (yes vs. no)

12.4.8. Multiple comparison/multiplicity

This trial is a parallel design with two endpoints. Two interim analyses are included for OS. To control the overall type I errors, the α is allocated as follows:

PFS: $\alpha = 0.005$ (one-sided)

OS: $\alpha = 0.020$ (one-sided)

The O'Brien-Fleming method is used for the α spending in the interim analysis and final analysis of OS. See section 12.4.6 for details.

12.4.9. Exploratory analysis

The following exploratory endpoints will be analyzed using descriptive statistics:

- Evaluation of the relationship between PD-L1 expression in tumor tissues and efficacy;
- Determination of the proportion of subjects showing anti-SHR-1210 antibodies.

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.

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 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

Implemented by: CRA.

Monitoring content: To confirm that whether the study protocol is adhered to; whether the records on eCRF are correct and complete, and consistent with the source documents such as study medical records and laboratory test reports, and whether there are errors or omissions in the data. According to the monitoring plan, the CRA will verify the completeness, consistency, and accuracy of 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.

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 CRA, data manager, and medical personnel 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 mainly to determine the analysis data set (including the ITT set, 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. 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 shall 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 termination of the clinical trial.

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.

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

15. QUALITY ASSURANCE AND QUALITY CONTROL

To ensure data quality, the sponsor and investigator will discuss and formulate the clinical trial 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 study drugs, including receipt, storage, dispensing, return, and destruction (if applicable).

According to the GCP guidelines, necessary measures must be taken at the design and implementation phases of the study to ensure that all collected data are accurate, consistent, intact, and reliable. All observed results and abnormal findings in the clinical trial 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 trial must have stringent specifications and be operated under normal conditions.

The investigator will input data required by the protocol into the eCRF. The CRA will check whether the eCRF is completely and accurately filled and guide the study site personnel for 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 shall be conducted by persons 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 approval is obtained. The clinical approval number for SHR-1210 is 2016L01455.

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

- Provisions for Drug Registration;
- Good Clinical Practices;
- 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;
- Other applicable laws and regulations.

16.2. Ethical Standards

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

16.4.1. ICFs and other written information for subjects

The ICF describes the investigational product and study process in detail and fully explains the risks of the study to the subjects. Written documentation of informed consent must be obtained before starting any study-related procedures. The following informed consent materials will be submitted along with the protocol:

Informed consent form;

Recruitment advertisement.

16.4.2. Informed consent process and records

Informed consent begins before an individual decides to participate in the clinical trial and continues during the entire clinical trial. 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 a patient refuses to participate in this study, his or her rights will be fully protected, and the nursing quality will not be affected.

16.5. Confidentiality of Subject Information

The confidentiality of subject information will be strictly enforced by the investigator, participated 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 shall not to be disclosed to any unauthorized third-party without prior written approval from the sponsor.

Other authorized representatives of the sponsor, IRB, or regulatory authorities 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. When the study has ended, all the records will be kept in a secure place based on the time limit specified by local IRB and regulations.

The study data of 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.

16.5.1. Use of samples, specimens or data

- Planned use: The samples and data collected in accordance with this protocol will be used for exploratory studies to evaluate the relationship between PD-L1 expression and efficacy, and will not be used for any unrelated purposes.
- Storage: Samples and data will be numbered for storage in this study. The data in the computer will also be password protected. Only the investigator can have access to these samples and data.

16.5.2. Future use of archival specimens

In this study, archival specimens will not be used for purposes other than those specified in the protocol.

17. PUBLISHING OF STUDY RESULTS

The study outcomes belong to 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 study drug or not. However, the investigator should let the sponsor have the opportunity to review any proposed publication or other forms of publication before document submission or publication to prevent unintentional leakage of confidential information or unprotected inventions. The investigator should provide Hengrui with the manuscript, abstract, or full text of all planned publications (poster, invited lectures, or guest lectures) at least 30 days prior to submission for publication or other forms of release. To protect the intellectual property, 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 12 months after 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: October 2018

Anticipated enrollment of the last subject: April 2020

Anticipated study completion: October 2021

19. REFERENCES

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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

Appendix IV TNM Staging of Esophageal Cancer (8th Edition)

T Staging

Tx: Primary tumor cannot be assessed

T0: No evidence of primary tumor

Tis: High-grade dysplasia

T1: Tumor invades the lamina propria, muscularis mucosae, or submucosa

T1a: Tumor invades the lamina propria or muscularis mucosae

T1b: Tumor invades the submucosa

T2: Tumor invades the muscularis propria

T3: Tumor invades the fibrous membrane

T4: Tumor invades adjacent structures

T4a: Tumor invades the pleura, pericardium, azygos vein, diaphragm, or peritoneum

T4b: Tumor invades other adjacent structures such as aorta, vertebral body, or trachea

N Staging

Nx: Not assessable

N0: No regional lymph node metastasis

N1: Metastasis in 1-2 regional lymph nodes

N2: Metastasis in 3-6 regional lymph nodes

N3: Metastasis in 7 or more regional lymph nodes

M Staging

M0: No distant metastasis.

M1: With distant metastasis.

Tumor Differentiation (G)

Gx: Differentiation cannot be assessed;

G1: Well-differentiated, with prominent keratinization with pearl formation and a minor component of nonkeratinizing basal-like cells, tumor cells arranged in sheets, and mitotic counts low;

G2: Moderately differentiated, with variable histologic features ranging from parakeratotic to poorly keratinizing lesions and pearl formation generally absent;

G3*: Poorly differentiated, consisting predominantly of basal-like cells forming large and small nests with frequent central necrosis and with the nests consisting of sheets or pavement-like arrangements of tumor cells that are occasionally punctuated by small numbers of parakeratotic or keratinizing cells;

* If the "undifferentiated" cancer tissue is further tested as a squamous cell component, or if it is still undifferentiated after further testing, it is classified as G3 squamous cell carcinoma.

Esophageal segments are divided according to the center of the tumor into:

Esophageal Segment	**Site of Primary Lesion**
Cervical Esophageal Segment	From hypopharynx (upper esophageal sphincter) to the thoracic inlet (suprasternal notch)
Upper Thoracic Esophageal Segment	From the thoracic inlet to the lower edge of arch of azygos vein
Middle Thoracic Esophageal Segment	From the lower edge of arch of azygos vein to the level of inferior pulmonary vein
Lower Thoracic Esophageal Segment	From the level of inferior pulmonary vein to lower esophageal sphincter
Esophagogastric Junction	When the midpoint of the tumor is within 2 cm from the cardia (formerly Siewert types I/II), it will be staged based on the staging of esophageal cancer; when the midpoint of the tumor is 2 cm away from the cardia, even if it invades the cardia, it will be staged based on the staging of gastric cancer.

cTNM Staging

	cT	**cN**	**M**
0	Tis	N0	M0
I	T1	N0-1	M0
II	T2	N0-1	M0
	T3	N0	M0
III	T3	N1	M0
	T1-3	N2	M0
IVA	T4	N0-2	M0
	Any T	N3	M0
IVB	Any T	Any N	M1

pTNM Staging

	pT	pN	M	G	Segment
0	Tis	N0	M0	N/A	Any
IA	T1a	N0	M0	G1	Any
	T1a	N0	M0	GX	Any
IB	T1a	N0	M0	G2-3	Any
	T1b	N0	M0	G1-3	Any
	T1b	N0	M0	GX	Any
	T2	N0	M0	G1	Any
IIA	T2	N0	M0	G2-3	Any
	T2	N0	M0	GX	Any
	T3	N0	M0	Any	Lower segment
	T3	N0	M0	G1	Upper segment/middle segment
IIB	T3	N0	M0	G2-3	Upper segment/middle segment
	T3	N0	M0	GX	Any
	T3	N0	M0	Any	Unknown
	T1	N1	M0	Any	Any
IIIA	T1	N2	M0	Any	Any
	T2	N1	M0	Any	Any
IIIB	T2	N2	M0	Any	Any
	T3	N1-2	M0	Any	Any
	T4a	N0-1	M0	Any	Any
IVA	T4a	N2	M0	Any	Any
	T4b	N0-2	M0	Any	Any
	Any T	N3	M0	Any	Any
IVB	Any T	Any N	M1	Any	Any

pTNM Staging

	ypT	**ypN**	**M**
I	T0-2	N0	M0
II	T3	N0	M0
IIIA	T0-2	N1	M0
IIIB	T3	N1	M0
	T0-3	N2	M0
	T4a	N0	M0
IVA	T4a	N1-2	M0
	T4a	Nx	M0
	T4b	N0-2	M0
	Any T	N3	M0
IVB	Any T	Any N	M1

Summary of Amendments to Protocol of a Randomized, Double-Blind, Placebo-Controlled, Multi-Center Phase III Clinical Study of Anti-PD-1 Antibody SHR-1210 Combined with Paclitaxel and Cisplatin vs. Placebo Combined with Paclitaxel and Cisplatin as First-line Treatment of Advanced Esophageal Cancer

(Version 1.0, Date: 12 Jun., 2018 - Version 2.0, Date: 8 Aug., 2018)

Page/Title/Line	Original Content (Version 1.0, Date: 12 Jun., 2018)	Revision (Version 2.0, Date: 8 Aug., 2018)	Reason for Modification
Cover Page, Page 5	Title "A Randomized, Open-Label, Controlled, Multi-Center Phase III Clinical Study of Anti-PD-1 Antibody SHR-1210 Combined with Paclitaxel and Cisplatin vs. Paclitaxel Combined with Cisplatin as First-Line Treatment of Advanced Esophageal Cancer"	A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Phase III Clinical Study of Anti-PD-1 Antibody SHR-1210 Combined with Paclitaxel and Cisplatin vs. Placebo Combined with Paclitaxel and Cisplatin as First-line Treatment of Advanced Esophageal Cancer	◆ This study was changed to a double-blind, placebo-controlled study
Pages 5 and 24	Primary objective "To compare the ... of SHR-1210 combined with paclitaxel and cisplatin vs. paclitaxel combined with cisplatin" Secondary objectives "To compare the ... of SHR-1210 combined with paclitaxel and cisplatin vs. paclitaxel combined with cisplatin; To evaluate the ... of SHR-1210 combined with paclitaxel and cisplatin vs. paclitaxel combined with cisplatin"	Primary objective To compare the progression-free survival (PFS) (IRC-assessed) and overall survival (OS) of SHR-1210 combined with paclitaxel and cisplatin vs. placebo combined with paclitaxel and cisplatin in the treatment of patients with advanced esophageal cancer. Secondary objectives To compare the PFS (investigator-assessed), 6-month and 9-month OS rates, objective response rate (ORR), and disease control rate (DCR) of SHR-1210 combined with paclitaxel and cisplatin vs. placebo combined with paclitaxel and cisplatin in the treatment of patients with advanced esophageal cancer, and to evaluate the duration of response (DoR) of the two groups; To evaluate the safety of SHR-1210 combined with paclitaxel and cisplatin vs. placebo combined with paclitaxel and cisplatin in the treatment of patients with advanced esophageal cancer.	◆ This study was changed to a double-blind, placebo-controlled study

