Title: A Randomized, Open-Label, Active-Controlled, Multi-Center, Phase III Clinical Study of Anti-PD-1 Antibody SHR-1210 vs. Investigator's Choice of Chemotherapy in Subjects with Locally Advanced or Metastatic Esophageal Cancer

NCT number: NCT03099382

Date: 12 Apr., 2018

A RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED, MULTI-CENTER, PHASE III CLINICAL STUDY OF ANTI-PD-1 ANTIBODY SHR-1210 VS. INVESTIGATOR'S CHOICE OF CHEMOTHERAPY IN SUBJECTS WITH LOCALLY ADVANCED OR METASTATIC ESOPHAGEAL CANCER

Protocol No.: SHR-1210-III-301-ESC
Study Phase: III
Compound Code: SHR-1210

Medical Director: [redacted]

Institution of Principal Investigator: 307 Hospital of the Chinese People's Liberation Army
Principal Investigator: Prof. Jianming Xu

Institution of Principal Investigator: Cancer Hospital Chinese Academy of Medical Sciences
Principal Investigator: Prof. Jing Huang

Version No.: 5.0
Version Date: 12 Apr., 2018

Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Sponsor's Signature Page

I have read and confirmed this clinical study protocol (protocol number: SHR-1210-III-301-ESC, version number: 5.0, version date: 12 Apr., 2018). I agree to fulfill my duties in accordance with Chinese laws, the Declaration of Helsinki, the Chinese GCP, and this study protocol.

Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

[redacted]		
Medical Director (print)	Medical Director (signature)	Signature Date (DD/MM/YYYY)

Principal Investigator's Signature Page (Leading Center)

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

Study Center: The 307th Hospital of the Chinese People's Liberation Army

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

Principal Investigator's Signature Page (Leading Center)

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

Study Center: Cancer Hospital, Chinese Academy of Medical Sciences

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

Principal Investigator's Signature Page (Participating Center)

I will carefully execute the duties as an investigator in accordance with the Chinese GCP, and personally participate in or directly lead this clinical study. I have received the Investigator's Brochure for the investigational drug; I have read the materials of preclinical studies of the investigational drug and the protocol for this clinical study. 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 medical records in a truthful, accurate, complete, and timely manner. I agree to be monitored and audited by the clinical research associate or auditor assigned by the sponsor, and to be inspected by the drug regulatory authorities, to ensure the quality of the clinical study. I will keep the personal information of and matters related to the subjects confidential. I agree to disclose my full name and occupation to the sponsor, and the expenses related to the clinical study upon request. I agree not to engage in any commercial and economic activities related to this study. I agree for the study results to be used for drug registration and publication. I will provide a resume before the start of the study, submit it to the ethics committee, and to the drug regulatory authority for filing purposes.

Study Center: _____

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

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PROTOCOL SYNOPSIS

Study Title	A Randomized, Open-Label, Active-Controlled, Multi-Center, Phase III Clinical Study of Anti-PD-1 Antibody SHR-1210 vs. Investigator's Choice of Chemotherapy in Subjects with Locally Advanced or Metastatic Esophageal Cancer
Protocol No.	SHR-1210-III-301-ESC
Version No.	5.0
Sponsor	Jiangsu Hengrui Pharmaceuticals Co., Ltd.
Principal Investigators	Prof. Jianming Xu 307 Hospital of the Chinese People's Liberation Army Prof. Jing Huang Cancer Hospital Chinese Academy of Medical Sciences
Participating Study Centers	Approximately 40 centers in China
Study Objectives	Primary objective: To evaluate the efficacy of SHR-1210 vs. investigator's choice of chemotherapy in subjects with locally advanced or metastatic esophageal cancer who are refractory to the first-line chemotherapy. Secondary objective: To evaluate the safety of SHR-1210 vs. investigator's choice of chemotherapy in subjects with locally advanced or metastatic esophageal cancer who are refractory to the first-line chemotherapy. Exploratory objectives: (1) To evaluate the relationship between biomarkers in tumor tissue and/or blood (such as PD-L1) and the efficacy of SHR-1210. (2) To evaluate the immunogenicity of SHR-1210 in subjects with locally advanced or metastatic esophageal cancer, and to investigate the correlation between immunogenicity and drug trough concentration, efficacy and safety.
Study Population	Patients with locally advanced or metastatic esophageal cancer who are refractory to the first-line chemotherapy
Study Design	This is a randomized, open-label, active-controlled, multi-center study. A total of 438 eligible subjects with locally advanced or metastatic squamous cell carcinoma of the esophagus who are refractory to first-line chemotherapy will be randomized to investigational treatment group or control group in a 1:1 ratio and stratified by: 1. locally advanced lesion vs. distant metastasis; 2. ECOG PS (0 vs. 1). Subjects in the investigational treatment group will receive SHR-1210 (200 mg/dose, on Day 1 of each 2-week cycle) until confirmed disease progression, intolerable toxicity, voluntary withdrawal by the subject, or treatment discontinuation determined by the investigator. Temporary accelerated tumor growth, i.e., pseudoprogression, may occur soon after immunotherapy is started; therefore, when a subject who has PD in the first assessment is clinically stable, the treatment can be continued, and a tumor assessment should be performed again 4 weeks (±7 days) later; when a non -PD result is confirmed using both iRECIST and RECIST v1.1 criteria, the treatment may be continued, and otherwise, the treatment should be discontinued. For subjects who are clinically unstable, treatment should be discontinued after the first PD, and a new imaging assessment is not required. Subjects in the control group will receive the investigator's choice of chemotherapy, either docetaxel (75 mg/m^2, on Day 1 of each 3-week cycle) or irinotecan (180 mg/m^2, on Day 1 of each 2-week cycle). Chemotherapy will continue until the occurrence of disease progression, intolerable toxicity, voluntary withdrawal by the subject, or discontinuation determined by the investigator.

	The study procedure is divided into three stages. The screening period is 28 days. After completing the screening examination and evaluation, the eligible subjects enter the treatment period and undergo visits by the dosing frequency. Relevant examinations and assessments must be completed before each dose. In particular, tumor imaging will be assessed once every 8 weeks (±7 days) (including the chemotherapy control group). All subjects must complete safety examinations and tumor assessments before the end of treatment. These subjects then enter the follow-up period. The safety follow-up visits of all subjects should be carried out 90 days after the last dose. The follow-up visits scheduled for 30 days after the last dose should be carried out at the study center, while those scheduled for 60 days and 90 days after the last dose via telephone. Survival follow-up visits should begin from the last dose and be carried out once a month; subjects ending the treatment due to reasons other than progressive disease should continue to undergo imaging assessment once every 8 weeks (±7 days) until progressive disease, initiation of new anti -cancer treatments or death.
Study Drugs	Investigational drug: SHR-1210 Control drugs: docetaxel or irinotecan
Method of Administration	**Investigational treatment group**: SHR-1210, 200 mg/dose, intravenous infusion over 30 min (no less than 20 min and no more than 60 min) on Day 1 of each 2-week cycle. The treatment will continue until the occurrence of confirmed PD, intolerable toxicity, voluntary withdrawal by the subject, or treatment discontinuation determined by the investigator. **Control group**: Investigator's choice of chemotherapy (previously-adopted chemotherapy not available). Choose one of the active drugs below for treatment. Docetaxel: 75 mg/m^2, intravenous infusion over approximately 1 h (drip rate may be adjusted accordingly) on Day 1 of each 3-week cycle. The treatment will continue until the occurrence of PD, intolerable toxicity, voluntary withdrawal by the subject, or discontinuation determined by the investigator. Irinotecan: 180 mg/m^2, intravenous infusion over approximately 1 h (drip rate may be adjusted accordingly) on Day 1 of each 2-week cycle. The treatment will continue until the occurrence of PD, intolerable toxicity, voluntary withdrawal by the subject, or discontinuation determined by the investigator.
Inclusion Criteria	Patients must meet all of the following criteria to be eligible for this study: 1. Aged 18-75 years, male or female; 2. Patients with histologically or cytologically confirmed squamous cell carcinoma of the esophagus, unresectable locally advanced, locally recurrent or distant metastasis; 3. Patients who have received first-line systemic chemotherapy (which may include chemotherapies based on platinum, paclitaxel or fluorouracil) and showed disease progression or intolerance (patients who have progression in maintenance treatment after first-line chemotherapy can also be included). Concurrent chemoradiotherapy for postoperative recurrence or metastasis is considered as first-line treatment; For radical concurrent chemoradiotherapy and neoadjuvant/adjuvant therapy (chemotherapy or chemoradiotherapy), it should be considered as first-line treatment failure when progressive disease occurs during the treatment or within 6 months after the treatment discontinued; 4. Patients with at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1), and the measurable lesion(s) should not have been locally treated such as radiotherapy (lesions in previous radiotherapy sites may also be selected as target lesions when PD is confirmed and RECIST v1.1 are met);

	5. Patients with available tissue samples for biomarker (such as PD-L1) analysis; fresh tissue is preferred; archival samples of 5-8 paraffin embedded sections that are 5 μm thick are also acceptable when a fresh biopsy is not accessible; 6. ECOG PS: 0-1 (see Appendix I); 7. Life expectancy ≥ 12 weeks; 8. Major organ functions must meet the following rules (no blood components or cell growth factors are allowed to be used within 2 weeks before the start of study treatment): 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 and AST ≤ 2.5 × ULN; for liver metastasis, ALT and AST ≤ 5 × ULN; f. CrCl ≥ 50 mL/min (Cockcroft-Gault, see Appendix II); 9. Female patients of childbearing potential must have a negative urine or serum pregnancy test result within 72 h before the first dose of study drugs and must be willing to use effective contraceptive measures during the study and within 3 months after the last dose of SHR-1210 (180 days after the last dose for the control group). Male patients with partners of childbearing potential must be willing to take effective contraceptive measures during the study and within 3 months after the last dose of SHR-1210 (180 days after the last dose for the control group); 10. Patients must participate voluntarily, sign the informed consent form, have good compliance, and cooperate with follow-up visits.
Exclusion Criteria	Patients meeting any of the following are ineligible to participate in this study 1. Patients who are diagnosed with other malignant tumors (excluding curatively treated basal cell carcinoma of skin and squamous cell carcinoma of skin, and/or curatively resected cervical carcinoma *in situ* and/or breast cancer *in situ*) within 5 years from the first dose of study drugs; 2. Patients with central nervous system (CNS) metastasis; 3. Patients with active autoimmune disease or history of autoimmune diseases (such as interstitial pneumonia, uveitis, enteritis, hepatitis, hypophysitis, vasculitis, myocarditis, nephritis, hyperthyroidism, hypothyroidism (enrollment is not restricted when hormone replacement therapy is effective)); patients with vitiligo or who had completely resolved pediatric asthma requiring no intervention after adulthood may be enrolled, while those still requiring medical intervention with bronchodilators should not be enrolled; 4. Patients with uncontrolled cardiac symptoms or disease, such as: (1) > NYHA Class II heart failure, (2) unstable angina, (3) myocardial infarction within the past year, and (4) clinically significant supraventricular or ventricular arrhythmias requiring clinical intervention; 5. Patients with active infection or unexplained fever > 38.5 ℃ within 2 weeks before randomization (patients with tumor-induced fever, as determined by the investigator, may be enrolled); 6. Patients with a known history or evidence of interstitial lung disease or pneumonitis that has been treated with corticosteroids;

	7. Patients with congenital or acquired immune deficiency (such as HIV infection), active hepatitis B (HBV-DNA ≥ 10^4 copies/mL or 2000 IU/mL), or hepatitis C (positive anti-HCV antibodies, and HCV RNA titer higher than the lower limit of detection of the analytical method); 8. Patients with a BMI less than 18.5 kg/m^2 or weight loss of ≥ 10% within 2 months before screening (at the same time, the effect of massive pleural effusions and ascites on body weight should be considered); 9. Previous treatment with other anti-PD-1 antibodies or immunotherapy targeting PD-1/PD-L1; 10. Patients with known allergies to macromolecular protein preparations or any components of SHR-1210, or allergic reaction, hypersensitivity reaction, or contraindications to any components of docetaxel or irinotecan, or their in-preparation components; 11. Patients who require systemic treatment with corticosteroids (prednisone of > 10 mg/day or equivalent) or other immunosuppressive medications within 14 days before the administration of study drugs. 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 is permitted; 12. Patients who received anti-tumor treatment with monoclonal antibodies (mAbs), chemotherapy, targeted small molecule therapy, or radiotherapy within 4 weeks before the first dose of study drugs or with adverse events caused by previously-received medications but not recovered (Grade ≤ 1 or baseline reached). Note: Except for patients with Grade ≤ 2 neuropathy or Grade ≤ 2 alopecia. If the patient has undergone major surgery, toxicities and/or complications resulting from the surgical intervention must be fully recovered before the study treatment. 13. Patients who currently participate in or participated in another clinical study within 4 weeks before the first dose of study drugs (for patients in the follow-up period, calculation will be carried out using the time of the last use of study drugs or devices); 14. Patients who inoculated with live vaccine within 4 weeks before the first dose of study drugs; injections of inactivated influenza vaccine for seasonal influenza are permitted, but not live attenuated influenza vaccines for intranasal use; 15. Pregnant or lactating women; 16. Patients with other factors, as determined by the investigator, which may result in study termination; 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 collection of study data.
Immunogenicity Study	Collection time for immunogenicity and drug trough concentration blood samples: Within 30 min before the first, second, third, fifth, and seventh doses, within 30 min before every four doses thereafter, and at visits carried out on Day 30, Day 60 (optional), and Day 90 (optional) after the last treatment.
Study Endpoints	**(I) Efficacy** **Primary endpoint** 1 Overall survival (OS); **Secondary endpoints** 1. Progression-free survival (PFS); 2. Objective response rate (ORR); 3. Quality of life score (EORTC QLQ-C30, EORTC QLQ-OES18);

	Exploratory endpoints 1. To evaluate the relationship between the expression of PD-L1 and/or other biomarkers and the efficacy of SHR-1210. 2. To evaluate the incidence of anti-SHR-1210 antibody (ADA), time to the first positive ADA result, duration of ADA, incidence of anti-SHR-1210 antibody with neutralizing activity, and the correlation between immunogenicity and drug trough concentration, efficacy and safety. **(I) Safety** Adverse events, laboratory measurements.
Sample Size Determination	This is parallel study with its primary endpoint being OS. Subjects will be randomized in a 1:1 ratio. Assuming that the median OS of the control group is 7 months and the median OS of the investigational treatment group is 9.5 months (the investigational treatment group is extended by 2.5 months compared with that of the control group), the inter-group OS distribution will be compared using a stratified log-rank test at an overall significance level $\alpha = 0.025$ (one-sided); when the duration of enrollment is assumed to be 18 months and the entire study lasts for 36 months, at least 365 OS events need to be collected to obtain a power of 80% according to the calculation by East v6.3. Furthermore, assuming a drop-out rate of 20%, a total of 438 subjects need to be enrolled in this study (219 in the investigational treatment group and 219 in the control group).
Statistical Methods	**Analysis Set/Population** • Informed consent set (ICS) All subjects who have signed the informed consent form will be included in this analysis set. • Full analysis set (FAS) Based on the intention-to-treat (ITT) principle, all randomized subjects who have received study drug at least once will be included in FAS. • Per-protocol set (PPS) PPS is a subset of FAS, defined as subjects who do not have major protocol deviations or do not have protocol deviations that may have major impacts on study results. • Immunogenicity analysis set Subjects who have received at least one dose of SHR-1210 and have baseline and at least one post-baseline immunogenicity evaluation data constitute the immunogenicity analysis set. • Safety set (SS) All subjects who have received study drug at least once (whether they have participated in randomized grouping or not) constitute the safety set. **Statistical Methods** **Basic methods** This is a parallel-controlled study. Unless otherwise stated, all data will be analyzed by treatment group (SHR-1210 group and investigator selected chemotherapy group) and appropriate statistics will be applied according to the data type: measurement data will be summarized by mean, standard deviation (STD), median, minimum, and maximum; count data will be summarized by frequency and proportion for descriptive statistics; for time-to-event data, median time and the corresponding overall 95% confidence interval will be estimated by the Kaplan-Meier method. **Primary efficacy endpoint analysis** **1. Primary analysis** The primary analysis is to evaluate the efficacy difference between investigational treatment group and control group based on the FAS. In the primary analysis, the null hypothesis that the distributions of OS are identical between groups will be verified by the stratified log-rank test with randomized stratification factors considered.

