Title: An Open-Label, Multi-Center, Phase II Study of Anti-PD-1 Antibody SHR-1210 Plus Capecitabine and Oxaliplatin Sequenced by SHR-1210 with Apatinib Mesylate or Apatinib in Patients with Previously Untreated Advanced or Metastatic Gastric (GC) or Gastroesophageal Junction (GEJ) Cancer

NCT number: NCT03472365

Date: 8 Aug., 2018

AN OPEN-LABEL, MULTI-CENTER, PHASE II STUDY OF ANTI-PD-1 ANTIBODY SHR-1210 PLUS CAPECITABINE AND OXALIPLATIN SEQUENCED BY SHR-1210 WITH APATINIB MESYLATE OR APATINIB IN PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED OR METASTATIC GASTRIC (GC) OR GASTROESOPHAGEAL JUNCTION (GEJ) CANCER

Protocol No.:	SHR-1210-II-207
Study Phase:	II
Version No.:	6.0
Version Date:	8 Aug., 2018

Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

VERSION HISTORY/REVISION HISTORY

Document	Version Date	Amendment Rationale and Summary of Changes
Initial version (1.0)	1 Nov., 2017	Not applicable
2.0	15 Dec., 2017	Added the information on the clinical study progress of SHR-1210 combined with apatinib (section 1.1.4); Inaccurate text description: The legend "Table 17. Sample size calculation" in the list of tables in version 1.0 was actually Table 16 in the text. Checked the protocol text and modified the table to "Table 16. Sample size calculation" to keep the description correct and consistent.
3.0	9 Jan., 2018	For more details, refer to independent document "List of Study Protocol Amendments Version 3.0". The main revisions are as follows: Deleted immunogenicity and PK tests; Deleted biomarker test; Deleted overall survival from the secondary endpoints; Modified "Incidence and severity of adverse events (AEs) and serious adverse events (SAEs) and laboratory abnormalities" to "incidence and severity of adverse events (AEs) and serious adverse events (SAEs), vital signs, ECG, and laboratory abnormalities" in the secondary endpoints. Deleted "Subjects shall be first included into cohort 1. The enrollment of cohort 2 is started only after the enrollment of cohort 1 is completed" from the study design. Deleted exclusion criterion 9 "The ascites is still uncontrollable after treatment". Modified the descriptions "treatment group 1" and "treatment group 2" in the study design of the protocol synopsis to "cohort 1" and "cohort 2" to keep the text correct and consistent.
4.0	22 Jan., 2018	The study design adopts a randomized method to assign the subjects to cohort 1 or cohort 2. Added Section 4.3 Randomization and Blinding. Recalculated the sample size according to the requirement for randomization. Nineteen subjects will be enrolled into cohort 1 and cohort 2 at the first stage, respectively. If at least 4 subjects achieve objective response, the second stage will be initiated. Besides, considering the 10% non-evaluable subjects, 48 and 62 subjects should be enrolled into cohort 1 and 2, respectively.

5.0	5 Jun., 2018	Updated the treatment of cohort 1. Updated the original treatment for cohort 1 (at least four cycles of SHR-1210 combined with capecitabine and oxaliplatin sequenced by SHR-1210 monotherapy as maintenance treatment) to the following: SHR-1210 + capecitabine + oxaliplatin for 4-6 cycles, followed by SHR-1210 + apatinib in the treatment of the subjects without disease progression. Based on the above revisions, relevant contents including the title of the study, were updated: The title was updated to "An Open-Label, Multi-Center, Phase II Study of Anti-PD-1 Antibody SHR-1210 Plus Capecitabine and Oxaliplatin Sequenced by SHR-1210 with Apatinib Mesylate or Apatinib in Patients with Previously Untreated Advanced or Metastatic Gastric (GC) or Gastroesophageal Junction (GEJ) Cancer"; The study objectives were updated to "Primary objective: To evaluate the efficacy of the sequential therapy of SHR-1210 combined with capecitabine and oxaliplatin or SHR-1210 combined with apatinib mesylate as the first-line therapy for advanced or metastatic gastric (GC) or gastroesophageal junction (GEJ) cancer"; Secondary objective: "To evaluate the safety of the sequential therapy of SHR-1210 combined with capecitabine and oxaliplatin or SHR-1210 combined with apatinib mesylate for the treatment of advanced or metastatic gastric (GC) or gastroesophageal junction (GEJ) cancer". According to the latest CDE requirements on drug safety, relevant contents in the study were updated: a) AEs: AEs are recorded from the date of signing informed consent to the end of the safety follow-up (90 days after the last dose) or the start of a new anti-cancer therapy. b) Death caused by the symptoms and signs of PD will be reported as an SAE. c) "Definitely related", "possibly related" and "unlikely related" and "indeterminable" are all listed as adverse drug reactions. d) The collection and follow-up duration of AE/SAE are reinforced (see section 7.4.1). e) The CFDA and the National Health and Family Planning Commission have changed to other names but the GCP and Provisions for Drug Registration have not been updated yet. Therefore, the reporting of SAEs was updated: "The SAE must be reported to the relevant regulatory authorities, the sponsor, and the ethics committee within 24 hours of knowing of the event. The sponsor's email address for safety data is: hengrui_drug_safety@hrglobe.cn."

6.0	8 Aug., 2018	1. The safety data by 7 Aug., 2018 showed that the safety and tolerance of SHR-1210 combined with apatinib (500 mg/d) were poor: Among 11 patients receiving SHR-1210 + apatinib treatment, there were 4 SAEs related to apatinib (including grade 3 transaminase increased, grade 3 erythema multiforme, grade 3 upper gastrointestinal hemorrhage, and grade 4 skin toxicity). By referring to the latest data from other studies of SHR-1210 plus apatinib treatment and after discussion with PI, it is planned to reduce the dose of SHR-1210 plus apatinib to 375 mg/d. For more details, see section 5.1.5 Regimen of the drugs. Section 5.2.3 Dose Modification of Apatinib Mesylate has also been updated accordingly based on the above changes in the dose of apatinib: Depending on the initial dose of apatinib, the dose of apatinib mesylate can be reduced to 375 mg qd or 250 mg qd. 2. Blood sampling for Pharmacokinetic study and for anti-drug antibodies were added to fully investigate the properties of SHR-1210 combined with apatinib and to more effectively analyze the safety and efficacy of the combined treatment (see section 3.1). 3. Blood sampling burden is minimized as much as possible for the subjects based on the current medical practice while satisfying the medical requirements. For the HBV DNA test, the following requirement was proposed: If the Hepatitis B five items test indicates HBV infection [HBsAg positive] or a history of HBV infection, HBV DNA quantification shall be performed (see section 6.1). 4. Capecitabine (0.15 g/tablet) and oxaliplatin (100 mg/bottle) were added to facilitate the subjects to receive the study drug based on the current medical practice (see section 5.1.2). 5. In section 5.2.3 Dose Modification of Apatinib Mesylate, "dose delay" was revised to "dose interruption" to improve the correctness of description. 6. In section 7.4.5 Pregnancy Report, reporting to the ethics committee was added with improvement of wording: "Female subjects who become pregnant during the study must withdraw from the study. If a female partner of a male subject becomes pregnant, the male subject will continue participation in the clinical study. The investigators must fill out the "Pregnancy Report/Follow-up Form for Hengrui's Clinical Studies" and report to the sponsor within 24 hours after becoming aware of the pregnancy, and report to the ethics committee promptly".

SPONSOR'S SIGNATURE PAGE

I have read and confirmed this clinical study protocol (protocol no.: SHR-1210-II-207, version no.: 6.0, version date: 8 Aug., 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.

_____	_____	_____
Medical Director (print)	Medical Director (signature)	Date of Signature

PRINCIPAL INVESTIGATOR'S SIGNATURE PAGE (LEADING CENTER)

I will carefully execute the duties as an investigator in accordance with the Chinese GCP, and personally participate in or directly lead this clinical study. I have received the Investigator's Brochure for the study drugs; I have read the materials of preclinical studies of the study drugs and the protocol for this clinical study. I agree to fulfill my duties in accordance with Chinese laws, the Declaration of Helsinki, the Chinese GCP, and this study protocol. I agree that any modifications to the protocol must be reviewed and approved by the sponsor, and can only be implemented upon approval by the ethics committee, unless measures must be taken to protect the safety, rights, and interests of the subjects. It is my responsibility to make clinically relevant medical decisions to ensure appropriate and timely treatments in subjects experiencing adverse events during the study period, and to document and report such adverse events in accordance with relevant state regulations. I will document all data in a truthful, accurate, complete and timely manner. I agree to be monitored and audited by the clinical research associate or auditor assigned by the sponsor, and to be inspected by the drug regulatory authorities, to ensure the quality of the clinical study. I will keep the personal information 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)	Date of Signature

PRINCIPAL INVESTIGATOR'S SIGNATURE PAGE (PARTICIPATING CENTER)

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

Study Center: _____

_____	_____	_____
Principal Investigator (print)	Principal Investigator (signature)	Date of Signature

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PROTOCOL SYNOPSIS

Study Title	An Open-Label, Multi-Center, Phase II Study of Anti-PD-1 Antibody SHR-1210 Plus Capecitabine and Oxaliplatin Sequenced by SHR-1210 with Apatinib Mesylate or Apatinib in Patients with Previously Untreated Advanced or Metastatic Gastric (GC) or Gastroesophageal Junction (GEJ) Cancer
Protocol No.	SHR-1210-II-207
Version No.	6.0
Sponsor	Jiangsu Hengrui Pharmaceuticals Co., Ltd.
Study Objectives	Primary objective: • To evaluate the efficacy of the sequential therapy of SHR-1210 combined with capecitabine and oxaliplatin or SHR-1210 combined with apatinib mesylate as the first-line therapy for advanced or metastatic gastric (GC) or gastroesophageal junction (GEJ) cancer. Secondary objectives: • To evaluate the safety of the sequential therapy of SHR-1210 combined with capecitabine and oxaliplatin or SHR-1210 combined with apatinib mesylate for the treatment of advanced or metastatic gastric (GC) or gastroesophageal junction (GEJ) cancer.
Study Endpoints	Primary endpoint: • Objective response rate (ORR) Secondary endpoints: • Progression free survival (PFS); • Duration of response (DoR); • Disease control rate (DCR); • Incidence and severity of adverse events (AEs) and serious adverse events (SAEs), vital signs, ECG, and laboratory abnormalities.
Study Population	Patients with unresectable, advanced or metastatic GC or GEJ cancer without previous systemic treatment.
STUDY DESIGN	This is a randomized, open-label, multi-center, phase II clinical study. A total of 98 patients with previously untreated advanced or metastatic gastric cancer or gastroesophageal junction cancer will be enrolled. The subjects are randomized in a 1:1 ratio into the sequential therapy of SHR-1210 combined with capecitabine and oxaliplatin treatment group (cohort 1, n = 43) or the SHR-1210 combined with apatinib treatment group (cohort 2, n = 55). • Cohort 1 (sequential therapy of SHR-1210 combined with capecitabine and oxaliplatin): SHR-1210 + capecitabine + oxaliplatin for 4-6 cycles, followed by SHR-1210 + apatinib for subjects without progressive disease (PD); • Cohort 2 (SHR-1210 combined with apatinib): SHR-1210 + apatinib.

	A two-stage design is adopted to minimize the exposure of subject to ineffective treatment. Nineteen subjects will be enrolled into cohort 1 and cohort 2 at the first stage, respectively. If at least 4 subjects achieve objective response (complete response or partial response), the second stage will be initiated. And more subjects will be enrolled in cohort 1(to 43 subjects) and in cohort 2 (to 55 subjects), respectively. In this study, the screening period should be no more than 28 days. After completing screening examinations and assessments, eligible subjects will enter the treatment period (21 days/cycle) and begin the study treatment and study visits according to the protocol. Tumor imaging assessment will be performed once in every 2 cycles (6 weeks ± 7 days) during the first 12 months (the first 16 cycles) of the study treatment period and once every 3 cycles (9 weeks ± 7 days) thereafter. The subjects will complete safety examinations and imaging assessments upon discontinuation of the study treatment. Thereafter, the subjects will enter the follow-up period. Safety follow-up starts from the last dose of study treatment. The follow-up is performed once every 30 days (± 7 days) until 90 days after the last dose. The first safety follow-up is carried out at the study center; the second and the third follow-up visit are made via telephone calls. The survival follow-up period starts after the end of the safety follow-up period. The survival follow-up period ends upon the subject's death, lost to follow-up, withdrawal of informed consent, or study termination by sponsor. During this period, a follow-up shall be conducted every month via telephone or other effective methods to collect information on subject survival and subsequent treatments. For subjects who show no evidence of radiographic progression, an imaging evaluation should be continued at the frequency of response evaluations specified in the protocol, until progressive disease, death, lost to follow-up, withdrawal of informed consent, start of other anti-cancer treatments, or trial termination by the sponsor.
Study Drugs and Method of Administration	**Cohort 1**: SHR-1210 + capecitabine + oxaliplatin for 4-6 cycles, followed by SHR-1210 + apatinib for subjects without disease progression: • SHR-1210, 200 mg, infuse over 30 min (the total infusion time should be no less than 20 min and no more than 60 min, including rinsing period), q3w; • Capecitabine, 1000 mg/m^2, administered orally twice daily within 30 min after meals (once in the morning and once in the evening, with total daily dose of 2000 mg/m^2). Two weeks of treatment is followed by 1 week of treatment interruption (i.e., drug administration from Day 1 to Day 14, and drug interruption from Day 15 to Day 21). One treatment cycle lasts for 3 weeks; • Oxaliplatin, 130 mg/m^2, mixed with 250-500 mL of 5% glucose solution, continuously administered by intravenous drip infusion for 2-6 h. Administered on Day 1 of each treatment cycle, once every 3 weeks; • Apatinib mesylate, 375 mg, administered orally once daily. Administered with warm water approximately half an hour after meals (administration time should be the same in each day whenever possible). During the treatment of SHR-1210 combined with chemotherapy, SHR-1210 will be administered intravenously followed by oxaliplatin at least 30 min later on Day 1 of each cycle. **Cohort 2**: SHR-1210 + apatinib mesylate • SHR-1210, 200 mg, infuse over 30 min (the total infusion time should be no less than 20 min and no more than 60 min, including rinsing period), q3w; • Apatinib mesylate, 375 mg, administered orally once daily. Administered with warm water approximately half an hour after meals (administration time should be the same in each day whenever possible).

	All subjects should continue to receive the study treatment until progressive disease, intolerable toxicity, voluntary treatment discontinuation or study withdrawal by the subject, or discontinuation determined by the investigator. SHR-1210 is an immune checkpoint inhibitor and according to the experience of similar drugs, some subjects may experience delayed or early pseudo progression after receiving immunotherapy drugs. For subjects in the treatment group experiencing progressive disease (PD) for the first time, they may continue with the original treatment if they meet the criteria in section 4.6 Criteria for Continuing Treatment Beyond Disease Progression. Subjects who do not have progressive disease or intolerable toxicities may continue the SHR-1210 treatment for no more than 24 months. Subjects who do not have progressive disease after 24-month treatment may continue the apatinib monotherapy according to the prescribing information of apatinib.
Inclusion Criteria	Patients must meet all of the following criteria to be eligible. 1. Pathologically or cytologically confirmed GC or GEJ cancer, with evidence of being unresectable, locally advanced, or metastatic; histologically confirmed adenocarcinoma mainly. 2. Aged 18 or above, male and female. 3. Patients who have not received systemic treatment (including HER-2 inhibitors) for advanced or metastatic GC/GEJ. Subjects who have received adjuvant or neoadjuvant therapy (including chemotherapy, radiotherapy, or radiochemotherapy) for GC/GEJ must have completed the last treatment at least 6 months prior to the first dose of study treatment. Palliative radiotherapy is permitted, but it must be completed 2 weeks prior to the start of study treatment. 4. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1. 5. With measurable lesion as per RECIST 1.1 criteria. 6. Life expectancy > 12 weeks. 7. All acute toxicities due to previous anti-tumor treatments or surgeries must have resolved to Grade 0–1 (as per NCI CTCAE 4.03) or to the level specified in the inclusion/exclusion criteria. Other toxicities such as alopecia, which do not pose a safety risk to the subjects evaluated by investigators, are excluded. 8. With adequate organs and bone marrow functions, as defined below: a) Absolute neutrophil count (ANC) ≥ 1500/mm^3 (1.5×10^9/L); b) Platelet count (PLT) ≥ 100,000/mm^3 (100×10^9/L); c) Hemoglobin (Hb) ≥ 9 g/dL (90 g/L); d) Serum creatinine ≤ 1.5 × upper limit of normal (ULN), or creatinine clearance ≥ 60 mL/min; e) Total bilirubin (BIL) ≤ 1.5 × ULN; f) Aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) ≤ 2.5 × ULN; for patients with liver metastasis, ALT and AST should be ≤ 5 × ULN; g) International normalized ratio (INR) ≤ 1.5, prothrombin time (PT) and activated partial thromboplastin time (APTT) ≤ 1.5 × ULN;

	h) Urine protein < 2+; If urine protein is ≥ 2+, then the 24-hour urine protein must be ≤ 1 g; i) Thyroid stimulating hormone (TSH) ≤ ULN; in case of abnormalities, T3 and T4 levels should be measured; if T3 and T4 levels are normal, the subject can be enrolled. 9. Female patients of childbearing potential must have a negative serum pregnancy test within 3 days prior to the first dose, and be willing to use a recognized effective contraceptive measure (such as intra-uterine contraceptive devices, contraceptive pills, and condoms) during the study and within 3 months after the last dose of the study drugs; male patients with female partners of childbearing potential must either be surgically sterilized or agree to take effective contraceptive measures during the study and within 3 months after the last dose of the study drugs. 10. Subjects must agree and have signed the informed consent form, be willing and able to follow the scheduled visits, study treatment, laboratory tests, and other study procedures.
Exclusion Criteria	Patients meeting any one of the followings are not eligible to participate in this study: 1. Known HER2-positive. 2. Prior treatment with anti-PD-1/PD-L1 antibodies, CTLA-4 antibodies, or other treatments targeting PD-1/PD-L1 and/or VEGFR inhibitors. 3. Known allergies to the study drug or their excipients; severe allergic reactions to other monoclonal antibodies. 4. Having received immunosuppressive drugs within 14 days prior to the first dose of SHR-1210, excluding intranasal and inhaled corticosteroids or systemic steroids of physiological doses (i.e., no more than 10 mg/d of prednisolone or equivalent). 5. Having received live, attenuated vaccines within 4 weeks before the first dose or had such vaccination plan during the study. 6. Presence of known uncontrolled or symptomatic active central nervous system (CNS) metastases, manifested as clinical symptoms, cerebral edema, spinal cord compression, carcinomatous meningitis, leptomeningeal disease, and/or progressive growth. Patients with a history of metastases to the central nervous system or spinal cord compression may be eligible if they are clearly treated and clinically stable 4 weeks after discontinuation of anticonvulsants and steroids before the first dose of study treatment. 7. Presence of Grade > 1 peripheral neuropathy. 8. Advanced diseases that are symptomatic, disseminated to viscera, and at risk of life-threatening complications in the short term (including uncontrollable massive [pleural, pericardial, and abdominal] exudate, pulmonary lymphangitis, and more than 30% of hepatic involvement). 9. Presence of any active autoimmune diseases or a history of autoimmune diseases (including but not limited to autoimmune hepatitis, interstitial pneumonia, uveitis, enteritis, hepatitis, hypophysitis, vasculitis, nephritis, hyperthyroidism, hypothyroidism; adult subjects with vitiligo or completely relieved childhood asthma can be enrolled if they do not require any intervention; patients with asthma requiring medical interventions with bronchodilators cannot be enrolled). 10. Having been diagnosed with any other malignancies within 3 years before the enrollment, excluding adequately treated basal cell carcinoma or squamous cell skin cancer, or cervical carcinoma *in situ*.

	11. Infection with human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS), active hepatitis B (HBV DNA ≥ 500 IU/mL), hepatitis C (hepatitis C antibody being positive and HCV-RNA being above the lower limit of detection of the assay), or co-infection of hepatitis B and C. 12. Any of the following conditions observed within 6 months prior to the enrollment: myocardial infarction, severe/unstable angina, > NYHA Class II cardiac insufficiency, poorly controlled arrhythmia (including males with QTcF > 450 ms and females with QTcF > 470 ms, QTcF interval calculated with the Fridericia's formula), symptomatic congestive cardiac failure, or cerebrovascular accident (including transient ischemic attack or symptomatic pulmonary embolism). 13. Hypertension uncontrolled by antihypertensives (systolic pressure > 140 mmHg or diastolic pressure > 90 mmHg). 14. Abnormal coagulation function (INR > 1.5 or activated partial thromboplastin time (APTT) > 1.5 × ULN), bleeding tendency, or receiving thrombolytics or anticoagulant therapy. 15. Known hereditary or acquired hemorrhage and thrombophilia (hemophilia, coagulopathy, thrombocytopenia, hypersplenism, etc.). 16. Obvious hemoptysis or a daily amount of hemoptysis of half a teaspoon (2.5 mL) or more within 2 months before the enrollment. 17. Clinically significant hemorrhage symptoms or clear bleeding tendency within 3 months prior to participation in this study, such as GI bleeding, hemorrhagic gastric ulcer, baseline fecal occult blood++ and above, or vasculitis. 18. Events of arterial/venous thrombosis within 6 months prior to participation in this study, such as cerebrovascular accidents (including transient ischemic attacks, cerebral hemorrhage, and cerebral infarction), deep vein thrombosis, and pulmonary embolism. 19. Known hereditary or acquired hemorrhage and thrombophilia (hemophilia, coagulopathy, thrombocytopenia, hypersplenism, etc.). 20. Requiring long-term anticoagulant therapy with warfarin or heparin; or requiring long-term antiplatelet therapy (aspirin ≥ 300 mg/day or clopidogrel ≥ 75 mg/day). 21. Complicated with severe infection (such as one requiring intravenous infusion of antibiotics, antifungals, or antivirals) within 4 weeks prior to the first dose, or any unexplained fever of > 38.5 °C observed during screening period/prior to the first dose. 22. Known history of allogeneic organ transplantation or allogeneic hematopoietic stem cell transplantation. 23. Having participated in clinical studies concerning any other drugs within 4 weeks prior to the first dose, or less than 5 half-lives from the last dose of study drugs. 24. Known history of psychotropic substance abuse or drug abuse. 25. Patients with other severe physical or psychiatric disorders or laboratory abnormalities, which may increase the risk of participating in this study or interfere with the study results, as well as those deemed unsuitable by the investigator.