Page/Title/Line	Original Content (Version 1.0, Date: 12 Jun., 2018)	Revision (Version 2.0, Date: 8 Aug., 2018)	Reason for Modification
Pages 6, 7, 25, 26, and 37	Method of administration "The treatment group is given SHR-1210 (200 mg, D1) combined with paclitaxel (175 mg/m^2, D1) and cisplatin (75 mg/m^2, D1) in 3-week cycles, for up to 6 cycles, followed by SHR-1210 (200 mg, D1) monotherapy as maintenance treatment until disease progression, unacceptable toxicity, withdrawal of informed consent, or when the investigator judges that the subject should withdraw from the study treatment. The longest duration of administration with SHR-1210 is 2 years." The control group is given paclitaxel (175 mg/m^2, D1) combined with cisplatin (75 mg/m^2, D1) in 3-week cycles, for up to 6 cycles; no systemic anti-tumor treatment is allowed before disease progression, while best supportive care and local palliative treatment are allowed until disease progression.	The treatment group is given paclitaxel (175 mg/m^2, D1) and cisplatin (75 mg/m^2, D1) combined with SHR-1210 (200 mg, D2) in 3-week cycles, for up to 6 cycles of chemotherapy. The control group is given paclitaxel (175 mg/m^2, D1) and cisplatin (75 mg/m^2, D1) combined with placebo (D2) in 3-week cycles, for up to 6 cycles of chemotherapy. After the end of 6 cycles of chemotherapy, SHR-1210 (200 mg, D1)/placebo (D1) monotherapy is given as maintenance treatment, until disease progression, unacceptable toxicity, start of new anti-tumor treatment, withdrawal of informed consent, or when the investigator judges that the subject should withdraw from the study treatment. The longest duration of administration with SHR-1210/placebo is 2 years.	◆ Added placebo administration for the control group ◆ Considering the preventive hormone therapy for chemotherapy, the dosing regimen was changed to: paclitaxel + cisplatin on D1, SHR-1210/placebo on D2
Pages 6, 15, 25, 48, 51, and 54	Safety follow-up is conducted for 90 days in the treatment group and for 30 days in the control group	Safety follow-up is conducted for a total of 90 days	◆ Due to the double-blind design, the duration of follow-up should be kept the same for the two groups
Page 7		In Section "Study Drug", added the placebo and its manufacturer	◆ Due to the double-blind design, placebo administration was added
Pages 7 and 28	Inclusion Criterion 2 "(Patients with adenosquamous carcinoma with squamous cell carcinoma accounting for more than 50% may be screened)"	Deleted	◆ Based on the opinion from the Investigator Meeting, patients with adenosquamous carcinoma are not recommended to be enrolled

Page/Title/Line	Original Content (Version 1.0, Date: 12 Jun., 2018)	Revision (Version 2.0, Date: 8 Aug., 2018)	Reason for Modification
Pages 8 and 28	Inclusion Criterion 9 "at least 3 months after the last dose of SHR-1210"	at least 3 months after the last dose of SHR-1210/placebo	◆ Due to the double-blind design, placebo administration was added, and the corresponding part of the protocol was modified
Pages 8 and 29	Exclusion Criterion 3 "Significant tumor invasion into adjacent organs (aorta or trachea) of esophageal lesions leading to higher risk of bleeding or fistula"	Significant tumor invasion into adjacent organs (aorta or trachea) of esophageal lesions leading to higher risk of hemorrhage or fistula	◆ Standardized the wording
Pages 9 and 29	Exclusion Criterion 6 Item d "Received the last dose of anti-tumor treatment (including chemotherapy, radiotherapy, targeted therapy) within ≤ 4 weeks before the first dose of the study drug"	Received the last dose of anti-tumor treatment (including radiotherapy) within ≤ 4 weeks before the first dose of the study drug	◆ Contradictory to the inclusion criteria
Pages 9 and 29	Exclusion Criterion 9 "Patients with asthma requiring medical intervention with bronchodilators cannot be enrolled"	Deleted	◆ Not necessary to be excluded
Pages 10, 15, 32, and 47	ADA study "For the treatment group only, blood samples are collected once before administration on C1D1, C2D1, C4D1, C6D1, and C9D1"	Blood samples are collected once before administration of SHR-1210/placebo on C1D2, C2D2, C4D2, C6D2, and C9D1.	◆ Due to the double-blind design, blood sampling is required for both groups ◆ Changed blood sampling time to D2 because SHR-1210 should be administered on D2 during the first 6 cycles of the combined medication with chemotherapy

Page/Title/Line	Original Content (Version 1.0, Date: 12 Jun., 2018)	Revision (Version 2.0, Date: 8 Aug., 2018)	Reason for Modification
Pages 10, 31, and 38	Study Treatment Discontinuation Criteria "When judged as disease progression as per RECIST v1.1 criteria, administration shall be discontinued for the control group; subjects in the treatment group who meet the criteria of clinical stability (see section 7.1.5) may continue administration of SHR-1210 combined with chemotherapy or SHR-1210 monotherapy, until PD is confirmed or the subjects no longer clinically benefit from the treatment as per the investigator's judgment"	When judged as disease progression as per RECIST v1.1 criteria, subjects who meet the criteria of clinical stability (see section 7.1.5) may continue the treatment, until PD is confirmed or the subjects no longer clinically benefit from the treatment as per the investigator's judgment;	◆ Due to the double-blind design, changes were made correspondingly
Pages 11 and 64	Study Dates "Anticipated enrollment of the first subject: August 2018 Anticipated enrollment of the last subject: February 2020 Anticipated study completion: August 2021"	Anticipated enrollment of the first subject: October 2018 Anticipated enrollment of the last subject: April 2020 Anticipated study completion: October 2021	◆ Delayed due to protocol amendment
Page 15	Schedule of Activities "SHR-1210 administration: Day 1 of each 3-week cycle"	SHR-1210/placebo administration: on Day 2 of each cycle during the combined treatment, and on Day 1 of each cycle during the maintenance treatment period, with every cycle containing 3 weeks.	◆ Modified according to the double-blind design and dosing regimen
Page 25	Table 2, control group "paclitaxel + cisplatin", maintenance treatment period "best supportive care and local palliative care"	Control group "placebo + paclitaxel + cisplatin", "placebo" for the maintenance treatment	◆ Modified according to the double-blind design
Page 25	Subjects may experience pseudoprogression after receiving the immunotherapy drugs … the subject may continue to receive SHR-1210 combined with chemotherapy or SHR-1210 monotherapy ... the subject must discontinue SHR-1210 combined with chemotherapy or SHR-1210 monotherapy ... obtaining approval, the subject may continue treatment until the subjects no longer	Subjects may experience pseudoprogression after receiving the immunotherapy drugs ... the subject may continue treatment ... the subject must discontinue treatment ... obtaining approval, the subject may continue treatment after re-signing an informed consent form for continuing treatment beyond disease progression, until the subjects no longer clinically benefit as per the investigator's judgment.	◆ Modified according to the double-blind design ◆ Subjects should re-sign an informed consent form for continuing treatment after confirmation of PD

Page/Title/Line	Original Content (Version 1.0, Date: 12 Jun., 2018)	Revision (Version 2.0, Date: 8 Aug., 2018)	Reason for Modification
	clinically benefit as per the investigator's judgment.		
Page 27		Added "The same packaging will be adopted for SHR-1210 and placebo to maintain the blind. Double-blind technique will be used. SHR-1210 and placebo will be prepared by non-blinded nurses, and blinded study nurses are responsible for the administration. Subjects, investigators, and staff of the sponsor or designated personnel who participate in the treatment or clinical evaluation of the subjects are not aware of the grouping status."	◆ Added blinding procedures
Page 27	Section 4.2.1 "No blinding is applied in this study. In order to reduce deviations, the frequency of imaging assessment of the treatment group and the control group remains the same. The imaging assessments of tumor lesions are performed according to RECIST v1.1 criteria. The primary efficacy endpoint, PFS, is assessed by the Independent Review Committee (IRC) under blinded state. The final analysis strategy will be determined before the primary efficacy endpoint analysis database is locked, including defining data censoring rules in advance. The efficacy analysis will only be carried out at the time specified in the protocol."	Moved to Section 4.2.2 Blinded assessment	◆ Modified according to the double-blind design
Page 27	4.2.3 Unblinding not applicable	Changed to "This study will remain blinded to the subjects, investigators or agents, study sites, and the sponsor until the study is completed or	◆ Modified according to the double-blind design

Page/Title/Line	Original Content (Version 1.0, Date: 12 Jun., 2018)	Revision (Version 2.0, Date: 8 Aug., 2018)	Reason for Modification
		terminated. To minimize the possibility of bias, treatment randomization information will be kept confidential during the course of the study and will not be disclosed to the blinded team before the study database is locked. Treatment randomization information will be stored in a third-party IWRS, and access permissions will be strictly controlled. The established database will be locked and unblinded after being confirmed correct per the blinded review, with the issuance of a blinded review report. After the database is locked, the data must be properly stored for future reviews. The blind code and the database should be statistically analyzed by the statistician. In case of emergencies (e.g., occurrence of serious adverse events) where the investigator needs to determine the drug and dosage for the subject, the treatment identification information may be unblinded. Unless necessary, the subject should be kept blinded as much as possible. When the investigator needs to confirm the drug and dosage for the subject in cases of emergencies, the responsible investigator at the study site shall submit the application, and the medical director of the sponsor and the principal investigator shall make a joint decision on whether to unblind. The investigator will use the IWRS to unblind the subject and report the unblinding to the sponsor. Before unblinding, the investigator must enter the toxicity level of the observed adverse event, the correlation with the study drug, and the causes in the medical record and other documents. Subjects whose treatment allocation is unblinded	

Page/Title/Line	Original Content (Version 1.0, Date: 12 Jun., 2018)	Revision (Version 2.0, Date: 8 Aug., 2018)	Reason for Modification
		by the investigator and/or non-study physician must discontinue the study treatment, but should continue to be monitored during the trial. Upon unblinding, the circumstances of the unblinding (e.g., the date, causes, and the person responsible for unblinding) must be documented immediately, and the sponsor's CRA must be notified as soon as possible. In the event of an emergency unblinding, the principal investigator, study site personnel, and sponsor's personnel may be unblinded to provide the subject with appropriate subsequent medical care."	
Page 34		Made changes to the labels of SHR-1210/placebo	◆ Modified according to the double-blind design
Page 37		Section 7.1.5, added "The preparation of drug in this study is blinded. Non-blinded nurses should prepare drugs in a separate treatment room to prevent unblinding. They may hand the drugs over to blinded nurses after ensuring that the appearance, packaging, label, and other characteristics are the same."	◆ Modified according to the double-blind design
Page 50		Independent Data Monitoring Committee, added "An unblinded independent statistician will provide the results of the interim analysis to the IDMC. As the principal reviewer of the safety and primary efficacy analysis results, IDMC will advise the sponsor whether to terminate the study. If the IDMC recommends to terminate the study, the safety and efficacy results may be unblinded to the sponsor, such that the sponsor can take action on these recommendations. The unblinded independent statistician will record the degree of unblinding for the interim analysis results by relevant personnel."	◆ Modified according to the double-blind design

Page/Title/Line	Original Content (Version 1.0, Date: 12 Jun., 2018)	Revision (Version 2.0, Date: 8 Aug., 2018)	Reason for Modification
Page 54	The investigator should report the pregnancy to the sponsor within 24 h after becoming aware of the event.	The investigator should report the pregnancy to the sponsor and ethics committee within 24 h after becoming aware of the event.	◆ Changed according to the latest company procedures
Page 58	Interim analysis "with a corresponding HR (treatment group/control group) of 0.72, the comparison between the treatment group and the control group is determined to be statistically significant"	With a corresponding HR (treatment group/control group) of 0.72, the comparison between the treatment group and the control group is determined to be statistically significant and the trial is terminated.	◆ The trial is terminated when the interim analysis achieves statistical significance
Page 70	Esophageal segments: unknown, upper, middle, and lower	Esophageal segments: cervical segment, upper thoracic segment, middle thoracic segment, lower thoracic segment, and esophagogastric junction	◆ Modified according to the eighth edition of TNM staging of esophageal cancer

Abstract of Amendment to Informed Consent Form

Page/Title/Line	Original Content (Version 1.0, Date: 16 Mar., 2016)	Revisions (Version 1.1, Date: 5 Aug., 2016)	Reason for Modification
			◆
			◆
			◆

Abstract of Amendment to Diary Card

Page/Title/Line	Original Content (Version 1.0, Date: 15 Feb., 2016)	Revisions (Version 2.0, Date: 5 Aug., 2016)	Reason for Modification
Page 1	Enrollment No.	Subject No.	◆
			◆
			◆

