Title: A Randomized, Parallel-Controlled, Multicenter Phase II/III Clinical Study Evaluating Anti-PD-1 Antibody SHR-1210 in Patients with Advanced Hepatocellular Carcinoma (HCC) Who Have Previously Received Systemic Therapy
Clinical trial registration number: NCT02989922
Version Date: 3 Apr., 2018

A RANDOMIZED, PARALLEL-CONTROLLED, MULTICENTER PHASE II/III CLINICAL STUDY EVALUATING ANTI-PD-1 ANTIBODY SHR-1210 IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA (HCC) WHO HAVE PREVIOUSLY RECEIVED SYSTEMIC THERAPY

Study Protocol

Protocol Number:	SHR-1210-II/III-HCC
Version No.:	5.0
Version Date:	3 Apr., 2018
Principal Investigator:	[redacted]
Leading Site of Clinical Study:	[redacted]
Sponsor:	Jiangsu Hengrui Pharmaceuticals Co., Ltd.

VERSION HISTORY/REVISION HISTORY

Version No.	Version Date	Amendment Rationale and Summary of Changes
1.0	13 Oct., 2016	NA
2.0	28 Dec., 2016	See separate document: Protocol Version 2.0 Amendment
3.0	22 Jun., 2017	See separate document: Protocol Version 3.0 Amendment
4.0	25 Aug., 2017	See separate document: Protocol Version 4.0 Amendment
5.0	3 Apr., 2018	See separate document: Protocol Version 5.0 Amendment

Sponsor's Signature Page

I have read and confirmed this clinical study protocol (protocol number: SHR-1210-II/III-HCC; version number: 5.0; version date: 3 Apr., 2018). I agree that relevant responsibilities must be fulfilled in accordance with Chinese laws, Helsinki Declaration, Chinese GCP and this study protocol.

Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Sponsor's Medical Director: _____ (print)

_____ (signature)

Date of Signature: _____

Contact Number: _____

[redacted]

Principal Investigator's Signature Page (Leading Site)

I will fulfill the investigator's responsibilities carefully in accordance with Chinese GCP, participate or directly instruct this clinical study by myself. I have received the investigator's brochure of the investigational drug for this clinical study; I have known and read the preclinical data of the investigational drug and the protocol of this clinical study. I agree that relevant responsibilities must be conducted in accordance with Chinese laws, Helsinki Declaration, Chinese GCP and this study protocol. Unless for the purpose of protection of subject's safety, rights and benefits, I will amend the protocol only after informing the sponsor and obtaining the consent, and put into effect upon agreement by the ethics committee. I am responsible for making medical decisions related with clinical practice, so as to ensure prompt and appropriate treatment for subjects when any adverse event occurs during the study, and record and report these adverse events in accordance with national relevant regulations. I will ensure the authentic, accurate, complete and prompt entry of the data into the study medical record. I will accept the monitoring and auditing by monitors and auditors appointed by the sponsor, and inspection by the drug regulatory authority, so as to guarantee the quality of the clinical trial. I commit to the confidentiality on subject's personal information and relevant affairs. I agree to publicize my full name and occupation to the sponsor as well as own expenditure related with the clinical study as requested, and prohibit any commercial or economic behavior related with the study. I agree upon the use of study results for the drug registration and publication. I will provide a curriculum vitae of the principal investigator to the ethics committee, and submit to the drug regulatory agency for filing prior to the start of the study.

Study Site: _____

Principal Investigators: _____ (print)

_____ (signature)

Date of Signature:

Contact Number:_____

Address: _____

Zip code: _____

Principal Investigator's Signature Page (Participating Site)