Study withdrawal criteria	Reasons for withdrawal may include: • Withdrawal of informed consent and refusal of further follow-ups by subjects; • Continuing participation in the study violating the patient's optimal benefit due to clinical AEs, laboratory abnormalities, or concurrent diseases, as assessed by the investigator; • Other investigator-assessed reasons requiring withdrawal, such as the inability to provide voluntary consent due to imprisonment or quarantine; • Lost to follow-up; • Death; • Study termination by the sponsor.
Criteria for Study Termination	The study treatment must be discontinued when any of the following occurs: • Requests to discontinue the study treatment by subjects; • Radiographic or clinical evidence of progressive disease, unless the subject meets the criteria for continuing treatment after progression; • Occurrence of pregnancy during the study; • Any clinical AEs, laboratory abnormalities, or other medical conditions indicating that the subject can no longer benefit from the treatment; • Comprehensive deterioration of health status and inability to continue study participation; • Significant protocol deviations such as ineligibility found after enrollment; • Lost to follow-up; • Study termination by the sponsor; • Death; • Other reasons as determined by the investigator.
Determination of Sample Size	The sample size will be calculated using Simon's two-stage design, with a power of 80% and a one-sided α of 0.05. The optimal method is used, that is, minimizing the subjects' exposure to ineffective treatment. Assuming that in the cohort 2 (SHR-1210 + apatinib), uninteresting level ORR (P0) = 15% and desirable target level ORR (P1) = 30%. The first stage requires 19 subjects, and the treatment should be effective in > 3 subject (i.e. a minimum of 4) before proceeding to the second stage. The first and the second stages require a total of 55 subjects, and the treatment should be effective in > 12 subjects (i.e., a minimum of 13) to be considered effective. Assuming that in the cohort 1 (sequential therapy of SHR-1210 + capecitabine + oxaliplatin), the uninteresting level ORR (P0) = 35% and desirable target level ORR (P1) = 55%. Under the condition that the power of test is 80% and α is 0.05 (one-sided), the first stage requires 19 subjects in both cohort 1 and cohort 2 for the purpose of consistency. The treatment should be effective in > 3 subjects (i.e. a minimum of 4) before proceeding to the second stage. The first and the second stages require a total of 43 subjects, and the treatment should be effective in > 20 subjects (i.e., a minimum of 21) to be considered effective.

	The number of subjects and the required minimum number of subjects responding to the treatment at each stage for both cohorts are shown in the table below: **P0** **P1** **N1** **R1** **N** **R** **Cohort 1** 35% 55% 19 3 43 20 **Cohort 2** 15% 30% 19 3 55 12 N1: Number of subjects at the first stage; R1: Number of subjects responding to the treatment at the first stage shall be greater than this number; N: Final number of subjects; R: Final number of subjects responding to the treatment shall be greater than this number. At the first stage, 19 subjects are enrolled into each cohort. If ≥ 4 subjects in cohort 1 achieve response (CR or PR), the second stage will be initiated, and 24 more subjects are enrolled (more subjects are enrolled into cohort 1 until there are 43 subjects); if ≥ 4 subjects in cohort 2 achieve response, the second stage will be initiated, and 36 more subjects are enrolled (more subjects are enrolled into cohort 2 until there are 55 subjects). Considering the 10% non-evaluable subjects, 48 and 62 subjects should be enrolled into cohort 1 and 2, respectively.
Data Analysis/ Statistical Methods	■ General analysis For this study, efficacy data will be summarized in accordance with the following general principles using descriptive statistics, unless otherwise stated. Two-category and multi-category data will be summarized using frequency and percentage. Multi-category ordinal data will be summarized using cumulative frequency and percentage. Measurement data will be summarized using mean, standard deviation, median, maximum, and minimum. For time-event data, the survival rate and median survival time for the time of interest will be estimated using the Kaplan-Meier method. Serum drug concentrations will be summarized using mean or geometric mean, standard deviation, coefficient of variation or geometric coefficient of variation, median, maximum, and minimum. All statistical analyses will be performed using SAS version 9.2 or later. ■ Efficacy analysis In addition to the general principles of efficacy analysis described above, the analysis of primary and secondary efficacy indicators also includes: Objective response rate (ORR) and disease control rate (DCR): The 95% CI for ORR will be calculated using the Clopper-Pearson method. Progression-free survival (PFS): Survival curves will be plotted using the Kaplan-Meier method, and the 95% CI for median survival will be calculated using the Brookmeyer-Crowley method. Duration of response (DOR) will be analyzed using the same general principles, but the 95% confidence interval for the median and a survival curve may be added if appropriate.

	■ Safety analysis The AEs, SAEs, and adverse drug reactions will be analyzed mainly using descriptive statistics. Laboratory tests that are normal before the study but become abnormal after starting treatment will be described. ■ PK analysis PK analysis is performed based on the PK analysis set. PK concentrations and PK parameters (maximum and minimum concentration) are summarized by descriptive statistics. Apart from the statistics listed in the general analysis, PK concentration and PK parameter data (maximum and minimum concentration) will be also summarized descriptively using geometric mean (GM), coefficient of variation (CV%), and geometric CV% (GCV%). The correlation between drug exposure and toxicity is analyzed based on the maximum and minimum concentration of SHR-1210 and apatinib. ■ Immunogenicity analysis The immunogenicity will be analyzed based on the ADA analysis set. The concentration of anti-SHR-1210 antibodies (ADAs) will be analyzed using descriptive statistics. Treatment-emergent adverse events may be analyzed separately in the ADA-negative and ADA-positive groups.

SCHEDULE OF ACTIVITIES

Study Procedures	Screening Period		Cycle 1	Cycle 2 and beyond	End of Treatment/ Withdrawal	Follow-Up Period (at the end of treatment)	
	D-28 ~ D-1	D-7 ~ D-1	D1 ± 3[22]	D1 ± 3		Safety Follow-Up[23]	Survival Follow-Up[24]
Signing of Informed Consent Form[1]	×						
Demographics	×						
Medical History and Treatment History[2]	×						
Verification of Eligibility		×					
ECOG PS[3]		×	×	×	×	×	
Vital Signs[4]		×	×	×	×	×	
Physical Examination[5]		×	×	×	×	×	
Virology[6]	×						
Hematology[7]		×	×	×	×	×	
Urinalysis[8]		×	×	×[8]	×	×	
Fecal Occult Blood Test[9]		×		×[9]	×	×	
Clinical Chemistry[10]		×	×	×	×	×	
Coagulation Function[11]		×	×	×	×	×	
Thyroid Function[12]		×	×	×[12]	×	×	
12-Lead ECG[13]		×	×	×	×	×	
Echocardiography[14]		×			×		

Study Procedures	Screening Period		Cycle 1	Cycle 2 and beyond	End of Treatment/ Withdrawal	Follow-Up Period (at the end of treatment)	
	D-28 ~ D-1	D-7 ~ D-1	D1 ± 3[22]	D1 ± 3		Safety Follow-Up[23]	Survival Follow-Up[24]
Pregnancy Test[15]		×			×		
Oncology Imaging Examination[16]	×			×[16]	×[16]	×[16]	×[16]
Study Treatment[17]			×	×			
Blood Sampling for PK Study[18]			×[19]	×[19]	×	×	
Blood Sampling for ADA Detection[19]			×[20]	×[20]	×	×	
Adverse Events [20]	×	×	×	×	×	×	×
Concomitant Medications/Concomitant Treatments[21]	×	×	×	×	×	×	

Note: Other than the examinations and time points listed in the table, the investigator may add visits and other examinations if needed. Results should be documented in the corresponding sections of the electronic case report form (eCRF) (e.g., "Unscheduled Visit Examination").

[1] Except for tumor imaging evaluation and tumor tissue biopsies performed within the specified time limit prior to the first dose, written informed consent must be obtained from subjects before any study procedures. Subjects who have failed previous screening may be screened again in this study. The informed consent form must be re-signed and a new subject number should be given for re-screening.

[2] Medical history and treatment history: including tumor history (diagnosis, surgery, radiotherapy, chemotherapy history) and history of other concurrent diseases. Among them, tumor diagnosis should include: the results of the histological diagnosis, pathological classification, histological grade, clinical stage, and time of first diagnosis prior to enrollment.

[3] ECOG PS: The ECOG PS is evaluated within 7 days prior to the first dose, before drug administration on Day 1 of each cycle, at the end of treatment/upon withdrawal, and upon the first visit during the safety follow-up period.

[4] Vital signs: Pulse rate, respiratory rate, body temperature and blood pressure; the vital signs are evaluated within 7 days prior to the first dose, before drug administration on Day 1 of each cycle, at the end of treatment/upon withdrawal, and upon the first visit during the safety follow-up period.

[5] Physical examination: Within 7 days prior to the first dose and at the end of treatment/upon withdrawal, a comprehensive physical examination (including 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 and mental state) is performed; before drug administration on Day 1 of each cycle and upon the first visit of the safety follow-up period, symptom-directed physical examination can be performed if clinically indicated.

[6] Virology: HBsAg, HBsAb, HBeAg, HBeAb, HBcAb, HBV DNA (if the Hepatitis B five items test indicates HBV infection [HBsAg positive] or if the subjects have a history of HBV infection, HBV DNA quantification should be performed), HCV-Ab (if the result is positive, HCV RNA quantification should be performed), and HIV-Ab.

[7] Hematology: Red blood cell count (RBC), hemoglobin (Hb), platelet count (PLT), white blood cell count (WBC), absolute neutrophil count (ANC), and lymphocyte count; hematology test is performed within 7 days prior to the first dose, before drug administration on Day 1 of each cycle, at the end of treatment/upon withdrawal, and upon the first visit of the safety follow-up period.

[8] Urinalysis: WBC, RBC, and urine protein. If the urine protein ≥ 2+, the 24-h urine protein quantification should be performed; the urinalysis is performed within 7 days prior to the first dose, before drug administration on Day 1 of every two cycles, at the end of treatment/upon withdrawal, and upon the first visit during the safety follow-up period.

[9] Fecal occult blood test: Fecal occult blood test is performed within 7 days prior to the first dose (if the fecal occult blood is positive, the test should be performed again. If the result is still positive, gastrointestinal endoscopy should be performed), before drug administration on Day 1 of every two cycles, at the end of treatment/upon withdrawal, and upon the first visit during the safety follow-up period.

[10] Blood biochemistry: Alanine transaminase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (γ-GT), total bilirubin (TBIL), direct bilirubin (DBIL), alkaline phosphatase (AKP), blood urea nitrogen (BUN, preferred) or urea, total protein (TP), albumin (ALB), creatinine (Cr), blood glucose (GLU), K^+, Na^+, Ca^{2+}, Mg^{2+} and Cl^-. The blood biochemistry test is performed within 7 days prior to the first dose, before the drug administration on Day 1 of each cycle, at the end of treatment/upon withdrawal, and upon the first visit of the safety follow-up period.

[11] Coagulation function: Activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), fibrinogen (FIB), and international normalized ratio (INR); coagulation function is evaluated within 7 days prior to the first dose, before drug administration on Day 1 of each cycle, at the end of treatment/upon withdrawal, and upon the first visit during the safety follow-up period.

[12] Thyroid function: Thyroid stimulating hormone (TSH), free tri-iodothyronine (FT3), and free thyroxine (FT4). If FT3 and FT4 are unavailable, T3 and T4 can be used instead. The thyroid function is evaluated within 7 days prior to the first dose, before drug administration on Day 1 of every two cycles, at the end of treatment/upon withdrawal, and upon the first visit during the safety follow-up period.

[13] 12-Lead ECG: Attentions should be paid to QT, QTc, and PR-intervals. Performed within 7 days prior to the first dose, on Day 1 of each cycle before administration (retest is not required prior to the first dose if ECG is completed within 7 days prior to the first dose at screening), at the end of treatment/study withdrawal, and at the first visit during the safety follow-up period.

[14] Echocardiography: Echocardiography is performed within 7 days prior to the first dose and at the end of treatment/upon withdrawal if clinically indicated.

[15] Pregnancy test: Serum pregnancy test will be performed for women of childbearing potential. The serum pregnancy test is performed 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 chest, abdomen, and pelvis. Brain MRI is required when brain metastasis is suspected and confirmed (if MRI is contraindicated, CT can be used instead). Bone scan is performed only when clinically indicated and must be performed within 42 days before the first dose.

- ✓ At screening, tumor evaluations up to 4 weeks before the first dose and before signing the informed consent may be used as long as they meet the RECIST 1.1.
- ✓ During the treatment period, imaging examination is performed once every two cycles (6 weeks) in the first 12 months (the first 16 cycles), then once every 3 cycles (9 weeks) thereafter. Imaging examination should be also performed if new lesions are suspected. Imaging examination should be performed when subjects withdraw from the study for any reason (± 4 weeks; the imaging examination does not need to be repeated if the time from the last examination is no more than 4 weeks). Imaging conditions should be the same as those at baseline (including slice thickness and contrast agent). The time window for tumor evaluation is ± 7 days. Additional tumor evaluations may be performed if PD is suspected (for example, worsening of symptoms).
- ✓ During safety follow-ups and survival follow-ups, subjects in whom no radiographic progression is observed should continue to undergo imaging assessment at the original frequency until PD, death, lost to follow-up, or start of other anti-cancer treatments.
- ✓ Subjects who discontinue treatment for reasons other than radiographically confirmed PD must also undergo imaging examination at the frequency specified in the protocol whenever possible until documented PD, start of a new anti-tumor treatment, or death.

[17] Study treatment: Each cycle lasts for 21 days. Depending on the group of subjects, the following treatments are administered (for the administration method of the drugs, please refer to section 5.1.5):

- ✓ Cohort 1 (sequential therapy of SHR-1210 combined with capecitabine and oxaliplatin): SHR-1210 200 mg, intravenous infusion, once every 3 weeks; capecitabine 1000 mg/m^2, administered orally, twice daily, 2 weeks of treatment followed by 1 week of drug interruption; oxaliplatin 130 mg/m^2, intravenous infusion, once every 3 weeks; subjects in whom no radiographic progression is observed, after 4-6 cycles of the above treatment, continue to receive the SHR-1210 + apatinib (375 mg, administered orally, once daily) treatment.
- ✓ Cohort 2 (SHR-1210 combined with apatinib): SHR-1210 200 mg, intravenous infusion, once every 3 weeks; apatinib 375 mg, administered orally, once daily, continuous administration.

[18] Blood sampling for PK study: Blood samples are collected for PK study from subjects receiving SHR-1210 plus apatinib. Blood samples are collected once within 0.5 h before the administration of SHR-1210 + apatinib on Day 1, once at 3 h (± 5 min) after the drug administration, and once within 0.5 h before the administration of apatinib on Day 7 (a total of 3 blood sampling time points in the first cycle of SHR-1210 + apatinib). PK blood samples are collected at the same time points above for each cycle afterwards, for 6 cycles in total (including the first cycle of SHR-1210 plus apatinib). PK blood samples are collected once at 30 days (± 7 days), 60 days (± 7 days), and 90 days (± 7 days) after the last dose of study treatment, respectively (depending on the visit schedule if applicable).

[19] Blood sampling for ADA detection: Blood samples are collected within 0.5 h before the drug administration on C1D1, C2D1, C4D1, C6D1, and C9D1, respectively. ADA blood samples are collected once every 4 cycles within 0.5 h before the drug administration since Cycle 9. ADA blood samples are collected once at 30 days (± 7 days), 60 days (± 7 days), and 90 days (± 7 days) after the last dose of study treatment, respectively (depending on the visit schedule if applicable).

[20] AEs: AEs are recorded from the date of signing informed consent to the end of the safety follow-up (90 days after the last dose) or the start of a new anti-cancer therapy. The adverse events should be followed up until they are resolved, return to baseline levels or Grade ≤ 1, reach a stable state, or are reasonably explained (e.g., lost to follow-up, death).

[21] Concomitant medications/concomitant treatments: Concomitant medications/concomitant treatments are recorded from within 30 days before the first dose until the end of the safety follow-up. After the end of treatment or withdrawal, only concomitant medications/concomitant treatments related to the treatment-related AEs are documented.

[22] There is no need to repeat the laboratory tests (hematology, urinalysis, clinical chemistry, coagulation function, and thyroid function) and ECG before drug administration on D1 of Cycle 1, if such tests have already been performed at baseline within 7 days before the first dose.

[23] Safety follow-up: Safety follow-up starts from the last dose of study treatment, once every 30 days (± 7 days) until 90 days after the last dose. The first safety follow-up visit (30 days ± 7 days) is carried out at the study center where the evaluations specified in the protocol will be completed. The second (60 days ± 7 days) and the third (90 days ± 7 days) follow-up are made via telephone calls. The information on survival, concomitant medications/concomitant treatments and AEs are collected.

[24] Survival follow-up: At the end of the safety follow-up period, the subjects will enter the survival follow-up period until death, lost to follow-up, withdrawal of informed consent or termination of the clinical study by the sponsor. During this period, visit will be conducted via telephone or other effective methods once every month to collect information on subject survival and subsequent treatments (if the subjects start a new anti-tumor treatment, the therapeutic regimen and the start and end time should be recorded).

ABBREVIATIONS

Abbreviations	Full Name
12-Lead ECG	12-Lead electrocardiogram
ADA	Anti-drug antibody
AE	Adverse event
AKP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute Neutrophil Count
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CDK	Cyclin-dependent kinase
Cl^-	Blood chlorine
Cr	Creatinine
CR	Complete Response
CRF	Case report form
CRO	Contract research organization
CTLA-4	Cytotoxic T Lymphocyte Antigen 4
D	Day
DC	Dendritic Cell
DCR	Disease Control Rate
DoR	Duration of Response
EC	Ethics committee
ER	Estrogen Receptor
FAS	Full Analysis Set
GC	Gastric Cancer
GCP	Good Clinical Practice
GEJ	Gastroesophageal Junction cancer
h	Hour
Hb	Hemoglobin
HER-2	Human epidermal growth factor receptor 2
HR	Hazard Ratio
HUVEC	Human umbilical vein endothelial cells
IB	Investigator's brochure
IC_{50}	Half maximal inhibitory concentration
irAE	Immune-related Adverse Event
IU	International unit
K^+	Serum potassium
kg	Kilogram

Abbreviations	Full Name
LDH	Lactate dehydrogenase
mg	Milligram
mL	Milliliter
mm	Millimeter
MTD	Maximum tolerated dose
Na^+	Plasma sodium
NEUT	Neutrophil
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
NYHA	New York Heart Association
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PD-1	Programmed Death-1
PD-L1	Programmed death-ligand 1
PDGFR	Platelet-derived growth factor receptors
PFS	Progression-Free Survival
PK	Pharmacokinetics
PKS	Pharmacokinetics set
PPS	Per-Protocol Set
PR	Partial Response
PLT	Blood platelet
RBC	Red blood cell count
RECIST	Response Evaluation Criteria In Solid Tumors
sec	Second
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable Disease
SS	Safety Set
sUA	Serum uric acid
T-BIL	Total bilirubin
TEAE	Treatment Emergent Adverse Event
UA	Uric acid
URBC	Urine red blood cell
VEGF	Vascular endothelial growth factor
WBC	White blood cell count

1 INTRODUCTION: BACKGROUND AND SCIENTIFIC RATIONALE

1.1. Background

Gastric cancer (GC) is one of the common malignancies with poor prognosis, seriously threatening human health. In 2012, there were approximately 951 thousand new cases of GC and approximately 723 thousand GC-related deaths worldwide, ranking the 5th in incidence and the 3rd in mortality of all malignant tumors. China is a country with a high prevalence of GC. The number of cases developing GC and deaths related to GC in China accounted for 42.6% and 45.0%, respectively, the data worldwide. In the past decade, the incidence and mortality of GC have remained stable in urban areas of China, but numbers of male were on the rise in rural areas and there was little change in rural females. According to the latest statistics from the National Center for Cancer Registry, in 2015, there were approximately 679 thousand newly diagnosed cases of GC and approximately 498 thousand GC-related deaths in China.

Surgery is the primary treatment for early GC, and the 5-year survival rate of GC patients receiving surgical treatment is about 40-50%. However, early GC is usually asymptomatic, which makes the diagnosis difficult. For this reason, early GC may remain undetected. At present, the five-year survival rate of GC is about 27% in China. For patients with advanced or metastatic gastric cancer, chemotherapy can relieve symptoms and achieve survival benefit compared with best supportive care. Combination chemotherapy based on fluorouracil and platinum is the mainstream first-line treatment at present. The median survival of GC patients receiving this combination chemotherapy is 9.5 to 13 months. Therefore, there is an urgent clinical need to develop more effective treatment regimen to improve the current treatment of advanced GC.

This study involves recombinant humanized anti-PD-1 monoclonal antibody injection (SHR-1210), a new class 1 therapeutic biological product that has not been marketed either in China or abroad. Preclinical studies have shown that SHR-1210 has comparable *in vivo* pharmacological and safety profiles to those of drugs of the same class abroad, and may have a better clinical potential for anti-tumor treatment. Phase I clinical studies have been conducted on SHR-1210 in Australia and China since 2015. Several clinical studies are currently underway.

This study also involves apatinib mesylate (trade name: Aitan), which was launched in 2014 by Jiangsu Hengrui Pharmaceuticals Co., Ltd. Apatinib is a small molecule targeted medicine and acts as a tyrosine kinase inhibitor of vascular endothelial growth factor receptor (VEGFR). Apatinib exerts its anti-angiogenic effect to treatment cancer mainly by inhibiting VEGFR. China Food and Drug Administration (CFDA, now National Medical Products Administration, NMPA) approved apatinib for the treatment of advanced GC and gastroesophageal junction (GEJ) adenocarcinoma on 17 Nov., 2014.

This study is a clinical study on the inhibitor targeting the VEGF-VEGFR pathway combined PD-1 monoclonal antibody for the treatment of advanced GC. The goal is to lay a solid foundation for new combination therapies urgently needed in clinical practice. The present study has important clinical and academic significance.

1.1.1. Information on SHR-1210

1.1.1.1. Pharmacology and mechanism of action

Programmed death-1 (PD-1) is a protein receptor expressed on the surface of T cells 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-4. It is primarily expressed on 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. In contrast, the expression of PD-L2 is mainly restricted to antigen presenting cells, such as activated macrophages and DCs. Humanized anti-PD-1 monoclonal antibody can specifically bind to PD-1, block the interaction between PD-1 and its ligands, and restore T cell immune response to tumor cells.