Summary of Amendments to Protocol of a Randomized, Double-Blind, Placebo-Controlled, Multi-Center Phase III Clinical Study of Anti-PD-1 Antibody SHR-1210 Combined with Paclitaxel and Cisplatin vs. Placebo Combined with Paclitaxel and Cisplatin as First-line Treatment of Advanced Esophageal Cancer

(Version 2.0, Date: 8 Aug., 2018 - Version 3.0, Date: 12 Oct., 2018**)**

Page/Title/Line	**Original Content (Version 2.0, Date: 8 Aug., 2018)**	**Revision (Version 3.0, Date: 12 Oct., 2018)**	**Reason for Modification**
Page 6, Study Design	The treatment group is given paclitaxel (175 mg/m^2, D1) and cisplatin (75 mg/m^2, D1) combined with SHR-1210 (200 mg, D2) in 3-week cycles, for up to 6 cycles of chemotherapy. The control group is given paclitaxel (175 mg/m^2, D1) and cisplatin (75 mg/m^2, D1) combined with placebo (D2) in 3-week cycles, for up to 6 cycles of chemotherapy.	The treatment group is given paclitaxel (175 mg/m^2, D1) and cisplatin (75 mg/m^2, D1) combined with SHR-1210 (200 mg, D1) in 3-week cycles, for up to 6 cycles of chemotherapy. The control group is given paclitaxel (175 mg/m^2, D1) and cisplatin (75 mg/m^2, D1) combined with placebo (D1) in 3-week cycles, for up to 6 cycles of chemotherapy.	At present, there is no evidence that hormone pretreatment for chemotherapy will affect the efficacy, and thus the same design of similar studies (pembrolizumab and nivolumab) in China and abroad is adopted. Also, the administration is more convenient for the subjects.
Page 7, Method of Administration	Treatment group: Intravenous drip infusion of study drugs. Paclitaxel 175 mg/m^2 and cisplatin 75 mg/m^2 are given sequentially on Day 1 of each cycle, and SHR-1210 200 mg is given on Day 2, in 3-week cycles, for up to 6 cycles of chemotherapy with camrelizumab. Control group: Intravenous drip infusion of study drugs. Paclitaxel 175 mg/m^2 and cisplatin 75 mg/m^2 are given sequentially on Day 1 of each cycle, and placebo is given on Day 2, in 3-week cycles, for up to 6 cycles of chemotherapy.	Treatment group: Intravenous drip infusion of study drugs. Paclitaxel 175 mg/m^2, cisplatin 75 mg/m^2, and SHR-1210 200 mg are given sequentially on Day 1 of each 3-week cycle, for up to 6 cycles of chemotherapy with camrelizumab. Control group: Intravenous drip infusion of study drugs. Paclitaxel 175 mg/m^2, cisplatin 75 mg/m^2, and placebo are given sequentially on Day 1 of each 3-week cycle, for up to 6 cycles of chemotherapy.	
Page 15, Notes under the Schedule of Activities	SHR-1210/placebo administration: on Day 2 of each cycle during the combined treatment, and on Day 1 of each cycle during the maintenance treatment period, with every cycle containing 3 weeks.	Administration of SHR-1210/placebo: on Day 1 of each cycle during the combined treatment, and on Day 1 of each cycle during the maintenance treatment period, with every cycle containing 3 weeks.	
Page 26, Study Design Schematic	SHR-1210 (200 mg, IV D2)/Placebo (D2)	SHR-1210 (200 mg, IV D1)/Placebo (D1)	

Page/Title/Line	Original Content (Version 2.0, Date: 8 Aug., 2018)	Revision (Version 3.0, Date: 12 Oct., 2018)	Reason for Modification
Page 37, Table 3	SHR1210/Placebo Administration time: D2; Administration sequence of combined medications: paclitaxel and cisplatin on Day 1. SHR-1210/ placebo on Day 2.	SHR1210/Placebo Administration time: D1; Administration sequence of combined medications: paclitaxel, cisplatin, and SHR-1210/placebo on Day 1.	
Page 10, ADA Study/Page 15, Notes for ADA Blood Sampling under the Schedule of Activities/ Page 47, ADA Blood Sampling/ Page 32, 6.1.1 Blood sampling time points	Collected once before administration of SHR-1210/placebo on C1D2, C2D2, C4D2, C6D2, and C9D1; thereafter, once every 4 cycles before administration; once upon withdrawal from study treatment; and once 30 days after the last dose (if applicable).	Collected once before administration of SHR-1210/ placebo on C1D1, C2D1, C4D1, C6D1, and C9D1; thereafter, once every 4 cycles before administration; once upon withdrawal from study treatment; and once 30 days after the last dose (if applicable).	Due to the change of the administration of SHR-1210 to Day 1, the blood sampling time was correspondingly changed to Day 1
Page 45, 8.1 Screening	History of concomitant disease, past medications, medication allergies;	History of concomitant disease, past medications, medication allergies, smoking and alcohol drinking;	Completed past history, considering that they may be related to disease

Summary of Amendments to Protocol of a Randomized, Double-Blind, Placebo-Controlled, Multi-Center Phase III Clinical Study of Anti-PD-1 Antibody SHR-1210 Combined with Paclitaxel and Cisplatin vs. Placebo Combined with Paclitaxel and Cisplatin as First-line Treatment of Advanced Esophageal Cancer

(Version 3.0, Date: 12 Oct., 2018 - Version 4.0, Date: 26 Nov., 2018)

Page/Title/Line	Original Content (Version 3.0, Date: 12 Oct., 2018)	Revision (Version 4.0, Date: 26 Nov., 2018)	Reason for Modification
Pages 6 and 37	The treatment group is given **paclitaxel (175 mg/m^2, D1) and cisplatin (75 mg/m^2, D1) combined with SHR-1210 (200 mg, D1)** in 3-week cycles, for up to 6 cycles of chemotherapy. The control group is given **paclitaxel (175 mg/m^2, D1) and cisplatin (75 mg/m^2, D1) combined with placebo (D1)** in 3-week cycles, for up to 6 cycles of chemotherapy.	The treatment group is given **SHR-1210 (200 mg, D1) combined with paclitaxel (175 mg/m^2, D1) and cisplatin (75 mg/m^2, D1)** in 3-week cycles, for up to 6 cycles of chemotherapy. The control group is given **placebo (D1) combined with paclitaxel (175 mg/m^2, D1) and cisplatin (75 mg/m^2, D1)** in 3-week cycles, for up to 6 cycles of chemotherapy.	Considering the convenience of clinical operation and the side effects after chemotherapy, the order of medication was changed with SHR-1210 administered first.
Page 7, Method of Administration	Treatment group: Intravenous drip infusion of study drugs. **Paclitaxel 175 mg/m^2, cisplatin 75 mg/m^2, and SHR-1210 200 mg** are given sequentially on Day 1 of each 3-week cycle, for up to 6 cycles of chemotherapy. Control group: Intravenous drip infusion of study drugs. **Paclitaxel 175 mg/m^2, cisplatin 75 mg/m^2, and placebo** are given sequentially on Day 1 of each 3-week cycle, for up to 6 cycles of chemotherapy.	Treatment group: Intravenous drip infusion of study drugs. **SHR-1210 200 mg, paclitaxel 175 mg/m^2, and cisplatin 75 mg/m^2** are given sequentially on Day 1 of each 3-week cycle, for up to 6 cycles of chemotherapy. Control group: Intravenous drip infusion of study drugs. **Placebo, paclitaxel 175 mg/m^2, and cisplatin 75 mg/m^2** are given sequentially on Day 1 of each 3-week cycle, for up to 6 cycles of chemotherapy.	
Page 26, Study Design Schematic	Paclitaxel (175 mg/m^2, IV, D1) + Cisplatin (75 mg/m^2, IV, D1) + SHR-1210 (200 mg, IV, D1) Paclitaxel (175 mg/m^2, IV, D1) + Cisplatin (75 mg/m^2, IV, D1) + Placebo (D1)	SHR-1210 (200 mg, IV, D1) + Paclitaxel (175 mg/m^2, IV, D1) + Cisplatin (75 mg/m^2, IV, D1) Placebo (D1) + Paclitaxel (175 mg/m^2, IV, D1) + Cisplatin (75 mg/m^2, IV, D1)	

Page/Title/Line	Original Content (Version 3.0, Date: 12 Oct., 2018)	Revision (Version 4.0, Date: 26 Nov., 2018)	Reason for Modification
Pages 10, 15, and 32	Collected once before administration of SHR-1210/placebo on **C1D1, C2D1, C4D1, C6D1, and C9D1**; thereafter, once every 4 cycles before administration; once upon withdrawal from study treatment; and once 30 days after the last dose (if applicable).	Collected once before the **1st, 2nd, 4th, 6th, and 9th** administration of SHR-1210/placebo; thereafter, once every 4 doses of SHR-1210/placebo before administration; once upon withdrawal from study treatment; and once 30 days after the last dose (if applicable).	Samples for ADA testing are only collected before the administration of SHR-1210/placebo; thus clarified the description for cycles without administration
Page 47	• ADA blood sampling: Collected once before administration of SHR-1210/placebo on **C1D1, C2D1, C4D1, and C9D1**; thereafter, once every 4 cycles before administration.	• ADA blood sampling: Collected once before the 1st, 2nd, 4th, 6th, and 9th administration of SHR-1210/placebo; thereafter, once every 4 doses of SHR-1210/placebo before administration.	
Page 37, 7.1.5 Use of drug	/	For the pretreatment of paclitaxel chemotherapy, the requirements on the package insert and local clinical practice may be referenced. The following is a pretreatment recommendation for chemotherapy: dexamethasone, 20 mg, divided into 2 doses, orally administered 12 h and 6 h before chemotherapy; diphenhydramine, 50 mg, intravenously injected 30–60 min before chemotherapy (or equivalent dose of other similar drugs); cimetidine (300 mg) or ranitidine (50 mg), intravenously injected 30–60 min before chemotherapy.	Added recommendations on paclitaxel pretreatment
Page 37, 7.1.5 Use of drug	/	To prevent renal toxicity, cisplatin needs to be fully hydrated. When used, cisplatin needs to be hydrated for 3 days, i.e., D0–D2. The recommended dosage is 1500 mL/m^2. Also, potassium chloride, mannitol, and furosemide should be used to maintain a daily urine output of 2000–3000 mL. Cisplatin is a highly emetic chemotherapeutic drug. NK-1 receptor antagonists (aprepitant) combined with 5-HT3 receptor antagonists are recommended for antiemetic treatment when cisplatin is	Added recommendations for hydration of cisplatin at high doses

Page/Title/Line	Original Content (Version 3.0, Date: 12 Oct., 2018)	Revision (Version 4.0, Date: 26 Nov., 2018)	Reason for Modification
		first used; also, antiemetics such as dopamine receptor blockers (metoclopramide) and antihistamines (e.g., phenergan and diphenhydramine) are recommended in combination. While, long-term, continuous use of glucocorticoid is not recommended for chemotherapy-related nausea and vomiting.	
Page 37, Table 3, Notes for Method of Administration	/	If the subject's weight fluctuates less than 10% from baseline (the day of the first administration), the baseline weight is used to calculate the body surface area, based on which the dosage of chemotherapy is calculated. Otherwise, the dosage of chemotherapy is calculated based on the actual body weight on the day of scheduled administration. For the convenience of administration, a deviation of ± 5% for the calculated total dosage per infusion is allowed as per the protocol.	Added regulations for calculating the dosage of chemotherapy based on body surface area

Summary of Amendments to Protocol of a Randomized, Double-Blind, Placebo-Controlled, Multi-Center Phase III Clinical Study of Anti-PD-1 Antibody SHR-1210 Combined with Paclitaxel and Cisplatin vs. Placebo Combined with Paclitaxel and Cisplatin as First-line Treatment of Advanced Esophageal Cancer

(Version 4.0, Date: 26 Nov., 2018 - Version 5.0, Date: 17 May 2019)