	2. Secondary analysis The hazard ratio (HR) of OS of investigational treatment group to control group will be estimated using a Cox proportional hazards model, and the corresponding 95% confidence interval will be calculated. In the fitting of the primary analysis based on this model, treatment group will be set as a fixed effect. In addition, to explore the effects of other factors on efficacy, stratification factors [1. locally advanced lesion vs. distant metastasis; 2. ECOG PS (0 vs. 1)], gender, and PD-L1 expression level can also be used to fit the model except for the treatment group. The above analysis for the primary efficacy endpoint will be repeated in FAS and PPS. **Secondary efficacy endpoint analysis** The analysis of secondary efficacy endpoints in this study will be based on FAS only and will be carried out for all efficacy endpoints except OS (progression-free survival (PFS), objective response rate (ORR), and quality of life score EORTC QLQ-C30 and EORTC QLQ-OES18). For PFS, the inter-group differences will be compared using the log-rank test, and meanwhile, HR of PFS will be estimated using a Cox proportional hazards model and the effects of factors other than treatment group on the differences in PFS will be investigated, with both test and model similar to those of OS-related analysis. For ORR, the difference in ORR between the two groups and the corresponding 95% confidence interval will be estimated. **Analysis of exploratory endpoints** Based on the immunogenicity analysis set, descriptive statistics for the time to the first positive ADA result and the duration of ADA will be summarized. The incidence of ADA, the incidence of anti-SHR-1210 antibody with neutralizing activity, and the correlation between immunogenicity and drug trough concentration, efficacy and safety will be calculated. **Safety analysis** The safety analysis is based on the safety set (by actual treatment received). According to Hengrui's Standard Reporting Procedures, safety will be summarized using descriptive statistics, including but not limited to the following: • Subject disposition and populations; • Subjects' basic characteristics (including demographics, medical history, and medication history); • Discontinuations; • Summary of adverse events (of all causes and treatment-related); • Incidence and severity of adverse events (of all causes and treatment-related); • Summary of serious adverse events; • Causality analysis of adverse events; • Laboratory measurements, vital signs, ECG, and their changes from baseline; • Number and rate of laboratory measurements, vital signs, and ECG data "changed from normal to abnormal" or "exacerbated abnormally" after the trial. In this study, adverse events will be evaluated by NCI-CTCAE v4.03.
End of Study	The study will end upon the completion of the final analysis.
Study Date	Anticipated enrollment of the first subject: Apr. 2017 Anticipated enrollment of the last subject: Oct. 2018 Anticipated study completion: Apr., 2019

SCHEDULE OF ACTIVITIES

Schedule of Activities for Investigational Treatment Group (SHR-1210)

	Screening Period				End of Treatment/Withdrawal (+ 3 days)	After End of Treatment	
			C1	C2+			
Visit Window	**D-28 to D-1**	**D-7 to D-1**	**D1**	**D1 ±3**		**90 days (±7 days) after the last dose**[24]	**Survival follow-up (±7 days)** [25]
Signing of Informed Consent Form[1]	√						
Verification of Eligibility		√					
Demographics	√						
Medical History[2]	√						
ECOG PS[3]		√		√	√		
Vital Signs[4]		√		√	√		
Physical Examination[5]		√		√	√		
Hematology[6]		√		√	√	√	
Urinalysis[7]		√		√	√		
Fecal Occult Blood[8]		√		√			
Clinical Chemistry[9]		√		√	√	√	
Thyroid Function[10]		√		√	√	√	
Coagulation Function[11]		√					
Virological Examination[12]	√						
ECG[13]		√		√	√		
Echocardiography[14]		√					
Pregnancy Test[15]		√			√		

	Screening Period		C1	C2+	End of Treatment/Withdrawal (+ 3 days)	After End of Treatment	
Visit Window	**D-28 to D-1**	**D-7 to D-1**	**D1**	**D1 ±3**		**90 days (±7 days) after the last dose**[24]	**Survival follow-up (±7 days)** [25]
Tumor Imaging Evaluation[16]	√		√				
Randomization		√					
Administration of SHR-1210[17]			√	√			
Adverse Events[18]	√	√	√	√	√	√	
Concomitant Medication[19]	√	√	√	√	√	√	
Quality of Life Score[20]			√	√	√	√	
Blood Sampling for Immunogenicity and Drug Trough Concentration[21]			√	√		√	
Biomarker Blood Sampling[22]			√	√			
Tumor Tissue[23]	√						

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

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

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

[3] ECOG PS: within 7 days prior to the first dose, before administration on Day 1 of each cycle (do not need to be tested for the first dose if completed within 7 days prior to the first dose at screening), and at the end of treatment/upon withdrawal.

[4] Vital signs: blood pressure, heart rate, body temperature and respiratory rate; within 7 days prior to the first dose, before administration on Day 1 of each cycle (do not need to be tested for the first dose if completed within 7 days prior to the first dose at screening), and at the end of treatment/upon withdrawal.

[5] Physical examination: within 7 days prior to the first dose and at the end of treatment/upon withdrawal, a comprehensive physical examination (including head and face, skin, lymph nodes, eyes, ears, nose and throat, mouth, respiratory system, cardiovascular system, abdomen, reproductive and urinary system, musculoskeletal system, nervous system and mental state) is performed; before administration on Day 1 of each cycle (do not need to be tested for the first dose if completed within 7 days prior to the first dose at screening), symptom-directed physical examination can be performed when 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 (do not need to be tested for the first dose if completed within 7 days prior to the first dose at screening), at the end of treatment/upon withdrawal, and 30 days after the last dose.

[7] Urinalysis: WBC, RBC, and urine protein. Within 7 days prior to the first dose, before administration on Day 1 of every 2 cycles, and at the end of treatment/upon withdrawal. In the case of urine protein ≥ 2+, a 24-h urine protein test (quantitative) must be added.

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

[9] Clinical chemistry: 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 (do not need to be tested for the first dose if completed within 7 days prior to the first dose at screening), at the end of treatment/upon withdrawal, and 30 days after the last dose.

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

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

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

[13] ECG: within 7 days prior to the first dose, pre-administration on Day 1 of each cycle (do not need to be tested for the first dose if completed within 7 days prior to the first dose at screening), and at the end of treatment/upon withdrawal.

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

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

[16] Tumor imaging evaluation: CT or MRI of the neck, chest and abdomen (including pelvic cavity). Brain MRI is required when brain metastasis is suspected and confirmed (if MRI is contraindicated, CT can be used instead). Bone scan is performed only when clinically indicated and must be performed within 42 days before the first dose.

- ✓ At screening, tumor evaluations up to 4 weeks before randomization and before informed consent may be used as long as they meet the RECIST 1.1.
- ✓ During the treatment period, lesions found at baseline should be examined every 8 weeks. Examinations should also be performed as appropriate when new lesions are suspected. Tumor evaluations should be performed when subjects withdraw due to any reason (±4 weeks, bu t do not need to be repeated if the time from the last evaluation is no more than 4 weeks). Imaging conditions should be the same as those at baseline (including slice thickness and contrast agent).
- ✓ The time window for imaging examination is ±7 days. Unscheduled imaging examination may be perform ed if PD is suspected (for example, worsening of symptoms). Except for imaging confirmed PD, subjects who discontinue the study treatment for any other reasons must also undergo a tumor evaluation every 8 weeks until documentation of confirmed PD, start of a new anti-tumor treatment, lost to follow-up, or death.

[17] SHR-1210 administration: on Day 1 of each 2-week cycle.

[18] Adverse events: AEs collection begins from signing of informed consent form to 90 days after the last dose. Only treatment-related AEs, including AEs of special interest (AESI), will be collected 30 days after the last dose.

[19] Concomitant medications: Concomitant medications from 30 days before the first dose to 90 days after the last dose should be collected; only concomitant medications for treatment-related AEs should be collected from 30 days after the end of treatment.

[20] Quality of life score (EORTC QLQ-C30, EORTC QLQ-OES18): before the first dose, every 8 weeks, at the end of treatment, 30 days after the last dose, with a time window of ±7 days. It is recommended to be performed prior to administration as well as AE and tumor evaluations.

[21] Collection time for immunogenicity and drug trough concentration blood samples: within 30 min before the first, second, third, fifth, and seventh doses, within 30 min before every four doses thereafter, and at visits carried out on Day 30, Day 60 (optional), and Day 90 (optional) after the last treatment.

[22] Biomarker blood sampling: before the first dose, at the occurrence of first tumor response, and at the presence of progressive disease.

[23] Tumor tissue: Fresh biopsy is preferred, otherwise use archival tumor tissue specimens.

[24] 90 days after the last dose: Subjects must return to the study center for a follow-up on Day 30 after the last dose, and the safety information are obtained via telephone calls on Day 60 and Day 90 after the last dose (including AE outcomes, new SAEs, and AEs of special interest); the time window is ±7 days.

[25] Survival follow-up: once per month, with a time window of ±7 days.

Schedule of Activities for Control Group (Docetaxel)

	Screening Period		Treatment Period		End of Treatment/Withdrawal (+ 3)	After End of Treatment	
			C1	C2+			
Visit Window	**D-28 to D-1**	**D-7 to D-1**	**D1**	**D1 ±3**		**90 days (±7 days) after the last dose**[22]	**Survival follow-up (±7 days)** [23]
Signing of Informed Consent Form[1]	√						
Verification of Eligibility		√					
Demographics	√						
Medical History[2]	√						
ECOG PS[3]		√		√	√		
Vital Signs[4]		√		√	√		
Physical Examination[5]		√		√	√		
Hematology[6]		√		√	√	√	
Urinalysis[7]		√		√	√		
Fecal Occult Blood[8]		√		√			
Clinical Chemistry[9]		√		√	√	√	
Thyroid Function[10]		√		√	√	√	
Coagulation Function[11]		√					
Virological Examination[12]	√						
ECG[13]		√		√	√		
Echocardiography[14]		√					

	Screening Period		Treatment Period		End of Treatment/Withdrawal (+ 3)	After End of Treatment	
			C1	C2+			
Visit Window	**D-28 to D-1**	**D-7 to D-1**	**D1**	**D1 ±3**		**90 days (±7 days) after the last dose**[22]	**Survival follow-up (±7 days)** [23]
Pregnancy Test[15]		√			√		
Tumor Imaging Evaluation[16]	√		√		√		
Randomization		√					
Docetaxel Administration[17]			√	√			
Adverse Events[18]	√	√	√	√	√	√	
Concomitant Medication[19]	√	√	√	√	√	√	
Quality of Life Score[20]			√	√	√	√	
Tumor Tissue[21]	√						

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

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

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

[3] ECOG PS: within 7 days prior to the first dose, before administration on Day 1 of each cycle (do not need to be tested for the first dose if completed within 7 days prior to the first dose at screening), and at the end of treatment/upon withdrawal.

[4] Vital signs: blood pressure, heart rate, body temperature and respiratory rate; within 7 days prior to the first dose, before administration on Day 1 of each cycle (do not need to be tested for the first dose if completed within 7 days prior to the first dose at screening), and at the end of treatment/upon withdrawal.

[5] Physical examination: within 7 days prior to the first dose and at the end of treatment/upon withdrawal, a comprehensive physical examination (including head and face, skin, lymph nodes, eyes, ears, nose and throat, mouth, respiratory system, cardiovascular system, abdomen, reproductive and urinary system, musculoskeletal system, nervous system and mental state) is performed; before administration on Day 1 of each cycle (do not need to be tested for the first dose if completed within 7 days prior to the first dose at screening), symptom-directed physical examination can be performed when 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 (do not need to be tested for the first dose if completed within 7 days prior to the first dose at screening), at the end of treatment/upon withdrawal, and 30 days after the last dose.

[7] Urinalysis: WBC, RBC, and urine protein. Within 7 days prior to the first dose, before administration on Day 1 of every 2 cycles, and at the end of treatment/upon withdrawal. In the case of urine protein ≥ 2+, a 24-h urine protein test (quantitative) must be added.

[8] Fecal occult blood: within 7 days before the first administration and after enrollment when clinically indicated.

[9] Clinical chemistry: 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 (do not need to be tested for the first dose if completed within 7 days prior to the first dose at screening), at the end of treatment/upon withdrawal, and 30 days after the last dose.

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

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

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

[13] ECG: within 7 days prior to the first dose, pre-administration on Day 1 of each cycle (do not need to be tested for the first dose if completed within 7 days prior to the first dose at screening), and at the end of treatment/upon withdrawal.

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

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

[16] Tumor imaging evaluation: CT or MRI of the neck, chest and abdomen (including pelvic cavity). Brain MRI is required when brain metastasis is suspected and confirmed (if MRI is contraindicated, CT can be used instead). Bone scan is performed only when clinically indicated and must be performed within 42 days before the first dose.

- ✓ At screening, tumor evaluations up to 4 weeks before randomization and before informed consent may be used as long as they meet the RECIST 1.1.
- ✓ During the treatment period, lesions found at baseline should be examined every 8 weeks. Examinations should also be performed as appropriate when new lesions are suspected. Tumor evaluations should be performed when subjects withdraw due to any reason (±4 weeks, bu t do not need to be repeated if the time from the last evaluation is no more than 4 weeks). Imaging conditions should be the same as those at baseline (including slice thickness and contrast agent).
- ✓ The time window for imaging examination is ±7 days. Unscheduled imaging examination may be performed if PD is suspected (for example, worsening of symptoms). Except for imaging confirmed PD, subjects who discontinue the study treatment for any other reasons must also undergo a tumor evaluation every 8 weeks until documentation of confirmed PD, start of a new anti-tumor treatment, lost to follow-up, or death.

[17] Docetaxel administration: on Day 1 of each 3-week cycle.

[18] Adverse events: AE collection begins from signing of informed consent form to 90 days after the last dose. Only treatment-related AEs, including AEs of special interest (AESIs), will be collected 30 days after the last dose.

[19] Concomitant medications: Concomitant medications from 30 days before the first dose to 90 days after the last dose should be collected; only concomitant medications for treatment-related AEs should be collected from 30 days after the end of treatment.

[20] Quality of life score (EORTC QLQ-C30, EORTC QLQ-OES18): before the first dose, every 8 weeks, at the end of treatment, 30 days after the last dose, with a time window of ±7 days. It is recommended to be performed prior to administration as well as AE and tumor evalu ations.

[21] Tumor tissue: Fresh biopsy is preferred, otherwise use archival tumor tissue specimens.

[22] 90 days after the last dose: Subjects must return to the study center for a follow-up on Day 30 after the last dose, and the safety information are obtained via telephone calls on Day 60 and Day 90 after the last dose (including AE outcomes, new SAEs, and AEs of special interest); the time window is ±7 days.

[23] Survival follow-up: once per month, with a time window of ±7 days.