I will fulfill the investigator's responsibilities carefully in accordance with Chinese GCP, participate or directly instruct this clinical study by myself. I have received the investigator's brochure of the investigational drug for this clinical study; I have known and read the preclinical data of the investigational drug and the protocol of this clinical study. I agree that relevant responsibilities must be conducted in accordance with Chinese laws, Helsinki Declaration, Chinese GCP and this study protocol. Unless for the purpose of protection of subject's safety, rights and benefits, I will amend the protocol only after informing the sponsor and obtaining the consent, and put into effect upon agreement by the ethics committee. I am responsible for making medical decisions related with clinical practice, so as to ensure prompt and appropriate treatment for subjects when any adverse event occurs during the study, and record and report these adverse events in accordance with national relevant regulations. I will ensure the authentic, accurate, complete and prompt entry of the data into the study medical record. I will accept the monitoring and auditing by monitors and auditors appointed by the sponsor, and inspection by the drug regulatory authority, so as to guarantee the quality of the clinical trial. I commit to the confidentiality on subject's personal information and relevant affairs. I agree to publicize my full name and occupation to the sponsor as well as own expenditure related with the clinical study as requested, and prohibit any commercial or economic behavior related with the study. I agree upon the use of study results for the drug registration and publication. I will provide a curriculum vitae of the principal investigator to the ethics committee, and submit to the drug regulatory agency for filing prior to the start of the study.

Study Site: _____

Principal Investigators: _____ (print)

_____ (signature)

Date of Signature:

Contact Number:_____

Address: _____

Zip code: _____

TABLE OF CONTENTS

VERSION HISTORY/REVISION HISTORY **2**
TABLE OF CONTENTS **6**
LIST OF TABLES **8**
LIST OF FIGURES **8**
SYNOPSIS **9**
STUDY PROCEDURES **15**
ABBREVIATIONS AND DEFINITIONS **22**
1. STUDY BACKGROUND **24**
1.1 Epidemiology and Current Treatment Status of Hepatocellular Carcinoma 24
1.2 Advances in the Treatment of Hepatocellular Carcinoma 24
1.3. Background of Immunotherapy 25
1.4 Background on Development of Anti-PD-1 Antibody SHR-1210 26
1.5 Preclinical Studies Result of SHR-1210 27
2 STUDY OBJECTIVES AND ENDPOINTS **30**
2.1 Study Objectives 30
2.2 Primary Study Endpoints 30
2.3 Secondary Study Endpoints 30
2.4 Exploratory Study Endpoints 30
3 STUDY PLAN **30**
3.1 Study Design 30
3.2. Study Procedures 31
4. RANDOMIZATION AND BLINDING **35**
5 SELECTION AND WITHDRAWAL OF SUBJECTS **35**
5.1 Inclusion Criteria 35
5.2 Exclusion Criteria 37
5.3 Concomitant Medications and Treatments 39
5.4 Criteria for Re-screening of Subjects 40
5.5 Criteria for Subjects' Withdrawal from the Study or Termination of Study Treatment 41
5.6 Criteria for Termination of Study Treatment 41
5.7 Subject ID 42
6 STUDY TREATMENT **42**
6.1 Information of Investigational Drug 42
6.2 Drug Dispensation 42
6.3 Drug Storage and Management 43
6.4 Disposal of Remaining Drugs 43

6.5 Dose Regimen 43
6.6 Common Recommendations on Safety Management 43
7 DOSE ADJUSTMENT AND SAFETY MANAGEMENT 46
7.1 Dose Level and Regimen 46
7.2 Dose Modification 46
8 EFFICACY EVALUATION 50
8.1 Primary Endpoints and Observation Method 50
8.2 Secondary Endpoints and Observation Method 51
8.3 Independent Tumor Imaging Evaluation 51
9. SAFETY EVALUATION 51
9.1 Adverse Events 51
9.2 Serious Adverse Event (SAE) 53
9.3 Pregnancy 55
9.4 AEs of Special Interest 56
9.5 Emergency Unblinding 56
10 DATA MANAGEMENT 56
10.1 Material Collection and Data Management 56
11 DATA ANALYSIS AND STATISTICAL METHODS 58
11.1 Determination of Sample Size 58
11.2 Analysis Populations 58
11.3 Statistical Analysis 59
12 INFORMED CONSENT AND ETHICS 60
12.1 Informed Consent 60
12.2 Ethical Principles 60
12.3 Regulatory Considerations 61
12.4 Security Measures of Subject Information 61
13 QUALITY CONTROL AND QUALITY ASSURANCE 61
14 PUBLICATION OF STUDY RESULTS 62
15 SCHEDULE OF THE TRIAL 62
16 PROTOCOL COMPLIANCE 62
17 STUDY SITE AND PARTICIPATING PERSONNEL 63
17.1 Leading Site 63
17.2 Sponsor 63
17.3 Other Study Participating Personnel 63
18 REFERENCES 64
Annex 1 Response Evaluation Criteria in Solid Tumors RECIST Version 1.1 66
Annex 2 Child-Pugh Classification on Hepatic Function 76