Page/Title/Line	Original Content (Version 4.0, Date: 26 Nov., 2018)	Revision (Version 5.0, Date: 17 May 2019)	Reason for Modification
Pages 7 and 28	Those whose last dose of chemotherapy is more than 6 months from recurrence or progression may be screened	Those whose last dose of treatment is more than 6 months from recurrence or progression may be screened	For previous treatments that are chemoradiotherapy, this revision covers the case where radiotherapy ends later than chemotherapy
Pages 8 and 28	Use of any blood components, cell growth factors, leukopoietic agents, thrombopoietic agents, or anti-anemic agents is not allowed within 14 days before the first dose of the study drug	Use of any blood components and cell growth factors is not allowed within 14 days before the screening examinations	To avoid the influence of drugs at screening. In addition, some leukopoietic, thrombopoietic, and anti-anemic proprietary Chinese medicines do not require a washout
Pages 9 and 30	Baseline chest radiography suggesting presence of active lung inflammation, infection symptoms and signs present within 2 weeks prior to the first dose of the study drug, or requiring treatment by oral or intravenous administration of any antibiotic	Baseline chest radiography suggesting presence of active lung inflammation, infection symptoms and signs present within 2 weeks prior to the first dose of the study drug requiring treatment by oral or intravenous administration of any antibiotic	Patients with infections do not need a washout; only patients with infections who have used antibiotics need a washout
Pages 10 and 30	Diagnosed with any other malignancy within 5 years prior to the first dose of the study drug	Diagnosed with any other malignancy prior to the first dose of the study drug	Patients who have previously been diagnosed with other malignant tumors are excluded due to the difficulty of ruling out recurrence of previous malignant tumors
Page 27	and nurses for preparing drugs do not participate in the operation on subjects	and nurses for preparing drugs do not participate in the operation on subjects as much as possible during the	Updated relevant description on the procedures based on the actual

Page/Title/Line	Original Content (Version 4.0, Date: 26 Nov., 2018)	Revision (Version 5.0, Date: 17 May 2019)	Reason for Modification
	during the trial.	trial; other study nurses are responsible for the administration.	situations of clinical study sites.
Page 36	The preparation of drug in this study is blinded. Non-blinded nurses should prepare drugs in a separate treatment room to prevent unblinding. They may hand the drugs over to blinded nurses after ensuring that the appearance, packaging, label, and other characteristics are the same. The blinded study nurses are responsible for the administration.	The preparation of drug in this study is blinded. Nurses for preparing drugs should prepare drugs in a separate treatment room to prevent unblinding. Drugs should be kept the same in the appearance, packaging, label, and other characteristics. Nurses for preparing drugs do not participate in the operation on subjects as much as possible during the trial; other study nurses are responsible for the administration.	Updated relevant description on the procedures based on the actual situations of clinical study sites.
Page 45	Granulocyte colony stimulating factor (G-CSF) is not allowed as primary prophylaxis. For retrospective assessments in the second or subsequent chemotherapy cycles, if subjects have experienced febrile neutropenia or dose-limiting neutropenia events in the previous chemotherapy cycle, prophylactic use of G-CSF may be considered, and dose delay or reduction may also be adopted to reduce the risk of recurrence. The investigator may make judgment based on clinical situations.	For patients with high or medium risk factors for febrile neutropenia or myelosuppression (including but not limited to: aged > 65 years old, have previously received radiotherapy/chemotherapy, with persistent neutropenia, recent surgery or open trauma, hepatic insufficiency, renal insufficiency, tumors involving bone marrow, febrile neutropenia in the past) as judged by the investigator, preventive use of G-CSF is allowed in the first cycle. The investigator may determine the use of G-CSF based on clinical situations.	Modified in consideration that the current chemotherapy regimen involves a large dose and a high incidence of bone marrow suppression as well as with reference to the "Guidelines for the Standardized Management of Neutropenia Related to Tumor Radiotherapy and Chemotherapy"

Summary of Amendments to Protocol of a Randomized, Double-Blind, Placebo-Controlled, Multi-Center Phase III Clinical Study of Anti-PD-1 Antibody SHR-1210 Combined with Paclitaxel and Cisplatin vs. Placebo Combined with Paclitaxel and Cisplatin as First-line Treatment of Advanced Esophageal Cancer

(Version 5.0, Date: 17 May 2019 - Version 6.0, Date: 28 Sep., 2020)

Page/Title/Line	Original Content (Version 5.0, Date: 17 May 2019)	Revision (Version 6.0, Date: 28 Sep., 2020)	Reason for Modification
Pages 6 and 25	In this study, an interim analysis will be conducted when about 269 (66%) OS events (about 22.1 months) are collected.	In this study, an interim analysis will be conducted when about 269 (66%) OS events (about 22.1 months) and about 347 (85%) OS events (about 28.4 months) are collected, respectively.	Added the second interim analysis. The reasons for adding another interim analysis are as follows: Considering that subsequent anti-tumor treatments will affect OS and considering the interests of patients, patients with esophageal squamous cell carcinoma should receive second-line immunotherapy earlier. Thus, another interim analysis of OS was added while holding other conditions of the study unchanged. The analysis will be performed when 85% of OS events are collected, following the completion of the existing interim analysis.
Pages 11 and 56	An interim analysis is planned for the OS. The Lan-DeMets α spending function will be used to allocate the α, and the O'Brien & Fleming method will be used to preset the superiority boundary (EAST 6.4.1) to control the overall one-sided α = 0.02. The interim analysis will be performed when 269 (66%) OS events (approximately 22.1 months) are collected.	Two interim analyses are planned for the OS. The Lan-DeMets α spending function will be used to allocate the α, and the O'Brien & Fleming method will be used to preset the superiority boundary (EAST 6.4.1) to control the overall one-sided α = 0.02. The first interim analysis will be performed when 269 (66%) OS events (approximately 22.1 months) are collected, and the second interim analysis will be performed when 347 (85%) OS events (approximately 28.4 months) are collected.	Described the number of events that must be collected and the time of the second interim analysis.

Page/Title/Line	Original Content (Version 5.0, Date: 17 May 2019)	Revision (Version 6.0, Date: 28 Sep., 2020)	Reason for Modification
Page 51	An interim analysis will be performed when about 269 (66%) OS events are collected. The IDMC will make recommendations on whether to continue or terminate the study based on the safety and efficacy data and results.	Interim analyses will be performed when about 269 (66%) OS events and 347 (85%) OS events are collected. The IDMC will make recommendations on whether to continue or terminate the study based on the safety and efficacy data and results.	Added the second interim analysis and specified the time point for IDMC analysis.
Page 57	Full analysis set (FAS): According to the ITT principle, all subjects who have passed the screening and received at least one dose of the study drugs are included in this set. The FAS is the primary analysis set for the efficacy analysis of this study.	Intent-to-treat (ITT) set: According to the ITT principle, all subjects who have passed the screening and have been enrolled and randomized. The ITT set is the primary analysis set for the efficacy analysis of this study.	According to the CDE's "Guidelines on the Statistical Design of Clinical Trials of Anti-Tumor Drugs", updated the primary analysis set of the efficacy analysis.
Page 57	The primary efficacy endpoints of this study are PFS and OS. An interim analysis of the efficacy is planned for the OS. The final analysis for the PFS will be performed when 378 PFS events are collected (about 22 months). It is expected that the interim analysis of OS will be performed when 269 (66%) events (about 22.1 months) are collected.	The primary efficacy endpoints of this study are PFS and OS. Two interim analyses of the efficacy are planned for the OS. The final analysis of PFS will be performed when 378 PFS events (about 22 months) are collected; at the same time, the first interim analysis of OS will be performed, when about 269 (66%) events (about 22.1 months) are collected. The second interim analysis of OS will be performed when about 347 (85%) events (about 28.4 months) are collected.	Described the second interim analysis

<table>
<tr><th>Page/Title/Line</th><th>Original Content
(Version 5.0, Date: 17 May 2019)</th><th>Revision
(Version 6.0, Date: 28 Sep., 2020)</th><th>Reason for Modification</th></tr>
<tr><td>Page 57</td><td>Table 11. Termination criteria and α spending in the primary analyses of PFS and OS.<table><tr><th>Study Endpoint</th><th>Planned Analysis Time Point</th><th>Number of Events</th><th>Z Value of Superiority Boundary (HR of superiority boundary) (treatment group/control group)</th><th>α Spending</th></tr><tr><td>PFS</td><td>Final analysis (about 22 months)</td><td>378</td><td>-2.576 (HR = 0.65)</td><td>0.005</td></tr><tr><td>OS</td><td>Interim analysis (about 22.1 months)</td><td>About 269 (66%)</td><td>-2.638 (HR = 0.72)</td><td>0.004</td></tr><tr><td>OS</td><td>Final analysis (about 36 months)</td><td>408</td><td>-2.081 (HR = 0.81)</td><td>0.019</td></tr></table></td><td>Table 11 Boundary value and α spending at the analysis time point of PFS and OS.<table><tr><th rowspan="2">Study Endpoint</th><th rowspan="2">Planned Analysis Time Point</th><th rowspan="2">Number of Events</th><th>Z Value of Superiority Boundary (HR of superiority boundary) (treatment group/control group)</th><th>α Spending (one-sided)</th></tr><tr><td>Effective (≤ Lower Limit)</td><td></td></tr><tr><td>PFS</td><td>Final analysis (about 22 months)</td><td>378</td><td>-2.576 (HR = 0.767)</td><td>0.005</td></tr><tr><td rowspan="3">OS</td><td>First interim analysis (about 22.1 months)</td><td>About 269 (66%)</td><td>-2.638 (HR = 0.725)</td><td>0.004</td></tr><tr><td>Second interim analysis (about 28.4 months)</td><td>About 347 (85%)</td><td>-2.312 (HR = 0.780)</td><td>0.010</td></tr><tr><td>Final analysis (about 36 months)</td><td>408 (100%)</td><td>-2.137 (HR = 0.809)</td><td>0.016</td></tr></table></td><td>Added the second interim analysis of OS, using the Lan-DeMets α spending function to allocate α, using the O'Brien & Fleming method to preset the superiority boundary, and giving the corresponding Z value, HR value, and one-sided boundary of P-value after the adjustment.</td></tr>
<tr><td>Page 59</td><td></td><td>According to Table 11, when the P-value (one-sided) based on the stratified Log-Rank test in the second interim analysis of OS is < 0.010, and the Z value exceeds the efficacy boundary Z value of -2.312, the comparison between the treatment group and the control group is determined to be statistically significant and the trial is discontinued. If, in the second interim analysis, the actual number of observed events does not reach or exceed 347, the boundary should be timely monitored and adjusted using EAST.</td><td>Described in details the boundary of the one-sided P-value and Z value in the second interim analysis, and the rules for judgment.</td></tr>
</table>

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER PHASE III CLINICAL STUDY COMPARING PD-1 ANTIBODY SHR-1210 IN COMBINATION WITH PACLITAXEL AND CISPLATIN VS. PLACEBO IN COMBINATION WITH PACLITAXEL AND CISPLATIN AS THE FIRST-LINE TREATMENT OF ADVANCED ESOPHAGEAL CANCER

Statistical Analysis Plan

SAP

Written by: Yi Zhu

Company: Jiangsu Hengrui Medicine Co., Ltd.

Version: V1.0/final version

Date: 28 Nov., 2020

This SAP has been reviewed by the following personnel before being approved and effective.

Functional Role	Reviewer
Senior Statistical Director	Ping Yan
Senior Medical Director	Qing Yang

CONTENT

LIST OF TABLES

LIST OF FIGURES

1. REVISION

None.

2. INTRODUCTION

This SAP is formulated for a phase III study comparing the efficacy and safety of SHR-1210 in combination with paclitaxel and cisplatin vs. placebo in combination with paclitaxel and cisplatin in patients with advanced esophageal cancer to provide the specific methods or strategies for statistical analysis and reporting. This SAP is formulated based on the latest version of the study protocol (version No., V6.0; version date, 28 Sept., 2020).