1.1.1.2. Pharmacodynamics

Experiments on the binding affinity of SHR-1210 antibody to human, monkey and rat antigens (Table 1) showed that the affinities of SHR-1210 to human and monkey PD1 antigens were quite close at 6.9 nM and 4.1 nM, respectively, but no binding was detected with rat PD-1 antigens. SHR-1210 shows an affinity of 3.0 nM for the antigen (human PD-1) and its activity is comparable to that of the control antibodies Nivolumab and Pembrolizumab (Table 2).

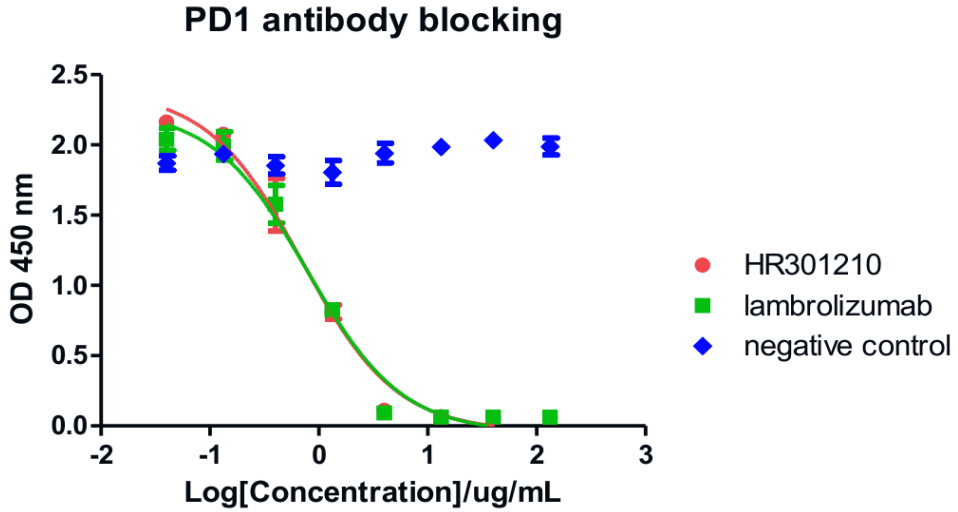
Stationary Phase	Mobile Phase	Affinity (nM)
SHR-1210	Human PD-1 antigen	6.9
SHR-1210	Murine PD-1 antigen	Extremely weak signals, no binding detected
Monkey PD-1 antigen (-hFc)	SHR-1210	4.1

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

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

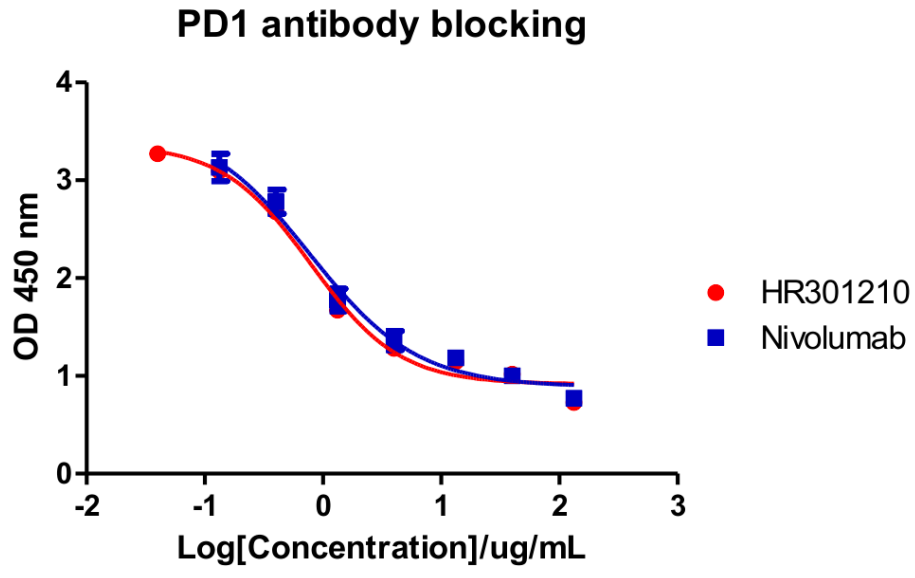
Table 2. Inhibition of PD-1/PD-L1 binding by SHR-1210

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



	HR301210	lambrolizumab
IC50	0.7007	0.7864

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



	HR301210	Nivolumab
IC50	0.7913	0.7745

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

1.1.1.3. Toxicology studies

In a pre-clinical acute toxicity experiment in cynomolgus monkeys, 8 cynomolgus monkeys (half male and half female) were randomly divided into 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, continuous intravenous administration of SHR-1210 at 20, 50, and 100 mg/kg for 4 weeks (5 total doses) was well-tolerated in both sexes. Clinical symptoms, including injection site irritation, or changes in body weight, food intake, body temperature, ECG, blood pressure, heart rate and respiratory measurements related to SHR-1210 were not observed. No changes in B and T cell differentiation, cytokines, immunoglobulins, and complements were observed. No changes in organ weight, gross lesions, or histopathological changes associated with SHR-1210 were observed.

Apatinib primarily caused slight changes in body weight, food intake, liver function, and bone in rats. After 4 weeks of drug discontinuation, all other changes were recovered except that the bone changes were partially recovered. 15 mg/(kg•d): The safe dose in male and female rats. 50 mg/(kg•d): The toxicity dose of male and female rats, and female rats are more sensitive. The 3-month oral application of 30 mg/(kg•d) of apatinib capsules in Beagle dogs showed no significant toxicity.

1.1.1.4. Pharmacokinetic study

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

Dosage (mg/kg)	Gender	$T_{1/2}$ (hr)	Tmax (hr)	Cmax (μg/ml)	AUClast (hr×μg/ml)	Vz (ml/kg)	Cl (ml/hr/kg)	MRTlast (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

Dosage (mg/kg)	Gender	$T_{1/2}$ (hr)	Tmax (hr)	Cmax (μg/ml)	AUClast (hr×μg/ml)	Vz (ml/kg)	Cl (ml/hr/kg)	MRTlast (hr)
	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
2	Male	113.54± 8.26	1.67±0.58	71.65±10.85	6380.24±2062.85	47.05±27.05	0.47±0.12	127.10± 59.24
	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	124.01± 49.13
	Female	169.70± 38.96	2.17±1.76	217.46± 20.22	31357.28± 9338.28	41.24±24.76	0.33±0.1	179.68±73.6
3	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

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

1.1.1.5. Progress in the clinical studies of SHR-1210

Since 2015, Jiangsu Hengrui Pharmaceuticals Co., Ltd. has conducted 4 phase I clinical studies of SHR-1210 at multiple sites in Australia and China, which preliminarily validated the safety, tolerability and efficacy of SHR-1210 in patients with advanced solid tumors who have failed existing standard treatments.

By the end of 2016, 140 subjects with solid tumor had been enrolled in China and abroad, including 116 subjects enrolled in China and 24 subjects enrolled in Australia. Tolerability observation showed that different doses of SHR-1210 (1 mg/kg, 3 mg/kg, 6 mg/kg, 10 mg/kg and fixed doses of 60 mg, 200 mg, and 600 mg) were well tolerated. No DLTs were observed in any of the dose groups during the tolerability observation period, i.e., the maximum tolerated dose (MTD) is greater than 10 mg/kg or 600 mg.

The investigator-assessed adverse drug reactions possibly related to the investigational drug (SHR-1210) mainly included the following: reversible capillary proliferation, rash, pruritus, fatigue, asthenia, fever, anemia, nausea, vomiting, headache, dizziness, diarrhea, serum transaminase increased, serum bilirubin increased, prolonged QT interval, hypothyroidism, hyperthyroidism and hypophysitis. The majority of the adverse drug reactions were Grade 1-2 and could be controlled with or without medical intervention.

1.1.2. Information on apatinib mesylate

Apatinib is a potent and selective inhibitor of vascular endothelial growth factor receptor-2 (VEGFR-2). The activity assay showed that its inhibitory effect against VEGFR-2 is stronger than that of drugs of same class (sorafenib, sunitinib, pazopanib, etc.); its selectivity for VEGFR-2 is ≥ 30 times stronger than that of other targets (VEGFR-1/PDGFR, SRC, etc.). Apatinib can effectively inhibit the *in vitro* lumen formation of Human Umbilical Vein Endothelial Cells (HUVEC) and the formation of arterial ring capillaries in rats, and has a strong inhibitory effect against neovascularization.

The efficacy and safety of apatinib monotherapy in advanced GC were evaluated in two randomized controlled studies. The efficacy and safety of apatinib in the treatment of advanced GC were evaluated in a multicenter, randomized, double-blind, placebo-controlled phase III clinical study. A total of 267 patients with advanced gastric cancer, including gastroesophageal junction adenocarcinoma, who had failed second-line treatment (definition of treatment failure: intolerable toxic and side effects, progressive disease during treatment, or recurrence after the end of treatment) were enrolled in the study. The median age of patients treated with apatinib was 58 years old, and 75% were male; 27% had an ECOG PS of 0 and 73% had an ECOG PS of 1; about 60% of the patients had once received radical surgery, including about 22% with total gastrectomy and 35% with gastrectomy; 68% of the primary lesions were GC, and 22% were GEJ adenocarcinoma; 21% of the patients had more than 2 organs affected by metastases cumulatively, and 56% of the patients had liver metastases; 92% of the patients were clinically classified as stage IV; 66% of the patients had once received at least 2 types of systemic chemotherapy; the basic drugs used in first-line chemotherapy included fluorouracil, platinum, paclitaxel, and doxorubicin; the second-line chemotherapy is primarily based on irinotecan. The investigational treatment group and the placebo group were comparable in baseline features and demographics of subjects. The subjects were randomized in a 2:1 ratio to receive either apatinib tablet 850 mg treatment once daily (n = 176) or placebo once daily (n = 91) in 28-day cycle. The mean chemotherapy cycles were 2.9 in the treatment group, with 72% of the subjects receiving 2 or more cycles of treatment.

The primary efficacy endpoint was overall survival (OS). The secondary efficacy endpoints included progression-free survival (PFS), disease control rate (DCR), and objective response rate (ORR). The median overall survival in the investigational treatment group was prolonged compared with the placebo group, while the death risk was reduced by about 30%. The secondary endpoints PFS and DCR were also higher in the treatment group than those in the placebo group. Generally, no symptoms specific to advanced GC or deterioration of health-related life quality were caused. Table 4. lists the primary efficacy results, and Figure 3. shows the survival curves.

Endpoint	Treatment Group (n = 176)	Placebo Group (n = 91)
Overall survival (OS)		
Median (mOS, month)	6.5	4.7
HR (95% CI)	0.709 (0.537, 0.937)	
Progression-free survival (PFS)		
Median (mPFS, month)	2.6	1.8
HR (95% CI)	0.444 (0.331, 0.595)	
Objective Response Rate (CR + PR)	2.84%	0
Clinical Benefit Rate (CR + PR + SD)	42.05%	8.79%

Table 4. Efficacy results of the phase III clinical study of apatinib in GC (FAS)

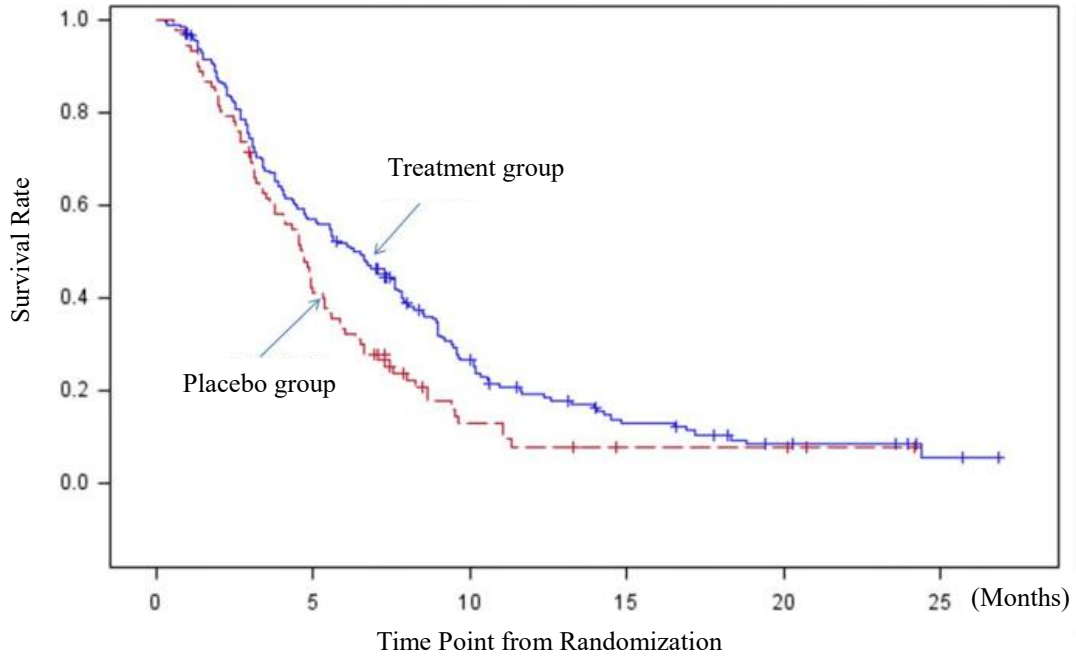


Figure 3. Survival analysis of the phase III clinical study of apatinib in GC (FAS)

In the treatment group and the placebo group, the incidences of adverse drug reactions were 92.05% and 71.43%, respectively; the incidences of Grade 3/4 adverse drug reactions were 51.70% and 24.18%, respectively. Among the common adverse drug reactions (incidence ≥ 5%), the ones that were statistically different between the two groups in incidence included hematologic toxicities (WBC decreased, granulocytopenia, and thrombocytopenia) and non-hematologic toxicities (proteinuria, hypertension, hand-and-foot syndrome, asthenia, and hoarse voice). The incidences of serious adverse drug reactions in the investigational treatment group and the control group were 6.25% and 6.59%, respectively. The common serious adverse drug reaction was upper gastrointestinal hemorrhage in both groups.

Another multi-center, randomized, double-blind, placebo-controlled, parallel-group phase II clinical study also targeted advanced GC patients who failed second-line chemotherapy. A total of 141 subjects were enrolled, including 48 subjects in the placebo group, 47 subjects in the 850 mg qd group, and 46 subjects in the 425 mg bid group. Each cycle lasted for 28 days, and the primary endpoint was PFS. Results: The mPFS was 3.7 months in the 850 mg QD group and 3.2 months in the 425 mg bid group, with statistically significant differences compared with the placebo group ($P < 0.0001$). The median survival and the ORR in the two treatment groups were higher than those in the placebo group. Table 5 lists the data on primary efficacy results.

Endpoint	850 mg QD Group (n = 47)	Placebo Group (n = 48)
Overall survival (OS)		
Median (mOS, month)	3.7	1.4
HR (95% CI)	0.232 (0.133, 0.406)	
Progression-free survival (PFS)		
Median (mPFS, month)	4.8	2.5
HR (95% CI)	0.513 (0.319, 0.826)	
Objective Response Rate (CR + PR)	6.38%	0
Clinical Benefit Rate (CR + PR + SD)	51.06%	10.42%

Table 5. Efficacy results of the phase II clinical study of apatinib in advanced GC (FAS)

In this study, the incidences of adverse drug reactions in the apatinib 850 mg QD group and placebo group were 78.72% and 56.25%, respectively; the incidences of Grade 3/4 adverse drug reactions were 30.04% and 16.67%, respectively.

The National Medical Products Administration (NMPA) approved apatinib for the treatment of advanced GC and GEJ cancer in 2014.

1.1.3. Information on capecitabine and oxaliplatin

Capecitabine and oxaliplatin have already been marketed as routine first-line cytotoxic drugs for advanced GC. Refer to their respective prescribing information for details.

1.1.4. Progress in the Clinical Studies of SHR-1210 plus Apatinib

As of 25 Aug., 2017, Hengrui had conducted two clinical studies of SHR-1210 plus apatinib.

SHR-1210-APTN-II-202-NSCLC is an ongoing phase II study. The objective is to evaluate the safety and efficacy of SHR-1210 plus apatinib in non-squamous NSCLC subjects who had metastases or disease progression after multimodal therapy. SHR-1210 is infused intravenously at a fixed dose of 200 mg Q2W for a 28-day cycle with a maximum treatment period of 2 years. In the meantime, apatinib tablet 250 mg, 375 mg or 500 mg is given orally once daily for 28 consecutive days as a cycle.

SHR-1210-APTN-II-203-PLC is an ongoing open-label phase II clinical study. The objective is to evaluate the safety and tolerability of SHR-1210 plus apatinib mesylate or FOLFOX4 (OXA + calcium levofolinate + 5-Fu) in untreated advanced primary liver cancer (PLC) subjects and advanced PLC subjects who failed or were intolerant of systemic treatment, molecular targeted therapy, or systemic chemotherapy. Subjects are enrolled into treatment group A or B based on whether they have received systemic treatment, targeted therapy or systemic chemotherapy before. Subjects in Group A (having received systemic treatment) receive SHR-1210 plus apatinib mesylate (APTN) treatment, in which SHR-1210 is intravenously infused at 3 mg/kg Q2W. The optimal dose of apatinib is explored by elevating from low to high dose. Apatinib tablets 125 mg, 250 mg, 375 mg or 500 mg are given orally once daily for 28 consecutive days as a cycle. Subjects in Group B (having received no systemic treatment) receive SHR-1210 plus FOLFOX4 regimen, in which SHR-1210 is infused intravenously at 3 mg/kg Q2W, and FOLFOX4 regimen Q2W.

A total of 18 subjects in the above two studies have received SHR-1210 plus apatinib treatment. None of the subjects experienced DLT, serious adverse events, or unexpected adverse drug reactions, and no subject discontinued treatment due to adverse drug reactions. The SHR-1210 combined with apatinib at a dose level of 375 mg/day is currently being investigated.

1.2. Scientific Rationale

Cancer immunotherapy is a long-time hot spot in the field of cancer treatment, in which the cancer immunotherapy using T cells is at the core position. Cancer immunotherapy fully utilizes and mobilizes killer T cells in patients to kill tumors, which may be the most effective and safest way to treat tumors. Tumor immune escape is a great challenge in cancer immunotherapy. Cancer cells' suppressive effect on the immune system promotes uncontrolled tumor growth. There is an extremely complex relationship between the immune escape mechanism of tumors and the body's immune response. Specific killer T cells have certain biological activities in the early stage of the cancer development, but they lose their cytotoxicity in the late stage of tumor growth. Therefore, the cancer immunotherapy aims to maximize a patient's own immune response against the tumor. It not only activates the original immune response in the body, but also maintains the duration and intensity of the immune responses which is the key to the cancer immunotherapy.

With better understanding of the mechanism of controlling host response to tumor at the molecular level, the identification of signaling pathways that restrict anti-cancer immune response has been further promoted. The programmed death-1 (PD-1) pathway, one of the most critical checkpoint pathways responsible for regulating tumor-induced immunosuppression, has been substantiated. PD-1 is a protein receptor expressed on the surface of T cells and mainly responsible for regulating cell apoptosis. PD-1 is a member of the CD28 family and has a 23% consistency amino acid sequence with cytotoxic T lymphocyte antigen 4 (CTLA-4). However, its expression is different

from that of CTLA-4. PD-1 is mainly expressed on activated T cells, B cells and myeloid cells. PD-1 has two ligands, PD-L1 and PD-L2. PD-L1 is mainly expressed on T cells, B cells, macrophages, and dendritic cells (DCs), and is up-regulated on activated cells. PD-L1 is up-regulated in many cancers. PD-L1 expression is closely related to shortened survival and poor prognosis in various cancers, including lung cancer, kidney cancer, pancreatic cancer and ovarian cancer. Tumor-infiltrating lymphocytes in patients with cancers usually express PD-1 and their anti-tumor function is impaired. Pre-clinical studies have shown that blocking PD-1 or PD-L1 can enhance T-cell function and promote tumor cell lysis.

A number of pharmaceutical companies are currently developing monoclonal antibodies targeting PD-1/PD-L1. By blocking the binding of PD-1/PD-L1, these monoclonal antibodies maximize a patient's own immune response against tumors, thereby achieving the purpose of killing tumor cells. Bristol-Myers Squibb (BMS) and Merck have jointly developed PD-1 monoclonal antibodies (nivolumab and pembrolizumab), which have been approved by FDA for anti-tumor treatment of various cancers. In Jul. 2014, nivolumab was approved by the Japanese Ministry of Health, Labour and Welfare for the treatment of advanced melanoma. It was approved by the FDA for the treatment of melanoma in Dec. 2014, approved by the FDA for the treatment of non-small cell lung cancer in Mar. 2015, and approved by the FDA for the treatment of renal cell carcinoma in Nov. 2015. In 2016, nivolumab was approved for use in the treatment of classical Hodgkin's lymphoma. In Sep. 2014, Pembrolizumab was approved by the FDA for the treatment of advanced melanoma. In Oct. 2015, Pembrolizumab was approved by the FDA for the treatment of non-small cell lung cancer.

PD-1/PD-L1 inhibitors will play a very important role in the combination anti-cancer treatment regimens. These drugs will revolutionize the current treatment regimens and become the backbone of the combination therapy. This view has already been verified for the treatment of melanoma. CheckMate-069 study showed that nivolumab combined with CTLA-4 inhibitor ipilimumab reduced the mortality by 60% (HR=0.40; 95% CI, 0.22-0.71; $P < 0.002$) compared with ipilimumab monotherapy. For melanoma patients harboring wild-type BRAF, the ORR of the combination therapy was 60%, while the ORR of ipilimumab monotherapy was 11%. Therefore, the FDA accelerated the approval of nivolumab in combination with ipilimumab as a treatment for patients with unresectable or metastatic melanoma who harbor wild-type BRAF V600. According to the reports in the 2016 Annual Meeting of the American Gastroenterological Association and the annual meeting of the American Society of Clinical Oncology, in the CheckMate-032 study, nivolumab was administered to 59 patients with intermediate to advanced esophageal cancer and gastric cancer. The overall response rate was 14%. The response rate of PD-L1 positive (> 1%) patients was 27%, including one case of complete response. The 1-year survival rate was 36%.

Several studies on the anti-tumor mechanism have laid the basis for immunotherapy combined with targeted therapy. Some evidence suggests that targeted molecular therapies can enhance certain aspects of the "cancer-immunity cycle" (such as tumor antigenicity, T cell activation/transport/infiltration, etc.) to synergistically enhance the efficacy of the immunotherapy. In particular, targeted molecular therapies targeting the MAPK and the VEGF pathways can have a direct impact on cancer cell growth and tumor angiogenesis, as well as on tumor antigenicity and intratumoral T cell infiltration. Studies have shown that molecular targeted drugs can induce tumor cell death. Dead tumor cells can release tumor autoantigens, which are taken up by antigen-presenting cells and presented to tumor-specific T lymphocytes. PD-1 antibody inhibits the PD-1/PD-L1 signaling pathway by binding to PD-1 on T lymphocytes, thereby activating the specific killing effect of T lymphocytes on tumor cells. In addition, the release of tumor autoantigens caused by targeted therapy reduces attacks of T lymphocytes on non-tumor antigens, thereby reducing immunotherapy-related adverse drug reactions. This provides a strong basis for tumor immunotherapy combined with targeted therapy.