Schedule of Activities for Control Group (Irinotecan)

	Screening Period		Treatment Period		End of Treatment/Withdrawal (+ 3 days)	After End of Treatment	
			C1	C2+			
Visit Window	**D-28 to D-1**	**D-7 to D-1**	**D1**	**D1 ±3**		**90 days (±7 days) after the last dose**[22]	**Survival follow-up (±7 days)** [23]
Signing of Informed Consent Form[1]	√						
Verification of Eligibility		√					
Demographics	√						
Medical History[2]	√						
ECOG PS[3]		√		√	√		
Vital Signs[4]		√		√	√		
Physical Examination[5]		√		√	√		
Hematology[6]		√		√	√	√	
Urinalysis[7]		√		√	√		
Fecal Occult Blood[8]		√		√			
Clinical Chemistry[9]		√		√	√	√	
Thyroid Function[10]		√		√	√	√	
Coagulation Function[11]		√					
Virological Examination[12]	√						
ECG[13]		√		√	√		
Echocardiography[14]		√					

	Screening Period		Treatment Period		End of Treatment/Withdrawal (+ 3 days)	After End of Treatment	
			C1	C2+			
Visit Window	**D-28 to D-1**	**D-7 to D-1**	**D1**	**D1 ±3**		**90 days (±7 days) after the last dose**[22]	**Survival follow-up (±7 days)** [23]
Pregnancy Test[15]		√			√		
Tumor Imaging Evaluation[16]	√		√		√		
Randomization		√					
Irinotecan Administration[17]			√	√			
Adverse Events[18]	√	√	√	√	√	√	
Concomitant Medication[19]	√	√	√	√	√	√	
Quality of Life Score[20]			√	√	√	√	
Tumor Tissue[21]	√						

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

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

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

[3] ECOG PS: within 7 days prior to the first dose, before administration on Day 1 of each cycle (do not need to be tested for the first dose if completed within 7 days prior to the first dose at screening), and at the end of treatment/upon withdrawal.

[4] Vital signs: blood pressure, heart rate, body temperature and respiratory rate; within 7 days prior to the first dose, before administration on Day 1 of each cycle (do not need to be tested for the first dose if completed within 7 days prior to the first dose at screening), and at the end of treatment/upon withdrawal.

[5] Physical examination: within 7 days prior to the first dose and at the end of treatment/upon withdrawal, a comprehensive physical examination (including head and face, skin, lymph nodes, eyes, ears, nose and throat, mouth, respiratory system, cardiovascular system, abdomen, reproductive and urinary system, musculoskeletal system, nervous system and mental state) is performed; before administration on Day 1 of each cycle (do not need to be tested for the first dose if completed within 7 days prior to the first dose at screening), symptom-directed physical examination can be performed when 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 (do not need to be tested for the first dose if completed within 7 days prior to the first dose at screening), at the end of treatment/upon withdrawal, and 30 days after the last dose.

[7] Urinalysis: WBC, RBC, and urine protein. Within 7 days prior to the first dose, before administration on Day 1 of every 2 cycles, and at the end of treatment/upon withdrawal. In the case of urine protein ≥ 2+, a 24-h urine protein test (quantitative) must be added.

[8] Fecal occult blood: within 7 days before the first administration and after enrollment when clinically indicated.

[9] Clinical chemistry: 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 (do not need to be tested for the first dose if completed within 7 days prior to the first dose at screening), at the end of treatment/upon withdrawal, and 30 days after the last dose.

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

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

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

[13] ECG: within 7 days prior to the first dose, pre-administration on Day 1 of each cycle (do not need to be tested for the first dose if completed within 7 days prior to the first dose at screening), and at the end of treatment/upon withdrawal.

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

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

[16] Tumor imaging evaluation: CT or MRI of the neck, chest and abdomen (including pelvic cavity). Brain MRI is required when brain metastasis is suspected and confirmed (if MRI is contraindicated, CT can be used instead). Bone scan is performed only when clinically indicated and must be performed within 42 days before the first dose.

- ✓ At screening, tumor evaluations up to 4 weeks before randomization and before informed consent may be used as long as they meet relevant criteria.
- ✓ During the treatment period, lesions found at baseline should be examined every 8 weeks. Examinations should also be performed as appropriate when new lesions are suspected. Tumor evaluations should be performed when subjects withdraw due to any reason (±4 weeks, but do not n eed to be repeated if the time from the last evaluation is no more than 4 weeks). Imaging conditions should be the same as those at baseline (including slice thickness and contrast agent).
- ✓ The time window for imaging examination is ±7 days. Unscheduled imaging examination may be performed if PD is suspected (for example, worsening of symptoms). Except for imaging confirmed PD, subjects who discontinue the study treatment for any other reasons must also undergo a tumor evaluation every 8 weeks until documentation of confirmed PD, start of a new anti-tumor treatment, lost to follow-up, or death.

[17] Irinotecan administration: on Day 1 of each 2-week cycle.

[18] Adverse events: AE collection begins from signing of informed consent form to 90 days after the last dose. Only treatment-related AEs, including AEs of special interest (AESIs), will be collected 30 days after the last dose.

[19] Concomitant medications: Concomitant medications from 30 days before the first dose to 90 days after the last dose should be collected; only concomitant medications for treatment-related AEs should be collected from 30 days after the end of treatment.

[20] Quality of life score (EORTC QLQ-C30, EORTC QLQ-OES18): before the first dose, every 8 weeks, at the end of treatment, 30 days after the last dose, with a time window of ±7 days. It is recommended to be performed prior to administration as well as AE and tumor evalu ations.

[21] Tumor tissue: Fresh biopsy is preferred, otherwise use archival tumor tissue specimens.

[22] 90 days after the last dose: Subjects must return to the study center for a follow-up on Day 30 after the last dose, and the safety information are obtained via telephone calls on Day 60 and Day 90 after the last dose (including AE outcomes, new SAEs, and AEs of special interest); the time window is ±7 days.

[23] Survival follow-up: once per month, with a time window of ±7 days.

ABBREVIATIONS

Abbreviation	Full Name
AKP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the curve
BUN	Blood urea nitrogen
CFDA	China Food and Drug Administration
CR	Complete response
Cr	Creatinine
CRF	Case report form
CRO	Contract research organization
D	Day
DLT	Dose-limiting toxicity
EC	Ethics committee
EDC	Electronic data collection
FAS	Full analysis set
FT3	Free triiodothyronine
FT4	Free thyroxine
GCP	Good Clinical Practice
GGT	Gamma glutamyl transpeptidase
h	Hour
Hb	Hemoglobin
IB	Investigator's brochure
IC_{50}	Half maximal inhibitory concentration
ICS	Informed consent set
irAE	Immune-related adverse event
iRECIST	Immune-related response evaluation criteria in solid tumors
IU	International unit
kg	Kilogram
LDH	Lactate dehydrogenase
mg	Milligram
min	Minute
mL	Milliliter
mm	Millimeter

Abbreviation	Full Name
MRI	Magnetic resonance imaging
ORR	Objective response rate
OS	Overall survival
PR	Partial response
PD	Progressive disease
PFS	Progression-free survival
PPS	Per-protocol set
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 set
T-BIL	Total bilirubin
TSH	Thyroid-stimulating hormone
UA	Uric acid
ULN	Upper limit of normal
WBC	White blood cell count

1. KEY FUNCTIONAL ROLES

Sponsor's Medical Director	[redacted], M.D., Clinical Medical Director [redacted]
Statistician	[redacted]
Project Manager	[redacted] Jiangsu Hengrui Pharmaceuticals Co., Ltd. No. 7 Kunlunshan Road, Lianyungang Economic and Technological Development Zone, Jiangsu [redacted]

2. INTRODUCTION: BACKGROUND AND SCIENTIFIC RATIONALE

2.1. Background

Esophageal cancer, a type of malignant tumor, occurs in the esophageal mucosa, including the tumor that arises in the gastroesophageal junction or within 5 cm of the junction and has invaded the lower esophagus or esophagogastric junction[1]. Worldwide, esophageal cancer ranks 8th in cancer incidence and 6th in mortality. China accounts for more than 50% of global cases[2]. In 2015, the number of new esophageal cancer patients in China was 477,900. From 2001 to 2011, the incidence ranked 5th and mortality 4th among all cancers in males. The incidence and mortality showed an annual decline in females[3]. About 90% of esophageal cancers are squamous cell carcinoma, and there are obvious regional differences. High-risk provinces/municipalities/autonomous regions include Hebei, Henan, Fujian, and Chongqing, followed by Xinjiang, Jiangsu, Shanxi, Gansu, and Anhui[1].

Endoscopic treatment is preferred for early esophageal cancer (involving mucosa or submucosa only). The 5-year survival rate is as high as 95%. However, as most patients are not treated early in the disease, the five-year survival rate for esophageal cancer is less than 20%[4]. The first-line treatment for advanced unresectable, relapsed, metastatic esophageal cancer is platinum-based combination chemotherapy, for example, cisplatin-5-fluorouracil and paclitaxel-cisplatin. The response rate is between 30-60% and median OS is 5-10 months[1, 5]. There is no standard

second-line treatment for patients who failed the first-line treatment. Even though paclitaxel, docetaxel, and irinotecan can be used as monotherapy or in combination with other treatments as the second-line treatment, the efficacy rates are low (see Table 1) and no large-scale studies confirm their efficacy. Therefore, there is a dire need to develop new drugs as the second-line treatment for esophageal cancer.

Table 1. Efficacy of existing second-line chemotherapies for esophageal cancer

Chemotherapy	Number of Subjects and Cases	ORR	TTP/PFS (Months)	OS (Months)
Paclitaxel[6]	53 patients with relapsed or advanced esophageal cancer; 51 cases of squamous cell carcinoma and 1 case of esophageal adenocarcinoma	44.2%	4.8	10.4
Docetaxel[7]	49 patients with metastatic esophageal cancer; 46 cases of squamous cell carcinoma, 1 case of adenocarcinoma, and 2 cases of other carcinomas	16%	Unknown	8.1
Docetaxel[8] Docetaxel Plus Platinum	85 patients with metastatic/relapsed squamous cell carcinoma of the esophagus; 41 cases in docetaxel group and 44 cases in docetaxel + platinum group	19.5% 29.5%	3.2 3.6	5.2 5.7
Docetaxel + Cisplatin[9]	35 patients with metastatic/relapsed squamous cell carcinoma of the esophagus	34.2%	4.5	7.4
Docetaxel + Nedaplatin[10]	33 patients with relapsed or unresectable squamous cell carcinoma of the esophagus	21.2%	2.3	6.9
Gemcitabine + Vinorelbine[11]	35 patients with advanced esophageal cancer, 34 cases of squamous cell carcinoma, 1 case of adenocarcinoma	31.3%	4.3	7.3
Irinotecan[12]	14 patients with advanced esophageal cancer, 7 cases of squamous cell carcinoma, 7 cases of esophageal adenocarcinoma	15%	2	5
Irinotecan[13]	13 patients with advanced esophageal cancer, 10 cases of esophageal squamous cell carcinoma (10), 3 cases of esophageal adenocarcinoma	10% (squamous cell carcinoma) 33% (adenocarcinoma)	3.8	6.1
Irinotecan + Docetaxel[14]	24 patients with locally advanced or metastatic esophageal cancer; 11 cases of squamous cell carcinoma and 13 case of adenocarcinoma	12.5%	Unknown	6.5
Vinorelbine[15]	46 patients with metastatic squamous cell carcinoma of the esophagus; 30 treatment-naive and 16 chemotherapy refractory	6% in relapsed patients	Unknown	6 (treatment-naive and relapsed)

2.2. Scientific Rationale

2.2.1. Study rationale

The programmed cell death protein-1 (PD-1) pathway is one of the most critical checkpoint pathways responsible for regulating tumor-induced immunosuppression. PD-1 is a protein receptor expressed on the surface of T cells discovered in 1992 and is involved in the process of cell apoptosis. PD-1 is a member of the CD28 family and has a 23% consistency in amino acid sequence with cytotoxic T lymphocyte antigen 4 (CTLA-4). However, its expression is different from CTLA. It is primarily expressed by activated T cells, B cells, and myeloid cells. PD-1 has two ligands, PD-L1 and PD-L2. PD-L1 is primarily expressed on T cells, B cells, macrophages, and dendritic cells (DCs), and is up-regulated on activated cells. According to the literature, about 41.4% of squamous cell carcinoma of the esophagus has PD-L1 expression (a meta-analysis of 1,350 Chinese and Japanese subjects), and the overexpression of PD-L1 may reduce OS[16]. Therefore, immune checkpoint inhibitors against PD-1/PD-L1 may be a new method of treating esophageal cancers.

An open-label, single-arm, multi-center, phase II study was conducted in Japan for nivolumab, a PD-1 inhibitor developed by Bristol-Myers Squibb. Patients with advanced esophageal cancer refractory or intolerant to more than one line of chemotherapy were treated with 3 mg/kg nivolumab every 2 weeks. A total of 65 subjects were enrolled, with 64 being assessable. ORR was 17.2% (1 CR/10 PR), DCR 42.2% (1 CR/10 PR/16 SD), and median OS 10.8 months, regardless of PD-L1 status[17]. In a phase Ib study involving pembrolizumab (MK-3475), a PD-1 inhibitor developed by Merck, 23 patients with advanced esophageal cancer (PD-L1+) refractory to standard treatment were enrolled and treated with 10 mg/kg drugs every 2 weeks. Among the 22 assessable subjects, ORR was 30% (7 PR) and DCR 40.9% (7 PR/2 SD). ORRs were 29% (5 PR) among the 17 patients with squamous cell carcinoma and 40% (2 PR) among the 5 with adenocarcinoma[18]. Currently, phase III clinical studies are underway for both nivolumab and pembrolizumab as second-line treatments for advanced esophageal cancer. Preliminary efficacy of PD-1/PD-L1 immune checkpoint inhibitors in the treatment of esophageal cancer suggests that it may be a new effective drug for treating esophageal cancers.

2.2.2. Rationale for drug development

Jiangsu Hengrui Pharmaceuticals Co., Ltd. used PD-1 as a target and recombinant PD-1 protein as an immunogen to obtain a series of PD-1 antibodies in mice. Through a large number of *in vitro* binding assays, *in vitro* ligand blocking assays, T cell proliferation assays, animal experiments, and antibody druggability assessments, an antibody prototype was selected. Then, a humanized design of the murine antibody prototype was carried out through computer

simulations, resulting in several humanized anti-PD-1 monoclonal antibodies. Finally, SHR-1210, the one with the highest activity among those antibodies, was selected for further development. Phase I clinical studies have been conducted by Hengrui in Australia and China since 2015. Several clinical studies are currently underway.

2.2.2.1. Preclinical study results of SHR-1210

2.2.2.1.1. Product name and physicochemical properties

[Generic Name]: SHR-1210 Injection

[English Name]: SHR-1210 Injection

[Molecular Weight]: approx. 146.3 kDa

2.2.2.1.2. Pharmacology and mechanism of action

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

2.2.2.1.3. Pharmacodynamics

(1) Affinity

Results from affinity assays involving SHR-1210 and human, monkey, and murine PD-1 antigens showed that the affinities of SHR-1210 for human and monkey PD-1 antigens were 6.9 nM and 4.1 nM, respectively. No binding was detected with murine PD-1 antigens. See Table 2 for details.

Table 2. Binding affinity of SHR-1210 to human, monkey, and murine PD-1 antigens

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

Results from the binding affinity assay showed that the binding affinity of SHR-1210 to human PD-1 antigen was 3.0 nM, similar to nivolumab and MK3475. See Table 3 for details.