2.1. Study Design

A randomized, double-blind, placebo-controlled, and multicenter study design is adopted for this study. It is planned to enroll 548 patients with unresectable locally advanced/recurrent or distant metastatic esophageal squamous cell carcinoma who have not received systematic anti-tumor treatment. Eligible subjects will be randomly assigned to the treatment group or the control group at a 1:1 ratio (see Table 1 for the study groups. The stratification factors are: Liver metastasis (Yes vs. No) and whether the subjects have received concurrent definitive chemoradiation (Yes vs. No)).

Table 1. Treatment groups.

Treatment Groups	**Combined Medication (3 Weeks/Treatment Cycle, up to 6 Cycles)**	**Maintenance Treatment (3 Weeks/Treatment Cycle)**
Treatment Group	SHR-1210 + Paclitaxel + Cisplatin	SHR-1210
Control Group	Placebo + Paclitaxel + Cisplatin	Placebo

The two groups of patients will receive the study drugs until the disease progresses, the toxicity becomes intolerable, the new anti-tumor therapy is initiated, the informed consent is withdrawn, the investigator judges that the subjects need to withdraw from the study treatment, or until the subjects have received SHR-1210/placebo treatment for up to 2 years.

The study design is shown in Figure 1.

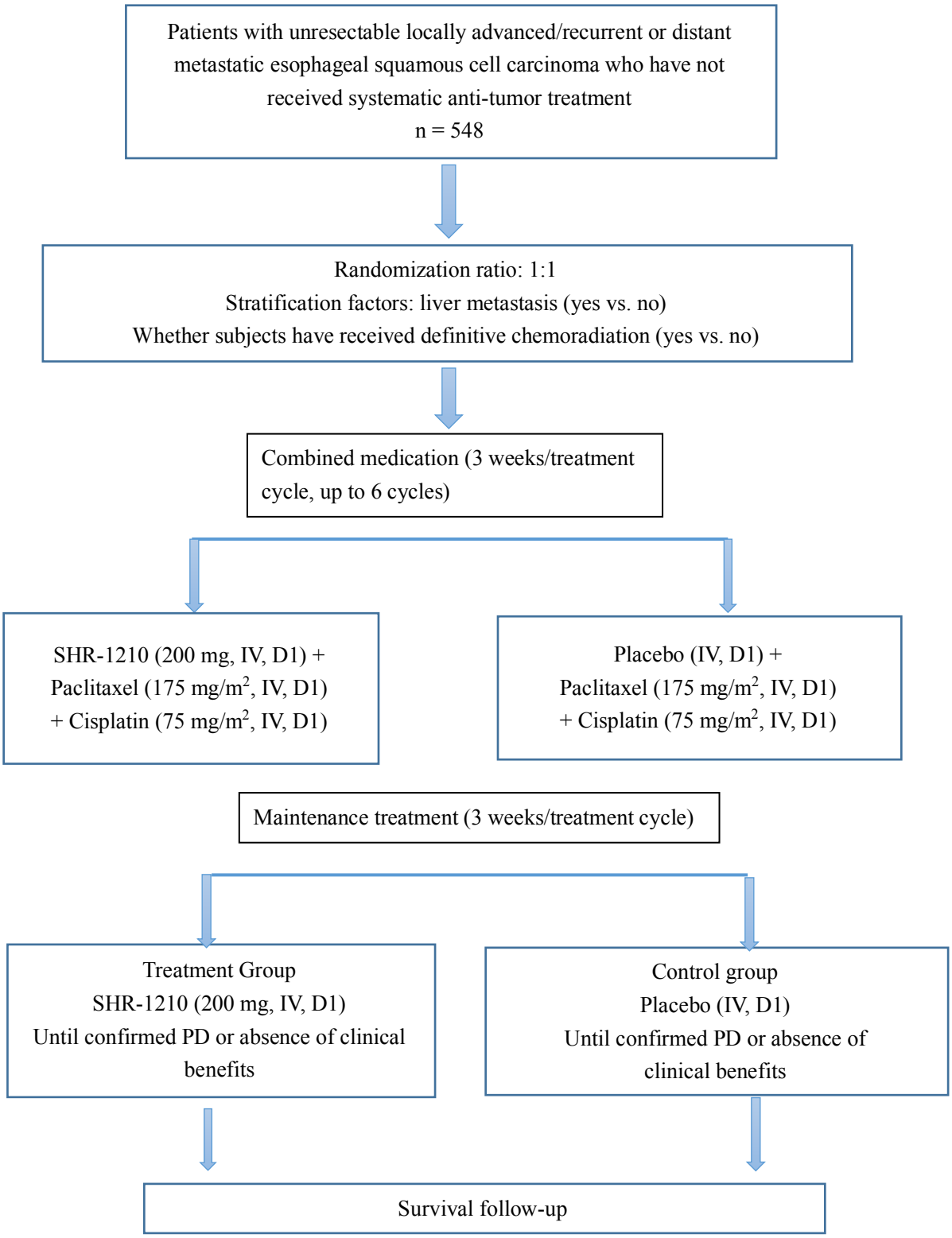

Figure 1. Schematic diagram of study design.

2.2. Study Objectives

2.2.1. Primary Objective

- To compare the progression-free survival (PFS) (assessed by IRC) and overall survival (OS) of patients with advanced esophageal cancer treated with SHR-1210 in combination with paclitaxel and cisplatin vs. placebo in combination with paclitaxel and cisplatin.

2.2.2. Secondary Objectives

- To compare the PFS (assessed by the investigator), OS rate, objective response rate (ORR) and disease control rate (DCR) of patients with advanced esophageal cancer treated with SHR-1210 in combination with paclitaxel and cisplatin vs. placebo in combination with paclitaxel and cisplatin, and to evaluate the duration of response (DoR) in the two groups;
- To compare the safety of SHR-1210 in combination with paclitaxel and cisplatin vs. placebo in combination with paclitaxel and cisplatin in patients with advanced esophageal cancer.

2.2.3. Exploratory Objectives

- To evaluate the relationship between the expression of PD-L1 in the tumor tissues and efficacy.

2.3. Sample Size

This study adopts the parallel design. The sample size is calculated based on the comparison of PFS and OS of the PD-1 antibody SHR-1210 in combination with paclitaxel and cisplatin (treatment group) vs. placebo in combination with paclitaxel and cisplatin (control group).

The assumption is as follows: the hazard ratio (HR) of PFS (treatment group/control group) is 0.67, the median PFS of the control group is 5 months, the hazard ratio (HR) of OS (treatment group/control group) is 0.73, and the median OS of the control group is 10 months. Under the one-sided $\alpha = 0.005$, it is planned to collect 378 PFS events to provide 90% power, and the estimated final analysis time of PFS is about 22.0 months. Two interim analyses are scheduled for OS, α will be allocated using the Lan-DeMets spending function, and the O'Brien & Fleming method will be employed to predefine the superiority boundary (EAST 6.4.1) so as to control the overall one-sided $\alpha = 0.020$. The first interim analysis will be performed when approximately 269 (66%) OS events are collected (approximately 22.1 months), and the second interim analysis will be performed when 347 (85%) OS events are collected (approximately 28.4 months). The final analysis of OS will be performed when 408 OS events are collected, and the power of greater than 85% can be

obtained while the overall type I error does not exceed the one-sided $\alpha = 0.020$. The enrollment period will last about 18 months, and the follow-up period will last about 18 months. According to the randomization ratio of 1:1, a total of about 520 subjects will be needed. Considering a dropout rate of 5%, it is scheduled to enroll about 548 subjects.

3. STATISTICAL HYPOTHESES

The main objective of this study is to compare the efficacy difference with respect to PFS (assessed by IRC, based on RECIST v1.1) and OS of SHR-1210 in combination with paclitaxel and cisplatin vs. placebo in combination with paclitaxel and cisplatin in patients with advanced esophageal cancer.

Null hypothesis H_{10}: The survival function of PFS of SHR-1210 in combination with paclitaxel and cisplatin (assessed by IRC) is the same as that of placebo in combination with paclitaxel and cisplatin (control group);

Alternative hypothesis H_{11}: the PFS of SHR-1210 in combination with paclitaxel and cisplatin (assessed by IRC) is superior to that of placebo in combination with paclitaxel and cisplatin (control group).

Null hypothesis H_{20}: The survival function of OS of SHR-1210 in combination with paclitaxel and cisplatin (treatment group) is the same as that of placebo in combination with paclitaxel and cisplatin (control group).

Alternative hypothesis H_{21}: the OS of SHR-1210 in combination with paclitaxel and cisplatin (treatment group) is superior to that of placebo in combination with paclitaxel and cisplatin (control group).

This trial has co-primary endpoints; specifically, OS includes two interim analyses. To control the overall type I error, α is allocated as follows:

PFS: $\alpha = 0.005$ (one-sided);

OS: $\alpha = 0.020$ (one-sided).

For PFS, the final analysis is scheduled when about 378 PFS events are collected (about 22 months). If the p value (one-sided) of the stratified Log-rank test is smaller than 0.005, then it is claimed that the PFS of the treatment group (assessed by IRC) is superior to that of the control group and the difference is statistically significant.

For OS, two interim analyses and one final analysis will be conducted. For the interim analyses and the final analysis of OS, to control the total type I error, the Lan-DeMets α spending function will be used, and the O'Brien & Fleming method will be used to predefine the superiority

boundary. It is scheduled to conduct the first interim analysis when about 269 OS events are collected (about 22.1 months). If the p value (one-sided) of the stratified Log-rank test is smaller than 0.004, then it is claimed that the OS of the treatment group is superior to that of the control group and the difference is statistically significant. The second interim analysis is scheduled when about 347 OS events are collected (about 28.4 months). If the p value (one-sided) of the stratified Log-rank test is smaller than 0.010, then it is claimed that the OS of the treatment group is superior to that of the control group and the difference is statistically significant. It is scheduled to conduct the final analysis when about 408 OS events are collected (about 36 months). If the p value (one-sided) of the stratified Log-rank test is smaller than 0.016, then it is claimed that the OS of the treatment group is superior to that of the control group and the difference is statistically significant.

If the number of events in the interim analysis of OS does not reach or exceeds the pre-defined number of events, timely monitoring and adjustment of boundary values can be made using the EAST software. The specific details for the interim analysis of OS is shown in Section 6.

4. STUDY ENDPOINTS

4.1. Efficacy Endpoints

4.1.1. Primary endpoints

4.1.1.1. Progression free survival (PFS)

PFS is defined as the time from the start of randomization to the first documentation of objective tumor progression or to death caused by any reason (whichever occurs first). The primary endpoint will be assessed by the Independent Review Committee (IRC). The secondary endpoint is based on the investigator's assessment.

4.1.1.2. Overall survival (OS)

OS is defined as the time from the start of randomization to death of the subject caused by any reason. OS is obtained during study treatment and during survival follow-up.

4.1.2. Secondary endpoints

4.1.2.1. Objective response rate (ORR)

ORR refers to the proportion of subjects whose best overall responses (BORs) are CR and PR in the number of subjects in each of the treatment group.

BOR is defined as the best tumor response from the start of randomization to the first documentation of objective tumor progression or to subsequent anti-tumor treatment or to death

(whichever occurs first). For those without documented progression or subsequent anti-tumor treatment or death, BOR will be determined based on the results of all response assessments.

4.1.2.2. Duration of response (DoR)

DoR refers to the time from the first PR or CR to the first PD or death (whichever occurs first).

4.1.2.3. Disease control rate (DCR)

DCR refers to the proportion of subjects whose best overall responses (BORs) are CR, PR and SD in the number of subjects in each of the treatment group.