Annex 3 Criteria for ECOG Performance Status 76
Annex 4 Recommended Rules for Management of Immune-related Adverse Events 77

LIST OF TABLES

Table 1 The binding affinity of antibody SHR-1210 to human, monkey, and mouse PD1 antigens 27
Table 2 The binding affinity of antibody SHR-1210, Nivolumab and MK3475 to PD-1 antigen 28
Table 3 Pharmacokinetic parameters of cynomolgus monkeys after single intravenous infusion of SHR-1210 at different doses 29
Table 4 Recommendations on management of immune related adverse reactions 44
Table 5 Recommendations on management of immune-related adverse events 45

LIST OF FIGURES

Figure 1 SHR-1210 and Pembrolizumab blocking the binding of PD-1 / PD-L1 28
Figure 2 SHR-1210 and Nivolumab blocking the binding of PD-1 / PD-L1 28
Figure 3 The schematic diagram for phase II study 31

SYNOPSIS

Study Title	A Randomized, Parallel-Controlled, Multicenter Phase II/III Clinical Study Evaluating Anti-PD-1 Antibody SHR-1210 in Patients with Advanced Hepatocellular Carcinoma (HCC) Who Have Previously Received Systemic Therapy
Protocol Number	SHR-1210-II/III-HCC
Sponsor	Jiangsu Hengrui Pharmaceuticals Co., Ltd.
Study Population	Patients with advanced hepatocellular carcinoma (HCC) who have failed systematic therapy
Study Objectives	To evaluate the efficacy and safety of SHR-1210 in subjects with advanced HCC who have previously received systematic therapy
Study Design	The master study comprises of a randomized, parallel-controlled, multicenter, phase II clinical study and a randomized, double-blind, placebo-controlled, phase III clinical study, aiming at evaluating the efficacy and safety of anti-PD-1 antibody SHR-1210 in subjects with advanced hepatocellular carcinoma (HCC) who have received systematic therapy previously. This study will be conducted in several sites throughout the country. The whole study includes two parts, i.e., the first stage (phase II) and the second stage (phase III). The first stage (phase II) will be elucidated in the study protocol. The first stage: a phase II clinical study with the primary objective to investigate the efficacy and safety of SHR-1210 in subjects with advanced HCC who have previously failed systematic therapy. Sixty subjects are planned to be enrolled initially in the study and randomized in a 1:1 ratio to receive SHR-1210 3 mg/kg, I.V, q2W (once every two weeks) or SHR-1210 3 mg/kg, I.V, q3W (once every three weeks) in 42-day cycles. In order to observe the treatment effect of this investigational drug in a larger sample size, the sample size is increased according to the protocol treatment (Version 4.0, 25 Aug., 2017), i.e., a total of 220 subjects are needed in the study. The second stage (phase III study) will not be included in the protocol temporarily, but using a separate protocol.
Study Endpoints	**Primary Endpoints:** 1) Objective response rate (ORR) 2) 6-month overall survival rate (6-month OS rate) **Secondary Endpoints:** 1) Duration of response (DoR) 2) Disease control rate (DCR) 3) Safety of SHR-1210 4) Time to progression (TTP) 5) Progression-free survival (PFS) 6) Overall survival (OS) **Exploratory Endpoint:** The relationship between PD-L1 expression level and efficacy.