Table 3. Binding affinity of SHR-1210, nivolumab, and MK3475 to PD-1 antigen

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

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

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

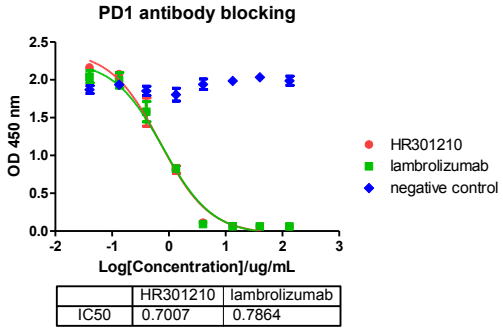

Figure 1. Inhibition of PD-1/PD-L1 binding by SHR-1210 and pembrolizumab

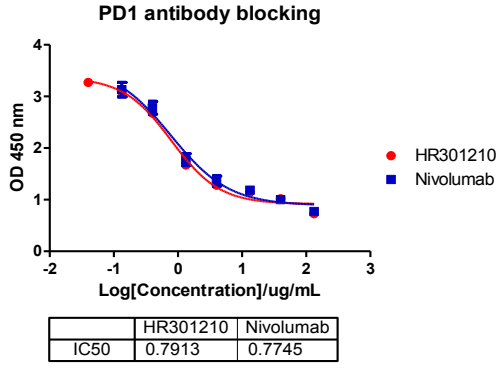

Figure 2. Inhibition of PD-1/PD-L1 binding by SHR-1210 and nivolumab

2.2.2.1.4. Toxicology studies

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

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

2.2.2.1.5. Pharmacokinetic study

For SHR-1210 PK parameters after a single intravenous infusion in cynomolgus monkeys, see Table 4.

Table 4. PK parameters after a single intravenous infusion of SHR-1210 at different doses in cynomolgus monkeys

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

2.2.2.2. Clinical study results

Four open-label, dose-escalation, phase I clinical studies are underway to evaluate the safety and tolerability of SHR-1210 in patients with advanced solid tumors refractory to existing standard treatment.

In 2015, the first-in-human study (INCSHR-1210-101) was initiated in Australia. It was an open-label, multi-center, non-randomized, dose-escalation, and tumor-expansion phase I study consisting of two stages. The first stage employed a 3+3 dose escalation design with 4 doses of 1 mg/kg, 3 mg/kg, 6 mg/kg, and 10 mg/kg being set (the first four weeks were the DLT observation period, with only one dose administered; thereafter, the drug was administered every 2 weeks); the phase 2a stage was a stage of monotherapy expansion and 600 mg (once every 4 weeks) was selected for the expansion. Approximately 52 patients with advanced endometrial cancer, thymic cancer, biliary tract cancer, and cancers of unknown origin refractory to standard treatment were enrolled. As of 15 Dec., 2016, a total of 32 subjects were enrolled.

In 2016, three phase I clinical trials were initiated in China: SHR-1210-101, SHR-1210-102, and SHR-1210-103. SHR-1210-101 was an open-label, single-center, dose-escalation, phase I study consisting of 3 stages. The first stage employed a 3+3 dose-escalation design with 4 doses of 1 mg/kg, 3 mg/kg, 200 mg/kg, and 10 mg/kg being set (the first four weeks were the DLT observation period, with only one dose administered; thereafter, the drug was administered every 2 weeks); the second stage was a stage of expansion, and the number of subjects was expanded to 8-12 for the 4 groups; in the third stage, a fixed dose of 200 mg (once every 2 weeks) was selected to expand the study clinically in patients with nasopharyngeal cancer and non-small cell lung cancer. As of 15 Dec., 2016, a total of 39 subjects were enrolled. SHR-1210-102 was an open-label, single-center, dose-escalation, phase I study prominently enrolling patients with advanced malignant melanoma refractory to standard treatment. The study consisted of 2 stages. The first stage employed a 3+3 dose-escalation design with 3 fixed doses of 60 mg, 200 mg, and 400 mg being set (the first eight weeks were the DLT observation period, with only one dose administered in the first four weeks and every 2 weeks thereafter); the second stage was a stage of expansion, and the number of subjects was expanded to 8-12 for the 3 groups. As of 15 Dec., 2016, a total of 16 subjects were enrolled. SHR-1210-103 was an open-label, single-center, dose-escalation, phase I study consisting of 3 stages. The first stage employed a 3+3 dose-escalation design with 3 doses of 60 mg, 200 mg and 400 mg being set (the first four weeks were the DLT observation period, with only one dose administered; the drug was administered every 2 weeks thereafter); the second stage was a stage of expansion and the number of subjects was expanded to 9-12 for the 3 groups; in the third stage, a fixed dose of 200 mg (every 2 weeks) was selected to expand the study clinically in patients with GI cancers (mainly esophageal cancer, liver cancer, and gastric cancer) and triple negative breast cancer. As of 15 Dec., 2016, a total of 61 subjects were enrolled.

As of 15 Dec., 2016, a total of 32 subjects were enrolled overseas and a total of 116 subjects were enrolled in China. DLT was not observed in all high-dose groups. Preliminary safety results suggested that SHR-1210 is safe and well-tolerated. The common hematologic AE was anemia and non-hematologic AEs were hemangioma of skin, pyrexia, ALT and AST increased, blood bilirubin increased, rash, and hypothyroidism (refer to the Investigator's Brochure for preliminary safety data). As of 28 Dec., 2016, a total of 36 patients with advanced esophageal cancer who were refractory to standard treatment were enrolled in Study 103. Among the 21 subjects who had at least one efficacy assessment, ORR was 23.8% (5 PR), and DCR 52.4% (5 PR and 6 SD). Preliminary results showed that SHR-1210 is effective in treating patients with advanced esophageal cancer to certain extents.

2.2.3. Basis of dosing regimen

PD-1 immune checkpoint inhibitors exert their effect on immunosuppression by blocking the binding of PD-1/PD-L1. Therefore, the receptor occupancy of these inhibitors is the basic pharmacological mechanism that reflects the ultimate anti-cancer effects. Phase I PK studies showed that serum drug concentrations dropped below 1000 ng/mL on Day 15 after a single dose of 1 mg/kg and a fixed dose of 60 mg and remained between 4000-9000 ng/mL after a single dose of 3 mg/kg and a fixed dose of 200 mg. Receptor occupancy assays suggested that a serum drug concentration of at least 2000 ng/mL is required to maintain the receptor saturation. Clinical results also suggested that a fixed dose of 200 mg every 2 weeks can maintain a saturated receptor occupancy. In phase I studies, the incidence of AEs did not increase with the dose, whether the drug was administered by weight or by dose fixed. Based on results from the studies described above and the convenience of clinical administration, a fixed dose of 200 mg every 2 weeks is selected as the treatment regimen for this study.

There are no second-line standard treatments for patients with locally advanced or metastatic esophageal cancer after being treated with the first-line standard chemotherapy. The NCCN guideline recommends docetaxel and irinotecan as the second-line chemotherapy for esophageal cancer. To demonstrate the clinical efficacy of SHR-1210 in patients with locally advanced or metastatic esophageal cancer, these two drugs are selected as the controls for this study.

2.3. Potential Risks and Benefits

Drugs similar to SHR-1210 have demonstrated efficacy in patients with advanced esophageal cancer. The control group will receive an investigator's choice of routine second-line chemotherapy for advanced esophageal cancer. Therefore, subjects will benefit from the study regardless of group allocation.

Refer to the Investigator's Brochure and the Informed Consent Form for detailed information on subject's benefits and risks.

3. OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

Primary objective: To evaluate the efficacy of SHR-1210 vs. investigator's choice of chemotherapy in subjects with locally advanced or metastatic esophageal cancer who are refractory to the first-line chemotherapy.

Secondary objective: To evaluate the safety of SHR-1210 vs. investigator's choice of chemotherapy in subjects with locally advanced or metastatic esophageal cancer who are refractory to the first-line chemotherapy.

Exploratory objectives: (1) To evaluate the relationship between biomarkers in tumor tissue and/or blood (such as PD-L1) and the efficacy of SHR-1210.

(2) To evaluate the immunogenicity of SHR-1210 in subjects with locally advanced or metastatic esophageal cancer, and to investigate the correlation between immunogenicity and drug trough concentration, efficacy and safety.

3.2. Study Endpoints

3.2.1. Primary endpoint

Overall survival (OS): defined as the time from the start of randomization to the death of the subject caused by any reason.

3.2.2. Secondary endpoints

Progression-free survival (PFS): defined as the time from the start of randomization to the first documented objective tumor progression or death caused by any reason, whichever occurs first.

Objective response rate (ORR): the proportion of subjects who achieved CR and PR.

Quality of life score: 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 impact). The EORTC QLQ-OES18 scale is mainly used for patients with esophageal cancer and contains 18 symptom items. The assessment should be completed at various time points based on the schedule of activities, starting from the first cycle until 30 days after the last dose.

3.2.3. Exploratory endpoints

To evaluate the relationship between the expression of PD-L1 and/or other biomarkers with the efficacy of SHR-1210.

To evaluate the incidence of ADA, time to the first positive ADA result, duration of ADA, incidence of anti-SHR-1210 antibody with neutralizing activity, and the correlation between immunogenicity and drug trough concentration, efficacy and safety.

Tumor tissues and/or blood obtained during the study may also be used in the future to determine tumor mutation burden, proteomics, or other analytes.

4. STUDY DESIGN

This is a randomized, open-label, active-controlled, multi-center study. A total of 438 eligible subjects with locally advanced or metastatic squamous cell carcinoma of the esophagus who are refractory to first-line chemotherapy will be randomized to investigational treatment group or control group in a 1:1 ratio and stratified by: 1. locally advanced lesion vs. distant metastasis; 2. ECOG PS (0 vs. 1).

Subjects in the investigational treatment group will receive SHR-1210 (200 mg/dose, on Day 1 of each 2-week cycle) and those in the control group will receive the investigator's choice of chemotherapy, either docetaxel (75 mg/m^2, on Day 1 of each 3-week cycle) or irinotecan (180 mg/m^2, on Day 1 of each 2-week cycle). Both investigational treatment group and control group will continue treatment until the occurrence of progressive disease (PD), intolerable toxicity, voluntary withdrawal by the subject, or treatment discontinuation determined by the investigator.

Based on SHR-1210 being an immune checkpoint inhibitor and the experience of similar drugs, some subjects may experience delayed or early tumor pseudoprogression after receiving the immunotherapy. Therefore, the use of RECIST v1.1 alone may underestimate the benefits of the immunotherapy. As a result, it is suggested in this study to carry out a comprehensive imaging assessment based on both RECIST v1.1 and iRECIST, i.e., for subjects experiencing progressive disease for the first time but whose clinical symptoms are stable, the investigator may decide to allow the subjects to continue using SHR-1210 and take the imaging assessment again after 4 weeks (±7 days); when the subsequent imaging assessment confirms progressive disease, the subjects need to discontinue SHR-1210 unless the investigator believes that the subjects can continue to gain clinical benefits from SHR-1210 and makes the decision following the discussion with the sponsor.

The study procedure is divided into three stages. The screening period is 28 days. After completing the screening examination and evaluation, the eligible subjects enter the treatment

period and undergo visits by the dosing frequency. Relevant examinations and assessments must be completed before each dose. In particular, tumor imaging will be assessed once every 8 weeks (±7 days) (including the chemotherapy control group). All subjects must complete safety examinations and tumor assessments before the end of treatment. These subjects then enter the follow-up period. The safety follow-up visits of all subjects will be carried out until 90 days after the last dose. The follow-up visits scheduled for 30 days after the last dose will be carried out at the study center, while those scheduled for 60 days and 90 days after the last dose via telephone. Survival follow-up visits begin from the last dose and are carried out once a month; subjects ending the treatment due to reasons other than PD will continue to undergo imaging assessment once every 8 weeks (±7 days) until PD, initiation of new anti -tumor treatment or death. Refer to Section 7 for specific study procedures.

Refer to
Figure 3 for study design.

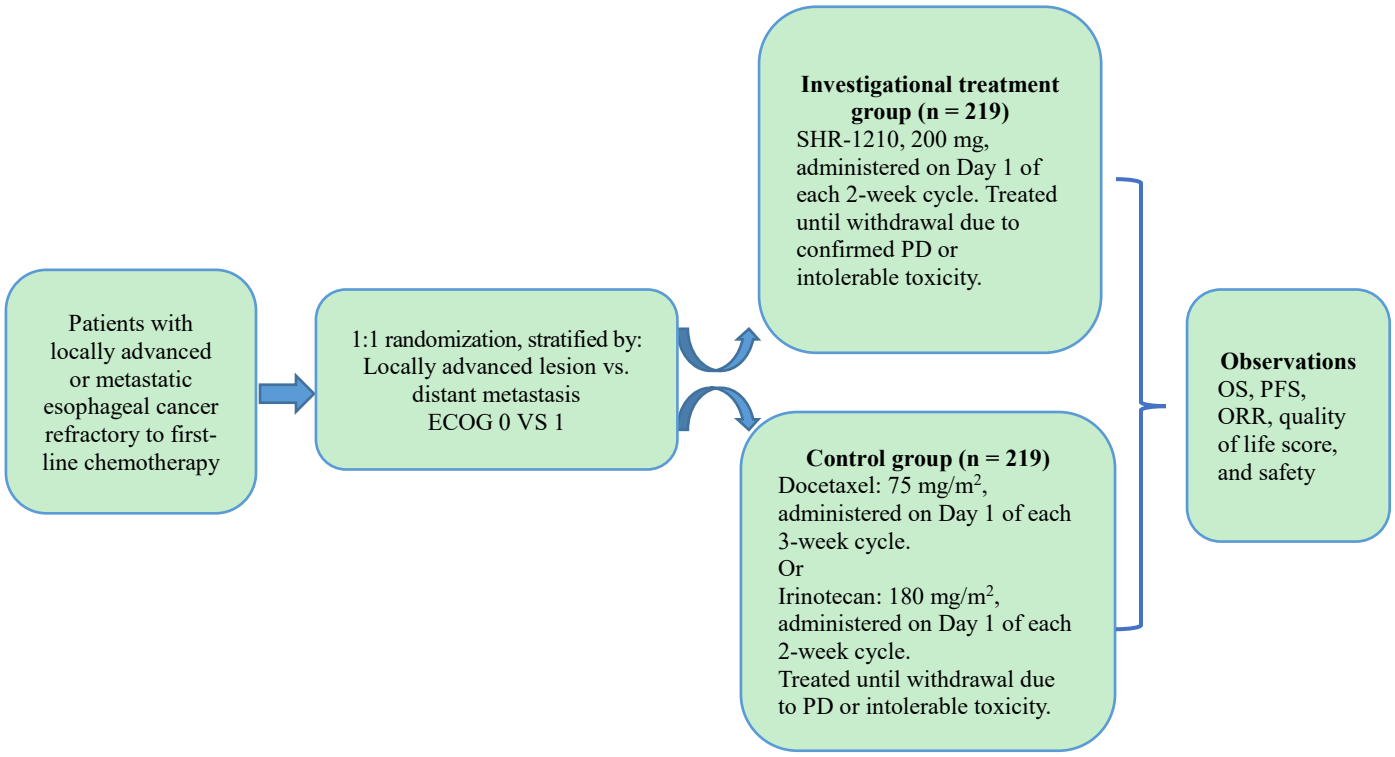

Figure 3. Study design schematic

5. SELECTION AND WITHDRAWAL OF SUBJECTS

5.1. Inclusion Criteria

Patients must meet all of the following criteria to be eligible.