4.1.2.4. Quality of life score (EORTC QLQ-C30, EORTC QLQ-OES18)

Quality of life score (EORTC QLQ-C30 and EORTC QLQ-OES18): As a core scale for all cancer patients, the EORTC QLQ-C30 scale comprises 30 items, 5 functional scales (physical, role, cognitive, emotional and social), 3 symptom scales (fatigue, pain and nausea and vomiting), 1 global health status/quality of life scale and 6 single-item scale (dyspnea, insomnia, loss of appetite, constipation, diarrhea and the financial difficulties). The EORTC QLQ-OES18 scale is mainly used for patients with esophageal cancer. It includes 18 items that can be divided into 4 scales (dysphagia, eating, reflux, and pain) and 6 symptom items (each as a scale).

4.2. Safety Endpoints

4.2.1. Adverse events

Including any AE occurring after signing the informed consent form (ICF) and being enrolled in the study.

Any AE occurring after the first dose and no later than 90 days after the last dose is defined as a treatment-emergent adverse event (TEAE). Including but not limited to the followings:

- Worsening of pre-existing (prior to start of study treatment) medical conditions/diseases after the start of study drug.
- Any new AE occurring after the start of study treatment.
- Clinically significant abnormal laboratory findings or results occurring after the start of study treatment.

If an event occurs during non-treatment period (e.g., treatment interruption or follow-up period after treatment discontinuation), then this event will still be considered to be treatment emergent and attributed to previous therapy.

4.2.2. Laboratory tests

Laboratory measurements including hematology, blood biochemistry, urinalysis, and fecal occult blood will be collected at the visit time points specified in the study protocol.

4.2.3. Vital signs

The vital signs such as blood pressure, pulse, body temperature, and respiratory rate will be collected at the time points predetermined in the study protocol.

4.2.4. Electrocardiogram (ECG)

The heart rate, PR interval, QC interval, and QTcF data will be collected at the time points predetermined in the study protocol.

4.2.5. Physical examinations

Physical examinations include general condition, head and face, neck, skin, lymph nodes, eyes, ears, nose, throat, oral cavity, respiratory system, cardiovascular system, abdomen, reproductive-urinary system, musculoskeletal system, nervous system, the mental state and others. These data will be collected at protocol-specified visit/time points.

4.2.6. Other safety endpoints

Examinations such as the ECOG PS score.

4.3. Exploratory Endpoints

- To evaluate the relationship between the expression of PD-L1 in the tumor tissues and efficacy.

5. STATISTICAL ANALYSIS

5.1. General Considerations

5.1.1. Analysis sets

- Informed Consent Set (ICS): all subjects who have signed the informed consent form.
- Intent-To-Treat Set (ITTS): all subjects who pass the screening and who are randomly enrolled into the groups according to the ITT principle. The ITT set represents the main analysis set for efficacy analyses of this study. The analysis is based on the groups assigned by randomization.
- Per-Protocol Set (PPS): a subset of subjects in the ITT set, excluding subjects with significant deviations from the protocol and such deviations judged to have a significant

impact on the results. The exclusion criteria are required to be finalized before the locking of the database, and the list of subjects who are included or removed from the PPS is required to be negotiated and determined by the principal investigator, statistician, and sponsor before the locking of the database.

- Safety Set (SS): subjects who have received the study drug at least once after randomization. Analyses will be performed according to the actual treatment group. The SS is the primary population used for the safety analysis. Subjects who receive the wrong study treatment during the treatment will be analyzed according to the group of the study treatment drug actually received for the first time.

5.1.2. General rules and analysis

Baseline

Unless otherwise stated, the "baseline" in this study is defined as the last non-missing measurement value obtained prior to the first use of the study drugs, including the measurements taken on the day of the first dose and prior to the administration of the first dose.

Study day

The day of the first dose is used as the start date of the study. On this basis, the number of study days corresponding to the examinations or events is calculated according to the following formula:

- Study days = examination date - start date of the study, if the date of an examination/event precedes the start date of study;
- Study days = examination date - start date of the study + 1, if the date of an examination/event is on or after the start day of study.

The start date of the study is used for the analysis of safety data. The randomization date is used for all the calculations of the time to events in the efficacy analysis. As specified in the study protocol, 21 days constitute one cycle.

General analysis

Unless otherwise specified, the following descriptive statistics will be summarized by the type of variables:

- Measurement data are summarized by the number of cases, mean, standard deviation, median, maximum and minimum.
- Count data are summarized by frequency and percentage;

- For time-to-event data, Kaplan-Meier method will be used to estimate the survival function and median time, and a survival curve will be plotted.

Number of decimal places

Unless otherwise specified, number of decimal places in the analysis report will be determined as per the following rules:

- The decimal places of the minimum and maximum will remain the same as that of raw data to be acquired; there should be one additional decimal place for the mean and median, and 2 additional decimal places for standard deviation, up to 4 decimal places.
- The percentage will be rounded to 1 decimal place. If the frequency is 0, the percentage is not displayed.
- The 95% confidence interval has 1 more decimal place than the raw data. If the raw data have no decimal places, then the 95% confidence interval will be rounded to 2 decimal places; if the raw data have 4 decimal places or more decimal places, the 95% confidence interval will retain at most 4 decimal places.
- Time to event (in months) will be rounded to one decimal place.
- HR will be rounded to three decimal places.

Analysis software

All statistical analyses will be conducted using SAS® 9.4 or above.

5.1.3. Derived variables

Time to first diagnosis (months) = (randomization date - date of first diagnosis + 1)/30.4375

The derivative variables related to drug exposure are shown in Section 5.5.1.

5.1.4. Factors and subgroups

The stratification factors include liver metastasis (yes vs. no), and whether the subjects have received definitive chemoradiation (yes vs. no). The stratification factors will be used in the fitting of the Cox proportional hazard model.

The subgroups include:

- Age (< 65 years vs. ≥ 65 years)

- Gender (male vs. female)

- Liver metastasis (yes vs. no)

- Whether the subjects have received definitive chemoradiation (yes vs. no)

- Body weight (< 60 kg vs. ≥ 60 kg)

- ECOG PS score (0 point vs. 1 point)

- PD-L1 expression level in the tumor tissue (< 1% vs. ≥ 1%; < 5% vs. ≥ 5%; < 10% vs. ≥ 10%)

- Cumulative organ number of metastatic lesions (1 vs. ≥ 2)

- Clinical staging (locally advanced vs. distant metastasis)

- Smoking (never smoke vs. currently smoking vs. already quit smoking)

- Drinking (never drink vs. currently drinking vs. already quit drinking)

5.1.5. Analysis window

Data obtained from post-baseline visits will be summarized by protocol visits shown in eCRF. There is no need to consider whether the visit window specified by the protocol has been exceeded.

In the analysis carried out based on visits, the statistical analysis will be performed according to the planned time points in the protocol, i.e., the time points of unplanned visits do not need to be shown.

For the analysis of quality of life score data, the analysis window is defined in Table 2 (calculated by the number of study days):

Table 2. Analysis window for the analysis of quality of life score data.

	Planned Time of Visit	Time Window of Analysis
Baseline	1	-7 - 1
Week 6	43	36 - 50
Week 12	85	78 - 92
Week 18	127	120 - 134
…	…	…

For the quality of life score, if the planned protocol visit is missing and if there is an unplanned visit in the time window of visit for the analysis, the unplanned visit will be used as a visit for analysis. If there are 2 or more unplanned visits in the analysis visit time window, the unplanned visit closest to the time of planned visit will be used for visit analysis. If the time of two unplanned visits is equal to the time of planned visit is equal, the unplanned visit of a later time will be used for visit analysis.

Analyses (other than the quality of life score) which are required to be summarized by visit (e.g., laboratory examinations, vital signs, ECG, physical examinations and tumor efficacy assessments), in addition to the baseline, will be summarized according to the protocol visits filled in the eCRF, and there is no need to consider whether the examinations have exceeded the time window specified in the protocol.

5.1.6. Handling of missing dates and missing data

- The onset dates and end dates, which are missing, of AEs and concomitant treatment will be imputed according to the following rules:

1) If all the dates of an event are missing, they are not imputed. If the day is missing but the year and month of the event occurrence are the same as those of study treatment, then the missing day is imputed with the day of starting study treatment, otherwise it is imputed with the first day of that month; if the day of the end date is missing, then it is imputed with the last day of that month;

2) If the month and day of the occurrence date are missing while the year of the occurrence is the same as that of the initiation of the treatment with the study drug, then the month and day of the initiation of the treatment with the study drug will be is used to impute. In other cases, 1 Jan. will be used to impute; if the month and day of the end date are missing, then 31 Dec. will be used to impute;

3) All imputed dates must precede the latest date available during the study.

- The date of first pathological diagnosis that is missing shall be imputed according to the following rules:

1) If all the dates are missing, then they will not be imputed; if the day is missing, then the first day of that month will be used to impute; if the month and day are missing, then 1 Jan. will be used to impute;

2) The imputed date shall be before the randomization date.

- The date of death that is missing shall be imputed according to the following rules:

1) If the date of death is completely missing, then the date of the last known survival status that is available + 1 day will be used as the date of death;

2) If the month and day of death date are missing, then they should be imputed with 1 Jan., and a comparison should be made with the date of the last known survival status that is available + 1 day, with the later date as the date of death;

3) If the day of death date is missing, then it should be imputed with the first day of that month, and a comparison should be made with the date of the last known survival status that is available + 1 day, with the later date as the date of death.

- Missing data of laboratory tests, ECG, and vital signs are not imputed.

5.1.7. Data cutoff rules

See the data cutoff plan for details.

5.2. Study Subjects

5.2.1. Subjects disposition

All enrolled subjects will be randomized and summarized by frequency and percentage.

In addition, in the disposition of subjects, the frequency and percentage of the following information will be summarized by dose group:

- Number of subjects failing screening and reason for screening failure;
- Number of enrolled subjects;
- Number of subjects discontinuing the treatment/reasons for discontinuation;
- Number of subjects terminating the study/reasons for termination;
- The number of subjects in each analysis set.

5.2.2. Demographics

Age, gender, ethnicity, height of the subjects are summarized using descriptive statistics, respectively. Measurement data such as age and height are summarized using descriptive statistics, such as number of evaluable subjects (n), mean and standard deviation, median, min and max. Categorical variables such as gender, ethnicity, presence or absence of liver metastasis, whether the subjects have received definitive chemoradiation, ECOG PS score, drinking, and smoking are summarized using descriptive statistics, including number of evaluable subjects per category and corresponding percentage of total population. Specifically, the presence or absence of liver metastasis and whether the subjects have received definitive chemoradiation are summarized by the actual baseline stratification and randomized stratification resepectively.

5.2.3. Medical history

The medical history will be summarized descriptively according to the same system organ classification (SOC) and/or preferred terms (PT).

5.2.4. Tumor diagnosis

The following tumor parameters will be summarized using relevant descriptive statistics, respectively:

- Time from the first pathological diagnosis to randomization
- Degree of differentiation (well differentiated G1, moderately differentiated G2, poorly differentiated G3, undifferentiated G4, and Gx whose grade cannot be assessed)
- Cumulative organ number with metastatic lesions (1 vs. ≥ 2)
- Metastatic lesions (the brain, liver, lung, bone, spleen, stomach, kidney, pancreas, lymph node, pleura, chest wall, adrenal gland, thyroid, pleural effusion, abdominal effusion, pericardial effusion, skin, and others)
- Clinical staging (locally advanced vs. distant metastasis)

5.2.5. Prior therapy and concomitant medication

Previous anti-tumor treatment: surgical treatment, local treatment or radiotherapy.

The systemic treatment will be classified and listed by treatment type and generic name.

All prior and concomitant medication will be classified and listed by treatment type and generic name.

5.2.6. Protocol deviations

Prior to database locking, data of all subjects during the study will be checked for major protocol deviation, if any. All potential major protocol deviations will be reviewed and evaluated by the investigator and the sponsor. Major protocol deviations will be summarized.

All major protocol deviations will be summarized and listed by group and type (including group, subject ID, and causes for protocol deviation) for analysis.