Sample Size Determination	This is a single-arm, open-label phase II study to observe the objective response rate (ORR) and survival rate at 6 months simultaneously. Referring to the study results on similar products, assuming the ORR is 15% for SHR-1210 in treatment of target population of this study, and the lower limit of 95% confidential interval of ORR obtained from this study is >7%, it can be considered as effective. 154 subjects need to be enrolled to obtain 90% power at a one-sided significance level of 0.025. Further assuming evaluable cases accounting for 80% of the enrolled subjects, 194 subjects are required to be enrolled. Assuming the survival rate at 6 months is 80% for SHR-1210 in treatment of target population, and the lower limit of 95% confidential interval is >70%, this therapy can be considered to have advantage in efficacy. 200 subjects need to be enrolled to obtain 90% power at a one-sided significance level of 0.025. Considering the drop-out rate of 10%, a total of 220 subjects are required to be enrolled. Therefore, the planned sample size of this study is 220.
Screening Criteria	**Inclusion Criteria:** 1. Age: 18 years old or older; male or female; 2. Had a histological or cytological diagnosis of advanced HCC, not amenable for surgical or local therapy, and having at least one measurable lesion as defined by RECIST v1.1 (major diameter of the measurable lesion ≥10 mm or minor diameter of malignant lymph node ≥15 mm in spiral CT scan in accordance with RECIST v1.1); 3. Failure of or intolerant to at least one systematic treatment for HCC: 1) the previous systematic treatment must be chemotherapy or sorafenib; 2) if not, the patient must be adequately informed by the treating physician that current therapeutic options include sorafenib and chemotherapy and should have refused these options, as recorded by investigator in a written form; a. Failure of treatment is defined as disease progression during treatment or recurrence after the end of treatment (the systematic chemotherapy must be ≥ 1 cycle, duration of sorafenib treatment must be ≥ 14 day); b. Intolerance to chemotherapy is defined as ≥ Grade 4 hematological toxicity or ≥ Grade 3 non-hematological toxicity or ≥ Grade 2 cardiac, hepatic or renal impairment during treatment; c. Intolerance to sorafenib is defined as: continuation or recurrence of CTCAE Grade 2 treatment-related adverse event (AE) after sufficient supportive treatment according to local standard, and dose interruption for at least 7 days and reduction of one dose level (until 400 mg qd); continuation or recurrence of CTCAE ≥ Grade 3 treatment-related adverse event after sufficient supportive treatment according to institutional standard, or dose interruption for at least 7 days and reduction of one dose level (until 400 mg qd); 4. The end of previous systematic treatment was ≥ 2 weeks from the start of the study (at least reaching drug elution period, i.e., 5 times of drug half-life) and treatment related AE recovered to NCI-CTCAE ≤ Grade 1 (except Grade 2 alopecia);

5. Child-Pugh scores of 7 or less (Child-Pugh A or B7);
6. ECOG PS before enrollment: 0–1;
7. With a life expectancy of ≥ 12 weeks;
8. Patients with chronic hepatitis B (HBV) infection: HBV- deoxyribonucleic acid (DNA) must be < 500 IU/ml; and the patients with positive hepatitis B surface antigen must receive antiviral therapy according to the treatment guideline; the patients with positive hepatitis C (HCV) must receive antiviral therapy according to the treatment guideline and have ≤ CTCAE Grade 1 elevated hepatic function;
9. Have adequate main organ function, which meets the following criterion:
   (1) Hematology: Complete blood cell count: (no blood transfusion, no use of granulocyte colony-stimulating factor (G-CSF) or corrective drug within 14 days prior to screening)
      a. Hemoglobin (HB) ≥ 90 g/L
      b. Absolute neutrophil count (ANC) ≥ 1.5×10^9/L
      c. Platelet count (PLT) ≥ 60×10^9 /L
   (2) Blood biochemistry: (no infusion of albumin (ALB) within 14 days)
      a. ALB ≥ 29 g/L
      b. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 5 × ULN
      c. Total bilirubin (TBIL) ≤ 1.5 × ULN
      d. Creatinine ≤ 1.5 × ULN
   (3) Pro-thrombin time (PT)- International normalized ratio (INR) ≤ 2.3 or PT ≤ 6 seconds exceeding the range of normal control;
   (4) Urine protein < 2+ or 24 hours urine protein quantification < 1.0 g;
10. Women of childbearing potential must receive serum pregnancy test within 72 hours prior to start dose of investigational drug, and have negative result, willing to use at least two highly effective contraceptive methods during the trial and 60 days after the last dose of investigational drug (about 5 drug half-lives + menstrual cycle). The male patients whose partner are women of childbearing potential should use at least two highly effective contraceptive methods during the trial and 120 days after the last dose of investigational drug (about 5 drug half-lives + sperm emptying cycle);
11. The patients are voluntary to participate in the study and sign the informed consent form, with good compliance and willingness to cooperate with follow-up.