1. Aged 18-75 years, male or female;
2. Patients with histologically or cytologically confirmed squamous cell carcinoma of the esophagus, unresectable locally advanced, locally recurrent or distant metastasis;
3. Patients who have received first-line systemic chemotherapy (which may include chemotherapies based on platinum, paclitaxel or fluorouracil) and showed disease progression or intolerance (patients who have progression in maintenance treatment after first-line chemotherapy can also be included). Concurrent chemoradiotherapy for postoperative recurrence or metastasis is considered as first-line treatment; for radical concurrent chemoradiotherapy and neoadjuvant/adjuvant therapy (chemotherapy or chemoradiotherapy), it should be considered as first-line treatment failure when disease progression occurs during the treatment or within 6 months after the treatment discontinued;

4. Patients with at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1), and the measurable lesion(s) should not have been locally treated such as radiotherapy (lesions in previous radiotherapy sites may also be selected as target lesions when PD is confirmed and RECIST v1.1 are met);
5. Patients with available tissue samples for biomarker (such as PD-L1) analysis; fresh tissue is preferred; archival samples of 5-8 paraffin embedded sections that are 5 μm thick are also acceptable when a fresh biopsy is not accessible;
6. ECOG PS: 0-1 (see Appendix I);
7. Life expectancy ≥ 12 weeks;
8. Major organ functions must meet the following rules (no blood components or cell growth factors are allowed to be used within 2 weeks before the start of study treatment):

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 and AST ≤ 2.5 × ULN; for liver metastasis, ALT and AST ≤ 5 × ULN;

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

9. Female patients of childbearing potential must have a negative urine or serum pregnancy test result within 72 h before the first dose of study drugs and must be willing to use effective contraceptive measures during the study and within 3 months after the last dose of SHR-1210 (180 days after the last dose for the control group). Male patients with partners of childbearing potential must be willing to take effective contraceptive measures during the study and within 3 months after the last dose of SHR-1210 (180 days after the last dose for the control group);
10. Patients must participate voluntarily, sign the informed consent form, have good compliance, and cooperate with follow-up visits.

5.2. Exclusion Criteria

1. Patients who are diagnosed with other malignant tumors (excluding curatively treated basal cell carcinoma of skin and squamous cell carcinoma of skin, and/or curatively resected cervical carcinoma *in situ* and/or breast cancer *in situ*) within 5 years from the first dose of study drugs;
2. Patients with central nervous system (CNS) metastasis;
3. Patients with active autoimmune disease or history of autoimmune diseases (such as interstitial pneumonia, uveitis, enteritis, hepatitis, hypophysitis, vasculitis, myocarditis, nephritis, hyperthyroidism, hypothyroidism (enrollment is not restricted when hormone replacement therapy is effective)); patients with vitiligo or who had completely resolved pediatric asthma requiring no intervention after adulthood may be enrolled, while those still requiring medical intervention with bronchodilators should not be enrolled;
4. Patients with uncontrolled cardiac symptoms or disease, such as: (1) > NYHA Class II heart failure, (2) unstable angina, (3) myocardial infarction within the past year, and (4) clinically significant supraventricular or ventricular arrhythmias requiring clinical intervention;
5. Patients with active infection or unexplained fever > 38.5 ℃ within 2 weeks before randomization (patients with tumor-induced fever, as determined by the investigator, may be enrolled);
6. Patients with a known history or evidence of interstitial lung disease or active non-infectious pneumonitis that has been treated with corticosteroids;
7. Patients with a BMI less than 18.5 kg/m^2 or weight loss of ≥ 10% within 2 months before screening (at the same time, the effect of massive pleural effusions and ascites on body weight should be considered);
8. Patients with congenital or acquired immune deficiency (such as HIV infection), active hepatitis B (HBV-DNA ≥ 10^4 copies/mL or 2000 IU/mL), or hepatitis C (positive anti-HCV antibodies, and HCV RNA titer higher than the lower limit of detection of the analytical method);
9. Previous treatment with other anti-PD-1 antibodies or immunotherapy targeting PD-1/PD-L1;

10. Patients with known allergies to macromolecular protein preparations or any components of SHR-1210, or allergic reaction, hypersensitivity reaction, or contraindications to any components of docetaxel or irinotecan, or their in-preparation components;
11. Patients who require systemic treatment with corticosteroids (prednisone of > 10 mg/day or equivalent) or other immunosuppressive medications within 14 days before the administration of study drugs. 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 is permitted;
12. Patients who received anti-tumor treatment with monoclonal antibodies (mAbs), chemotherapy, targeted small molecule therapy, or radiotherapy within 4 weeks before the first dose of study drugs or with adverse events caused by previously-received medications but not recovered (Grade ≤ 1 or baseline reached). Note: Except for patients with Grade ≤ 2 neuropathy or Grade ≤ 2 alopecia. If the patient has undergone major surgery, toxicities and/or complications resulting from the surgical intervention must be fully recovered before the study treatment.
13. Patients who currently participate in or participated in another clinical study within 4 weeks before the first dose of study drugs (for patients in the follow-up period, calculation will be carried out using the time of the last use of study drugs or devices);
14. Patients who inoculated with live vaccine within 4 weeks before the first dose of study drugs; injections of inactivated influenza vaccine for seasonal influenza are permitted, but not live attenuated influenza vaccines for intranasal use;
15. Pregnant or lactating women;
16. Patients with other factors, as determined by the investigator, which may result in study termination; 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 collection of study data.

5.3. Rescreening Criteria

Rescreening is permitted for this study; specifically, subjects who failed the screening and were not randomized can be screened again. Test/examination results from the first screening that meet the inclusion/exclusion criteria may be reused in the rescreening, provided that they are within the window period. A new screening number should be assigned during rescreening.

5.4. Randomization Criteria

Only eligible subjects (those who meet inclusion/exclusion criteria) may undergo randomization.

5.5. Withdrawal or Discontinuation

Subjects may withdraw informed consent at any time for any reason. The investigator may decide whether the study treatment should be discontinued for a subject based on the subject's clinical manifestations or adverse events. In addition, if the subject is not eligible for enrollment, has poor compliance, or is not suitable due to management and/or other safety reasons, the investigator or the sponsor may withdraw the subject from the study treatment.

5.5.1. Reasons for withdrawal or discontinuation

Reasons for treatment discontinuation may include:

- Refusal to receive further treatment and/or withdrawal of informed consent;
- Objective tumor progression as determined by the investigator using iRECIST and RECIST criteria;
- Comprehensive deterioration of health status and inability to continue study participation;
- Intolerable toxicity;
- Significant protocol deviations;
- Termination of the study by the sponsor;
- Pregnancy;
- Lost to follow-up;
- Death.

Reasons for withdrawal from study follow-ups may include:

- Refusal to receive follow-ups and withdrawal of informed consent;
- Study termination by the sponsor;
- Lost to follow-up;
- Death.

Note: Withdrawal of informed consent refers to the subject withdrawing the consent to be further contacted, or no longer agreeing to provide information from a previously authorized person. Whenever possible, subjects should notify the investigator in writing that they no longer agree to be followed. The investigator should specify the withdrawal of informed consent in the medical records, whether it is to discontinue study treatment, or to discontinue a study procedure and/or follow-up after completing the treatment period. Subject's survival status may only be determined using publicly available information in accordance with local laws. It should be noted that, unlike subjects withdrawing their informed consent, subjects who request a discontinuation will be remain in the trial and must be followed according to the specific follow-up procedures specified in the protocol.

5.5.2. Procedures for withdrawal or discontinuation

Subjects will undergo efficacy and safety assessments as specified in the protocol at the end-of-treatment/withdrawal visit as well as the visit 90 days after the last dose. All adverse events (AEs) and outcomes will be documented. The investigator may, based on the subject's conditions, suggest or provide new or alternative treatments. Subjects ending the treatment due to reasons other than PD should be followed for tumor progression, until PD, death, or start of a new anti-tumor treatment.

Survival status should still be followed even when the subject refuses to visit the study center, unless the subject withdraws the consent to provide further information or 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. Termination or Suspension of Study

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

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

- Unexpected, significant, or unacceptable risks being identified;
- Existing efficacy data supporting study termination;
- Poor compliance with study protocol and regulations;
- Inaccurate or incomplete documentation of data;
- Change in the sponsor's development strategy for the investigational drug;

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

6. INVESTIGATIONAL DRUG

6.1. Description of the Investigational Drug and Control Drugs

6.1.1. Access to drugs

SHR-1210 is manufactured by Suzhou Suncadia Biopharmaceuticals Co., Ltd. Docetaxel and irinotecan are provided by Jiangsu Hengrui Pharmaceuticals Co., Ltd.

6.1.2. Dosage form, appearance, packaging, and label

Investigational drug: SHR-1210 for injection

Manufacturer: Suzhou Suncadia Biopharmaceuticals Co., Ltd.

Dosage form: lyophilized powder

Strength: 200 mg in 20 mL vials

Batch number: see Certificate of Analysis

Route of administration: intravenous injection

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

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

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

A Randomized, Open-Label, Active-Controlled, Multi-Center, Phase III Clinical Study of Anti-PD-1 Antibody SHR-1210 vs. Investigator's Choice of Chemotherapy in Subjects with Locally Advanced or Metastatic Esophageal Cancer

For Clinical Study Use Only

Clinical study approval No.: 2016L01455

Indication: locally advanced or metastatic esophageal cancer

Strength: lyophilized powder for injection, 200 mg/vial

Method of administration: Prepare the solution according to study protocol, for intravenous injection only.

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

Batch No.:

Expiry date: DD/MM/20YY

Manufacturer: Suzhou Suncadia Biopharmaceuticals Co., Ltd.

Study drug: Docetaxel

Manufacturer: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Dosage form: injection

Strength: 0.5 mL: 20 mg; 1.5 mL: 60 mg

Batch number: see package insert

Method of administration: intravenous infusion

Shelf life: 24 months (0.5 mL: 20 mg); 18 months (1.5 mL: 60 mg)

Storage conditions: 2-8 ℃, sealed, away from light

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

Docetaxel

For Clinical Study Use Only

A Randomized, Open-Label, Active-Controlled, Multi-Center, Phase III Clinical Study of Anti-PD-1 Antibody SHR-1210 vs. Investigator's Choice of Chemotherapy in Subjects with Locally Advanced or Metastatic Esophageal Cancer

(Study number: SHR-1210-III-301-ESC)

Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Note: Please return the remaining products to the pharmacist

Study drug: Irinotecan

Manufacturer: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Dosage form: injection

Strength: 40 mg; 100 mg

Batch number: see package insert

Method of administration: intravenous infusion

Shelf life: 24 months

Storage conditions: away from light, sealed

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

Irinotecan

For Clinical Study Use Only

A Randomized, Open-Label, Active-Controlled, Multi-Center, Phase III Clinical Study of Anti-PD-1 Antibody SHR-1210 vs. Investigator's Choice of Chemotherapy in Subjects with Locally Advanced or Metastatic Esophageal Cancer

(Study number: SHR-1210-III-301-ESC)

Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Note: Please return the remaining products to the pharmacist

6.1.3. 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, access-controlled area that meets the storage conditions and complies with applicable regulatory requirements.

Study drugs should be stored under the storage conditions listed in Section 6.1.2. Where the protocol differs from other information, SHR-1210 will be stored according to the storage conditions listed on the label, and chemotherapies chosen by investigators will be stored according to the storage conditions outlined in the corresponding package insert.

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

Deviations will be reported immediately if the storage conditions are found to deviate from drug label or package insert. The study center should actively adopt measures to ensure that the corresponding drugs are restored as required 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. The use of affected study drugs without the approval of the sponsor is considered a protocol deviation. The sponsor will provide a detailed procedure on reporting temperature deviations to the study center.

6.1.4. Preparation of study drugs

Drugs used in this study are all administered via intravenous infusions. Therefore, these drugs should be prepared by qualified or experienced study staff such as a study nurse. The investigational drug SHR-1210 does not contain preservatives, and must be prepared using aseptic technique. Refer to the brochure for drug preparation.

The control drugs used in this study have been approved for marketing. They should be prepared according to the package insert.

6.1.5. Administration of study drugs

(1) Investigational drug

SHR-1210: 200 mg/dose, intravenous infusion over 30 min (no less than 20 min and no more than 60 min) on Day 1 of each 2-week cycle. The treatment will continue until the occurrence of confirmed PD, intolerable toxicity, voluntary withdrawal by the subject, or treatment discontinuation determined by the investigator.

Day 1 of Cycle 1 can be within 3 days from randomization, as close to the date of randomization as possible. For subsequent cycles, the drug may be administered 3 days before or after the scheduled Day 1 of the cycle. Administration beyond 3 days after the scheduled dosing day will be considered as a dose delay. Subsequent administrations will be based on the actual date of the previous dose. All required examinations and evaluations must be completed prior to each dose. The interval between two doses must not be less than 12 days.

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

Accelerated tumor growth may include any of the following:

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

If a subject develops PD as determined by RECIST v1.1, the investigator may decide whether treatment should be continued based on subject's overall clinical status, including performance status, clinical symptoms, and laboratory test results. Treatment can be continued when the subject is clinically stable, and a tumor assessment should be performed again 4 weeks (±7 days) later. If non-PD is confirmed by both iRECIST and RECIST v1.1, the treatment will be continued, and otherwise, the treatment will be discontinued, unless the investigator believes the subject may continue benefiting from the study; the sponsor must be consulted to allow a subject with confirmed PD to continue the treatment. For subjects who are clinically unstable, treatment should be discontinued after the first PD, and a new imaging assessment 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 disease progression;
- ✓ No progressive tumor requiring other urgent medical interventions at important anatomical sites (e.g., spinal cord compression);

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

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

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

(2) Control drugs

Investigator's choice of chemotherapy (prior chemotherapy should not be chosen). Subjects who once received docetaxel or irinotecan at the beginning of treatment must not switch to the other chemotherapy.

Docetaxel: 75 mg/m^2, intravenous infusion over approximately 1 h (drip rate may be adjusted accordingly) on Day 1 of each 3-week cycle. The treatment will continue until PD, intolerable toxicity, voluntary withdrawal by the subject, or treatment discontinuation determined by the investigator. Premedications should be given according to the clinical practice of the study center before treatment.

Day 1 of Cycle 1 can be within 3 days from randomization, and the premedication should be as close to the date of randomization as possible. The time window is 3 days for subsequent cycles. Administration beyond 3 days after the scheduled dosing day will be considered as a dose delay. Subsequent administrations will be based on the actual date of the previous dose. All required examinations and evaluations must be completed prior to each dose.

Irinotecan: 180 mg/m^2, the starting dose may being adjusted based on the results of the UGT1A1*28 assay. Intravenous infusion over approximately 1 h (drip rate may be adjusted accordingly) on Day 1 of each 2-week cycle. The treatment will continue until PD, intolerable toxicity, voluntary withdrawal by the subject, or treatment discontinuation determined by the investigator. Premedications should be given according to the clinical practice of the study center before treatment.

Day 1 of Cycle 1 can be within 3 days from randomization, and the premedication should be as close to the date of randomization as possible. The time window is 3 days for subsequent cycles. Administration beyond 3 days after the scheduled dosing day will be considered as a dose delay. Subsequent administrations will be based on the actual date of the previous dose. All required examinations and evaluations must be completed prior to each dose.

6.1.6. Route of Administration

SHR-1210 and the control drugs docetaxel and irinotecan are all administered via intravenous infusion.

6.1.7. Dose modifications and delay

6.1.7.1. Dose modification

(I) Dose modifications for SHR-1210

Adverse events related to SHR-1210 may be immune-related (irAEs), and may develop shortly after the first dose or months after the last dose. SHR-1210 should be suspended when events listed in Table 5 occur. During the study, the investigator must consult with the sponsor when, based on the benefit to risk ratio of subjects, SHR-1210 should not be interrupted or continued according to recommendations found in Table 5 or when the situation is not listed.