Major protocol deviations include but are not limited to the following:

- Serious violation of the inclusion and exclusion criteria;
- Use of any prohibited drug;
- Medication error.

5.3. Treatment Compliance

The duration of exposure to study drugs (weeks) is defined as: (date of last dose - date of first dose

+ 21)/7.

5.3.1. SHR-1210

According to the combined treatment phase and maintenance treatment phase, the dosing frequency of SHR-1210 in the subjects, the frequency and reasons of dose discontinuation, and the frequency and reasons of treatment delay will be summarized using descriptive statistics.

A detailed list of dosing of SHR-1210 will be provided. This listing will include the reasons for dose discontinuation and treatment delay.

5.3.2. Paclitaxel

The dosing frequency of paclitaxel in the subjects, the number and reasons of dose modifications, the frequency and reasons of dose discontinuation, and the frequency and reasons of treatment delay will be summarized using descriptive statistics.

A detailed list of dosing of paclitaxel will be provided. The listing will include the reasons for dose modification, dose discontinuation, and treatment delay.

5.3.3. Cisplatin

Descriptive statistics will be provided in a similar manner to paclitaxel.

5.4. Efficacy Analyses

Analyses of primary efficacy endpoints will be made based on the ITT set and PPS, with the ITT set being the main analysis set. Analyses of secondary efficacy endpoints will be made based on the ITT set.

5.4.1. Primary efficacy analyses

5.4.1.1. PFS, IRC

PFS is defined in Section 4.1.1.1.

- Primary Analysis

The IRC-assessed PFS is analyzed based on the ITT set and PPS, with the ITT set being the main analysis set.

The PFS between the groups is compared using stratified Log-Rank test, and the p value is given. The median time of PFS and the two-sided 95% confidence interval (Brookmeyer Crowley) based on Kaplan-Meier method will be provided and the survival curve will be plotted. The risk of the treatment group relative to the control group will be analyzed using the stratified Cox proportional hazard model, and HR and two-sided 95% confidence interval (Wald method) will be calculated. In

the model, group is used as a fixed effect, with the stratification factors (randomized stratification) being liver metastasis (yes vs. no) and whether the subjects have received definitive chemoradiation (yes vs. no).

The final analysis will be performed for PFS when there are 378 events. When the p value (one-sided) of the final analysis of PFS based on the stratified Log-Rank test is smaller than 0.005, exceeding the efficacy boundary Z value of -2.576, then the PD-1 antibody SHR-1210 in combination with paclitaxel and cisplatin (treatment group) will show a statistical significance as compared with placebo in combination with paclitaxel and cisplatin (control group).

Censoring rules for PFS:

- If the subject has no baseline tumor evaluation, the censoring date is the date of randomization.
- If there is no post-baseline objective tumor response assessment or death, then the date of randomization will be censored.
- If there is no PD or death as per RECIST 1.1, then the date of the last objective tumor response assessment will be censored.
- If there is no radiographic PD or death before the start of any new anti-tumor treatment, then the date of the last objective tumor response assessment prior to the start of new anti-tumor treatment will be censored.
- Before disease progression or death, if a subject has missed $\geq$ 2 consecutive scheduled imaging assessments (98 days ± window period), then the date of the last objective tumor efficacy assessment prior to the missing will be censored.

(Note: The new anti-tumor treatment in the censoring rules refers to the subsequent surgical treatment or subsequent radiotherapy for the target lesions, as well as any subsequent systemic anti-tumor treatment other than TCM.)

- Sensitivity analysis

1) Based on the ITT set and PPS, the above main analysis will be repeated using the method without considering the stratification factors.

2) Based on the ITT set and PPS, the Cox proportional hazard model will be used, with the randomized stratification as the stratification factor, and some of the subgroup factors defined in 5.4.3 will be included as covariates for model fitting. The hazard ratio and 95% CI (Wald method) of the treatment group relative to the control group will be calculated after adjustment of covariates.

In addition, the consistency between the IRC-assessed PFS and the investigator-assessed PFS will be compared based on the ITT set.

5.4.1.2. Overall survival (OS)

OS is defined in Section 4.1.1.2.

- Primary Analysis

The main analysis of OS will be performed based on the ITT set and PPS, with the ITT set being the main analysis set.

The OS between the groups is compared using stratified Log-Rank test, and the p value is given. The median OS and the two-sided 95% confidence interval (Brookmeyer Crowley) based on Kaplan-Meier method will be provided and the survival curve will be plotted. The risk of the treatment group relative to the control group will be analyzed using the stratified Cox proportional hazard model, and the HR and two-sided 95% confidence interval (Wald method) will be calculated. In the model, group is used as a fixed effect, with the stratification factors (randomized stratification) being liver metastasis (yes vs. no) and whether the subjects have received definitive chemoradiation (yes vs. no).

The details of the interim analysis and judgment of OS are shown in Section 6. If the interim analysis is unsuccessful, the final analysis will be performed for OS when there are 408 events. When the P-value (one-sided) of the final analysis of OS based on the stratified Log-Rank test is smaller than 0.016, exceeding the efficacy boundary Z value of -2.137 (see Section 6), then the PD-1 antibody SHR-1210 in combination with paclitaxel and cisplatin will show a statistical significance as compared with placebo in combination with paclitaxel and cisplatin. At the time of final analysis, when there are more than or less than 408 events actually observed, automatic adjustments can be made using the EAST software so as to control the overall type I error.

According to study design, there are two interim analyses for OS; the two-sided repeated confidence interval (RCI) of the OS HR between groups will be calculated using RCI method.

Censoring rules for OS:

- If there is no death during the study, the survival will be censored on the date of the last survival follow-up.
- If a subject is lost to follow-up, the censoring date is the last follow-up date when the survival status of the subject is obtained before the subject is lost to follow-up.

- Sensitivity analysis

1) Based on the ITT set and PPS, the above main analysis will be repeated using the method without considering the stratification factors.

2) Based on the ITT set and PPS, the Cox proportional hazard model will be used, with the randomized stratification as the stratification factor, and some of the subgroup factors defined in 5.4.3 will be included as covariates for model fitting. The hazard ratio and 95% CI (Wald method) of the treatment group relative to the control group will be calculated after adjustment of covariates.

3) If appropriate, the survival curves of the two groups do not meet the hypothesis of the proportional hazards, for example, the restricted mean survival time (RMST) of the treatment group and the control group at 1 and 2 years or other suitable time points and the difference between the two groups and 95% CI can, based on the ITT set, be calculated according to the Kaplan-Meier survival curve.

4) If appropriate, the survival curves of the two groups do not meet the hypothesis of the proportional hazards, for example, the Max-Combo test can be used to compare the differences in distribution between the two groups based on the ITT set. For the Max-Combo test, three different Fleming-Harrington (FH) weights will be adopted, namely FH(0,1), FH(1,0), and FH(1,1).

5.4.2. Secondary efficacy analyses

5.4.2.1. PFS, Investigator

PFS is defined in Section 4.1.1.1.

The investigator-assessed PFS is analyzed based on the ITT set, with the analysis method being the same as the main analysis method for IRC-assessed PFS.

5.4.2.2. Objective response rate (ORR) and disease control rate (DCR)

ORR is defined in Section 4.1.2.1.

DCR is defined in Section 4.1.2.3.

The subjects with assessment of efficacy missing are considered not applicable (NA), and those with unknown efficacy are considered not evaluable (NE).

Based on the ITT set, the investigator-assessed BORs are summarized, and ORR and DCR and their corresponding two-sided 95% confidence intervals are calculated using the Clopper-Pearson method. The differences between groups and the two-sided 95% confidence interval (Wald method) are calculated, and the differences between the groups are tested using the stratified

Cochran-Mantel-Haenszel test, with the stratification factors (randomized stratification) being liver metastasis (yes vs. no) and whether the subjects have received definitive chemoradiation (yes vs. no).

The investigator-assessed BORs are listed.

5.4.2.3. Duration of response (DoR)

DoR is defined in Section 4.1.2.2.

Based on the ITT set, the investigator-assessed DoR will be analyzed, the survival curve will be plotted using the Kaplan-Meier method, and the median DoR and the two-sided 95% confidence interval (Brookmeyer Crowley) will be provided. The DoR rates of the two groups (6, 9 and 12 months) and the corresponding 95% confidence interval (95% CI based on the log-log transformation is calculated by normal approximation and then it is subject to inverse transformation, with the standard error is calculated using Greenwood formula) will be estimated.

Censoring rules for DoR:

- If there is no PD or death as per RECIST 1.1, then the date of the last objective tumor response assessment will be censored.
- If there is no radiographic PD before the start of any new anti-tumor treatment, then the date of the last objective tumor response assessment prior to the start of new anti-tumor treatment will be censored.
- Before disease progression, if a subject has missed ≥ 2 consecutive scheduled imaging assessments, then the date of the last objective tumor efficacy assessment prior to the missing will be censored.

5.4.2.4. OS rate

Based on the ITT set and PPS, the OS rates of the two groups (6, 12 and 18 months) and the corresponding 95% confidence interval (95% CI based on the log-log transformation is calculated by normal approximation and then it is subject to inverse transformation, with the standard error is calculated using Greenwood formula) will be estimated using the Kaplan-Meier method.

5.4.2.5. Quality of life score (EORTC QLQ-C30, EORTC QLQ-OES18)

The converted standard scores of EORTC QLQ-C30 and EORTC QLQ-OES18 will be summarized by scales using descriptive statistics. The standard score conversion methods are shown in Appendix 9.2 and Appendix 9.3.

The quality of life score will be analyzed based on the ITT set.

The descriptive statistics of the above scores at each assessment time point and their changes from baseline values will be provided by treatment groups.

EORTC QLQ-C30 and EORTC QLQ-OES18 will be analyzed using Mixed Model of Repeated Measures (MMRM). The least squares mean and the 95% CI of changes from baseline in the treatment group and control group will be estimated, together with the least squares mean and 95% CI of the difference between the two groups, and the p value will be provided. In the model, the score at baseline will be used as a covariate, liver metastasis, whether the subjects have received definitive chemoradiation, study group, visit cycle, and study group * visit as the fixed effects, and subjects as the random effect. The unstructured (UN) covariance matrix will be selected, and if no converge is seen in the variance matrix, a covariance matrix with the structure of compound symmetry (CS) will be selected.

If necessary, the EORTC QLQ-C30 and EORTC QLQ-OES18 within a specific visit cycle will be analyzed using the Analysis of Covariance (ANCOVA) model, and the least squares mean and the 95% CI of changes from baseline in the treatment group and control group will be estimated, together with the least squares mean and 95% CI of the difference between the two groups, and the p-value will be provided. In the model, the baseline score is used as a covariate, and the liver metastasis, definitive chemoradiation received and the study group as the fixed effects.

5.4.3. Subgroup analysis

In order to determine the consistency in efficacy of this study among various subgroups, for the primary efficacy endpoints of IRC-assessed PFS and OS, the HR of OS and PFS of the treatment group relative to the control group and the 95% CI based on the Wald method will be estimated by using the Cox proportional hazard model based on all the categories of the following demographic characteristics and disease conditions at the baseline in the ITT set, and the forest plot will be generated. The model will be fitted using the treatment group as the only fixed effect while taking into account the randomized stratification factors. If the sub-group analysis itself is one of the randomized stratification factors, the model will be equivalent to a Cox model stratified using the remaining randomized stratification factors.

- Age (< 65 years vs. ≥ 65 years)
- Gender (male vs. female)
- Liver metastasis (yes vs. no)
- Whether subjects have received definitive chemoradiation (yes vs. no)
- Body weight (< 60 kg vs ≥ 60 kg)

- ECOG PS score (0 point vs. 1 point)
- PD-L1 expression level in the tumor tissue (< 1% vs. ≥ 1%; < 5% vs. ≥ 5%; < 10% vs. ≥ 10%)
- Cumulative organ number of metastatic lesions (1 vs. ≥ 2)
- Clinical staging (locally advanced vs. distant metastasis)
- Smoking (never smoke vs. currently smoking vs. already quit smoking)
- Drinking (never drink vs. currently drinking vs. already quit drinking)

5.4.4. Other analysis

None.