Chemotherapy can adjust the interactions between the tumor and immunity, thereby assisting the immune system to exert antitumor effects. Chemotherapy can cause death of tumor cells and as a result, more tumor antigens are produced and presented to the antigen-presenting cells. Tumor cell death can reduce soluble and membrane-bound factors that inhibit tumor-infiltrating T cells. In addition, chemotherapy affects the regulatory network of the immune system by reducing the amount of regulatory T cells. The immunogenic chemotherapy, such as oxaliplatin combined with immune checkpoint inhibitors, can trigger T-cell infiltration and have a synergistic anti-tumor effect. This treatment regimen is expected to exert a persistent anti-tumor effect. A phase I/II study of nivolumab showed that patients with advanced NSCLC who received nivolumab combined with chemotherapy (gemcitabine + cisplatin or pemetrexed + cisplatin) achieved an objective response rate of 33-47% (while historical data showed that the ORR of chemotherapy was 15-32%) and had a longer duration of response.

At present, many clinical studies have been conducted on PD-1-targeting treatment in advanced GC and achieved encouraging results. Several clinical studies of pembrolizumab have been carried out in advanced GC patients. KEYNOTE -012 study is a phase Ib clinical study of pembrolizumab monotherapy in advanced GC. A total of 39 (19 Asian patients from Japan, Korea, and Taiwan) PD-L1 positive patients with recurrent or metastatic GC or GEJ cancer were enrolled in the study. These patients were treated with pembrolizumab (10 mg/kg, q2w). Among 36 evaluable patients, 8 patients achieved partial response (PR), with an ORR of 22%. Compared with conventional chemotherapy, pembrolizumab was better tolerated. The common AEs were fatigue (18%), hypothyroidism (13%), itch (13%), and arthralgia (10%). Grade 3-4 AEs occurred in 5 subjects, including grade 3 fatigue in 2 subjects, grade 3 rash vesicular in 1 subject, grade 3 peripheral sensory neuropathy in 1 subject, and grade 4 pneumonia in 1 subject.

In a subsequent phase II study (KEYNOTE-059), the patients were divided into two cohorts. In cohort 1, 259 subjects with recurrent or metastatic GC or GEJ cancer who had received chemotherapy at least twice were enrolled and given pembrolizumab 200 mg q3w. The results showed that the ORR was 11.2% and the median duration of response was 8.1 months. Grade ≥ 3 treatment-related adverse events (TRAEs) were observed in 43 subjects (16.6%). The treatment was interrupted in 2 subjects due to TRAEs (abnormal liver function in 1 subject and bile duct stricture in 1 subject). Fatal AEs occurred in 2 subjects (acute renal failure in 1 subject and pleural effusion in 1 subject). In cohort 2, 25 subjects (including 17 Asian subjects) with untreated recurrent or metastatic HER2- GC/GEJ cancer were enrolled and given the following combination treatment regimen: Pembrolizumab (200 mg) + 5-FU (800 mg/m^2)/capecitabine (1000 mg/m^2, for Japanese subjects) + cisplatin (80 mg/m^2), once every 3 weeks. The ORR was 60%. The ORR of PD-L1 positive and PD-L1 negative patients was 68.8% and 37.5%, respectively. The median DoR was 4.6 months. The DoR of PD-L1 positive and PD-L1 negative patients was 4.6 months and 5.4 months, respectively. The median PFS was 6.6 months, and the median OS was 13.8 months. Grades 3-4 TRAEs occurred in 76% of the subjects. The treatment was interrupted in 3 subjects due to TRAEs (Grade 3 stomatitis in 1 subject, Grade 2 hypacusia in 1 subject, and creatinine increased in 1 subject). None of the TRAEs were fatal.

The CHECKMATE032 study evaluated the efficacy of nivolumab monotherapy or nivolumab in combination with ipilimumab in patients with advanced GC/GEJ cancer who had progression after previous chemotherapy. Among them, 59 patients were treated with nivolumab 3 mg/kg q2w. The ORR was 12%. The ORR of PD-L1 positive and PD-L1 negative patients was 18% and 12%, respectively. The median DoR was 7.1 months. The ORR of the N1I3 group (nivolumab 1 mg/kg + ipilimumab 3 mg/kg) and the N3I1 group (nivolumab 3 mg/kg + ipilimumab 1 mg/kg) was 24% and 8%, respectively. TRAEs were observed in 66% of the subjects. The common Grade 3 AEs were AST increased (5%) and ALT increased (3%). Other AEs included pneumonia, fatigue, diarrhea, vomiting and hypothyroidism.

In summary, preliminary results of immune checkpoint inhibitor in the treatment of advanced GC suggest that it may be a new effective treatment regimen for advanced GC.

1.3. Potential Risks and Benefits

1.3.1. Known potential risks

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

As of 25 Aug., 2017, a total of 539 patients with advanced cancer had been treated with SHR-1210 (either monotherapy or in combination with other drugs). Among them, 414 subjects (76.8%) reported ≥ 1 AE. The most common (incidence > 5%) treatment-related AEs were hemangioma (64.7%), hemangioma of skin (25.0%), asthenia (9.3%), capillary disorder (8.3%), aspartate

aminotransferase increased (8.2%), pruritus (7.8%), rash (7.6%), alanine aminotransferase increased (6.7%), fever (6.5%), white blood cell count decreased (6.1%), anemia (5.9%), blood bilirubin increased (5.9%), hypothyroidism (5.6%), and conjugated bilirubin increased (5.0%). There were a total of 38 SAEs related to SHR-1210, mainly including hemangioma of skin (6 events), abnormal liver function (4 events), interstitial pneumonia (3 events), and infectious pneumonia (2 events).

Investigator-assessed immune-mediated AEs were predominantly skin toxicities (such as rash and capillary proliferation). Most immune-mediated AEs were grade 1-2 in severity. The above data was compared with adverse drug reactions reported for other approved anti-PD-1 antibodies - nivolumab from BMS and pembrolizumab from Merck. The incidence and severity were both low. Overall, the adverse drug reactions of this product are expected to be similar to those of nivolumab and pembrolizumab. Recommended management of common side effects and protocol-specified dose modifications have been established for this study, so that, in the presence of clinical benefit, subjects may continue the SHR-1210 treatment.

All monotherapies using anti-PD-1 antibodies outperformed conventional chemotherapy and targeted therapy in terms of adverse drug reactions on the whole. However, immune-related adverse reactions still require special attention, mainly including immune-related interstitial pneumonia, rash, thyroiditis, as well as those with lower incidence (≤ 1%), such as vitiligo, colitis, nephritis, hepatitis, uveitis, adrenal insufficiency, and nerve paralysis. These immune-related adverse reactions are mostly mild and manageable. Very few are SAEs or potentially life-threatening. Thanks to established procedures for toxicity management, the majority of immune-mediated AEs can be adequately controlled.

Subjects receiving macromolecular protein monoclonal antibody drugs may also encounter other risks including infusion reactions, which prominently manifest as chills, shivers, facial and peripheral cyanosis, followed by fever and probably accompanied by nausea, vomiting, headache, dizziness, dysphoria, delirium, etc. In severe cases, there may be coma, fall in blood pressure, and symptoms such as shock and respiratory failure, etc. These risks may arise due to various factors during intravenous infusion, such as pyrogens, drugs, impurities, low temperature of drug formulation, high concentration of drug, and high rate of infusion, etc. SHR-1210 is a fully humanized monoclonal antibody. Its reported infusion reactions were low in incidence and mild in severity.

Capecitabine and oxaliplatin are common cytotoxic chemotherapeutic drugs with clear list of AEs. Clinical studies and medical practice have demonstrated that the common (≥ 5%) AEs associated with capecitabine plus oxaliplatin (XELOX regimen) include the following: neurotoxicity (19%), nausea (16%), diarrhea (15%), vomiting (11%), fatigue (8%), hand-and-foot syndrome (7%), neutrophils reduced (7%), anorexia (6%), and stomatitis (5%).

Medical examinations during the study may also pose risks to the subjects. Frequent tumor imaging examinations may expose subjects to low-dose radiation more frequently. However, since advanced or metastatic gastric cancer usually progresses rapidly, frequent imaging tumor examinations are necessary to determine the presence of progressive disease.

1.3.2. Known potential benefits

As mentioned before, gastric cancer (GC) is one of the common malignancies, seriously threatening human health and lives. Many GC patients have already miss the optimal surgical timing at the time of diagnosis. They usually have poor life quality and heavy disease burden. Despite an active combination chemotherapy, the median survival of patients with advanced or metastatic GC is only about 1 year. PD-1 inhibitors (used alone or in combination with other drugs) have achieved encouraging results in the treatment of GC. It is expected that more GC patients can benefit from PD-1 inhibitors.

2 OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

Primary objective:

- To evaluate the efficacy of the sequential therapy of SHR-1210 combined with capecitabine and oxaliplatin or SHR-1210 combined with apatinib mesylate as the first-line therapy for advanced or metastatic gastric (GC) or gastroesophageal junction (GEJ) cancer.

Secondary objectives:

- To evaluate the safety of the sequential therapy of SHR-1210 combined with capecitabine and oxaliplatin or SHR-1210 combined with apatinib mesylate for the treatment of advanced or metastatic gastric (GC) or gastroesophageal junction (GEJ) cancer.

2.2 Study Endpoints

Primary endpoint:

- Objective response rate (ORR).

Secondary endpoints:

- Progression free survival (PFS);
- Duration of response (DoR);
- Disease control rate (DCR);
- Incidence and severity of adverse events (AEs) and serious adverse events (SAEs), vital signs, ECG, and laboratory abnormalities.

3 STUDY DESIGN

This is a randomized, open-label, multi-center, phase II clinical study.

A total of 98 subjects with previously untreated advanced or metastatic gastric cancer (GC) or gastroesophageal junction cancer (GEJ) will be enrolled. The subjects are randomized in a 1:1 ratio into the sequential therapy of SHR-1210 combined with capecitabine and oxaliplatin treatment group (cohort 1, n = 43) or the SHR-1210 combined with apatinib treatment group (cohort 2, n = 55).

- Cohort 1 (sequential therapy of SHR-1210 combined with capecitabine and oxaliplatin): SHR-1210 + capecitabine + oxaliplatin for 4-6 cycles, followed by SHR-1210 + apatinib in the treatment of the subjects without disease progression;
- Cohort 2 (SHR-1210 combined with apatinib): SHR-1210 + apatinib;

A two-stage design is adopted to minimize the exposure of subject to ineffective treatment. Nineteen subjects will be enrolled into cohort 1 and cohort 2 at the first stage, respectively. If at least 4 subjects achieve objective response (complete response or partial response), the second stage will be initiated.

All subjects should continue to receive the study treatment until progressive disease, intolerable toxicity, voluntary treatment discontinuation or study withdrawal by the subject, or discontinuation determined by the investigator.

SHR-1210 is an immune checkpoint inhibitor and according to the experience of similar drugs, some subjects may experience delayed or early pseudo progression after receiving immunotherapy drugs. Therefore, for subjects in the treatment group experiencing progressive disease (PD) for the first time, they may continue with the original treatment if they meet the criteria in section 4.6 Criteria for Continuing Treatment Beyond Disease Progression. Subjects who do not have progressive disease or intolerable toxicities may continue the SHR-1210 treatment for no more than 24 months.

Subjects who do not have progressive disease after 24-month treatment may continue the apatinib monotherapy according to the prescribing information of apatinib.

In this study, the screening period is no more than 28 days, and eligible subjects will enter the study treatment period (every 21 days being a treatment cycle) after completing the screening and assessment and receive study treatment and visits as specified in the protocol. Tumor imaging assessment is performed once every 2 treatment cycles (6 weeks ±7 days) during the first 12 months (first 16 treatment cycles) of the study treatment period and once every 3 cycles (9 weeks ±7 days) thereafter. Subjects should complete corresponding safety examinations and

imaging assessments prior to exiting. Then, the subjects enter the safety follow-up period. They are followed up until 90 days after the last dose. After the safety follow-up is completed, subjects will then enter the survival follow-up period. Survival information will be collected once per month. During the follow-up period (including safety follow-ups and survival follow-ups), subjects who have no disease progression and withdraw should continue to undergo tumor assessment according to the original schedule until PD, death, lost to follow-up, withdrawal of informed consent, start of other anti-tumor treatments, or study termination by the sponsor. Specific study procedures is presented in section 6.

3.1 Pharmacokinetic and Immunogenicity Studies

The PK and ADA properties of SHR-1210 monotherapy and the PK properties of apatinib monotherapy in GC patients have already been evaluated in previous studies. However, there are only limited data regarding the PK and ADA available on the combined use of SHR-1210 and apatinib in GC patients. Although the probability of interactions between large and small molecules is very small, there is not enough evidence that SHR-1210 does not interact with apatinib in humans at all. Neither are there data to support the judgment of whether apatinib affects the immunogenicity of SHR-1210.

The existing clinical studies on the combined use of SHR-1210 and apatinib have indicated the toxic and side effects of the combination therapy. Therefore, it is of high importance to collect data on the blood drug concentration of apatinib to determine its toxic and side effects. The correlation between the toxic and side effects and the combined use of the two drugs can be further assessed based on the blood drug concentration of SHR-1210 and apatinib.

The PK and ADA data of SHR-1210 and apatinib are also crucial for interpreting the pharmacodynamic data. In addition, the improvement in pharmacodynamic effect with the combination therapy relative to the monotherapy of either drug can be compared at the same exposure dose. Such investigations are of high significance for subsequent clinical study design and dose selection. These data can also be comprehensively analyzed with the data from other studies to compare the exposure of combination therapy in patients with different tumors and provide further basis for how to use SHR-1210 and apatinib combination therapy in a more rational manner.

- PK blood samples are collected from subjects receiving SHR-1210 plus apatinib at the following time points:

  a) In the first treatment cycle of SHR-1210 + apatinib administration, blood samples are collected once within 0.5 h pre-administration, once at 3 h (± 5 min) post-administration on Day 1, and once within 0.5 h pre-administration of apatinib on Day 7. There are 3 time points for blood sampling during Cycle 1 of SHR-1210 plus apatinib;

b) After that, PK blood samples are collected at the above time points during each cycle, for 6 cycles in total (including the first cycle of SHR-1210 plus apatinib);

c) ADA blood samples are collected once at 30 days (± 7 days), 60 days (± 7 days), and 90 days (± 7 days) after the last dose of study treatment, respectively (depending on the visit schedule if applicable).

d) At each time point, 5 mL of venous blood is collected (2 mL for apatinib assay, and 3 mL for SHR-1210 assay).

◆ Time points for ADA blood sample collection:

a) Blood samples are collected within 0.5 h before the drug administration on C1D1, C2D1, C4D1, C6D1, and C9D1, respectively. ADA blood samples are collected once every 4 cycles within 0.5 h before the drug administration since the Cycle 9.

b) ADA blood samples are collected once at 30 days (± 7 days), 60 days (± 7 days), and 90 days (± 7 days) after the last dose of study treatment, respectively (depending on the visit schedule if applicable).

c) At each blood sampling time point, 4 mL of venous blood is collected.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

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

1. Pathologically or cytologically confirmed GC or GEJ cancer, with evidence of being unresectable, locally advanced, or metastatic; histologically confirmed adenocarcinoma mainly.
2. Aged 18 or above, male and female.
3. Patients who have not received systemic treatment (including HER-2 inhibitors) for advanced or metastatic GC/GEJ. Subjects who have received adjuvant or neoadjuvant therapy (including chemotherapy, radiotherapy, or radiochemotherapy) for GC/GEJ must have completed the last treatment at least 6 months prior to the first dose of study treatment. Palliative radiotherapy is permitted, but it must be completed 2 weeks prior to the start of study treatment.
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.
5. With measurable lesion as per RECIST 1.1 criteria.

6. Life expectancy > 12 weeks.

7. All acute toxicities due to previous anti-tumor treatments or surgeries must have resolved to Grade 0–1 (as per NCI CTCAE 4.03) or to the level specified in the inclusion/exclusion criteria. Other toxicities such as alopecia, which do not pose a safety risk to the subjects evaluated by investigators, are excluded.

8. With adequate organs and bone marrow functions, as defined below:

   a) Absolute neutrophil count (ANC) ≥ 1500/mm^3 (1.5×10^9/L);

   b) Platelet count (PLT) ≥ 100,000/mm^3 (100×10^9/L);

   c) Hemoglobin (Hb) ≥ 9 g/dL (90 g/L);

   d) Serum creatinine ≤ 1.5 × upper limit of normal (ULN), or creatinine clearance ≥ 60 mL/min;

   e) Total bilirubin (BIL) ≤ 1.5 × ULN;

   f) Aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) ≤ 2.5 × ULN; for patients with liver metastasis, ALT and AST should be ≤ 5 × ULN;

   g) International normalized ratio (INR) ≤ 1.5, prothrombin time (PT) and activated partial thromboplastin time (APTT) ≤ 1.5 × ULN;

   h) Urine protein < 2+; If urine protein is ≥ 2+, then the 24-hour urine protein must be ≤ 1 g;

   i) Thyroid stimulating hormone (TSH) ≤ ULN; in case of abnormalities, T3 and T4 levels should be measured; if T3 and T4 levels are normal, the subject can be enrolled.

9. Female patients of childbearing potential must have a negative serum pregnancy test within 3 days prior to the first dose, and be willing to use a recognized effective contraceptive measure (such as intra-uterine contraceptive devices, contraceptive pills, and condoms) during the study and within 3 months after the last dose of the study drugs; male patients with female partners of childbearing potential must either be surgically sterilized or agree to take effective contraceptive measures during the study and within 3 months after the last dose of the study drugs.

10. Subjects must agree and have signed the informed consent form, be willing and able to follow the scheduled visits, study treatment, laboratory tests, and other study procedures.

4.2 Exclusion Criteria

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

1. Known HER2-positive.
2. Prior treatment with anti-PD-1/PD-L1 antibodies, CTLA-4 antibodies, or other treatments targeting PD-1/PD-L1 and/or VEGFR inhibitors.
3. Known allergies to the study drug or their excipients; severe allergic reactions to other monoclonal antibodies.
4. Having received immunosuppressive drugs within 14 days prior to the first dose of SHR-1210, excluding intranasal and inhaled corticosteroids or systemic steroids of physiological doses (i.e., no more than 10 mg/d of prednisolone or equivalent).
5. Having received live, attenuated vaccines within 4 weeks before the first dose or had such vaccination plan during the study.
6. Presence of known uncontrolled or symptomatic active central nervous system (CNS) metastases, manifested as clinical symptoms, cerebral edema, spinal cord compression, carcinomatous meningitis, leptomeningeal disease, and/or progressive growth. Patients with a history of metastases to the central nervous system or spinal cord compression may be eligible if they are clearly treated and clinically stable 4 weeks after discontinuation of anticonvulsants and steroids before the first dose of study treatment.
7. Presence of Grade > 1 peripheral neuropathy.
8. Advanced diseases that are symptomatic, disseminated to viscera, and at risk of life-threatening complications in the short term (including uncontrollable massive [pleural, pericardial, and abdominal] exudate, pulmonary lymphangitis, and more than 30% of hepatic involvement).
9. Presence of any active autoimmune diseases or a history of autoimmune diseases (including but not limited to autoimmune hepatitis, interstitial pneumonia, uveitis, enteritis, hepatitis, hypophysitis, vasculitis, nephritis, hyperthyroidism, hypothyroidism; adult subjects with vitiligo or completely relieved childhood asthma can be enrolled if they do not require any intervention; patients with asthma requiring medical interventions with bronchodilators cannot be enrolled).
10. Having been diagnosed with any other malignancies within 3 years before the enrollment, excluding adequately treated basal cell carcinoma or squamous cell skin cancer, or cervical carcinoma *in situ*.

11. Infection with human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS), active hepatitis B (HBV DNA ≥ 500 IU/mL), hepatitis C (hepatitis C antibody being positive and HCV-RNA being above the lower limit of detection of the assay), or co-infection of hepatitis B and C.

12. Any of the following conditions observed within 6 months prior to the enrollment: myocardial infarction, severe/unstable angina, > NYHA Class II cardiac insufficiency, poorly controlled arrhythmia (including males with QTcF > 450 ms and females with QTcF > 470 ms, QTcF interval calculated with the Fridericia's formula), symptomatic congestive cardiac failure, or cerebrovascular accident (including transient ischemic attack or symptomatic pulmonary embolism).

13. Hypertension uncontrolled by antihypertensives (systolic pressure > 140 mmHg or diastolic pressure > 90 mmHg).

14. Abnormal coagulation function (INR > 1.5 or activated partial thromboplastin time (APTT) > 1.5 × ULN), bleeding tendency, or receiving thrombolytics or anticoagulant therapy.

15. Known hereditary or acquired hemorrhage and thrombophilia (hemophilia, coagulopathy, thrombocytopenia, hypersplenism, etc.).

16. Obvious hemoptysis or a daily amount of hemoptysis of half a teaspoon (2.5 mL) or more within 2 months before the enrollment.

17. Clinically significant hemorrhage symptoms or clear bleeding tendency within 3 months prior to participation in this study, such as GI bleeding, hemorrhagic gastric ulcer, baseline fecal occult blood++ and above, or vasculitis.

18. Events of arterial/venous thrombosis within 6 months prior to participation in this study, such as cerebrovascular accidents (including transient ischemic attacks, cerebral hemorrhage, and cerebral infarction), deep vein thrombosis, and pulmonary embolism.

19. Known hereditary or acquired hemorrhage and thrombophilia (hemophilia, coagulopathy, thrombocytopenia, hypersplenism, etc.).

20. Requiring long-term anticoagulant therapy with warfarin or heparin; or requiring long-term antiplatelet therapy (aspirin ≥ 300 mg/day or clopidogrel ≥ 75 mg/day).

21. Complicated with severe infection (such as one requiring intravenous infusion of antibiotics, antifungals, or antivirals) within 4 weeks prior to the first dose, or any unexplained fever of > 38.5 °C observed during screening period/prior to the first dose.