Exclusion Criteria:

1. Patients with known hepatocholangiocarcinoma, mixed cell carcinoma and lamellar cell carcinoma; other active malignant tumor within 5 years or simultaneously. Cured localized tumor, for example, basal cell carcinoma of skin, squamous cell carcinoma of skin, superficial bladder cancer, carcinoma in situ of prostate, carcinoma in situ of cervix, breast cancer in situ may be enrolled;

2. Plan to receive or previously received organ or bone marrow transplantation;
3. Ascites with clinical symptoms, i.e., requiring therapeutic abdominal puncture or drainage, or Child-Pugh score > 2;
4. History of gastrointestinal hemorrhage within 6 months prior to the start of study treatment or clear tendency of gastrointestinal hemorrhage, for example, esophageal varices with hemorrhagic risk, locally active ulcer, persistent fecal occult blood (+);
5. Abdominal fistula, gastrointestinal perforation or abdominal abscess within 28 days prior to the start of study treatment;
6. Previous or current presence of metastases to central nervous system;
7. Grade 2 or higher myocardial ischemia, myocardial infarction, or poorly controlled arrhythmia (including QTc interval ≥ 450 ms for man and ≥ 470 ms for woman) (QTc interval is calculated using Fridericia formula);
8. Grade 3−4 cardiac insufficiency in accordance with New York Heart Association (NYHA) or color Doppler echocardiography: left ventricular ejection fraction (LVEF) < 50%;
9. History of hepatic encephalopathy;
10. Untreated active hepatitis (hepatitis B: HBsAg positive and HBV-DNA ≥ 500 IU/mL; hepatitis C: HCV-RNA positive and obviously abnormal hepatic function); hepatitis B and hepatitis C co-infection;
11. Human immunodeficiency virus (HIV) infection;
12. Previous and current history of pulmonary fibrosis, interstitial pneumonia, pneumoconiosis, radiation pneumonitis, treatment-related pneumonia, serious pulmonary impairment that may interfere with the detection and management of suspected treatment-related pulmonary toxicity;
13. Known active or suspected autoimmune disease. Patients who have stable disease and do not require systemic immunosuppressive therapy can be enrolled;
14. Within 14 days prior to any dose of the investigational drug, use of corticosteroid (prednisone at the therapeutic dose > 10 mg/day) or other immunosuppressant for systematic treatment. With no active autoimmune disease, inhaled or local use of steroids and adrenaline equivalent to > 10 mg/day prednisone therapeutic dose is allowed for replacement;
15. Use of any local therapy for the hepatic lesion (including but not limited to surgery, radiotherapy, hepatic artery embolism, TACE, hepatic artery perfusion, radiofrequency ablation, cryoablation or percutaneous ethanol injection) within 4 weeks prior to participation in the study;
16. Palliative radiotherapy to control symptoms is allowed, and must be completed at least 2 weeks prior to the start of study treatment, and no additional radiotherapy for the same lesion is planned; adverse event (AE) induced by radiotherapy haven't recovered to ≤ CTCAE Grade 1;
17. Patients may receive other anti-cancer therapies during the study, such as chemotherapy, targeted therapy, or radiation therapy; Patients have previously received other anti–PD-1 antibodies or other immunotherapies against PD-1/PD-L1;