Table 5. SHR-1210 dose modifications

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

Treatment-Related Immune-Related Adverse Events (irAEs)	Severity Grades for Treatment Interruption	Resumption	Discontinuation
Type I Diabetes Mellitus (New Onset) or Hyperglycemia	New-onset type I diabetes mellitus or Grade 3-4 hyperglycemia accompanied with evidence of β-cell depletion	After clinical and metabolic conditions are stabilized	Continue SHR-1210 treatment.
Renal Failure or Nephritis	2	Recovery to Grade 0-1 and corticosteroids reduction to ≤ 10 mg of prednisone or equivalent.	Do not resolve within 12 weeks from the last dose, or the dose of corticosteroids cannot be reduced to ≤ 10 mg of prednisone or equivalent within 12 weeks.
	3-4	Discontinuation	Discontinuation
Infusion Reaction	2	Symptoms disappear	Re-administer at 50% of the initial rate after symptoms resolve. If no reaction occurs within 30 min, restore the original infusion rate (100%). Closely monitor. If the symptoms recur, the administration of the current SHR-1210 dose will be discontinued.
	3-4	Discontinuation	Discontinuation
Other Treatment-Related Adverse Events	3	Recovery to Grade 0-1 and corticosteroids reduction to ≤ 10 mg of prednisone or equivalent.	Do not resolve within 12 weeks from the last dose, or the dose of corticosteroids cannot be reduced to ≤ 10 mg of prednisone or equivalent within 12 weeks.
	4	Discontinuation	Discontinuation

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

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

The investigator may consider interrupting SHR-1210 in subjects who develop intolerable or persistent grade 2 treatment-related AEs.

The treatment should be terminated when a persistent grade 2 adverse drug reaction does not resolve to grade 0-1 within 12 weeks after the last dose.

(II) Dose modifications for docetaxel and irinotecan

The investigator will determine the criteria for the dose modifications of docetaxel and irinotecan as well as their treatment/resumption according to clinical practices. This section is used for the reference of investigators.

The starting dose for docetaxel is 75 mg/m^2, which may be reduced to 60 mg/m^2 based on toxicities (refer to Table 6). The dose cannot be increased after being reduced. Treatment should be terminated for subjects who cannot tolerate the reduced dose. The treatment should be terminated for subjects who develop ≥ grade 3 or greater peripheral neuropathy or severe hypersensitivity reactions.

Table 6. Docetaxel dose modifications

Adverse Event	Resumption
Febrile neutropenia	Reduce dose after recovery
Grade 4 neutropenia persisting more than 1 week	Reduce dose after return to Grade ≤ 1
Severe or accumulated skin reactions	Reduce dose after return to Grade ≤ 1
Grade 3-4 non-hematological toxicities	Reduce dose after return to Grade ≤ 1

Table 7. Criteria for docetaxel treatment/resumption

Laboratory Tests	Criteria for Treatment
Absolute Neutrophil Count	> 1500/mm^3 (1.5 ×10 ^{9}/L)
Blood Bilirubin	Normal or return to the baseline level
AST, ALT, and AKP	ALT and/or AST ≤ 1.5 × ULN and AKP ≤ 2.5 × ULN

The starting dose for irinotecan is 180 mg/m^2, which may be reduced by 25% based on toxicities (refer to Table 8). The dose cannot be increased after being reduced. Treatment should be terminated for subjects who still cannot tolerate the drug after dose reductions twice.

Table 8. Irinotecan dose modifications

Adverse Event	Resumption
Febrile Neutropenia	Reduce dose after recovery
Grade 3/4 Neutropenia, Leukopenia, Thrombocytopenia, and Anemia	Reduce dose after return to Grade ≤ 1
Grade 3/4 Diarrhea	Reduce dose after recovery
Grade ≥ 2 Non-Hematological Toxicity	Reduce dose after return to Grade ≤ 1

Table 9. Criteria for irinotecan treatment/resumption

Laboratory Tests and Clinical Manifestations	Criteria for Treatment
Absolute Neutrophil Count	≥ 1500/mm^3 (1.5 ×10 ^{9}/L)
Platelet Count	≥ 100 × 10^9/L
Diarrhea	Complete recovery

6.2. Drug Management, Dispensation and Return

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 6.1.5. Remaining or expired drugs should be returned to the sponsor and may not be used for non-participants.

When drugs transport to the study center, a drug receipt form should be signed by both parties, one copy for the study center and the other 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 CRA is responsible for monitoring the supply, use, and storage of study drugs, and disposal of remaining medications.

6.2.1. Disposal of study drugs

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

7. STUDY PROCEDURES

7.1. Study Procedures/Assessments

7.1.1. Screening

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

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

- Signing the informed consent form;
- Collecting demographics: gender, date of birth, ethnicity, height, and weight.
- Tumor diagnosis: site of primary tumor, the date of pathological diagnosis, pathological staging, and the location of the metastatic lesion.
- History of cancer treatment
  - ✓ History of tumor surgery: name of surgery, date of surgery, postoperative TNM staging, and date of postoperative recurrence;
  - ✓ History of radiotherapy: site, dose, and start and end dates.
  - ✓ History of neoadjuvant chemotherapy: chemotherapy regimen, cycles, and start and end dates;
  - ✓ History of adjuvant chemotherapy: chemotherapy regimen, cycles, and start and end dates;
  - ✓ Rescue therapy: regimen, cycles, start and end dates, best overall response, reasons for changes in treatment;
  - ✓ History of concurrent disease, past medications, and medication allergies;
  - ✓ Serology (completed within 14 days before the first dose): HBsAg (if positive, HBV-DNA test required), HBsAb, HBeAg, HBeAb, HBcAb, HCV-Ab (if positive, HCV-RNA test required), and HIV-Ab;
  - ✓ Fresh (preferred) or archival tumor tissue specimens;

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

- ✓ ECOG PS;
- ✓ Vital signs: heart rate, respiratory rate, body temperature, and blood pressure;
- ✓ Comprehensive physical examination: general condition, head and face, skin, lymph nodes, eyes, ears, nose and throat, mouth, respiratory system, cardiovascular system, abdomen, reproductive and 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 the case of urine protein ≥ 2+, a 24-h urine protein test (quantitative) must be added;
- ✓ Fecal occult blood;
- ✓ Clinical chemistry: ALT, AST, GGT, total bilirubin, direct bilirubin, AKP, blood urea nitrogen (preferred) or urea, total protein, albumin, creatinine, blood glucose, lactate dehydrogenase, K^+, Na^+, Ca^{2+}, Mg^{2+}, and Cl^-;
- ✓ Thyroid function: TSH, FT3, and FT4;
- ✓ Coagulation function: APTT, PT, FIB, INR;
- ✓ Echocardiography: including LVEF assessment. Perform when clinically indicated.
- ✓ 12-Lead ECG: additional necessary investigations required when an abnormality is seen as determined by the investigator;
- ✓ Pregnancy test (for women of childbearing potential);
- ✓ Imaging assessment: CT or MRI of neck, chest, and abdomen (including pelvic cavity). Brain MRI is required when brain metastasis is suspected and confirmed (if MRI is contraindicated, CT can be used instead). Bone scan is performed only when clinically indicated and must be performed within 42 days before the first dose. At screening, tumor evaluations up to 4 weeks before randomization and before informed consent may be used as long as they meet relevant criteria.
- ✓ Adverse events: Documented from the signing of ICF.
- ✓ Concomitant medications: Concomitant medications within 30 days before the first dose will be collected;

7.1.2. Treatment period/follow-up visits

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

- All examinations and assessments (except quality of life score and tumor imaging assessment) should be completed within 3 days before administration. The following items should be examined/assessed before the administration in each cycle; items are not required for examination/assessment in the first cycle when they have been examined/assessed at screening within 7 days before the first administration.

- ✓ ECOG PS;
- ✓ Vital signs: heart rate, respiratory rate, body temperature, and blood pressure;
- ✓ Targeted physical examination: required when clinically indicated;
- ✓ Hematology: RBC count, hemoglobin, platelet count, WBC count, neutrophil count, and lymphocyte count;
- ✓ Clinical chemistry: 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;
- ✓ Adverse events: document AEs in detail;
- ✓ Concomitant medications: concomitant medications will be documented;

- The following investigations should be completed every 2 cycles before administration:
  - ✓ Urinalysis: WBC, RBC, and urine protein In the case of urine protein ≥ 2+, a 24-h urine protein test (quantitative) must be added;
  - ✓ Fecal occult blood (SHR-1210 group: before or after administration; control group: when clinically indicated);
  - ✓ Thyroid function: TSH, FT3, and FT4;
- Quality of life score (EORTC QLQ-C30 and EORTC QLQ-OES18): It should be obtained once every 8 weeks, with a time window of ±7 days, and it is recommended to be obtained before administration and AE and tumor assessments.
- Imaging assessment: Lesions found at baseline should be assessed every 8 weeks, or when new lesions are suspected. For lesions of bone metastases, bone scans are only required when the assessment result of other lesions is CR and it is necessary to confirm the presence of lesions of bone metastases or when clinically indicated. For subjects ending the treatment for any reason, a tumor imaging assessment should be performed at the time of withdrawal when an assessment has not been carried out within 4 weeks before ending treatment. Imaging conditions should be the same as those at baseline (including slice thickness and contrast agent). The time window for imaging examination is ±7 days. Unscheduled imaging examination may be performed if PD is suspected (for example, worsening of symptoms). Time of imaging evaluation will not be adjusted due to dose delays.

Subjects in the SHR-1210 group who are clinically stable should have a confirmation scan 4 weeks (±7 days) after the first occurrence of PD based on iRECIST and RECIST v1.1. The subsequent tumor assessment will be performed at the pre-specified time point.

- Blood sampling for immunogenicity and drug trough concentration (treatment group only): within 30 min before the first, second, third, fifth, and seventh doses and within 30 min before every four doses thereafter.
- Biomarker blood sampling (investigational treatment group only): before the first dose, at the occurrence of first tumor response, and at the presence of progressive disease.

7.1.3. End of Treatment/Withdrawal Visit

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

- ✓ ECOG PS;
- ✓ Vital signs: heart rate, respiratory rate, body temperature, and blood pressure;
- ✓ Comprehensive physical examination: general condition, head and face, skin, lymph nodes, eyes, ears, nose and throat, mouth, respiratory system, cardiovascular system, abdomen, reproductive and 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 urine protein ≥ 2+, an additional 24-h urine protein test (quantitative) is required); clinical chemistry: ALT, AST, GGT, total bilirubin, direct bilirubin, AKP, BUN or urea (BUN preferred), total protein, albumin, creatinine, blood glucose, lactate dehydrogenase, K^+, Na^+, Ca^{2+}, Mg^{2+}, and Cl^-;
- ✓ Thyroid function: TSH, FT3, and FT4;
- ✓ ECG;
- ✓ Quality of life score;

- ✓ Imaging assessment: An imaging assessment should be performed at the end of treatment/upon withdrawal when it has not been done within 4 weeks before withdrawal. Subjects who discontinue treatment for reasons other than imaging-confirmed PD must also undergo a tumor assessment every 8 weeks until documentation of confirmed PD, start of a new anti-cancer treatment, or death.
- ✓ Adverse events: document AEs in detail;
- ✓ Concomitant medications: concomitant medications will be documented;

7.1.4. Follow-up visit 90 days after the last dose

Subjects should return to the study center for a follow-up visit 30 days after the last treatment. Safety information will be obtained via telephone follow-up visits on 60 days and 90 days after the last treatment (including AE outcome, newly-occurred SAE, and AESI). In addition, patients from the treatment group will be asked to go back to the study center to collect their immunogenicity and drug trough concentration blood samples whenever possible.

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

- ✓ Hematology: RBC count, hemoglobin, platelet count, WBC count, neutrophil count, and lymphocyte count;
- ✓ Clinical chemistry: 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;
- ✓ Blood sampling for immunogenicity and drug trough concentration (investigational treatment group only): at visits carried out on Day 30, Day 60 (optional), and Day 90 (optional) after the last treatment.
- ✓ Quality of life score;
- ✓ Adverse events: document AEs in detail;
- ✓ Concomitant medications: Concomitant medications within 90 days after the last treatment will be collected. Only concomitant medications for treatment-related AEs will be collected 30 days after the last treatment.

7.1.5. Unscheduled Visit

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

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

7.1.6. Survival follow-up

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

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

7.2. Concomitant Treatment

Prohibited medications and vaccines specifically found in the exclusion criteria are prohibited during the entire course of the study. If the subject develops a concurrent condition that requires the use of a prohibited drug, then study treatment may need to be stopped or 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.

7.2.1. Permitted concomitant medications

Topical use of corticosteroids such as ophthalmic, nasal, intra-articular, and inhaled is permitted (only for the treatment group; pre-treatment with corticosteroids is permitted for the control group).

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

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

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

All concomitant medications should be documented in the eCRF. Concomitant medications from 30 days before the first dose to 90 days after the last dose will be documented; only concomitant medications for treatment-related AEs will be documented from 30 days after the end of treatment.

7.2.2. Prohibited concomitant medications

- Anti-tumor systemic chemotherapy and biological therapy;
- Modern TCM preparations approved by CFDA (now NMPA) for anti-cancer treatment (refer to Appendix III);
- Immunotherapy not specified in the protocol;
- Chemotherapy not specified in the protocol;
- Immunomodulators with auxiliary anti-tumor effects, such as thymosin, lentinan, interleukin-12, etc.
- Inoculation of live vaccines within 4 weeks before the first dose and during the study. Live vaccines include, but not limited to, rubeola, epidemic parotitis, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid. Injections of inactivated influenza vaccine for seasonal influenza are permitted, but not live attenuated influenza vaccines for intranasal use;
- Applicable to the investigational treatment group only: Physiological doses of systemic corticosteroids for purposes other than the relief of symptoms due to immunological causes may, after the consultation with the sponsor, be approved (inhaled steroids are permitted as a part of fixed treatment for asthma or chronic obstructive pulmonary disease). Corticosteroids may be used prophylactically to prevent allergic reactions (such as intravenous contrast agent);

- Subjects receiving docetaxel should avoid strong CYP3A4 inhibitors. If it cannot be avoided, the dose of docetaxel should be reduced according to the package insert;
- Refer to the package insert for other prohibited medications in terms of investigator's choice of chemotherapy.

7.2.3. Supportive care

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

1. Hemangioma of skin

Subjects with skin hemangioma should undergo biopsy and pathological examination whenever possible. Endoscopic and MRI examinations are recommended for subjects with relatively severe or long-lasting skin hemangioma to confirm the involvement of internal organs and/or mucosa.

2. Diarrhea/Colitis

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

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

3. AST, ALT, or bilirubin increased

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

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 intravenous corticosteroids followed by oral corticosteroids. Corticosteroids should begin to taper after symptoms improve to grade 1 or lower. Taper will last for no less than 4 weeks. During the tapering process, appropriate hormone replacement therapy may be required.
- Thyroid hormone replacement therapy may be considered for Grade 2-4 hypothyroidism (such as levothyroxine).

5. Pneumonia

    - Subjects with Grade 2 pneumonia should receive systemic corticosteroids. Corticosteroids should begin to taper after symptoms improve to Grade 1 or lower. Taper will last for no less than 4 weeks.
    - If 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. Corticosteroids should begin to taper after symptoms improve to Grade 1 or lower. Taper will last for no less than 4 weeks. During the tapering process, appropriate hormone replacement therapy may be required.

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

7. Type I diabetes mellitus

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

8. Renal failure or nephritis

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

9. Infusion reactions

CTCAE Grade	Clinical Symptoms	Clinical Management	SHR-1210 Treatment
Grade 1	Mild and transient reactions	Bedside observation and close monitoring until recovery. Pre-administration prophylactics are recommended for subsequent infusions: 50 mg of diphenhydramine or equivalent and/or 325-1000 mg of acetaminophen at least 30 min before SHR-1210 being given.	Continue
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 infusion of normal saline, IV of 50 mg of diphenhydramine or equivalent and/or 325-1000 mg of acetaminophen; Bedside observation and close monitoring until recovery. Corticosteroids or bronchodilators can be considered based on clinical needs; The amount of study drug infused should be recorded in the original medical record; Pre-administration prophylactics are recommended for subsequent infusions: 50 mg of diphenhydramine or equivalent and/or 325-1000 mg of acetaminophen at least 30 min before SHR-1210 is given. Corticosteroids (equivalent to 25 mg of hydrocortisone) should be used when necessary.	Interrupt. Re-administer at 50% of the initial rate after symptoms resolve. If no reaction occurs within 30 min, restore the original infusion rate (100%). Closely monitor. If the symptoms recur, the administration of the current SHR-1210 dose will be discontinued.