22. Known history of allogeneic organ transplantation or allogeneic hematopoietic stem cell transplantation.
23. Having participated in clinical studies concerning any other drugs within 4 weeks prior to the first dose, or less than 5 half-lives from the last dose of study drugs.
24. Known history of psychotropic substance abuse or drug abuse.
25. Patients with other severe physical or psychiatric disorders or laboratory abnormalities, which may increase the risk of participating in this study or interfere with the study results, as well as those deemed unsuitable by the investigator.

4.3 Randomization and Blinding

Only Patients who meet all the inclusion criteria shall be randomly enrolled in this study. In the event that an ineligible patient is randomized, or erroneously start the treatment, or an enrolled subject no longer meets the eligibility criteria before starting the study treatment, the sponsor's representative and the investigator must jointly discuss whether the subject should continue or withdraw from the study. The sponsor should ensure that appropriate documentation is retained with regards to such decisions.

This study is an open-label study and does not involve blinding.

4.4 Rescreening Criteria

In this study, rescreening is allowed. That is, subjects who sign the informed consent form and enter the screening process but do not meet the inclusion criteria and have not yet started the treatment may be rescreened. 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. During rescreening, a new subject No. is assigned.

4.5 Withdrawal or Discontinuation

Subjects may withdraw the informed consent and withdraw from the study at any time. The investigator can determine whether the subject needs to withdraw from the study based on the occurrence of AEs. In addition, if the subject is not eligible for enrollment or violates the protocol, or due to management and/or other safety reasons, the investigator or the sponsor may withdraw the subject from the study.

4.5.1 Study withdrawal criteria

Reasons for withdrawal may include:

- Withdrawal of informed consent and refusal of further follow-ups by subjects;
- Continuing participation in the study violating the patient's optimal benefit due to clinical AEs, laboratory abnormalities, or concurrent diseases, as assessed by the investigator;
- Other investigator-assessed reasons, such as the inability to provide voluntary consent due to imprisonment or quarantine, or significant protocol violations;
- Lost to follow-up;
- Death;
- Study termination by the sponsor.

The reasons for the subject's withdrawal from the study must be recorded in CRF and the subject's medical record.

It is noteworthy that withdrawal of informed consent refers to the subject withdrawing the consent to be further contacted, or no longer agreeing to provide information via 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 and record the withdrawal of the informed consent. That is, whether the subject no longer consents to continue study treatment, or whether the subject no longer consents to receive the follow-up visits specified in the protocol either.

4.5.2 Criteria for treatment discontinuation

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

- Requests to discontinue the study treatment by subjects;
- Radiographic or clinical evidence of progressive disease, unless the subject meets the criteria for continuing treatment beyond progression (see Section 4.6);
- Occurrence of pregnancy during the study;
- Any clinical AEs, laboratory test abnormalities, or other medical conditions indicating that the subject can no longer benefit from the treatment;
- Comprehensive deterioration of health status and inability to continue study participation;
- Significant protocol deviations such as ineligibility found after enrollment or incompliance;

- Lost to follow-up;
- Study termination by the sponsor;
- Death;
- Other reasons as determined by the investigator.

4.5.3 Procedures for withdrawal or discontinuation

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

Unlike subjects withdrawing their informed consent to withdraw from the study, subjects who request discontinuation of study treatment will remain in the studies and should be followed up according to the study procedures specified in the protocol.

Survival status should still be followed even if the subject refuses further visits, unless the subject withdraws the consent to provide further information or the consent to be further contacted. In such case, no study assessment is performed, nor any data are collected.

4.6 Criteria for Continuing Treatment Beyond Disease Progression

Some subjects receiving immunotherapy can still benefit from continuing treatment after radiographic progression. The tumor of some subjects may be enlarged, but remarkable necrosis or denaturation may occur inside the tumor, with CT showing decreased internal density of the tumor lesion. It is generally considered to be beneficial to subjects under this circumstance. The study treatment may be continued beyond progressive disease (PD) defined per RECIST 1.1 for subjects who meet the criteria below:

- The investigator deems that it is in the best interest of the subject to continue treatment, and subject is not required to start other anti-tumor treatment immediately;
- The subject is able to tolerate continued study treatment;
- No obvious deterioration in subject's performance status, and no marked worsening of cancer-related symptoms;
- Subjects must sign the informed consent form prior to continuing study treatment, in which potential risks, discomforts, and other treatment options shall be included;
- Continued study treatment must be reviewed and approved by the principal investigator of the study center.

The assessment of clinical benefit must consider whether the subject has clinical exacerbations and whether the subject can benefit from continuing treatment. It is recommended that the investigator should discuss with the sponsor whether the subject should continue treatment after the disease progression.

If it is decided that the subject will continue the study treatment beyond progression, the subject should continue to be treated, evaluated, and followed up according to the protocol requirements.

Subjects should withdraw from the study if further disease progression is observed at the next assessment. The initial date of investigator-assessed progression should be used for all statistical analyses involving progression, regardless of whether the subject continues the study treatment beyond progression.

If the subject discontinues treatment due to deterioration of the general condition without objective evidence for progressive disease, the progression will be reported as "general deterioration". More objective evidences (eg., imaging confirmation) of progressive disease of these subjects should be obtained whenever possible after treatment discontinuation.

For subjects who withdraw from the study due to unacceptable toxicity without radiographic disease progression observed, the imaging examination should be performed at the same frequency, until PD or initiation of other anti-tumor treatments. The radiographic evidence of PD of these subjects must be obtained whenever possible.

4.7 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, the sponsor reserves the right to terminate the research and development of SHR-1210 at any time. The party who decides to suspend/terminate the study should notify the investigator, sponsor, and regulatory authorities in writing, documenting the reasons for suspension/termination. The investigator must immediately notify the ethics committee and sponsor, and provide relevant reasons.

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

- Confirmed unexpected, major, or unacceptable risks to the subjects;
- Existing efficacy data supporting study termination;
- Confirmed ineffectiveness of the study treatment;
- A major error in the protocol found during the implementation of the study;

- Extreme difficulties in completing the study due to poor compliance with protocol, such as severe delays in subject recruitment or frequent protocol deviations;
- Incomplete or undetectable data;
- Changes in the sponsor's development strategy for the investigational drug;
- Valueless study results.

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

4.8 Definition of End of Study

End of the study is defined as the last subject last visit (LSLV) or the last subject completing 24 months of study treatment after enrollment (whichever occurs first).

5 STUDY TREATMENT

5.1 Overview of the Study Drugs

5.1.1 Access to the drugs

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

5.1.2 Drug information

Investigational drug: SHR-1210 for injection

Manufacturer: Suzhou Suncadia Biopharmaceuticals Co., Ltd.

Dosage form: lyophilized powder.

Strength: 200 mg (proposed) in 20-mL vials.

Batch No.: 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 °C in refrigerator. Do not freeze.

Apatinib Mesylate Tablets

Manufacturer: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Dosage form: tablet.

Strength: 250 mg/tablet; 375 mg/tablet

Batch No.: see Certificate of Analysis

Route of administration: oral administration after meals (best to take the two drugs at the same time each day).

Shelf life: 2 years.

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

Capecitabine Tablet

Manufacturer: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Dosage form: tablet.

Strength: 0.5 g/tablet; 0.15 g/tablet.

Batch No.: see Certificate of Analysis

Route of administration: oral administration after meals.

Shelf life: 24 months.

Storage conditions: kept in a cool and dry place.

Oxaliplatin for Injection

Manufacturer: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Dosage form: injection.

Strength: 50 mg/bottle or 100 mg/bottle.

Batch No.: see Certificate of Analysis

Route of administration: intravenous infusion.

Shelf life: 24 months.

Storage conditions: sealed and stored below 25 °C.

5.1.3 Drug storage and management

The investigator or authorized personnel (such as a pharmacist) is responsible for ensuring that all study drugs are stored in a safe zone with appropriate storage conditions and controlled access, and that the storage is in compliance with regulatory requirements.

The study drugs should be stored in their original containers according to the storage conditions in section 5.1.2, and the storage conditions are consistent with the label. For inconsistencies between the storage conditions on the label with those in other materials (e.g., Investigator's Brochure), the storage conditions on the label should be followed.

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

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

Study drugs that are affected by temperature deviations must be temporarily quarantined until approved by the sponsor for further use, and such case is not considered 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.

For subjects who take the medications at home, the staff at the study center will provide guidance for the subjects on the proper method of drug storage as the storage conditions.

The study drugs are not allowed to be used in treatments outside of this study.

5.1.4 Preparation of study drugs

The study drugs should be prepared by qualified or experienced study staff (such as study nurse) according to the drug brochures or package insert of marketed drugs.

SHR-1210 does not contain preservatives, and must be prepared using aseptic technique. Refer to the brochure for drug preparation.

Other study drugs (apatinib mesylate, capecitabine and oxaliplatin) have already been marketed and should be prepared according to the package inserts.

5.1.5 Administration of study drugs

SHR-1210

SHR-1210, intravenous infusion at a fixed dose of 200 mg over 30 min (the total infusion time should be no less than 20 min and no more than 60 minutes, including rinsing period), once every 3 weeks.

Apatinib Mesylate Tablets

375 mg, administered orally once daily. Administered with warm water approximately half an hour after meals (administration time should be the same in each day whenever possible).

Capecitabine

1000 mg/m^2, administered orally twice daily 30 min after meals (once in the morning and once in the evening; with a total daily dose of 2000 mg/m^2). Two weeks of treatment is followed by 1 week of rest period (i.e., drug administration from Day 1 to Day 14, and drug interruption from Day 15 to Day 21) in 3 week cycle.

Oxaliplatin

130 mg/m^2, intravenous infusion with 250-500 mL of 5% glucose solution, given over 2-6 h; administered on Day 1 of each treatment cycle, once every 3 weeks.

SHR-1210 will be administered intravenously followed by oxaliplatin at least 30 min interval on Day 1 of each cycle.

Study Treatment	Drug	Treatment Cycle (21 days)	
Cohort 1	SHR-1210 200 mg	Day 1	
	Capecitabine 1000 mg/m^2	Day 1-Day 14	4-6 cycles
	Oxaliplatin 130 mg/m^2	Day 1	
	SHR-1210 200 mg	Day 1	
	Apatinib 375 mg	Day 1-Day 21	
Cohort 2	SHR-1210 200 mg	Day 1	
	Apatinib 375 mg	Day 1-Day 21	

Table 6. Administration plan of the study drugs

5.2 Dose Modification of Study Drugs

5.2.1 Dose modification of SHR-1210

Dose increases and reductions of SHR-1210 are not permitted. If SHR-1210 treatment is interrupted due to a toxicity, the subject may resume the treatment at the original dose after the toxicity is resolved. AEs related to SHR-1210 may be immune toxicities, and may occur shortly after the first dose or several months after the last dose. If the conditions listed in Table 7 occur, the use of SHR-1210 should be interrupted. During the study, the investigator must consult with the sponsor if the investigator considers that an adjustment listed in Table 7 is inappropriate based on the benefit-to-risk ratio of subjects or that SHR-1210 treatment should be interrupted or resumed due to a condition not listed in the table.

Table 7. Dose modification criteria for SHR-1210 due to immune-related toxicity

SHR-1210-Related Toxicity	Grade for Interruption	Resumption	Discontinuation
Diarrhea/Colitis	Grade 2-3	Recovered to Grade 0-1	Toxicity has not resolved by 12 weeks after the last dose, or the corticosteroid dose cannot be reduced to prednisone 10 mg/day (or equivalent) or lower within 12 weeks after the last dose.
	Grade 4	Discontinuation	Discontinuation
AST/ALT or Bilirubin Increased	Grade 2	Recovered to Grade 0-1	Toxicity has not resolved by 12 weeks after the last dose, or the corticosteroid dose cannot be reduced to prednisone 10 mg/day (or equivalent) or lower within 12 weeks after the last dose.
	Grade 3-4	Discontinuation[a]	Discontinuation
Type 1 Diabetes Mellitus (new onset) or Hyperglycemia with Signs of β-cell Failure	Grade 3-4 or new-onset type 1 diabetes	SHR-1210 treatment may only be resumed after the clinical and metabolic conditions of the subject are stabilized.	
Hyperthyroidism	Grade 3	Toxicity reduced to Grade 0-1	Toxicity has not resolved by 12 weeks after the last dose, or the corticosteroid dose cannot be reduced to prednisone 10 mg/day (or equivalent) or lower within 12 weeks after the last dose.
	Grade 4	Discontinuation	Discontinuation
Hypothyroidism	Grade 2-4	Study treatment can be continued after starting thyroxine replacement therapy	

SHR-1210-Related Toxicity	Grade for Interruption	Resumption	Discontinuation
Pneumonia	Grade 2	Toxicity reduced to Grade 0-1	Toxicity has not resolved by 12 weeks after the last dose, or the corticosteroid dose cannot be reduced to prednisone 10 mg/day (or equivalent) or lower within 12 weeks after the last dose.
	Grade 3-4	Discontinuation	Discontinuation
Immune-Related Hypophysitis	Grade 2-3	The SHR-1210 treatment may continue after the toxicity reduces to Grade 0-1 and the hormone replacement therapy starts.	Toxicity has not resolved by 12 weeks after the last dose, or the corticosteroid dose cannot be reduced to prednisone 10 mg/day (or equivalent) or lower within 12 weeks after the last dose.
	Grade 4	Discontinuation	Discontinuation
Renal Failure or Nephritis	Grade 2	Toxicity reduced to Grade 0-1	Toxicity has not resolved by 12 weeks after the last dose, or the corticosteroid dose cannot be reduced to prednisone 10 mg/day (or equivalent) or lower within 12 weeks after the last dose.
	Grade 3-4	Discontinuation	Discontinuation
Infusion reactions	Grade 2[b]	Symptoms disappeared	Discontinue the drugs if the symptoms recur after adequate premedication.
	Grade 3-4	Discontinuation	Discontinuation
Other T-related toxicities[c]	Grade 3	Toxicity reduced to Grade 0-1	Toxicity has not resolved by 12 weeks after the last dose, or the corticosteroid dose cannot be reduced to prednisone 10 mg/day (or equivalent) or lower within 12 weeks after the last dose.
	Grade 4	Discontinuation	Discontinuation

Treatment should be discontinued if any grade ≥ 3 treatment-related AE recurs (grade ≥ 2 pneumonia) or any life-threatening event recurs.

a) For subjects with liver metastasis and grade 2 AST or ALT increased at baseline, if the AST or ALT increased ≥ 50% from baseline persists for at least 1 week, the treatment shall be discontinued.

b) If the symptoms resolve within 1 hour after dechallenge, and the infusion can be resumed at 50% of the initial infusion rate. Otherwise, the treatment can only be resumed until symptoms are fully resolved. Premedication is required prior to the next dose. Refer to section 5.6.2 "Recommendations on infusion reaction management" for further management.

c) For subjects with intolerable or persistent grade 2 treatment-related AEs, the investigator may consider interrupting SHR-1210 treatment if appropriate, and the treatment should be discontinued if toxicity fails to decrease to Grade 0-1 within 12 weeks after the last dose.

5.2.2 Dose modification of capecitabine and oxaliplatin

For subjects receiving SHR-1210 combined with capecitabine and oxaliplatin (XELOX regimen), dose modification can be made based on toxicities.

For non-severe or non-fatal toxicities (eg., alopecia, appetite change and nail discoloration), dose modification may not be necessary as judged by the investigator.

Dose modification caused by toxicities of a single drug in the combination therapy will not affect the usage of other drugs according to the plan.

This is because the capecitabine- and/or oxaliplatin-related toxicities cannot resolve within one same treatment cycle. The administration of capecitabine and/or oxaliplatin can be delayed for no more than 6 weeks. If the toxicities still do not resolve by 6 weeks, the capecitabine and/or oxaliplatin treatment will be discontinued, unless the investigator considers that the subjects will benefit from the continuing treatment of the capecitabine and/or oxaliplatin.

- Dose modification of capecitabine

Toxicities caused by capecitabine can be managed by symptomatic treatment and/or interruption or dose reduction. The recommended dose modification criteria for capecitabine are shown in Table 8. The dose cannot be increased again after the reduction.

Grading of Adverse Drug Reactions	**Modification During Treatment**	**Dose Modification in the Next Cycle (% initial dose)**
Grade 1	Maintain original dose	Maintain original dose
Grade 2		
First occurrence	Interrupt until recovery to Grade 0-1	100% (1000 mg/m^2)
Second occurrence		75% (750 mg/m^2)
Third occurrence		50% (500 mg/m^2)
Fourth occurrence	Permanently discontinue the treatment	
Grade 3		
First occurrence	Interrupt until recovery to Grade 0-1	75% (750 mg/m^2)
Second occurrence		50% (500 mg/m^2)
Third occurrence	Permanently discontinue the treatment	

Grading of Adverse Drug Reactions	Modification During Treatment	Dose Modification in the Next Cycle (% initial dose)
Grade 4		
First occurrence	Permanently discontinue the treatment Or if the investigator believes that continuing treatment is beneficial to the subjects, then interrupt the treatment until the AE recovers to Grade 0-1 before resuming treatment.	50% (500 mg/m^2)

Table 8. Dose modification criteria for capecitabine

- Dose modification of oxaliplatin

Dose modification due to neurotoxicity

- For Grade 2 peripheral sensory neurotoxicity (moderate paresthesia or dysesthesia) or limited instrumental activities of daily living, oxaliplatin may be interrupted. After the toxicity recovers to grade ≤ 1, oxaliplatin can be resumed at 75% of the initial dose. If oxaliplatin treatment has been interrupted for more than 4 weeks due to neurotoxicity (2 consecutive doses), oxaliplatin treatment should be discontinued permanently.
- For grade ≥ 3 peripheral sensory neurotoxicity (severe paresthesia or dysesthesia) or limited activities of daily living, oxaliplatin should be discontinued permanently.

Dose modification due to renal injury

- There is no need to adjust the dose of oxaliplatin for mild or moderate renal function impairment (CrCl > 50 mL/min).
- For severe renal function impairment, the dose of oxaliplatin should be adjusted to 75% of the initial dose.

Dose modification due to hematologic toxicities

- For Grade 2 or 3 thrombocytopenia, the dose of oxaliplatin should be adjusted to 75% of the initial dose. For Grade 4 thrombocytopenia, the dose of oxaliplatin should be adjusted to 50% of the initial dose.
- For Grade 3 or 4 neutropenia or febrile neutropenia, the dose of oxaliplatin should be adjusted to 75% of the initial dose.

5.2.3 Dose modification of apatinib mesylate

Dose modifications caused by apatinib-related toxicities include the following: treatment interruption (no more than 28 days), dose reduction (to 375 mg qd or 250 mg qd, depending on the initial dose of apatinib), and permanent discontinuation.

The treatment may be delayed and the dose be reduced for Grade ≥ 3 hematologic toxicity or ≥ 2 non-hematologic toxicity; for non-hematologic toxicity, manageable nausea and vomiting, and fever (below 38 ℃) of dete rmined cause, active symptomatic treatment can be administered first. There is no need to immediately delay the treatment or reduce the dose.

In case of apatinib-related toxicity, administration should be delayed until recovery, and then the original dose should be resumed or the dose should be reduced by one dose level. The minimum dose allowable is 250 mg/d. If the dose is still intolerable at the reduced dose of 250 mg/d, apatinib should be permanently discontinued (refer to Table 9 for the recommended dose modification method). Dose increase of apatinib is not allowed during the study period.

Table 9. Recommended dose modification of apatinib

Apatinib-Related Toxicities	Grade	Dose Delay or Not	Criteria for Resuming	Dose Modification Method	Criteria for Discontinuation
Hematologic Toxicity	Grade 1-2	No	—	—	—
	Grade 3	Yes	Until the toxicity recovers to Grade ≤ 2	Resume at original dose	Apatinib interruption for more than 28 days
	Grade 4		Until the toxicity recovers to Grade ≤ 2	Reduce the dose by one level	
Non-Hematologic Toxicity	Grade 1	No	—	—	—
	Grade 2 (last for ≥ 7 days)	Yes	Until the toxicity recovers to Grade ≤ 1	Resume at original dose	Apatinib interruption for more than 28 days
	Grade 3	Yes	Until the toxicity recovers to Grade ≤ 1	Reduce the dose by one level	
Hypertension	Grade 3 (after corrective treatment)	Yes	Until the toxicity recovers to Grade ≤ 1	Reduce the dose by one level	Apatinib interruption for more than 28 days
Proteinuria (without significant increase in blood creatinine)	Grade 3 (24-h urine protein quantification)	Yes	Until the toxicity recovers to Grade ≤ 2	Reduce the dose by one level	Apatinib interruption for more than 28 days

Apatinib-Related Toxicities	Grade	Dose Delay or Not	Criteria for Resuming	Dose Modification Method	Criteria for Discontinuation
Hand-and-Foot Syndrome	Grade 3	Yes	Until the toxicity recovers to Grade ≤ 1	Reduce the dose by one level	Apatinib interruption for more than 28 days
Headache	Grade 2 (last for ≥ 7 days) or Grade 3	Yes	Until the toxicity recovers to Grade ≤ 1	Reduce the dose by one level	Apatinib interruption for more than 28 days

In this study, the minimum dose of apatinib allowable is 250 mg/d. If the subjects still cannot tolerate the dose of 250 mg/d, apatinib should be permanently discontinued.

For subjects with gastrointestinal perforation, wound dehiscence needing clinical management, fistula, severe hemorrhage, nephrotic syndrome or hypertensive crisis, apatinib should be permanently discontinued.

5.3 Duration of Treatment

All subjects should continue to receive the study treatment until progressive disease, intolerable toxicity, voluntary treatment discontinuation or study withdrawal by the subject, or discontinuation determined by the investigator.

SHR-1210 is an immune checkpoint inhibitor and according to the experience of similar drugs, some subjects may experience delayed or early pseudo progression after receiving immunotherapy drugs. For subjects in the treatment group experiencing progressive disease (PD) for the first time, they may continue with the SHR-1210 treatment if they meet the criteria in section 4.6 Criteria for Continuing Treatment Beyond Disease Progression. Subjects who do not have progressive disease or intolerable toxicities may continue the SHR-1210 treatment for no more than 24 months. Subjects who do not have progressive disease after 24-month treatment may continue the apatinib monotherapy according to the prescribing information of apatinib.

5.4 Drug Management, Dispensation, Return and Disposal

Designated personnel are responsible for management, dispensation, and return 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 5.1.4. Remaining or expired drugs should be returned to the sponsor or destroyed at the study center according to the specified procedures, and may not be used for non-participants.

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

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

- **Disposal of study drugs**

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

5.5 Recording of concomitant medications and concomitant treatments

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

All concomitant medications, blood products, and non-drug interventions (eg., paracentesis) that are given to the subjects from 30 days prior to the first dose to the end of the safety visit must be strictly documented in the CRF according to GCP requirements.