	18. Known history of serious allergy to any monoclonal antibody; 19. Pregnant or breast-feeding women; 20. Known to have a history of psychiatric substance abuse or drug abuse; Patients who have stopped drinking can be enrolled; 21. Other factors that may affect the study results or lead to forced early termination of the study as judged by investigators, such as other serious illnesses, with serious laboratory examination abnormalities which may affect patient's safety, or with family or social factors which may affect the collection of trial data and samples. 22. Patients who had participated in "the randomized, double-blind, parallel-controlled, multi-center, phase III clinical study on apatinib sulfonate tablets as the second line therapy for patients with advanced HCC" previously and been randomized to any medication cannot be enrolled before the primary study endpoint is reached in this study. **Criteria for Termination of Study Treatment** 1. Subjects withdraw informed consent and require to withdraw from the study. 2. Medical imaging examination shows progression of disease, unless the subjects meet the criteria on post-progression continuation of therapy (see Section 3.2.4); 3. Occurrence of clinical adverse events, abnormal laboratory examination or co-morbidities, and continued participation in the study is judged by investigators as violating the subjects' optimal benefit; 4. Other reasons for inability to continue study treatment, as considered by investigators, for example, loss of the ability to express freely due to custody or isolation; 5. Pregnancy in female subject; 6. Termination of study by sponsor.
Investigational Drug and Dose Regimen	**Group A**: SHR-1210, 3 mg/kg, i.v., q2w, in a 42-day cycle; **Group B**: SHR-1210, 3 mg/kg, i.v., q3w, in a 42-day cycle;
Data Analysis and Statistical Methods	**General analysis** The following methods will be used for descriptive statistics summary in this study, unless otherwise noted. The continuous variables will be summarized with mean, standard deviation, median, maximum, and minimum value; the categorical variables will be summarized with frequency and percentage; Kaplan-Meier method will be used to estimate the survival rate and median survival time for time to event data. The corresponding 95% confidential interval will be provided for the above analyses, if necessary. **Efficacy analysis** The 95% confidential interval of overall percentage for ORR and DCR will be calculated by Clopper-Pearson method.

	Safety analysis The safety analysis will be based on descriptive summary statistics. The AE, serious adverse event (SAE), treatment-related AE, AE leading to dose modification, AE leading to withdrawal from the trial, and laboratory data will be summarized according to CTCAE 4.0. The above AEs, laboratory tests, vital signs, and ECG will be analyzed and summarized using the existing criteria for clinical trial report from Hengrui. The criteria include but not limited to the following analyses and summaries: AEs (all-causality and treatment-related); The incidence and severity of AEs (all-causality and treatment-related); Summary of SAEs; Analysis of causality between AE and investigational drug; Laboratory parameters, vital signs, and changes from baseline; Number and percentage of "normal to abnormal" or "exacerbation of abnormal" in laboratory parameters and vital signs after the trial. **Exploratory analysis** The relationship between PD-L1 expression level and efficacy will be analyzed based on descriptive statistics.
Version No.	5.0
Expected Study Period	Oct. 2016 to May 2018 (primary endpoint analysis)

STUDY PROCEDURES

1. Screening Period

Items	Screening period (baseline[1], Day -28)	Comment
Enrollment assessment		
Signing of informed consent form	√	The signed informed consent form for subjects' enrollment in this study needs to be completed during screening period. Any screening procedure specified in this study cannot be performed without the written informed consent form: there is a special provision on the radiological examination of tumors at baseline. Refer to the note in the radiological evaluation of tumors in the flow chart for details. The subjects with failure of screening prior to treatment are permitted to be given another chance for re-screening in this study[2], must re-perform the informed consent and re-register so as to obtain a new subject number at the re-screening group.
Verification of eligibility	√	Evaluated in screening period (including the re-screening period)
Demographics	√	
Medical history	√	Including previous medical history, tumor history (initial diagnosis, course of treatment, etc.)
Child-Pugh score	√	It will be completed within 14 days prior to the first dose
Safety assessments		
ECOG PS	√	It will be completed within 14 days prior to the first dose
Physical examination	√	It will be completed within 14 days prior to the first dose
Vital signs	√	Including blood pressure, heart rate, body temperature, and respiratory rate. Conducting at screening visit and within 72 hours prior to the first dose. If the assessment is completed within 72 hours prior to the first dose during screening period, no additional detection is required prior to the first dose.
Concomitant medications/treatments	√	Including the concomitant therapies information within one month prior to signing informed consent form
Collection of AE	√	Including symptoms, body signs
12-Lead ECG	√	It will be completed within 14 days prior to the first dose
Echocardiography	√	Including LVEF evaluation, performed within 14 days prior to the first dose