CTCAE Grade	Clinical Symptoms	Clinical Management	SHR-1210 Treatment
Grade ≥ 3	Grade 3: Severe reaction without rapid recovery with treatment and/or interruption; or symptoms recur after alleviation; or the subject develops sequelae that requires hospitalization. Grade 4: life-threatening	Immediately discontinue SHR-1210; Administer normal saline by intravenous 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 1:10,000 adrenaline solution, and/or 50 mg of diphenhydramine + 100 mg of methylprednisolone or equivalent by intravenous injection when necessary; • Based on the guidelines for anaphylaxis of the study center; Bedside observation and close monitoring until recovery.	Discontinuation

8. IMMUNOGENICITY STUDY

8.1. Immunogenicity and Drug Trough Concentration Blood Sampling and Processing

8.1.1. Blood sampling timepoints

Within 30 min before the first, second, third, fifth, and seventh doses, within 30 min before every four doses thereafter, and at visits carried out on Day 30 (when a new anti-cancer treatment is started, the blood samples will be collected before the new treatment), Day 60 (optional), and Day 90 (optional) after the last treatment.

8.1.2. Processing and storage of blood samples

At each of the above time points, 4-6 mL of venous blood samples will be collected into serum separation tubes to collect the serum, which will be then transferred to 4 cryotubes (aliquoted equally into 3 test tubes, 1 for ADA, 1 for drug trough concentration, and 1 for antibody neutralizing activity, and 1 backup tube). The cryotubes will be stored in a low temperature freezer at ≤ -60 ℃ until they are transported to the central laboratory for test. Please ref er to the Laboratory Manual for specific operation details.

8.1.3. Shipping of clinical samples

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

9. BIOMARKER BLOOD SAMPLING

Before the first administration, at the occurrence of the first tumor response, and at the presence of progressive disease, one 4-mL tube of whole blood should be collected at each time point. Refer to the Biomarker Blood Sampling SOP for specific procedures.

10. SAFETY EVALUATION

10.1. Safety Parameters

Safety parameters for this study include vital signs, physical examination, laboratory test (hematology, urinalysis, clinical chemistry, fecal occult blood, thyroid function, and coagulation function), 12-Lead ECG, pregnancy test, and clinical symptoms.

10.1.1. Definition of adverse event

An **adverse event** refers to any untoward medical condition in a subject who has received a pharmaceutical product in a clinical trial. An AE is not necessarily related to the treatment that the subject receives. AEs should be documented starting from signing of the informed consent form to 90 days after the last administration of study drugs. From 30 days after the end of treatment, only treatment-related AEs will be collected. An AE may be any untoward and unexpected symptom, vital sign, laboratory test abnormality, or disease. AEs include the following:

1) Worsening of pre-existing (before enrollment) medical conditions/diseases (including symptoms, vital signs, and laboratory test abnormalities);
2) Any new adverse medical conditions (including symptoms, vital signs, and newly diagnosed diseases);
3) Clinically significant abnormal laboratory findings.

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

10.1.2. Definition of serious adverse event

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

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

AEs that lead to hospitalization or prolonged hospitalization during 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)
- Hospitalization or prolonged hospitalization unrelated to the worsening of an AE is not an SAE. For example:
- Hospitalization due to the pre-existing disease without new AEs and aggravation of the pre-existing disease (e.g., hospitalization to examine laboratory abnormalities that have persisted before the study until now);
- Hospitalization for management reasons (e.g., annual physical examination);
- Hospitalization during the study as specified in the study protocol (e.g., as required by the protocol);
- Elective hospitalization unrelated to worsening of AEs (e.g., elective surgery);
- Scheduled treatment or surgery that should be documented throughout the entire study protocol and/or in the subjects' individual baseline information;
- Hospitalization merely for use of blood products.

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

10.1.3. Progressive disease

Disease progression is defined as the worsening of clinical signs/symptoms of the target disease, appearance of a new metastatic lesion, or progression of existing lesions. Death, life-threatening event, hospitalization or prolonged hospitalization, permanent or severe disability/incapacity/impairment of working ability, congenital anomaly or birth defect resulting from vital signs and symptoms of progressive disease should not be reported as an SAE.

10.1.4. Definition of unexpected safety events

Unexpected safety events are events or outcomes that meet the following criteria:

SHR-1210 Investigator's Brochure and package inserts of docetaxel/irinotecan are used as references for predictive assessments of AEs. An event is considered unexpected when the nature, specificity, severity, or result of the event is not consistent with the description found in the Brochure and (or) package inserts.

10.2. Adverse Event Classification

10.2.1. Criteria for the severity of adverse events

The severity of AE is determined by NCI-CTCAE (v4.03). Refer to the following criteria for AEs not listed in NCI-CTCAE 4.03:

Grade	Clinical Description of Severity
1	Mild; asymptomatic or mild clinical symptoms; clinical or laboratory test abnormality only; intervention not indicated.
2	Moderate; minimal, local, or non-invasive interventions required; limited age-appropriate instrumental activities of daily living (ADL), e.g., cooking, shopping, using the telephone, counting money, 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	Death related to AE

10.2.2. Criteria for the causality between AEs and investigational drug

AEs include all unexpected clinical manifestations. All the AEs occurring after the signing of the ICF must be reported as an AE, regardless of whether the AEs are related to the study drugs, whether the subject is allocated to the investigational drug group, and whether the subject has been administered with the drug. Any discomforts complained by the subject or abnormal changes in laboratory tests during the treatment should be truthfully documented, noting event severity, duration, measures taken, and outcome. The clinical physician should comprehensively determine the relationship between event and study drugs and provide a causality assessment using the following five categories "definitely related, possibly related, unlikely related, not related, and indeterminable". "Definitely related, possibly related, and indeterminable" events are included as adverse drug reactions. The incidence of adverse drug reactions is calculated with events of these three categories as numerator and number of subjects used for safety evaluation as denominator.

Table 10. Criteria for causality between adverse events and study drugs.

Grade	Criteria
Definitely Related	An AE occurs in a plausible time relationship to drug administration. The event is a recognized pharmacological phenomenon of the suspected drug, or the event resolves with drug discontinuation and recurs with drug readministration.
Possibly Related	The AE occurs in a plausible time relationship to drug administration. The event is not a recognized pharmacological phenomenon of the suspected drug. It can also be explained by patient's clinical status or other treatments.
Unlikely Related	The AE does not occur in a plausible time relationship to drug administration. The event is not a recognized pharmacological phenomenon of the suspected drug. It can also be explained by patient's clinical status or other treatments.
Not Related	The AE does not occur in a plausible time relationship to drug administration. The event is not a recognized pharmacological phenomenon of the suspected drug. It can also be explained by patient's clinical status or other treatments. The event resolves when patient's clinical status improves or other treatments are discontinued. The event recurs upon restarting other treatment.
Indeterminable	The time relationship between the AE and drug administration is unclear. The event is similar to a recognized pharmacological phenomenon of the product. It can also be explained by combined medications.

10.3. Duration and Frequency of Adverse Event Assessment and Follow-Up Visit

AE and SAE are collected by investigators during routine visits and inquiries. All AEs, including systemic or local reactions that do not meet the criteria for SAE, will be documented in eCRF. The following information should be included: event description, start date, severity, causality (determined by qualified personnel), resolution/stabilization time. Each AE should be documented accurately regardless of the relationship with drugs. Each AE should be followed until being resolved or stabilized.

Conditions before the signing of informed consent form will be documented as baseline but not AEs. However, baseline medical conditions/diseases should be documented when they worsen or exacerbate during the trial.

Changes in the severity of AE should be documented to evaluate the duration of each severity grade. The start time and duration should be documented for all intermittent AEs.

All AEs reported after the informed consent form is signed should be documented. At each visit, the investigator should ask about AE/SAE that has/have occurred since the last visit. AEs should continue to be followed until being resolved or stabilized.

10.4. Reporting Procedures

10.4.1. Reporting of serious adverse events

The reporting period for SAE begins with the signing of the informed consent form until 90 calendar days (inclusive) after the last study drug treatment. Only treatment-related SAEs are reported from 30 days after the last dose. When an SAE occurs, regardless of being recorded in first report or follow-up report, the investigator must complete, sign, and date the "CFDA Serious Adverse Event Report Form" immediately. The event must be reported to the provincial/autonomous regional/municipal drug regulatory authorities, CFDA (via fax or EMS), health administration (via fax to bureau of medical administration), the sponsor (via email), and the ethics committee within 24 h after knowing the event. Refer to Table 11 below for contact details.

Reporting of SAEs that occur from 90 days after the last dose is generally not required unless they are suspected to be drug-related.

The symptoms, severity, causality with the study drug, time of onset, time of treatment, measures taken, time and method of follow-up, and outcome should be documented in detail in the SAE report. If the investigator believes that an SAE is not related to the study drug but potentially related to the study conditions (such as the termination of past treatment, or comorbidities during the study), then this relationship should be detailed in the description section of the SAE report form.

If the severity of an ongoing SAE or its relationship to the study drug changes, a follow-up report should be submitted immediately.

If an error is found in a previously reported SAE, such SAE may be revised, revoked, or downgraded in follow-up reports and reported in accordance with the SAE reporting procedure.

Table 11. SAE report contacts

Unit	Contact	Fax/Telephone/Address
Jiangsu Hengrui Pharmaceuticals Co., Ltd.	Drug Safety Group (SAE), Oncology Business Unit	Tel.: 021-60453192 ext. 818 Email: SHR1210safety@shhrp.com
China Food and Drug Administration Division of Drug Research Supervision, Department of Drug and Cosmetics Registration		Address: Building 2, No. 26, Xuanwumen West Street, Xicheng District, Beijing Postal Code: 100053 Tel.: 010-68313344-1003 Fax: 010-88363228
Medical Administration Bureau, Health Administration		Address: No. 38, North Lishi Road, Xicheng District, Beijing (100810) Tel.: 010-68792201 Fax: 010-68792734 (preferred)
Food and Drug Administration of Provinces, Autonomous Regions and Municipalities	Refer to the reporting requirements of the drug administration department of each province, autonomous region, or municipality	

10.4.2. Reports of adverse events of special interest

The sponsor should be notified of any of the following AEs that occur in subjects from the treatment group during the study within 24 h, even though the events do not meet the definition of SAE. The Hengrui Clinical Trial Adverse Event of Special Interest Report should be filled out and the CFDA Serious Adverse Event Report Form should also be filled out when the events are classified as SAEs. AESI should be reported 90 days after the last dose.

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

10.4.3. Pregnancy reporting

During the study, if a female subject becomes pregnant, she must discontinue the study drugs immediately. The investigator must report to the sponsor within 24 hours 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.

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

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

11. Data Analysis/Statistical Methods

Data analysis will be carried out without distinction of study centers (data from all participating study centers will be combined).

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

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

The statistical analysis in this study will be conducted when at least 365 OS events are collected. The analysis will be carried out after the database for the analysis is locked.

11.1. Statistical Analysis Plan

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

11.2. Statistical Hypotheses

The primary objective of this study is to compare the efficacy of SHR-1210 (treatment group) vs. investigator's choice of chemotherapy (control group) for the treatment of subjects with locally advanced or metastatic esophageal cancer who are refractory to the first-line chemotherapy. The primary efficacy endpoint is OS. In this study, the OS curve will be estimated by the Kaplan-Meier method and a stratified log-rank test will be used as the primary statistical method to test the null hypothesis that the distributions of OS are identical between the two groups (one-sided $\alpha = 0.025$).

Superiority criteria: When the P value obtained in the final analysis by the log-rank test is ≤ 0.025 and the median OS of the treatment group estimated by the Kaplan-Meier method is greater than that of the control group, the efficacy of the treatment group can be determined to be superior to that of the control group.

11.3. Analysis Set/Population

The following analysis sets will be involved in this study:

- Informed consent set (ICS)

All subjects who have signed the informed consent form will be included in this analysis set.

- Full analysis set (FAS)

Based on the intention-to-treat (ITT) principle, all randomized subjects who have received study drug at least once will be included in FAS. FAS is the main analysis set for this study. In the FAS-based analysis, subjects will be analyzed by group assigned by randomization (regardless of the actual treatment they receive).

- Per-protocol set (PPS)

PPS is a subset of FAS, defined as subjects who do not have major protocol deviations or do not have protocol deviations that may have major impacts on study results. Major protocol deviations or deviations that have major impacts on study results are defined as follows:

  - Violation of the inclusion and exclusion criteria;
  - Administration of drugs prohibited by the study;

The screening and determination of subjects with major protocol deviations or deviations that have major impacts on study results will be carried out before database locking, and these subjects (if any) will be removed from PPS. The PPS-based analysis will serve as a secondary/supportive analysis.

- Immunogenicity analysis set

Subjects who have received at least one dose of SHR-1210 and have baseline and at least one post-baseline immunogenicity evaluation data constitute the immunogenicity analysis set.

- Safety set (SS)

All subjects who have received study drug at least once (whether they have participated in randomized grouping or not) constitute the safety set. The SS is the primary analysis population used for the safety analysis. The SS-based analyses will be carried out by the actual treatment that patients receive.

11.4. Statistical Methods

11.4.1. Basic methods

This is a parallel-controlled study. Unless otherwise stated, all data will be analyzed by treatment group (SHR-1210 group and investigator selected chemotherapy group) and appropriate statistics will be applied according to the data type: measurement data will be summarized by mean, standard deviation (STD), median, minimum, and maximum; count data will be summarized by frequency and proportion for descriptive statistics; for time-to-event data, median time and the corresponding 95% confidence interval will be estimated by the Kaplan-Meier method.

11.4.2. Primary efficacy endpoint analysis

The primary efficacy endpoint is OS. In addition to the descriptive statistical summary of time-to-event data with basic methods listed in Section 10.4.1, the statistical analysis of OS will also include the following:

1. Primary analysis

The primary analysis is to evaluate the efficacy difference between investigational treatment group and control group based on the FAS. In the primary analysis, the null hypothesis that the distributions of OS are identical between the two groups will be tested using the stratified log-rank test based on randomized stratification factors (1. locally advanced lesion vs. distant metastasis; and 2. ECOG PS 0 vs. 1).

Missing data: This study will track subject survival until an OS event is observed where possible. Inevitably, when a subject drops out before an OS event is observed, the subject's survival time (from the start date of randomization of the subject) will be right-censored at the last known survival date (the actual survival time is greater than the recorded time). The survival time of drop-outs will be calculated using Hengrui's statistical criteria.

2. Secondary analysis

First, the above primary analysis will be repeated without the randomized stratification factors being considered.

Secondly, the hazard ratio (HR) of OS of investigational treatment group to control group will be estimated using a Cox proportional hazards model, and the corresponding 95% confidence interval will be calculated. In the fitting of the primary analysis based on this model, treatment group will be set as a fixed effect. In addition, to explore the effects of other factors on efficacy, stratification factors [1. locally advanced lesion vs. distant metastasis; 2. ECOG PS (0 vs. 1)], gender, and PD-L1 expression level can also be used to fit the model except for the treatment group.

Moreover, the 6-month and 12-month OS rates and their 95% confidence intervals will be estimated.

The above analysis for the primary efficacy endpoint will be repeated in FAS and PPS. The rule of missing data imputation is identical to that in the primary analysis.