Prohibited medications and vaccines specified in the study protocol are strictly prohibited during the entire course of study. If the subject develops a comorbidity requiring treatment with a prohibited drug, the investigator should consult with the sponsor before discontinuing the study treatment or using the prohibited drug. Whether the subject will continue the study treatment or receive a prohibited drug should be jointly decided by the investigator, the sponsor, and the subject.

In addition to the following contents, for subjects who receive apatinib mesylate, capecitabine and oxaliplatin treatment, the latest package insert of marketed drugs or medical practices regarding contraindications and precautions shall be also taken for reference.

5.5.1 Other anti-tumor treatments or investigational drugs

Other anti-tumor treatments not specified in the protocol are not permitted while subjects are receiving study treatment, including CDFA (NMPA)-approved Chinese herbal preparations for anti-tumor treatments (see Appendix 6 Prohibited Traditional Chinese Medicines During the Study Period) and immunomodulators (including but not limited to interferon, interleukin-2, and thymosin).

Participation in other drug/medical device clinical studies is not permitted.

Other systemic anti-tumor treatments such as chemotherapy, molecular targeted therapy, hormone therapy, immunotherapy, biological therapy, and radiotherapy are not permitted.

Subjects can receive bisphosphonate for the treatment of bone metastases. If systemic treatment or local analgesia is not effective in controlling painful lesions of bone metastases, a small area of palliative radiotherapy (the area of the radiotherapy must be < 5% of the bone marrow region, and the percent bone marrow in human is shown in Appendix 5 Percent Bone Marrow Content in Human Skeleton) is allowed.

Palliative treatment of local lesions that may cause obvious 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 also recommended to consult with the sponsor prior to starting palliative treatment.

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

5.5.2 Vaccines

Live attenuated vaccines should not be given within 4 weeks before the first dose or during the study period. Subjects who are expected to require live attenuated vaccines during the study period are not recommended for enrollment.

Inactivated vaccines for preventing infectious diseases, such as pneumonia, influenza, are permitted. Any other vaccines should be discussed with the sponsor before administration.

5.5.3 Immunomodulators and corticosteroids

Concomitant immunosuppressive therapy is not permitted (except when treating treatment-related adverse events).

Concomitant immunostimulants are not permitted (except when treating treatment-related AEs).

Long-term, systemic use of corticosteroids is prohibited. The use of corticosteroids for ≤ 1 week as premedication for chemotherapy or contrast media allergies as specified in the package insert is permitted. Systemic treatment with corticosteroids is permitted for individual subjects after discussing with the sponsor. Short term (≤ 3 weeks) use of corticosteroids for non-autoimmune diseases is permitted (such as delayed allergic reactions caused by contact allergens).

Emergency use, topical application, inhalation, eye drops, or local injections of corticosteroids are permitted. Physiological replacement doses (such as adrenal replacement doses) of systemic corticosteroids (≤ 10 mg/d of prednisone or equivalent) are permitted.

5.5.4 Hematopoietic growth factor and blood transfusion

Any granulocyte colony-stimulating factor, erythropoietin, thrombopoietin, and other hematopoietic stimulation factors, as well as blood transfusion and blood products (eg., albumin) are prohibited as primary prophylaxis before treatment. However, these treatments are allowed for treating AEs.

5.5.5 Anti-inflammatory treatment

Anti-inflammatory medications or narcotic analgesics can be given if there are no known or foreseeable drug interactions and if these drugs are not prohibited in the protocol.

5.5.6 Medications to be used with caution in subjects receiving apatinib during the study

Drugs that may affect the metabolism of apatinib or prolong QT interval should be used with caution in subjects in cohort 2 (SHR-1210 + apatinib).

- Drugs that may have drug-drug interactions with apatinib mesylate

In vitro metabolic enzymes studies have shown that apatinib is mainly metabolized by CYP3A4. When apatinib is used concomitantly with strong inhibitors of CYP3A4 (itraconazole, clarithromycin, voriconazole, telithromycin, saquinavir, and ritonavir), the plasma concentration of apatinib may rise up. When apatinib is used concomitantly with CYP3A4 inducers (dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital, and rifapentine), the plasma concentration of apatinib may decrease. When other combined medications are needed, it is recommended to choose alternative drugs that do not inhibit or induce CYP3A4. If a strong inducer or inhibitor of CYP3A4 enzyme must be used concomitantly, it is necessary to consider whether to modify the dose based on clinical observation.

- Drugs that prolong the QT interval of the heart

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

- Antibiotics: fluoroquinolones: sparfloxacin, gatifloxacin, levofloxacin, moxifloxacin, ofloxacin, ciprofloxacin; macrolides: erythromycin, clarithromycin, telithromycin, azithromycin, roxithromycin, and metronidazole.
- Antiarrhythmics: quinidine, procainamide, disopyramide, flecainide, propafenone, amiodarone, dronedarone, sotalol, dofetilide, and ibutilide.
- Drugs used to relieve angina: ranolazine and ivabradine.
- Antipsychotics: risperidone, fluphenazine, droperidol, haloperidol, thioridazine, pimozide, olanzapine, and clozapine.
- Antifungal drugs: voriconazole and posaconazole.
- Antimalarial drugs: mefloquine and chloroquine.
- Antihistamines: terfenadine, astemizole, and hydroxyzine.

- Gastrointestinal drugs: antiemetics: ondansetron, granisetron, dolasetron, droperidol (0.625-1.25 mg may be a safe dose), hydroxyzine; prokinetics: cisapride, domperidone, metoclopramide.
- Antidepressants: amitriptyline, imipramine, clomipramine, dosulepin, and doxepin.

5.5.7 Surgery

Any surgery conducted during the study period must be justified and necessary. The interval between the surgery and study treatment must not affect the recovery of the wound as much as possible and the investigation on hemorrhage of unknown cause. An interruption of study treatment 1 week before the surgery is recommended. Re-administration of the drugs after surgery will be determined on the basis of clinical assessment of wound healing and postoperative recovery.

5.5.8 Supportive care

Palliative and supportive care for disease-related symptoms should be based on the investigator's judgment and relevant guidelines (e.g., "American Society of Clinical Oncology Clinical Practice Guideline").

Subjects should be given optimal supportive care during the treatment.

It is not recommended to enroll subjects with uncontrolled cancer pain. Subjects requiring analgesics must have a stable analgesic regimen before enrollment. Palliative radiotherapy for symptomatic lesions (such as bone metastasis or perineural invasion) should be completed at least 2 weeks before enrollment. Local treatment should be considered before the start of study treatment, if appropriate, for asymptomatic metastatic lesions where further growth may result in dysfunction or intractable pain (e.g., epidural metastasis without spinal cord compression).

RANKL inhibitors (receptor activator of nuclear factor κB ligand inhibitor such as denosumab) are prohibited. Subjects with uncontrolled hypercalcemia (calcium ion > 1.5 mmol/L or calcium > 12 mg/dL or corrected serum calcium > ULN), or subjects who need to continue treatment with bisphosphonates or denosumab for symptomatic hypercalcemia are not recommended to be enrolled. Patients who receive bisphosphonate therapy only to prevent skeletal-related events and have no history of clinically significant hypercalcemia may be enrolled. Patients receiving denosumab prior to enrollment must agree to replace denosumab with a bisphosphate after entering the study.

Existing hormone replacement therapies are permitted. For example, subjects receiving treatment with a GnRH agonist can be enrolled in this study provided that the GnRH agonist has been well-tolerated for at least 3 months prior to enrollment. Likewise, patients with a history of autoimmune-mediated hypothyroidism who are receiving stable doses of thyroid hormone replacement therapy may be enrolled in this study. Patients with type 1 diabetes who are receiving on stable insulin therapy and have properly controlled blood glucose can be enrolled.

5.6 Recommended Symptomatic Treatment for Common Adverse Drug Reactions Related to SHR-1210

5.6.1 Safety management rules for immuno-oncological medications

AEs caused by immuno-oncology (I-O) medications are different from those of other anti-cancer drugs, especially in terms of severity and duration. SHR-1210 is one such drug, and therefore, early identification and management of adverse events is required to reduce the incidence of severe toxicities. The safety management procedures of similar approved drugs provide references to assist the investigator in assessing and dealing with adverse events involving the following systems: GI tract, kidneys, lungs, liver, endocrine, skin, and nervous system. Safety management rules for immuno-oncology drugs are presented in Appendix 4 Management Principles for Immune Related Adverse Events.

5.6.2 Infusion reactions

During the course of this study, the investigator should pay close attention to potential infusion and/or allergic reactions, especially acute immune-mediated adverse reactions (including cytokine storms).

SHR-1210 is a fully humanized monoclonal antibody with little potential for infusion or allergic reactions, and thus, in general, no prophylactic medications are required prior to SHR-1210 infusion. Based on published relevant information, an allergic reaction/event is most likely to occur within 24 h after infusion. If an allergic reaction/event occurs, the infusion should be slowed or interrupted based on the subject's condition, and supportive treatment should be given. In addition, prophylactics should be given before further administration. Possible allergic reactions include fever, chills, shiver, headache, rash, arthralgia, hypotension/hypertension, and bronchospasm.

Management of allergic reactions should be based on the medical practice and guidelines of the study center. The treatment recommendations for infusion reaction are shown below (Table 10) for reference.

Table 10. Treatment recommendations for infusion reaction related to SHR-1210

CTCAE Grade	Clinical Symptoms	Recommended Management	SHR-1210 Treatment
Grade 1	Mild and transient reactions	Bedside observation and close monitoring until recovery. Pre-dose prophylactics are recommended for subsequent administrations: 50 mg of diphenhydramine or equivalent, and/or 325–1000 mg of acetaminophen can be given at least 30 min before the administration of SHR-1210.	Continued use

CTCAE Grade	Clinical Symptoms	Recommended Management	SHR-1210 Treatment
Grade 2	Moderate reactions requiring treatment or interruption; rapidly resolve after symptomatic treatment (such as antihistamines, non-steroidal antiphlogistics, anesthetics, bronchodilators, intravenous fluids, etc.)	Intravenous administration of normal saline, 50 mg of diphenhydramine IV or equivalent and/or 325-1000 mg of acetaminophen; bedside observation and close monitoring should be given until recovery. Corticosteroids or bronchodilators can be considered based on clinical needs; The amount of study drug infused should be recorded in the original medical record; Pre-dose prophylactics are recommended for subsequent administrations: 50 mg of diphenhydramine or equivalent, and/or 325–1000 mg of acetaminophen can be given at least 30 min before the administration of SHR-1210. Corticosteroids (equivalent to 25 mg of hydrocortisone) can be used when necessary.	Interrupt. Re-administer at 50% of the initial rate after symptoms resolve. Restore the original infusion rate if no complications occur within 30 minutes. Closely monitor. If the symptoms recur, no more infusion shall be given.
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 is recommended. Intravenous infusion of diphenhydramine 50 mg and methylprednisolone 100 mg (or equivalent dose) can be given if necessary. Medical practices and guidelines for treating allergic reactions at the study center are followed. Bedside observation and close monitoring until recovery.	Discontinuation

6 STUDY PROCEDURES

6.1 Screening Period

The screening period is the time from the signing of the informed consent form until the 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.

- Obtain informed consent form signed by the subject.
- Collection of demographics: gender, date of birth, ethnicity, height, and weight.

- Collection of adverse events: Collect adverse events starting from the signing of ICF.
- Tumor diagnosis: date of pathological diagnosis, pathologic grade, pathologic stage (TNM), clinical stage, site of metastatic lesion, time to disease progression or recurrence from the last treatment.
- History of cancer treatment
  - ✓ History of tumor surgery: surgery, date;
  - ✓ 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;
  - ✓ History of concurrent disease, past medications, and medication allergies;
- Virology: HBsAg, HBsAb, HBeAg, HBeAb, HBcAb, HBV DNA (if the Hepatitis B five items test indicates HBV infection [HBsAg positive] or if the subjects have a history of HBV infection, HBV DNA quantification should be performed), HCV-Ab (if the result is positive, HCV RNA quantification should be performed), and HIV-Ab.
- Imaging examinations: CT or MRI of the chest, abdomen, and pelvic cavity. Brain MRI (if MRI is contraindicated, CT scan can be used instead) is required for suspected or confirmed brain metastases. Bone scan is performed only when clinically indicated and must be performed within 42 days prior to the first dose. At screening, tumor evaluations up to 4 weeks before the first dose of study treatment and before the signing of the informed consent may be used as long as they meet relevant requirements.
- Concomitant medications/concomitant treatments: Concomitant medications/ concomitant treatments within 30 days prior to the first dose of the study drug are documented.

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

- ECOG PS.
- Vital signs: pulse, respiratory rate, body temperature, and blood pressure.

- Comprehensive physical examination: general condition, head and face, skin, lymph nodes, eyes, ears, nose and throat, oral cavity, respiratory system, cardiovascular system, abdomen, reproductive-urinary system, musculoskeletal system, nervous system, mental state, etc.;
- Hematology: Red blood cell count (RBC), hemoglobin (Hb), platelet count (PLT), white blood cell count (WBC), absolute neutrophil count (ANC), and lymphocyte count.
- Urinalysis: WBC, RBC, and urine protein. If urine protein is ≥ 2+, then a quantitative 24-h urine protein test should be added.
- Fecal occult blood (OB) test: Fecal occult blood test is performed within 7 days prior to the first dose (if the fecal occult blood is positive, the test should be performed again. If the result is still positive, gastrointestinal endoscopy should be performed), on Day 1 of every two cycles, at the end of treatment/upon withdrawal, and upon the first visit during the safety follow-up period.
- Blood biochemistry: Alanine transaminase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (γ-GT), total bilirubin (TBIL), direct bilirubin (DBIL), alkaline phosphatase (AKP), blood urea nitrogen (BUN, preferred) or urea, total protein (TP), albumin (ALB), creatinine (Cr), blood glucose (GLU), K^+, Na^+, Ca^{2+}, Mg^{2+} and Cl^-.
- Thyroid function: Including serum thyroid stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4). If FT3 and FT4 cannot be obtained, T3 and T4 are allowed for substitution;
- Coagulation function: Activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), fibrinogen (FIB), and international normalized ratio (INR).
- 12-Lead ECG: Attentions should be paid to QT, QTc, and PR-intervals. The investigator may decide to add other investigations if the results are abnormal.
- Echocardiography: Including left ventricular ejection fraction (LVEF) assessment. Echocardiography is performed once within 7 days before the enrollment. After that, echocardiography is performed if clinically indicated and at the end of treatment/upon withdrawal.
- Pregnancy test (serum pregnancy test will be performed for women of childbearing potential).

6.2 Treatment Period/Follow-Up

The treatment period starts from the subject's first dose. The first dose of the study drugs should be given as close as possible to the time of completing the screening examinations and confirming the subjects' eligibility for the study. Each treatment cycle lasts for 21 days.

All examinations and evaluations (except for imaging evaluations) should be completed within 3 days pre-administration. There is no need to repeat the laboratory tests (hematology, urinalysis, blood biochemistry, coagulation function test, and thyroid function test) and electrocardiography on Day 1 of Cycle 1, if such tests have already been performed at the baseline within 7 days before the first dose.

- For subjects receiving the SHR-1210 + apatinib treatment for the first time, blood samples should be collected for PK and immunogenicity testing. The specific procedures can be found in the schedule of activities or section 3.1 "Pharmacokinetic and Immunogenicity Studies" in the protocol.
- The following evaluations should be completed before the drug administration in each cycle:
  - ECOG PS
  - Vital signs
  - Physical examination: Specific physical examination is performed if clinically indicated.
  - Hematology
  - Clinical chemistry
  - Coagulation function
  - 12-Lead ECG
  - Collection of AEs
  - Documentation of concomitant medications/concomitant treatments
- The following evaluations should be completed every 2 cycles prior to administration:
  - Urinalysis
  - Thyroid function
  - Fecal occult blood

- Imaging examination: Imaging examination is performed once every 2 cycles (6 weeks ± 7 days) in the first 12 months (the first 16 cycles), then once every 3 cycles (9 weeks ± 7 days). Imaging examination should be also performed if new lesions are suspected. Imaging examination should be performed when subjects withdraw from the study for any reason (the imaging examination does not need to be repeated if the time from the last examination is no more than 4 weeks). Imaging conditions should be the same as those at baseline (including slice thickness and contrast agent). The time window for imaging examination is ± 7 days. Unscheduled imaging examination may be performed if PD is suspected (for example, worsening of symptoms). The date of imaging examination is calculated by the calendar day and will not be adjusted due to dose delays.

Subjects with CR and PR should receive repeated imaging examination once to confirm the efficacy. Repeated tumor imaging should be performed at least 4 weeks after the initial response (4 weeks after the initial response or the next scheduled imaging evaluation). If the subject's imaging evaluation time is less than 4 weeks to the next scheduled imaging time, the next scheduled imaging evaluation is not required, and the imaging evaluation can be resumed at subsequent scheduled time point.

6.3 End of Treatment/Withdrawal Visit

If relevant assessments and examinations have not been performed within 7 days before the last dose, the following procedures should be followed:

- ECOG PS
- Vital signs
- Comprehensive physical examination: general condition, head and face, skin, lymph nodes, eyes, ears, nose and throat, oral cavity, respiratory system, cardiovascular system, abdomen, reproductive-urinary system, musculoskeletal system, nervous system, mental state, etc.;
- Hematology
- Urinalysis
- Fecal occult blood
- Clinical chemistry
- Coagulation function
- Thyroid function

- ECG
- Imaging examination: Imaging examination should be performed in time (± 4 weeks; there is no need to repeat the imaging examination upon withdrawal if the time from the previous examination to the discontinuation is less than 4 weeks). Subjects who discontinue treatment for reasons other than radiographically confirmed PD must also undergo imaging examination at the frequency specified in the protocol until documented of confirmed PD, start of a new anti-tumor treatment, or death.
- Collection of AEs
- Documentation of concomitant medications/concomitant treatments

6.4 Follow-up period

6.4.1 Safety follow-up period

Safety follow-up starts from the last dose of study treatment. The follow-up is performed once every 30 days (±7 day s) until 90 days after the last dose.

The first safety follow-up (30 days ±7 days) is carried out at the study center where the evaluations specified in the protocol are completed. The second (60 days ±7 days) and the third (90 days ± 7 days) follow-up are made via telephone calls. The information on survival, concomitant medications/concomitant treatments and AEs are collected.

◆ During the first safety follow-up (30 ± 7 days), the subjects should receive the following evaluations at the study center (if the subject has started a new anti-tumor treatment before the first safety follow-up, then the follow-up should be completed before starting the new anti-tumor treatment):

- ECOG PS
- Vital signs
- Physical examination: Specific physical examination is performed if clinically indicated.
- Hematology
- Urinalysis
- Fecal occult blood
- Clinical chemistry
- Thyroid function

- Coagulation function
- ECG
- Collection of AEs
- Documentation of concomitant medications/concomitant treatments

◆ For the second (60 days after the last dose) and the third safety follow-ups (90 days after the last dose), the subjects' survival information and AEs can be collected via telephone calls.

◆ Imaging examination: Subjects without radiographically confirmed disease progression should receive imaging examination at the same frequency as that during the treatment period.

6.4.2 Survival follow-up

The survival follow-up period starts after the end of the safety follow-up period. The survival follow-up period ends upon the subject's death, lost to follow-up, withdrawal of informed consent, or study termination by sponsor. During this period, an effective follow-up such as telephone follow-up is conducted once every month to collect information on subject survival and subsequent treatments (if the subject has started a new anti-cancer treatment, the therapeutic regimen and the start and end time should be recorded).

For subjects who show no evidence of radiographic progression, imaging evaluation will be continued at the same frequency of efficacy evaluations specified in the protocol, until progressive disease, death, lost to follow-up, withdrawal of informed consent, start of other anti-cancer treatment, or study termination by the sponsor. Evidence of radiographic progression should be collected as much as possible for these subjects.

6.5 Unscheduled Visit

The following shall be documented during unscheduled visits when subjects develop AEs during the study:

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

7 STUDY EVALUATION

7.1 Efficacy Evaluation

7.1.1 Efficacy endpoints

The primary efficacy endpoint of this study is objective response rate (ORR).

Objective response rate (ORR): the proportion of treated subjects with a best overall response (BOR) of complete response (CR) or partial response (PR) as per RECIST 1.1 criteria. If the subject achieves CR or PR, conformation should be done at least 4 weeks (28 days) after the first evaluation. Best overall response refers to the best response assessed by the investigator, or the best response from the date of enrollment to the first documentation of progression as per RECIST 1.1 or to the start of a new anti-tumor treatment (whichever comes first). For subjects without documented progression or new anti-cancer treatment, BOR will be determined based on all response evaluations. For subjects who continue SHR-1210 treatment beyond progression, the best overall response should be based on the efficacy assessment at the time of first documented progression as per RECIST 1.1. Efficacy evaluation should be performed once every 2 cycles (6 weeks ±7 days) in the first 12 months (first 16 cycles) from the study treatment. Then it is performed once every 3 cycles (9 weeks ±7 days) after 12 months until PD (or discontinuation of the study treatment for subjects continuing the SHR-1210 after PD), lost to follow-up, withdrawal of informed consent or death.

Secondary efficacy endpoints include progression free survival (PFS), duration of response (DoR) and disease control rate (DCR).

Progression-free survival (PFS): The time between the date of enrollment and the first documented tumor progression (as per RECIST 1.1 criteria, regardless of whether treatment is continued), or death due to any cause, whichever occurs first. When determining PFS, clinical exacerbations without definite evidence of progressive disease (as per RECIST 1.1) is not considered progressive disease. For subjects who die without any prior reports of progression, the date of death is considered the date of progression. Subjects without progressive disease or death will be censored on the date of their last evaluable tumor assessment. Subjects without tumor assessments during the study or death will be censored on their date of enrollment. Subjects who discontinue the treatment for reasons other than progressive disease (no subsequent tumor assessments) will be censored on their date of study discontinuation. For subjects who have not previously reported progressive disease but have initiated subsequent anti-tumor therapy, they will be censored on the date of their last evaluable tumor evaluation before starting the subsequent anti-tumor therapy, or they will be censored when starting the subsequent anti-tumor therapy. When subjects are not censored on the date of study discontinuation or the date of starting new anti-tumor treatment, the

scheduled sensitivity analysis will confirm PFS based only on the time of radiologically confirmed progression events. The occurrence of a new tumor will not be considered a progressive disease and is not censored.