5.5. Safety Analysis

All safety analyses will be made based on SS.

5.5.1. Adverse events

All AEs will be coded with MedDRA (version, 23.1) and graded using NCI-CTCAE v4.03. For the same SOC and/or PT, multiple cases of the same events occurred in one subject will be counted only once. For the same AE reported in one subject multiple times but varying in CTCAE grade, the AE of the greatest grade will be enumerated.

AEs will be sorted in descending order of proportion of SOC (treatment group), PTs under same SOC will be sorted in descending order (treatment group), and if 2 or more PTs have the same proportions, then they will be arranged alphabetically. If there is no AE under a SOC or PT, then analysis is not conducted.

In a listing of AEs, TEAEs will be analyzed by group, and frequencies and proportions will be statistically described. The listing comprises number of subjects experiencing at least one AE, number of subjects experiencing AE leading to treatment discontinuation, number of subjects experiencing AE leading to treatment delay or dose reduction, serious adverse event (SAE), drug-related AE, and CTCAE grade (≥ 3). All AEs and SAEs, AEs leading to treatment discontinuation, AEs of CTCAE grade ≥ 3, and AEs with an incidence ≥ 5% after treatment with the study drugs will be summarized according to System Organ Class (SOC) and Preferred Terms (PT). All drug-related AEs and SAEs, drug-related CTCAE of grades ≥ 3, and drug-related AEs with an incidence ≥ 5% that occur during the treatment will be summarized by SOC and PT. The incidence of AE is calculated based on the number of subjects having an AE, instead of the number of AE episodes. For TEAEs, drug-related AEs include definitely related, possibly related, and undeterminable AEs,

and such AEs that are missing will be regarded as drug-related AEs. AEs with any missing CTCAE grade will be analyzed based on the greatest grade.

All AEs will be listed. Drug-related AEs, AEs leading to treatment discontinuation, AEs leading to treatment delay or dose reduction, and deaths will be listed, respectively.

5.5.2. Laboratory Evaluations

Laboratory test baseline is defined as the latest non-missing test result prior to the first dose of investigational product.

The worst grades of baseline and post-baseline laboratory measurements in hematology, blood biochemistry, fecal occult blood, and urinalysis (normal, abnormal without clinical significance, or abnormal with clinical significance) will be summarized using shift tables.

For relevant laboratory measurements that can be graded as per CTCAE, the greatest grades at baseline and post-baseline will be summarized for analysis.

All laboratory measurements will be listed by subject ID, among which, abnormal values will be marked with H/L and indicated for clinical significance if any.

5.5.3. Vital signs

Vital signs will be summarized using descriptive statistics.

All vital signs will be listed.

5.5.4. 12-lead electrocardiogram

The test items of ECG include HR (beats/min), PR interval (ms), QT interval and QTcF. Measurements of each ECG variable at each time point will be analyzed using descriptive statistics.

The worst grades of the measurements at baseline and post-baseline will be summarized using shift tables.

Related data will also be reported in the form of listing.

5.5.5. ECOG PS Score

The highest grades of baseline and post-baseline ECOG PS scores will be summarized. All ECOG PS scores will be reported in the form of listing.

5.5.6. Physical examinations

Data of physical examination will be listed.

5.6. Exploratory Analyses

Based on the ITT set, for the expression level of PD-L1 in the tumor tissues at baseline, an exploratory analysis will be performed on the relationship between the expression level of PD-L1 and the primary efficacy endpoints of IRC-assessed PFS and OS, with the cut-off values being < 1% and ≥ 1%, < 5% and ≥ 5%, and < 10% and ≥ 10%, respectively. The HR of the IRC-assessed PFS and OS of the treatment group relative to the control group at the level of various factors and the 95% CI based on the Wald method will be estimated by using the Cox proportional hazard model, and the forest plot will be generated (see section 5.4.3 Subgroup analysis method). In addition, for IRC-assessed PFS and OS, the survival curves will be plotted based on the Kaplan-Meier method under each cut-off value of PD-L1.

6. INTERIM ANALYSIS

In this study, it is scheduled that interim analyses will be conducted when approximately 269 (66%) OS events (about 22.1 months) and approximately 347 (85%) OS events (about 28.4 months) are collected, respectively. It is scheduled that the final analysis of PFS and the first interim analysis of OS will be conducted simultaneously.

For the interim analyses and final analysis of OS, in order to control the total type I errors, the Lan-DeMets α spending function will be used, and the O'Brien & Fleming method will be used to predefine the superiority boundary.

Table 3. Boundary value and α spending at the analysis time point of PFS and OS.

Study Endpoints	**Scheduled Analysis Time Point**	**Events**	**Z Value of the Superiority Boundary (HR of the Superiority Boundary) (Treatment Group/Control Group)**	**α spending** (one-sided)
			Effective (≤ Lower Limit)	
PFS	Final analysis (About 22 months)	378	-2.576 (HR = 0.767)	0.005
OS	First interim analysis (About 22.1 months)	About 269 (66%)	-2.638 (HR = 0.725)	0.004
	Second interim analysis (About 28.4 months)	About 347 (85%)	-2.312 (HR = 0.780)	0.010
	Final analysis (About 36 months)	408 (100%)	-2.137 (HR = 0.809)	0.016

Note: The determination of the actual α spending value and the boundary during the interim analysis will be made based on the proportion of the number of events at that time. The results will be based on the Z value calculated using EAST 6.4.1. α will be allocated using the Lan-DeMets α spending function, and the superiority boundary will be predefined using the O'Brien & Fleming method.

The interim analyses will be completed by independent statisticians and programming team. The results of the interim analyses will be reviewed by the IDMC, and the recommendation on whether to continue the study or not will be made based on the results.

It is planned to use the data, of which the cutoff date is 30 Oct., 2020, to conduct the first interim analysis of OS. It is expected to collect 309 OS events (75.7%). The superiority boundary will be adjusted using the Lan-DeMets α spending function and the O'Brien & Fleming method. If the P-value (one-sided) of the stratified Log-rank test is smaller than 0.0075, then it is cliamed that the OS of the treatment group is superior to that of the control group and the difference is statistically significant at the first interim analysis of OS.

7. MULTIPLICITY

This trial has co-primary endpoints; specifically, OS includes two interim analyses. To control the total type I errors, the allocation of α is as follows:

PFS: $\alpha = 0.005$ (one-sided)

OS: $\alpha = 0.020$ (one-sided)

For the α spending for the interim analyses and final analysis of OS, the O'Brien-Fleming method will be used. See Section 6 for details.

8. REFERENCES

[1] WanCH, ChenMQ, ZhangCZ, et al. Assessment of Chinese version for EORTC QLQ-C30 for quality of life in patients with cancer [J]. Journal of Practical Oncology, 2005, 20(4): 353-355.

[2] Blazeby JM, Conroy T, Hammerlid E, et al. Clinical and psychometric validation of an EORTC questionnaire module, the EORTC QLQ-OES18, to assess quality of life in patients with esophageal cancer[J]. Eur J Cancer, 2003, 39(10):1384-1394.

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[4] Christopher Jennison, Bruce W. Turnbull. Repeated confidence intervals for group sequential clinical trials [J]. Controlled Clinical Trials, 1984, 5:33-45.

9. APPENDICES

Appendix 9.1 Time Point Response: Subjects with Target Lesions (Including or Excluding Non-Target Lesions)

Target Lesion	Non-Target Lesions	New lesion	Overall Response at the Time Point
CR	CR	Non	CR
CR	Non-CR/Non-PD	Non	PR
CR	Not evaluable	Non	PR
PR	Non-PD or not all evaluable	Non	PR
SD	Non-PD or not all evaluable	Non	SD
Not all evaluable	Non-PD	Non	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

Appendix 9.2 Scoring method for the Chinese version of EORTC QLQ—C30.

1. Item score calculation

EORTC's QLQ-C3O (V3) is a core scale for all cancer patients, including a total of 30 items. Item 29 and 30 has 7-point scales, scoring 1-7 points depending on the answer. Other items have 4-point scales: Not at all, A little, Quite a bit, and Very much, scoring 1-4 points.

2. Calculation of scale scores (raw scores)

For the convenience of statistical analysis and application, the scale is often divided into scales. A scale is an aspect of a quality of life component, also known as a dimension, which is analyzed as an independent variable. The EORTC QLQ—C30 (V3) scale comprises 30 items divided into 15 scales, including 5 functional scales (physical, role, cognitive, emotional and social), 3 symptom scales (fatigue, pain and nausea/vomiting), 1 global health status/quality of life scale, and 6 single-item scales (each one is a scale). To get the score of each scale, add up the scores of the items in each scale and divide by the number of items in each scale (Raw Score, RS). The details are shown in Table 4.

3. Calculation of standard scores

To compare the scores between each scale, a linear transformation is further carried out to standardize the RS so that the standard score (SS) ranges from 0-100. In addition, another purpose of the transformation is to reverse the direction of the score. Except for item 29 and 30 which are reversed items (the larger the score, the worse the quality of life), the scoring rules for QLQ-C30 clearly state that the higher the score for functional scale and global health status, the higher level of function status and QoL, but a high score for symptom status represents a high level of symptoms/problems (worse QoL). Therefore, the score of functional scale needs to be reversed when being standardized. Specifically, the following formula is used (where R is item range).

Functional scale: $SS = [1 - (RS - 1)/R] \times 100$

Global health status, symptom scale and 6 single-item scales: $SS = [(RS - 1)/R] \times 100$

Handling of missing data: For the global health status, functional scale, and symptom scale, if the number of answered items in the scale reaches ≥ 50%, the score is calculated using the above steps; otherwise the score of this scale is considered missing.

Table 4. QLQ-C30 (V3.0) scoring method for each scale (RS).

Scale (dimension)	Code	Property	Number of Items	Item Range (R)	Scoring method
Physical Functioning	PF	Functional scale	5	3	(Q1+Q2+Q3+Q4+Q5)/5
Role Functioning	RF	Functional scale	2	3	(Q6+Q7)/2
Emotional Functioning	EF	Functional scale	4	3	(Q21+Q2+Q23+Q24)/4
Cognitive Functioning	CF	Functional scale	2	3	(Q20+Q25)/2
Social Functioning	SF	Functional scale	2	3	(Q26+Q27)/2
Global Health Status	QL		2	6	(Q29+Q30)/2
Fatigue	FA	Symptom scale	3	3	(Q10+Q12+Q18)/3
Nausea and Vomiting	NV	Symptom scale	2	3	(Q14+Q15)/2
Pain	PA	Symptom scale	2	3	(Q9+Q19)/2
Dyspnoea	DY	Single-item scale	1	3	Q8
Insomnia	SL	Single-item scale	1	3	Q11
Appetite Loss	AP	Single-item scale	1	3	Q13
Constipation	CO	Single-item scale	1	3	Q16
Diarrhea	DI	Single-item scale	1	3	Q17
Financial Difficulties	FI	Single-item scale	1	3	Q28

Appendix 9.3 Scoring method for the Chinese version of EORTC QLQ—OES18.

	Abbreviation of the Scale	Number of Items	Item Range	eCRF Item Number
Functional scale				
Dysphagia	OESDYS	3	3	31 to 33
Symptom scale				
Eating	OESEAT	4	3	36 to 39
Reflux	OESRFX	2	3	44, 45
Pain	OESPA	3	3	46 to 48
Single-item scale				
Trouble Swallowing Saliva	OESSV	1	3	34
Choked When Swallowing	OESCH	1	3	35
Dry Mouth	OESDM	1	3	40
Taste Abnormality	OESTA	1	3	41
Trouble with Coughing	OESCO	1	3	42
Trouble Talking	OESSP	1	3	43

The calculation methods and handling of missing data of the functional scale, symptom scale, and single items are the same as those shown in Appendix 9.2.