11.4.3. Secondary efficacy endpoint analysis

The analysis of secondary efficacy endpoints in this study will be based on FAS only and will be carried out for all efficacy endpoints except OS (progression-free survival (PFS), objective response rate (ORR), and quality of life score EORTC QLQ-C30 and EORTC QLQ-OES18). Secondary efficacy endpoints will be summarized using descriptive statistics based on methods described in Section 10.4.1. Furthermore, for PFS, the inter-group differences will be compared using the log-rank test, and meanwhile, HR of PFS will be estimated using a Cox proportional hazards model and the effects of factors other than treatment groups on the differences in PFS will be investigated, with both test and model similar to those of OS-related analysis. For ORR, the difference in ORR between the two treatment groups and the corresponding 95% confidence interval will be estimated.

Missing data: they will adopt the imputation method for PFS identical to that for OS; no imputation method will be used for ORR or QoL score.

11.4.4. Analysis of exploratory endpoints

Based on the immunogenicity analysis set, descriptive statistics for the time to the first positive ADA result and the duration of ADA will be summarized. The incidence of ADA, the incidence of anti-SHR-1210 antibody with neutralizing activity, and the correlation between immunogenicity and drug trough concentration, efficacy and safety will be calculated. Safety analysis

The safety analysis is based on the safety set (by actual treatment received). According to Hengrui's Standard Reporting Procedures, safety will be summarized using descriptive statistics, including but not limited to the following:

- Subject disposition and populations;
- Subjects' basic characteristics (including demographics, life history, medical history, and medication history);
- Discontinuations;
- Summary of adverse events (of all causes and treatment-related);

- Incidence and severity of adverse events (of all causes and treatment-related);
- Summary of serious adverse events;
- Causality analysis of adverse events;
- Laboratory measurements, vital signs, ECG, and their changes from baseline;
- Number and rate of laboratory measurements, vital signs, and ECG data "changed from normal to abnormal" or "exacerbated abnormally" after the trial.

In this study, AEs will be evaluated and graded by NCI-CTCAE (v4.03).

11.4.5. Baseline descriptive statistics

Demographics (gender, age, body height, weight, etc.), medical history, and habituation of all randomized subjects will be summarized by treatment group after randomization using descriptive statistics based on FAS.

11.4.6. Multiple comparison/multiplicity

This study only involves one final analysis of the primary endpoint OS and multiplicity will not be involved. The secondary analysis in this study will be only used to provide supportive conclusions for the primary analysis and no α adjustments will be made for multiplicity.

11.4.7. Individual data listings

All data collected from this study will be presented in listings.

11.5. Sample Size

This is parallel study with its primary endpoint being OS. Subjects will be randomized in a 1:1 ratio. Assuming that the median OS of the control group is 7 months and the median OS of the investigational treatment group is 9.5 months (the investigational treatment group is extended by 2.5 months compared with that of the control group), the inter-group OS distribution will be compared using a stratified log-rank test at an overall significance level $\alpha = 0.025$ (one-sided); when the duration of enrollment is assumed to be 18 months and the entire study lasts for 36 months, at least 365 OS events need to be collected to obtain a power of 80% according to the calculation by East v6.3. Furthermore, assuming a drop-out rate of 20%, 438 subjects are required to be enrolled in this study (219 in the investigational treatment group and 219 in the control group).

11.6. Methods to Reduce Bias

11.6.1. Randomization and blinding

Randomization is the primary means of ensuring comparability between groups in this study. Personnel who participated in this study should ensure that the randomization procedure is strictly implemented where possible. The generation, review, quality assurance, testing, and validation of the randomized procedure will be in strict accordance with applicable Hengrui SOP (HRSOP STAT 01 Randomization and Blinding).

This study will use a stratified randomization method. Subjects will be randomized in a 1:1 ratio to groups of SHR-1210 or investigator's choice of chemotherapy (docetaxel or irinotecan) within each stratum. Stratification factors for this study are: 1. locally advanced lesion vs. distant metastasis; 2. ECOG PS (0 vs. 1). Randomization will be performed in the HRTAU RTSM system.

This is an open-label study. No blinding or subsequent procedures are involved.

11.6.2. Blinding evaluation

Not involved (see Section 10.6.1).

11.6.3. Unblinding

Not involved (see Section 10.6.1).

Not applicable in this study.

12. QUALITY ASSURANCE AND QUALITY CONTROL

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

All study centers must follow the SOPs for the management of study drugs, including drug receipt, storage, dispensing, retrieval, and disposal.

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

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

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

13. REGULATORY ETHICS, INFORMED CONSENT, AND SUBJECT PROTECTION

13.1. Regulatory Considerations

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

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

1) Provisions for Drug Registration
2) Good Clinical Practice
3) Consensus on ethical principles based on international ethics guidelines, including the Declaration of Helsinki and the Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
4) Other applicable laws and regulations

13.2. Ethical Standards

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

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

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

13.3. Independent Ethics Committee

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

13.4. Informed Consent

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

13.4.1. Informed consent process and records

Informed consent will begin before an individual decides to participate in the clinical study and continues during the entire clinical study. The risks and potential benefits of participating in the study should be discussed fully and in detail with subjects and their dependents. Subjects will be asked to read and review the ICF that has been approved by the IEC/IRB. The investigator will explain the clinical study to the subjects and answer any questions posed by the subjects. An informed consent discussion will be conducted for all subjects, and based on their understanding, the purpose, process, and potential risks of the study and their rights as study participants will be explained. Subjects will have opportunities to carefully read the written informed consent form (ICF) and pose questions before signing. Subjects will also have opportunities to discuss with their representatives on this study and fully think through it before agreeing to participate in the

study. Subjects can only participate in the study after they have signed the ICFs. During the clinical study, subjects can withdraw the informed consent form at any time. One copy of the signed ICF will be kept by the subjects. Even if subjects refuse to participate in this study, their rights will be fully protected. It will also be emphasized to subjects that the medical care quality they obtain will not be affected.

13.5. Confidentiality of Subject Information

During the course of this study, every effort shall be made to protect the privacy of all subjects. Study-related documents, study reports, publications, other published data will not include the name or other private information of subjects involved, except as required by law. To ensure the confidentiality of subjects' data, subject information will be collected, transmitted, processed, and stored in accordance with applicable laws and regulations.

14. DATA MANAGEMENT

14.1. Data Collection and Management

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

14.1.1. Medical records

As the source documents of the clinical trial, medical records should be retained in their entirety. The investigator is responsible for filling out and keeping medical records. Medical records should be neat and legible so that the sponsor's CRA could verify the data with eCRF at each inspection.

14.1.2. eCRF entry

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

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

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 error message prompt for questionable data. The investigator 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.

14.1.3. 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 CRA, data manager, and medical reviewer. After data cleaning is completed, the investigator will sign the completed eCRF for verification.

14.2. Data Monitoring

Implemented by: CRA.

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

14.3. Data Management

14.3.1. 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.

14.3.2. Data entry and verification

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

14.3.3. Database lock

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

14.3.4. Data archiving

After the study is completed, subject's eCRFs in PDF format must be generated from the EDC system and kept in non-rewritable disks (DVD). These disks will be archived by the sponsor and various institutions for auditing and/or inspection.

The preservation and management of the trial data must be in accordance with GCP requirements. The investigator must keep the clinical trial data at least 5 years after the termination of the clinical trial, and the sponsor must keep the clinical trial data at least 5 years after the approval of the drug for launching on the market.

14.4. Protocol Deviations

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

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

15. PUBLICATION OF STUDY RESULTS

The study results belong to Jiangsu Hengrui Pharmaceuticals Co., Ltd. Hengrui does not restrict the publication of any collected or research information by investigators, regardless of whether the results are beneficial to the investigational drug or not. However, the investigator should let the sponsor have the opportunity to review any proposed publication or other forms of publication before document submission or publication to prevent unintentional leakage of confidential information or unprotected inventions. The investigator should provide Hengrui with the manuscript, abstract, or full text of all planned publications (poster, invited lectures, or guest lectures) at least 30 days prior to submission for publication or other forms of release. To protect the intellectual property rights that need to be patented, the investigator should agree to delay publications, and the delay period should not exceed 60 days. Before open publication, Hengrui can require the investigator to delete any previously unpublished confidential information (except for study results). If this study is part of a multicenter study, the investigator must agree that the first publication is an integrated result from all study centers. However, if a

manuscript of the integrated analysis is not submitted 12 months after the study is completed or terminated in all study centers, the investigator can independently publish results based on other requirements in this section.

16. STUDY CENTER AND TRIAL STAFF

16.1. Study Center

16.1.1. Leading site

Name: The 307th Hospital of the Chinese People's Liberation Army

[redacted]

Principal Investigator: Jianming Xu

Name: Cancer Hospital Chinese Academy of Medical Sciences

[redacted]

Principal Investigator: Jing Huang

16.2. Sponsor

Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

[redacted]

17. CLINICAL STUDY PROGRESS

Anticipated enrollment of the first subject: Apr. 2017

Anticipated enrollment of the last subject: Oct. 2018

Anticipated study completion: Apr., 2019

18. REFERENCES

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Appendix I. ECOG PS

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

Appendix II. Creatinine Clearance Calculation

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

Serum Creatinine (mg/dL):

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

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

Serum Creatinine Concentration (μmol/L):

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

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

a Age in years, weight in kg.

Appendix III. 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

(T)umor Classification

Tx: Primary tumor that cannot be assessed

T0: No evidence of primary tumor

Tis: High-grade dysplasia

T1: Invasion of lamina propria, muscularis mucosae, or submucosa

T1a: Invasion of lamina propria or muscularis mucosae

T1b: Invasion of submucosa

T2: Invasion of muscularis propria

T3: Invasion of adventitia

T4: Invasion of adjacent structures

T4a: Resectable (pleura, pericardium, or diaphragm)

T4b: Unresectable (aorta, vertebral body, or trachea)

(N)ode Classification

Nx: Regional lymph nodes that cannot be assessed

N0: Absent

N1: 1-2 regional lymph nodes

N2: 3-6 regional lymph nodes

N3: ≥ 7 regional lymph nodes

(M)etastasis Classification

M0: Absent

M1: Present

Tumor Differentiation (G)

GX: Differentiation that cannot be assessed, use G1 for classification

G1: Well differentiated

G2: Moderately differentiated

G3: Poorly differentiated

G4: Undifferentiated, use G3 for classification

Tumor Cell Type

H1: Squamous cell carcinoma

H2: Adenocarcinoma

Stage	T	N	M	G	Site*
0	is (HGD)	0	0	1, X	Any
IA	1	0	0	1, X	Any
IB	1	0	0	2-3	Any
	2-3	0	0	1, X	Lower segment, X
IIA	2-3	0	0	1, X	Middle and upper segments
	2-3	0	0	2-3	Lower segment, X
IIB	2-3	0	0	2-3	Middle and upper segments
	1-2	1	0	Any	Any
IIIA	1-2	2	0	Any	Any
	3	1	0	Any	Any
	4a	0	0	Any	Any
IIIB	3	2	0	Any	Any
IIIC	4a	1-2	0	Any	Any
	4b	Any	0	Any	Any
	Any	3	0	Any	Any
IV	Any	Any	1	Any	Any

*The tumor site is defined by the position of the upper edge of the tumor in the esophagus, and X refers to the tumor site undocumented.

Appendix V. Response Evaluation Criteria in Solid Tumors

Response Evaluation Criteria in Solid Tumors Version 1.1 (Excerpt)

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

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

1 BACKGROUND

Omitted

2 PURPOSE

Omitted

3 MEASURABILITY OF TUMOR AT BASELINE

3.1 Definition

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

3.1.1 Measurable lesions

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

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

3.1.2 Non-measurable lesions

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

3.1.3 Special considerations regarding lesion measurability

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

Bone lesions:

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

Cystic lesions:

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

Lesions with prior local treatment:

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

3.2 Specifications by Methods of Measurements

3.2.1 Measurements of lesions

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

3.2.2 Method of Assessment

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

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

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

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

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

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

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

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

4 TUMOR RESPONSE ASSESSMENT

4.1 Assessment of Overall Tumor Burden and Measurable Disease

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

4.2 Baseline Documentation of "Target" and "Non-target" Lesions

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

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

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

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

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

4.3 Response Criteria

4.3.1 Evaluation of target lesions

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

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

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

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

4.3.2 Special notes on the assessment of target lesions

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

Target lesions that become "too small to measure". While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure". When this occurs, it is important that a value is recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph nodule is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false evaluation based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

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

4.3.3 Evaluation of non-target lesions

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

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

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

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

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

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

When the patient has only non-measurable disease: This circumstance arises in some phase III studies when it is not a criterion of study inclusion to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease load based on the change in non-measurable disease is comparable in magnitude to the increase that would be

required to declare PD for measurable disease. For example, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a peritoneal effusion from trace to large, an increase in lymphangiopathy from localized to widespread, or may be described in protocols as "sufficient to require a change in treatment". Examples include an increase in a pleural effusion from trace to large, an increase in lymphangitic disease from localized to widespread, or may be described in protocols as "sufficient to require a change in therapy". If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

4.3.5 New Lesion

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

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

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

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

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

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

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

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

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

4.4 Evaluation of Best Overall Response

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

4.4.1 Time point response

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

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

Target Lesion	Non-Target Lesion	New Lesion	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR

Target Lesion	Non-Target Lesion	New Lesion	Overall Response
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	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 = inevaluable

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

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

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

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

4.4.2 Missing assessments and unevaluable designation

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

4.4.3 Best overall response: all time points

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

BOR determination in studies where confirmation of complete or partial response is not required: BOR in these studies is defined as the best response across all time points (for example, a patient who has SD in evaluation at Cycle 1, PR at Cycle 2, and PD at the last cycle has a BOR of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time

calculated from baseline. If the minimum time is not met when SD is otherwise the BOR, the patient's BOR depends on the subsequent assessments. For example, a patient who has SD at Cycle 1, PD at Cycle 2 and does not meet minimum duration for SD, will have a BOR of PD. The same patient lost to follow-up after the first SD assessment would be considered not evaluable.

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

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

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

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.
[a]: If a CR is truly met at first time point, then efficacy of any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, will still evaluated as PD at that point (since disease will reappear after CR). Best response will depend on whether minimum duration for SD is met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

4.4.4 Special notes on response assessment

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

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

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

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

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

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

4.5 Frequency of Tumor Re-Evaluation

Frequency of tumor re-evaluation during treatment should be protocol-specific and consistent with the type and schedule of treatment. However, in the phase II studies where the beneficial effect of treatment is not known, follow-ups for every 6-8 weeks (timed to coincide with the end of a cycle) is reasonable. Interval adjustments can be justified in specific regimens or circumstances. The protocol should specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumor type under study)

and how often evaluations are repeated. Normally, all target and non-target sites are evaluated at each assessment. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when CR is identified in target disease or when progression in bone is suspected.

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

4.6 Confirmatory Measurement/Duration of Response

4.6.1 Confirmation

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

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

4.6.2 Duration of overall response

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

4.6.3 Duration of Stable Disease

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

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

4.7 PFS/TTP

4.7.1 Phase II clinical trials

This guideline is focused primarily on the use of objective response as study endpoints for phase II trials. In some circumstances, response rate may not be the optimal method to assess the potential anticancer activity of new agents/regimens. In such cases, PFS/PPF at landmark time points might be considered appropriate alternatives to provide an initial signal of biologic effect of new agents. It is clear, however, that in an uncontrolled trial, these measures are subject to criticism since an apparently promising observation may be related to biological factors such as patient selection and not the impact of the intervention. Thus, phase II screening trials utilizing these endpoints are best designed with a randomized control. Exceptions may exist where the behavior patterns of certain cancers are so consistent (and usually consistently poor), that a non-randomized trial is justifiable. However, in these cases it will be essential to document with care the basis for estimating the expected PFS or PPF in the absence of a treatment effect.