Disease control rate (DCR): the proportion of subjects with a best overall response of complete response (CR), partial response (PR), or stable disease (SD) as per RECIST 1.1 criteria. If the subject achieves CR or PR, conformation should be done at least 4 weeks (28 days) after the first evaluation. Best overall response refers to the best response assessed by the investigator, or the best response from the date of enrollment to the first documentation of progression as per RECIST 1.1 or to the start of a new anti-tumor treatment (whichever comes first). For subjects without documented progression or new anti-cancer treatment, BOR will be determined based on all response evaluations. For subjects who continue SHR-1210 treatment beyond progression, the best overall response should be based on the efficacy assessment at the time of first documented progression as per RECIST 1.1.

Duration of response (DoR) is defined as the period of time from the first documented tumor response (as per RECIST 1.1) to the first documented objective progression (as per RECIST 1.1) or death of any cause. Subjects without progressive disease or death will be censored on the date of their last tumor assessment. Subjects who start any subsequent anti-tumor therapy (excluding palliative radiotherapy of non-target bone lesions or central nervous system lesions during the study treatment) without previously reported progressive disease will be censored on the date of last tumor assessment prior to the start of new anti-tumor treatment, or on the date of starting the new anti-tumor treatment.

7.1.2 Criteria for efficacy evaluation

Objective response rate (ORR) as well as PFS, DCR and DoR based on tumor response will be evaluated by imaging examinations according to RECIST 1.1 (see Appendix 3 Response Evaluation Criteria in Solid Tumors).

For the record and assessment of survival, the subjects will be followed up by effective visits such as telephone calls on survival once every month after withdrawing from the study until death, lost to follow-up, withdrawal of informed consent, or study termination by the sponsor.

Assessments of tumor response include all known or suspected lesions.

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

Imaging assessment at screening must be performed within 28 days prior to the first study dose, and first tumor assessment during the treatment period should be performed 6 weeks (±7 days) after starting study treatment. Imaging evaluation should be performed once every 2 cycles (6 weeks ± 7 days) in the first 12 months (first 16 cycles) during the treatment. Then it is performed once every 3 cycles (9 weeks ±7 days) after 12 months until PD, lost to follow-up, death, withdrawal of informed consent, start of other anti-tumor treatment or study termination by the sponsor.

If the subject achieves CR or PR, conformation should be done at least 4 weeks (28 days) after the first evaluation. In case of SD, tumor assessment should be performed at least once after at least 6 weeks (±7 days) after enrollment, and the measurements must meet the criteria for SD at least once.

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

All subjects should continue to undergo tumor assessments according to the study protocol, regardless of dose interruptions or dose delays. If discontinuation is indicated due to deterioration of overall health in absence of objective evidence of progressive disease, such event shall be reported as symptomatic deterioration. Objective progressive disease (i.e. confirmed radiographically) should be documented even after treatment discontinuation.

Evaluation is done according to RECIST 1.1.

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

7.2 Safety Evaluation

7.2.1 Safety endpoints

Safety parameters for this study include clinical symptoms, vital signs, physical examination, laboratory tests (hematology, urinalysis, blood biochemistry, thyroid function, and coagulation function). AEs are evaluated according to NCI CTCAE Version 4.03, including type, incidence, severity, start and end date, whether it is an SAE, causality with the study drugs, and outcome.

7.2.2 Definition of adverse event

An adverse event (AE) refers to any untoward medical occurrence in a study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. In this study, AEs should be documented from signing informed consent until the end of the safety follow-up period (90 days after the last dose of the study drugs) or the start of new anti-tumor treatment. AEs include any adverse symptoms or signs, abnormal laboratory tests or diseases. AEs include the following:

1) Worsening of pre-existing (prior to enrollment) medical conditions/diseases (including symptoms, signs, and laboratory test abnormalities);

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

3) Clinically significant abnormal laboratory findings.

The investigator should record any AEs that have occurred in detail, including the description of the AEs and all relevant symptoms, time of occurrence, severity, relationship to the investigational drugs, duration, measures taken, and final results and outcomes.

7.2.3 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 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).

During the study, AEs resulting in hospitalization or prolonged hospitalization should be considered SAEs. Hospitalization does not include the following:

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

Hospitalization or prolonged hospitalization not related to the worsening of AEs is not considered an SAE. For example:

- ✓ Hospitalization due to the pre-existing disease without new AEs and aggravation of the pre-existing disease (e.g., hospitalization to examine laboratory abnormalities that have persisted from before the 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 an AE, it should be reported as so. For example, acute appendicitis during the AE reporting period should be reported as an AE, and the resulting appendicectomy shall be recorded as the treatment of the AE.

7.2.4 Progressive disease

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

7.2.5 Immune-mediated adverse events

Immune-mediated AE (IMAE) refers to specific events (including pneumonia, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, and endocrinopathy) related to immunosuppressive treatment. Endocrine events (hypothyroidism/thyroiditis, hyperthyroidism, hypophysitis, diabetes, and adrenal insufficiency) are often excluded, as they are usually unrelated to treatment and are usually managed in the absence of interventions with immunosuppressants. Preferred terms included in the IMAE analysis to support warnings and precautions are shown in Table 11.

IMAE Type	PT included in IMAE (MedDRA)
Pneumonia	Pneumonia, interstitial pneumonia
Diarrhea/Colitis	Diarrhea, colitis, enterocolitis
Hepatitis	Hepatotoxicity, hepatitis, hepatitis acute, autoimmune hepatitis, AST increased, ALT increased, bilirubin increased, ALP increased
Adrenal Insufficiency	Adrenal Insufficiency
Hypothyroidism/thyroiditis	Acute thyroiditis (collapse due to frequent thyroiditis), autoimmune thyroiditis (collapse due to frequent thyroiditis)
Hyperthyroidism	Hyperthyroidism
Hypophysitis	Hypophysitis
Diabetes Mellitus	Diabetes mellitus, diabetic ketoacidosis
Nephritis and kidney dysfunction	Nephritis, hepatitis acute, tubulointerstitial nephritis, renal failure acute, renal failure, creatinine increased
Rash	Rash, maculo-papular rash

Table 11. Preferred terms included in the IMAE analysis to support warnings and precautions

7.2.6 Potential drug-induced liver injury

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

Potential drug-induced liver injury is defined as follows (Table 12):

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

Table 12. Definition of potential drug-induced liver injury

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

Except for the reexaminations of AST and ALT, albumin, creatine kinase, TBIL, direct and indirect bilirubin, γ-GT, prothrombin time (PT)/international normalized ratio (INR), and ALP should also be examined. Detailed medical history should include history of alcohol use,

acetaminophen, soft drugs, various supplements, family diseases, occupational exposure, sexual behavior, travel, contact with jaundice patients, surgery, blood transfusion, hepatic diseases, and allergies. Further tests may include the testing for acute hepatitis A, B, C and E, and hepatic imaging (such as biliary tract). If the above laboratory criteria are confirmed upon re-examination, the possibility of potential drug-induced liver injury should be considered in the absence of any other causes of abnormal liver function, without waiting for all liver function test results. Potential drug-induced liver injury should be reported as an SAE.

7.2.7 Adverse Events of Special Interest

Special interest events include the following:

- Grade ≥ 3 infusion reactions;
- Grade ≥ 2 diarrhea/colitis, uveitis, and interstitial pneumonia;
- Grade ≥ 3 other immune-related AEs;
- Grade 4 amylase or lipase increased.

7.3 Classification of AEs and SAEs

7.3.1 Criteria for the severity of AEs

The severity of AEs is determined using NCI-CTCAE v4.03. Refer to the following criteria for AEs not listed in NCI-CTCAE v4.03 (Table 13):

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	Resulting in death

Table 13. Criteria for the severity of AEs

7.3.2 Criteria for causality between adverse events and study drugs

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 changes in objective laboratory measurements during the treatment period should be truthfully recorded. The severity,

duration, measures taken, and the outcome of AEs should also be documented. The study physician shall assess the relationship between the AE and the study drugs by considering the time sequence between the administration of study drug and the occurrence of AE, characteristics and toxicology of the study drug, concomitant medications, underlying diseases, medical history, family history, as well as dechallenge and rechallenge. The causality assessment will be provided using the following five categories "definitely related, possibly related, unlikely related, definitely unrelated, and indeterminable". Events that are assessed to be "definitely related", "possibly related", "unlikely related", and "indeterminable" will be listed as adverse drug reactions. When calculating the incidence of adverse events, the total of these four categories will be used as the numerator and the total number of subjects for safety evaluation will be used as the denominator.

7.4 Follow-up and Reporting of Adverse Events

7.4.1 Follow-up of AEs/SAEs

All AEs/SAEs should be followed up until they are resolved, return to baseline levels or Grade ≤ 1, reach a stable state, or are reasonably explained (e.g., lost to follow-up, death).

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

Table 14. Requirements for collection and follow-up of AEs/SAEs

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

7.4.2 Reporting of adverse events

AEs are recorded from the date of signing informed consent to the end of the safety follow-up (at 90 days after the last dose) or the start of a new anti-cancer therapy.

During each visit, the investigator should inquire about AEs that occur since the last visit. AEs should be followed-up until the end of the event, a stable state, returning to baseline levels or Grade ≤ 1, obtaining a reasonable explanation, lost to follow-up, or death. Follow-up information should be readily available when requested by the sponsor.

7.4.3 Reporting of serious adverse events

Serious adverse events (SAEs) that occur from the signing of the informed consent form until 90 calendar days (inclusive) after the last dose will be collected. In the event of an SAE, whether it is an initial report or a follow-up report, the investigator must complete the "NMPA Serious Adverse Event Report Form" immediately, with a signature and date. It must have been reported to the relevant regulatory authorities, the sponsor, and the ethics committee within 24 hours of knowing of the event.

The sponsor's email address for safety data is: hengrui_drug_safety@hrglobe.cn.

SAEs that occurred 90 days after the last study dose were generally not reported unless they were suspected to be related to the study drugs. 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 discontinuation of past treatment, or comorbidities during the study), the causality should be explained 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.

7.4.4 Reporting of Special Interest Events

For SIEs specified in the study protocol, the investigator must complete the "Report of Special Interest Event for Hengrui Clinical Studies" and report to the sponsor within 24 hours of knowing of the event.

If the SIE is also an SAE, the "NMPA Serious Adverse Event Report Form" should also be completed and reported to the relevant authorities according to the SAE reporting procedure.

SIEs are shown in section 7.2.7.

7.4.5 Pregnancy reporting

Female subjects who become pregnant during the study must withdraw from the study. If a female partner of a male subject becomes pregnant, the male subject will continue participation in the clinical study. The investigators must fill out the "Pregnancy Report/Follow-up Form for Hengrui's Clinical Studies" and report to the sponsor within 24 h after becoming aware of the pregnancy, and report to the ethics committee promptly.

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

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.

8 DATA ANALYSIS/STATISTICAL METHODS

Data analysis will be completed by Hengrui and/or a designated CRO. 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 have signed the informed consent form but have not receive any treatment) will not be included in any analysis. These subjects will be presented in a separate list.

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

8.1 Statistical Analysis Plan

The primary objective of this study is to evaluate the efficacy of the sequential therapy of SHR-1210 combined with capecitabine and oxaliplatin (cohort 1) or SHR-1210 combined with apatinib mesylate (cohort 2) as a first-line treatment for advanced or metastatic Gastric (GC) or gastroesophageal junction (GEJ) cancer. The primary efficacy endpoint is ORR.

Detailed summaries and methods of statistical analyses for the data collected from the study shall be included in the statistical analysis plan (SAP), which shall be finalized and filed by the sponsor. The SAP should be revised accordingly if there are any changes to the study protocol that may have a major impact on the SAP, as determined by the sponsor or principal investigator. Relevant content in statistical analysis plan that is relevant to this protocol may be revised. However, if revised content involves the main and/or key factors of the protocol (such as the definition of endpoints or their analysis), such content in the protocol will be revised.

8.2 Sample Size

The sample size will be calculated using Simon's two-stage design, with a power of 80% and a one-sided α of 0.05. The optimal method is used, that is, minimizing the subjects' exposure to ineffective treatment. Assuming that in the cohort 2 (SHR-1210 + apatinib), uninteresting level ORR (P0) = 15% and desirable target level ORR (P1) = 30%. The first stage requires 19 subjects, and the treatment should be effective in > 3 subject (i.e. a minimum of 4) before proceeding to the second stage. The first and second stage require a total of 55 subjects, and the treatment should be effective in > 12 subjects (i.e., a minimum of 13) to be considered effective.

Assuming that in the cohort 1 (sequential therapy of SHR-1210 + capecitabine + oxaliplatin), the uninteresting level ORR (P0) = 35% and desirable target level ORR (P1) = 55%. Under the condition that the power of test is 80% and α is 0.05 (one-sided), the first stage requires 19 subjects in both cohort 1 and cohort 2 for the purpose of consistency. The treatment should be effective in > 3 subjects (i.e. a minimum of 4) before proceeding to the second stage. The first and second stage require a total of 43 subjects, and the treatment should be effective in > 20 subjects (i.e., a minimum of 21) to be considered effective.

The number of subjects and the required minimum number of subjects responding to the treatment at each stage for both cohorts are shown in Table 15:

Cohort	P0	01	N1	R1	N	R
Cohort 1 (sequential therapy of SHR-1210 + capecitabine + oxaliplatin)	35%	55%	19	3	43	20
Cohort 2 (SHR-1210 + apatinib)	15%	30%	19	3	55	12

Table 15. Sample size calculation

N1: Number of subjects at the first stage

R1: Number of subjects responding to the treatment at the first stage shall be greater than this number

N: Final number of subjects

R: Final number of subjects responding to the treatment shall be greater than this number

At the first stage, 19 subjects are enrolled into each cohort. If ≥ 4 subjects in cohort 1 achieve response (CR or PR), the second stage will be initiated, and 24 more subjects are enrolled (more subjects are enrolled into cohort 1 until there are 43 subjects); if ≥ 4 subjects in cohort 2 achieve response, the second stage will be initiated, and 36 more subjects are enrolled (more subjects are enrolled into cohort 2 until there are 55 subjects).

Considering the 10% non-evaluable subjects, 48 and 62 subjects should be enrolled into cohort 1 and 2, respectively.

8.3 Analysis Population

This study will involve the following analysis sets:

- Full analysis set (FAS): All enrolled subjects who are randomized and received at least one dose of the study drugs. This analysis set will be used for the efficacy analysis.
- Per-protocol set (PPS): A subset of the FAS. Subjects with important protocol deviations judged to have a significant impact on treatment efficacy are excluded from this analysis set. The list of subjects included into or excluded from the PPS should be reviewed and determined by the sponsor and the investigator before the database is locked.
- Safety set (SS): All enrolled subjects who have received at least one dose of the study drugs and have post-administration safety data.
- Evaluable set (ES): A subset of the FAS, defined as the all enroll subjects receive at least one dose of the study drugs and receive post-baseline tumor assessment at least once.
- PK analysis set (PKS): Defined as all enrolled subjects who receive the study drugs and have evaluable post-dose PK data (concentration and/or parameters).
- Immunogenicity analysis set (ADA): All enrolled subjects who receive at least one dose of the study drugs and have baseline as well as at least one post-baseline evaluable ADA data.

8.4 Statistical Methods

8.4.1 General analysis

In this study, unless otherwise stated, all data will be summarized using descriptive statistics in accordance with the following general principles.

Continuous variables will be summarized using mean, standard deviation, median, maximum, and minimum; the categorical variables will be summarized using frequency and percentage; for time to event data, the survival rate will be estimated using the Kaplan-Meier method and the survival curves will be plotted; blood concentration data will be summarized using geometric mean, geometric standard deviation, geometric coefficient of variation, mean, standard deviation, coefficient of variation, median, maximum, and minimum.

8.4.2 Efficacy analysis

Efficacy analysis will be based on FAS and PPS. ORR is summarized using descriptive statistics by stage and dose group. PFS, DoR, and DCR are only summarized by treatment group.

ORR analysis provides the number and proportion of subjects with response (CR + PR) and estimates the two-sided 95% exact CI of overall ORR. In cohort 1 and cohort 2, 19 subjects will be analyzed in the first stage after completing the efficacy evaluation, respectively. Then, based on the judgment criteria in Table 15 and the safety data, it is determined whether to discontinue or continue the treatment in this cohort.

Both PFS and DoR are time-event data. Kaplan-Meier method will be used to draw survival curve and estimate median survival time. The 95% CI (two-sided) of overall median survival is also estimated if necessary. DCR will provide the number and proportion of subjects determined to achieve CR + PR + SD. The 95% CI (two-sided) of DCR is estimated if necessary.

8.4.3 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 only summarized using descriptive statistics, including but not limited to the following. The specific analysis is described in the statistical analysis plan:

- 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;
- Occurrence of abnormal laboratory measurements, vital signs, and ECG data.

8.4.4 PK analysis

PK analysis is performed based on PKS. PK concentrations and PK parameters (maximum and minimum concentration) are summarized by descriptive statistics. Apart from the statistics listed in the general analysis, PK concentration and PK parameter data (maximum and minimum concentration) will be also summarized descriptively using geometric mean (GM), coefficient of variation (CV%), and geometric CV% (GCV%).

The correlation between drug exposure and toxicity is analyzed based on the maximum and minimum concentration of SHR-1210 and apatinib.

8.4.5 Immunogenicity analysis

The immunogenicity will be analyzed based on the ADA analysis set. The concentration of anti-SHR-1210 antibodies (ADAs) will be analyzed using descriptive statistics. Treatment-emergent adverse events may be analyzed separately in the ADA-negative and ADA-positive groups.

9 SOURCE DOCUMENTS AND OBTAINING SOURCE DATA/DOCUMENTS

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

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

The investigator is responsible for ensuring that the source data is accurate, clear, contemporaneous, original and attributable, regardless of whether the data is handwritten or entered electronically. In routine clinical study activities, if the source data is created (first entered), modified, maintained, archived, retrieved, or transmitted through a computer system (and/or any other type of electronic device), such systems must comply with all applicable laws and regulations governing the use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical record/health record, adverse event follow-ups/reporting, evaluation required by the protocol and/or drug inventory records.

When written records obtained through such a system are used in place of the electronic version for specified activities, these written records must be certified copies. A certified copy consists of a copy of the verified original information, dated and signed, and is an exact copy with all attributes and information that are identical to the original document.

10 QUALITY ASSURANCE AND QUALITY CONTROL

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

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

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

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

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

11 REGULATIONS, ETHICS, INFORMED CONSENT, AND SUBJECT PROTECTION

11.1 Regulatory Considerations

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

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

1) Provisions for Drug Registration

2) Good Clinical Practice

3) Consensus on ethical principles based on international ethics guidelines, including the Declaration of Helsinki and the Council for International Organizations of Medical Sciences (CIOMS) International Ethics Guidelines

4) ICH Guidelines

5) Other applicable laws and regulations

11.2 Ethical Standards

This study protocol must first be reviewed and approved in writing by the IEC/IRB of the Hospital before being implemented. The study protocol, protocol revisions, ICF, and other relevant documents such as recruitment advertisements should be submitted to the ethics committee. This clinical study must comply with the "Declaration of Helsinki", NMPA's (former CFDA) "Good Clinical Practice" (GCP), and other 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 IEC/IRB only when in purpose of eliminating direct and immediate harm to the subject. Besides, the deviation or change and the corresponding reason, and the recommended protocol modification should be submitted to the IEC/IRB for review. The investigator must provide explanations and document any protocol deviation.

During the study, any changes to this study protocol must be submitted to the IEC/IRB. 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 IEC/IRB. 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.

11.3 IRB/IEC

Prior to the initiation of the study, the study protocol, informed consent form, subject recruitment materials and other materials provided to the subjects must first be approved by the IRB/IEC. Subjects may be enrolled only after the protocol and ICF have been approved. The revision of the study protocol should be approved by IRB/IEC. The investigator and the sponsor must provide a copy of the Investigator's Brochure or product information for subjects and any relevant updates to the IRB/IEC.

The investigator and the sponsor must submit reports, updates, or other data (e.g., expedited safety reports, modifications, and management letters) according to the requirements of the competent authority or institution's procedures to the IRB/IEC.

11.4 Informed Consent

11.4.1 ICFs and other written information for subjects

The ICF includes all the elements required by the ICH, GCP, and regulatory authorities, and is consistent with the ethical principles mentioned in the Declaration of Helsinki.

The ICF describes the study drugs and study process in detail and fully explains the risks of the study to the subjects. Written documentation of informed consent must be obtained before starting any study-related procedures.

All revisions to the ICF must be approved by the ethics committee, who will decide whether the subjects who have signed the previous version of the ICF are required to sign the new one.

The ICF should state that the identity of the subjects must be remained confidential, but the authorized representative of the sponsor and regulatory authorities are allowed to access the information.

11.4.2 Informed consent process and records

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

11.5 Confidentiality of Subject Information

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

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

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

Subject's study data that are collected for statistical analysis and scientific reports should not include the subject's contact information and identification information. Instead, individual subjects and their study data will be given a unique study identification number. The study data entry and study management system used by the study personnel at the study centers shall be confidential and password-protected. At the end of the study, all identification information in the study database will be erased and archived.

12 DATA MANAGEMENT

12.1 Data Recording

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

The investigator must retain all study records and source documents preferably as long as possible, up to the maximum time required by applicable regulations and guidelines, or SOP of the study center, or as specified by sponsor, whichever is longest. The investigator must first contact the sponsor prior to the destruction of any study-related records.

If the investigator withdraws from the study (e.g., change of positions, retirement), the records should be transferred to a designated personnel approved by both parties (e.g., another investigator). The sponsor must be notified in writing for such transfers.

12.1.1 Study medical records

As source documents, the medical records should be completely retained. The investigator should be responsible for filling and keeping the study medical record. The subject information on the cover of the medical record should be checked each time before filling the record. The medical record should be written in a neat and legible way so that the sponsor's CRA could verify the data with eCRF during each monitoring visit.

12.1.2 eCRF entry

Clinical study data are collected using the HRTAU EDC system.

Each staff that is authorized to sign the eCRF must meet the sponsor's training requirements and must only log in the electronic data capture system with the individual user account provided by the sponsor. The user account shall not be shared with others and shall not be assigned to another staff.

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

Modifications: The system instructions must be followed when correcting the eCRF data as needed, and the reason for data correction must be recorded. The logic verification program in the system will verify the integrity and logic of the clinical study data entered into the EDC system and generate an 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.

Laboratory tests: The investigator should conduct all tests as well as collect, input and report subject information and data according to the follow-up time window. As a source document, the laboratory test report must be complete and the results should be documented in the eCRF in a timely manner.

In addition, source data also include original copies of data recorded or generated by automated instruments, photographic negative, X-ray, CT or MRI, ECG records, and subject daily logs. These documents must at least indicate the subject number and date of the procedure performed. If possible, the medical review of these records should be documented, and signed and dated by the investigator. The information from these source documents must be entered into the eCRF in a timely manner.

12.1.3 eCRF review

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

12.1.4 Data monitoring and auditing

The authorized representatives (such as CRA, auditors, etc.) of sponsor must be allowed to regularly visit all the study centers to evaluate the quality of data and whether the study is complete and reliable. These representatives will perform an on-site review of the study records by directly comparing these records with the source documents, discuss the implementation of the study with the investigator, and confirm whether the study facilities still meet the requirements.

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

In addition, inspectors from regulatory departments may also evaluate the study. These personnel must also be allowed to review the eCRF, source documents, and other study documents, and to inspect the study facilities. Audit reports must be kept confidential. If the regulatory department plans to conduct an inspection, the investigator must immediately notify the sponsor and promptly provide the inspection report.

12.2 Data Management

12.2.1 EDC database establishment

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

12.2.2 Data entry and verification

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

12.2.3 Database lock

After the clinical study is completed, the study director, sponsor, statistician, and data manager will conduct a joint review before statistical analysis mainly to determine the analysis data set for each case, the judgment of missing values, and the handling of outliers.

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

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

12.2.4 Data archiving

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

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

12.3 Protocol Deviations

Protocol deviation refers to any practice that does not comply with study protocol, GCP or SOP. This non-compliance may occur in the subject and may also occur in the investigator or other study personnel. Study centers must prepare corresponding corrective measures and implement them immediately if a protocol 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 source documents and reported to the sponsor. 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.

13 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, synopsis, or full text of all planned publications (poster, invited lectures, or guest lectures) at least 30 days prior to submission for publication or other forms of release. To protect the intellectual property, especially before the acquisition of patent, the investigator should agree to delay the publication, and the delay period should not exceed 60 days. Before open publication, Hengrui can require 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.

14 EXPECTED STUDY SCHEDULE

Anticipated enrollment of the first subject: Dec. 2017

Anticipated enrollment of the last subject: Dec. 2018

Anticipated study completion: Dec. 2020

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Appendix 1 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.

Appendix 2 Cockroft-Gault Formula (for calculating the creatinine clearance)

Serum creatinine: mg/dL

$$\text{Creatinine clearance rate in males}\left(\frac{\text{ml}}{\text{min}}\right) = \frac{(140 - \text{Age}) \times \text{Weight}}{72 \times \text{Serum creatinine}}$$

$$\text{Creatinine clearance rate in females}\left(\frac{\text{ml}}{\text{min}}\right) = \frac{0.85 \times (140 - \text{Age}) \times \text{Weight}}{72 \times \text{Serum creatinine}}$$

Serum creatinine: μmol/L

$$\text{Creatinine clearance rate in males}\left(\frac{\text{ml}}{\text{min}}\right) = \frac{(140 - \text{Age}) \times \text{Weight}}{0.818 \times \text{Serum creatinine}}$$

$$\text{Creatinine clearance rate in females}\left(\frac{\text{ml}}{\text{min}}\right) = \frac{0.85 \times (140 - \text{Age}) \times \text{Weight}}{0.818 \times \text{Serum creatinine}}$$

Age in years, weight in kilogram (kg).

Appendix 3 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)

1 BACKGROUND

Omitted

2 PURPOSE

Omitted

3 MEASURABILITY OF TUMOR AT BASELINE

3.1 Definitions

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

3.1.1 Measurable

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

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

3.1.2 Non-measurable

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

3.1.3 Special considerations regarding lesion measurability

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

Bone lesions:

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

Cystic lesions:

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

Lesions with prior local treatment:

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

3.2 Specifications by Methods of Measurements

3.2.1 Measurement of lesions

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

3.2.2 Method of assessment

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

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

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

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

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

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

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

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

4 TUMOR RESPONSE EVALUATION

4.1 Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only 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 ≥ 15mm by CT scan. Only the short axis of these nodes needs to be measured at baseline. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by tumor metastasis. Nodule size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial,

sagittal or coronal). The smallest of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm ×30 mm with a short axis of 20 mm qualifies as a malignant and measurable node. In this example, 20 mm should be recorded as the node measurement. Nodes with short axis ≥ 10 mm but < 15 mm should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

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

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

4.3 Response Criteria

4.3.1 Evaluation of target lesions

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

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

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

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

4.3.2 Special notes on the assessment of target lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. CRFs or other data collection

methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

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

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

4.3.3 Evaluation of non-target lesions

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

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

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

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

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

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

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

4.3.5 New lesions

The appearance of new malignant lesions denotes PD; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of radiographically detected lesions; however, the finding of a new lesion should be unequivocal. For example, it

should not be attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some new bone lesions that may be simply healing, or re-occurrence of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a new cystic lesion, which it is not.

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

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

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

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up:
- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, PD is confirmed.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the imaging examination, this is not PD.

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: subjects with target (+/– non-target) disease

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

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

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

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

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

[a]: "Non-CR/non-PD" is preferred over SD for non-target disease. Since SD is increasingly used as an endpoint for response 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 three measured lesions with a baseline sum of 50 mm and only two lesions with a sum of 80 mm were assessed at a subsequent follow-up, the patient has 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 BOR 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

Overall Response at First Time Point	Overall Response at Subsequent Time Point	Best Overall Response
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; NE, not evaluable.
[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 be 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 are likely still present and in fact the subject has PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

4.4.4 Special notes on response evaluation

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

In trials where confirmation of response is required, repeated "NE" time point evaluations may complicate best response evaluation. 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 studies it is reasonable to consider a subject with time point responses of PR-NE-PR as a confirmed response.

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

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

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

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

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 studies

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

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

Appendix 4 Management Principles for Immune Related Adverse Events

The principles specified in this section can be used as reference for the investigator when managing immune-related AEs. The principles can be added after discussion with the representatives of the sponsor. The principles are applicable to all immuno-oncology drugs and regimens.

The general principle is that AEs should be carefully evaluated and the differential diagnosis be made in accordance with the standard medical practice. Non-inflammatory causes should be considered and properly handled.

Corticosteroids are preferable drug for immuno-oncology treatment-related AEs. An oral dose equivalent to the recommended IV dose can be considered for ambulatory patients with low grade toxicity. The low bioavailability of oral administration should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with an internist or surgeon is recommended, especially before an invasive diagnostic or therapeutic procedure.

The frequency and severity of related adverse events included in these protocols will depend on the cancer immunotherapy or regimen being used.

1. Management Principles for Gastrointestinal Adverse Events

Inflammatory causes of disease should be excluded. Opioids/anesthetics may mask the symptoms of perforation. Do not use infliximab in the case of perforation/sepsis.

Diarrhea/Colorectitis Grade (NCI CTCAE v4)	Handling	Follow-Up
Grade 1 Diarrhea: Increase of < 4 stools per day over baseline; Colitis: No symptom.	◆ Continue the immunotherapy according to the study protocol; ◆ Symptomatic treatment.	◆ Closely monitor aggravated symptoms. ◆ Educate subjects to report aggravated symptoms immediately. If it is aggravated: ◆ Provide treatment according to the method for grade 2 or grade 3/4 situations.
Grade 2 Diarrhea: Increase of 4-6 stools per day over baseline; intravenous infusion of < 24 h is required; daily living is not affected; Colitis: Abdominal pain; hematochezia.	◆ Delay the immunotherapy according to the study protocol; ◆ Symptomatic treatment.	If it is improved to Grade 1: ◆ Resume the immunotherapy according to the study protocol. If it lasts for > 5-7 days or relapses: ◆ Intravenous administration of 0.5-1.0 mg/kg/d methylprednisolone or an equivalent orally administrated dose; ◆ When the symptoms improve to grade 1, reduce the dose of steroids for at least 1 month and consider prophylactic antibiotics to prevent opportunistic infections, then resume the immunotherapy as per study protocol. If the symptoms aggravated or persisted after > 3-5 days of oral administration of steroids: ◆ Provide treatment according to the method for grade 3/4 situations.
Grade 3-4 Diarrhea (Grade 3): Increase of ≥ 7 stools per day over baseline; fecal incontinence; intravenous infusion of ≥ 24 h is required; daily living is affected; Colitis (Grade 3): Severe abdominal pain, indications for medical interventions, peritoneal signs; Grade 4: Life-threatening, perforation	◆ Terminate the immunotherapy according to the study protocol; ◆ Intravenous administration of 1.0-2.0 mg/kg/d methylprednisolone or an equivalent dose via intravenous injection; ◆ Add prophylactic antibiotics to prevent opportunistic infections; ◆ Consider lower GI endoscopy.	If symptoms improve: ◆ Continue steroid treatment until the symptoms recover to grade 1, then gradually reduce the dose of steroids for at least 1 month. If it lasts for > 3-5 days or relapses after improvement: ◆ Add 5 mg/kg infliximab (if there are no contraindications). Note: Do not use infliximab in the case of perforation/sepsis.

Once a patient given intravenous injections of steroids shows a sustained clinical improvement, the patient can switch to an equivalent dose of oral corticosteroids (e.g., prednisone) by the time or before the dose of steroid injections starts to be gradually reduced. When switching to oral corticosteroids with an equivalent dose, it should be considered that the bioavailability of oral corticosteroids is relatively low.

2. Management Principles for Pulmonary AEs

Inflammatory causes of disease should be excluded. If it is due to a non-inflammatory cause, a symptomatic treatment should be given while the immunotherapy should be continued. Imaging evaluation and consultations with the respiratory department should be performed.

Grade of Pneumonitis (NCI CTCAE v4)	Handling	Follow-Up
Grade 1 Only radiographic changes	◆ Consider delaying the immunotherapy; ◆ Monitor symptoms every 2-3 days; ◆ Consider consulting with respirologist and infectious diseases specialist.	◆ Repeat imaging examinations at least every 3 weeks. If it is aggravated: ◆ Provide treatment according to the method for grade 2 or grade 3/4 situations.
Grade 2 Mild to moderate new symptoms	◆ Delay the immunotherapy according to the study protocol; ◆ Consult with respirologist and infectious diseases specialist; ◆ Intravenous administration of 1.0 mg/kg/d methylprednisolone or an equivalent orally administrated dose; ◆ Consider bronchoscopy and lung biopsy.	◆ Repeat imaging examinations every 1-3 days. If symptoms improve: ◆ When symptoms return to near baseline levels, reduce the dose of steroids for at least 1 month and then resume the immunotherapy as per study protocol while considering prophylactic antibiotics. If the symptoms are not improved or aggravated after 2 weeks: ◆ Provide treatment according to the method for grade 3/4 situations.
Grade 3-4 Severe new symptoms; new onset/aggravation of hypoxia; life-threatening.	◆ Terminate the immunotherapy according to the study protocol; ◆ Consult with respirologist and infectious diseases specialist; ◆ Intravenous administration of 2-4 mg/kg/d methylprednisolone or an equivalent dose via intravenous injection; ◆ Add prophylactic antibiotics to prevent opportunistic infections; ◆ Consider bronchoscopy and lung biopsy.	If symptoms improve to the baseline level: ◆ Gradually reduce the dose of steroids for at least 6 weeks. If the symptoms are not improved or aggravated after 48 h: ◆ Add other immunosuppressants (e.g., infliximab, cyclophosphamide, intravenous immunoglobulin or mycophenolate mofetil).

Once a patient given intravenous injections of steroids shows a sustained clinical improvement, the patient can switch to an equivalent dose of oral corticosteroids (e.g., prednisone) by the time or before the dose of steroid injections starts to be gradually reduced. When switching to oral corticosteroids with an equivalent dose, it should be considered that the bioavailability of oral corticosteroids is relatively low.

3. Management Principles for Hepatic Adverse Events

Non-inflammatory causes of disease should be excluded. If it is due to a non-inflammatory cause, a symptomatic treatment should be given while the immunotherapy should be continued. Consider imaging examinations to rule out obstruction/tumor progression.

Elevation Grade in the Hepatic Function Test (NCI CTCAE v4)	Handling	Follow-Up
Grade 1 AST/ALT > 3 × ULN and/or TBIL>1 × ULN but ≤ 1.5 × ULN	◆ Continue the immunotherapy according to the study protocol.	◆ Continue hepatic function monitoring as per study protocol. If it is aggravated: ◆ Provide treatment according to the method for grade 2 or grade 3/4 situations.
Grade 2 AST/ALT > 3 × ULN, but ≤ 5 × ULN and/or TBIL> 1.5 × ULN but ≤ 3 × ULNN	◆ Delay the immunotherapy according to the study protocol; ◆ Increase the monitoring frequency to once every 3 days.	If symptoms recover to the baseline level: ◆ Resume routine monitoring and resume the immunotherapy according to the study protocol. If elevation persists for > 5-7 days or aggravates: ◆ Intravenous administration of 0.5-1 mg/kg/d methylprednisolone or an equivalent orally administrated dose. If LFT recovers to grade 1 or to the baseline level, reduce the dose of steroids for at least 1 month, and consider prophylactic antibiotics to prevent opportunistic infection and then resume the immunotherapy according to study protocol.
Grade 3-4 AST/ALT > 5 × ULN and/or TBIL> 3 × ULN	◆ Terminate the immunotherapy according to the study protocol*; ◆ Increase the monitoring frequency to once every 1-2 days; ◆ Intravenous administration of 1.0-2.0 mg/kg/d methylprednisolone or an equivalent dose via intravenous injection**; ◆ Add prophylactic antibiotics to prevent opportunistic infections; ◆ Consultation with the gastroenterology department.	If it recovers to Grade 2: ◆ Reduce the dose of steroids for at least 1 month. If not improving, or even aggravating or recurring after > 3-5 days: ◆ Add mycophenolate mofetil 1 g bid; ◆ If the symptoms are not relieved within 3-5 days, other immunosuppressants are considered based on local guidelines.

Once a patient given intravenous injections of steroids shows a sustained clinical improvement, the patient can switch to an equivalent dose of oral corticosteroids (e.g., prednisone) by the time or before the dose of steroid injections starts to be gradually reduced. When switching to oral corticosteroids with an equivalent dose, it should be considered that the bioavailability of oral corticosteroids is relatively low.

* If AST/ALT ≤ 8 × ULN and TBIL ≤ 5 × ULN, the immunotherapy can be delayed rather than discontinued.

**For Grade 4 hepatitis, the recommended starting dose of methylprednisolone intravenous injection is 2 mg/kg/d.

4. Management Principles for Endocrine Adverse Events

Non-inflammatory causes of disease should be excluded. If it is due to a non-inflammatory cause, a symptomatic treatment should be given while the immunotherapy should be continued. Visual field tests, endocrinology consultation and imaging examinations are considered.

Asymptomatic TSH elevation	◆ Continue the immunotherapy according to the study protocol; ◆ If TSH < 0.5 × LLN or TSH > 2 × ULN, or the results are out of range in 2 consecutive subsequent measurements: According to clinical indications, detect the level of free T4 in subsequent cycles; Consider endocrinology consultation.	
Symptomatic endocrinopathy	◆ Assess endocrine functions; ◆ Consider pituitary scans; ◆ <u>Observation of symptoms and abnormalities in laboratory test results/pituitary scans:</u> ◆ Delay the immunotherapy according to the study protocol; ◆ Intravenous administration of 1-2 mg/kg/d methylprednisolone or an equivalent orally administrated dose; ◆ <u>No abnormalities in laboratory test results/pituitary MRI but the symptoms persist:</u> ◆ Repeat the laboratory test within 1-3 weeks and repeat the pituitary MRI scan 1 month later.	<u>If there is improvement (with or without hormone replacement):</u> ◆ Reduce the dose of steroids for at least 1 month and consider prophylactic antibiotics to prevent opportunistic infections; ◆ Resume immunotherapy according to the study protocol; ◆ Patients with adrenal insufficiency may need to continue the use of mineralocorticoid-containing steroids.
Suspected Adrenal Crisis (e.g., severe dehydration, hypotension, and shock that does not match the severity of the disease)	◆ Terminate the immunotherapy according to the study protocol; ◆ Exclude sepsis; ◆ Intravenous administration of a stress dose of steroids containing mineralocorticoids; ◆ Intravenous infusion; ◆ Consult an endocrinologist; ◆ If adrenal crisis is ruled out, treat the symptomatic endocrinopathy using the methods described above.	

Once a patient given intravenous injections of steroids shows a sustained clinical improvement, the patient can switch to an equivalent dose of oral corticosteroids (e.g., prednisone) by the time or before the dose of steroid injections starts to be gradually reduced. When switching to oral corticosteroids with an equivalent dose in the lungs and liver, it should be considered that the bioavailability of oral corticosteroids is relatively low.

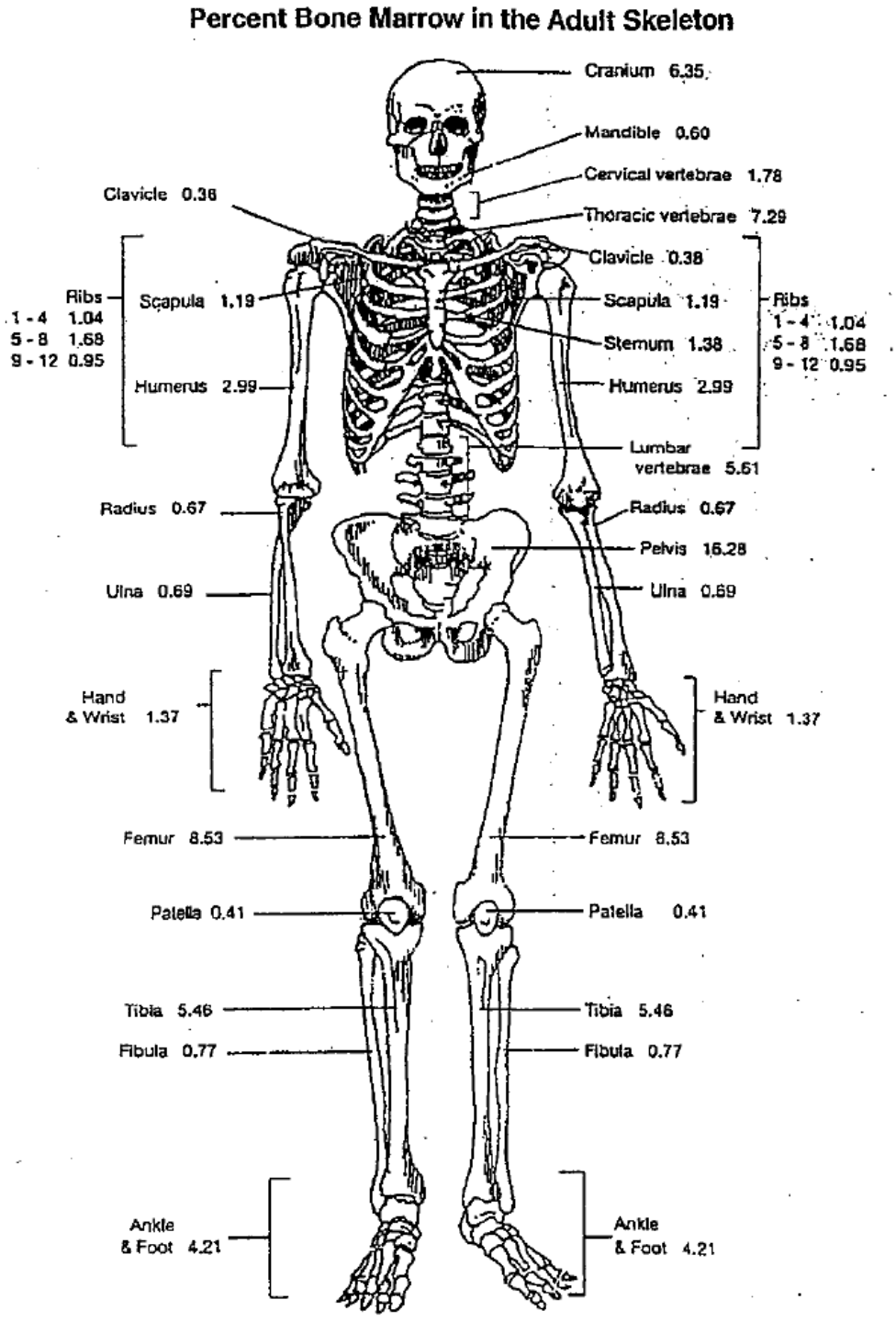
5. Management Principles for Skin Adverse Events

Rash Grade (NCI CTCAE v4)	Handling	Follow-Up
Grade 1-2 Coverage ≤ 30% body surface area (BSA)	◆ Symptomatic treatment (e.g., antihistamines, topical steroids); ◆ Continue the immunotherapy according to the study protocol.	<u>If symptoms persist for > 1-2 weeks or recur:</u> ◆ Consider skin biopsy; ◆ Delay the immunotherapy according to the study protocol; ◆ Consider intravenous administration of 0.5-1.0 mg/kg/d methylprednisolone or an equivalent orally administrated dose. Once improved, reduce the dose of steroids for at least 1 month and consider prophylactic antibiotics to prevent opportunistic infections, and resume immunotherapy according to the study protocol. <u>If it is aggravated:</u> ◆ Provide treatment according to the method for grade 3/4 situations.
Grade 3-4 Coverage ≥ 30% body surface area (BSA); or life-threatening results	◆ Delay or discontinue the immunotherapy as per the study protocol; ◆ Consider consultation with the Department of Dermatology; ◆ Intravenous administration of 1.0-2.0 mg/kg/d methylprednisolone or an equivalent dose via intravenous injection.	<u>If it is improved to Grade 1:</u> ◆ Reduce the dose of steroids for at least 1 month and add prophylactic antibiotics to prevent opportunistic infections; ◆ Resume the immunotherapy according to the study protocol.

Once a patient given intravenous injections of steroids shows a sustained clinical improvement, the patient can switch to an equivalent dose of oral corticosteroids (e.g., prednisone) by the time or before the dose of steroid injections starts to be gradually reduced. When switching to oral corticosteroids with an equivalent dose in the lungs and liver, it should be considered that the bioavailability of oral corticosteroids is relatively low.

(Weber JS, Postow M, Lao CD, Schadendorf D. Management of Adverse Events Following Treatment With Anti-Programmed Death-1 Agents. Oncologist. 2016 Jul 8: 2016-0055.)

Appendix 5 Percent Bone Marrow Content in Human Skeleton



Woodward Holoday E. A summary of the data of Mechanik on the distribution of human bone marrow. Phys Med Biol. 1960;5:57-59

Appendix 6 Prohibited Traditional Chinese Medicines During the Study Period

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

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