Items	Screening period (baseline[1], Day -28)	Comment
Hematology	√	Including complete blood cell count and category (white blood cell, red blood cell, lymphocyte, monocyte, neutrophil, basophil, eosinophil, hemoglobin), platelet count. The test will be conducted within 14 days prior to the first dose. If the test is completed within 72 hours prior to the first dose during screening period, no additional detection is required prior to the first dose.
Urinalysis	√	Including white blood cell, red blood cell, and urine protein. The test will be conducted within 14 days prior to the first dose. If urine protein is ≥ 2+ at screening period, 24 hours urine protein quantification must be detected additionally. If the test is completed within 72 hours prior to the first dose during screening period, no additional detection is required prior to the first dose.
Fecal occult blood	√	The test will be conducted within 14 days prior to the first dose.
Blood biochemistry	√	Including hepatic function (ALT, AST, TBIL, ALP), renal function [blood urea nitrogen (BUN) or serum urea level], albumin, creatinine, amylase (lipase must be detected additionally if amylase is abnormal and clinically significant), blood glucose, LDH. The test will be conducted within 14 days prior to the first dose. If the test is completed within 72 hours prior to the first dose during screening period, no additional detection is required prior to the first dose.
Blood electrolytes	√	Including K^+, Na^+, Ca^{++}, Mg^{++}, Cl^-. The test will be conducted within 14 days prior to the first dose. If the test is completed within 72 hours prior to the first dose during screening period, no additional detection is required prior to the first dose.
Coagulation function	√	INR and/or PT (if INR cannot be collected, PT will be used as judgment basis). The test will be conducted within 14 days prior to the first dose.
Alpha fetoprotein	√	The test will be conducted within 14 days prior to the first dose.
Thyroid function	√	Including TSH, FT3, and FT4. The test will be conducted within 14 days prior to the first dose.
Virology	√	Including HIV-Ab, HBV and HCV infection test. Requirement for HBV test: HBsAg will be detected during screening period to determine the presence of HBV infection, HBsAg (quantitative), HBsAb (qualitative), HBcAb (qualitative), HBeAg (qualitative), HBeAb (qualitative) and HBV-DNA (qualitative, quantitation needed additionally if positive) will be detected in case it is positive. Requirement for HCV test: HCV-Ab will be detected in screening period to determine HCV infection, HCV-RNA (qualitative, quantitation needed additionally if positive) will be quantified in case of positive result. The test will be conducted within 14 days prior to the first dose
Blood HCG test	√	Only for women of childbearing potential (WOCBP). The test will be conducted within 72 hours prior to the first dose.

Items	Screening period (baseline[1], Day -28)	Comment
Efficacy assessments		
Tumor imaging evaluation	√	The radiological evaluation at baseline must be performed in accordance with RECIST v1.1, including the enhanced computed tomography (CT) scan of chest, abdomen, pelvis and site of lesions. In case of allergy to the contrast agent for enhanced CT scan, thoracic plain CT scan + abdominal and pelvic magnetic resonance imaging (MRI) can be performed. Bone scan will be performed only when clinically indicated. If the routine radiological tumor evaluation has been performed before signing the informed consent form, CT or MRI does not need to be repeated during screening period as long as they are completed within 28 days prior to the start of investigational drug (42 days prior to the first administration is acceptable for bone scan). Brain MRI or enhanced CT Scan will be conducted during screening period.
Others		
Tumor tissue sample	√	When applicable. For detection of PD-L1 expression, also see Laboratory Manual.

2. Treatment Period

Items	Treatment period (One treatment cycle is 42 days)				Comment
	D1[3] (±3 days)	D15 (±3 days) (Group A)	D22 (±3 days) (Group B)	D29 (±3 days) (Group A)	
Randomization	√				It will be completed only within 3 days prior to the first dose.
Child-Pugh score	√				It will start from Cycle 2, and it will be finished at D1 of each cycle.
Safety assessments					
ECOG PS	√	√	√	√	It will be completed within 72 hours prior to each dose.
Physical examination	√	√	√	√	The physical examination will be performed for the target sites within 72 hours prior to each dose, at least include heart, lungs, abdomen, and skin.
Vital signs	√	√	√	√	Including blood pressure, heart rate, body temperature, respiratory rate. It will be conducted within 72 hours prior to each administration.

Items	Treatment period (One treatment cycle is 42 days)				Comment
	D1[3] (±3 days)	D15 (±3 days) (Group A)	D22 (±3 days) (Group B)	D29 (±3 days) (Group A)	
Concomitant medications/treatments	√	√	√	√	
Collection of AE	√	√	√	√	Including symptoms and signs.
12-Lead ECG					Performed according to local standard during the study, when clinically indicated.
Echocardiography					Performed according to local standard during the study, when clinically indicated.
Hematology	√	√	√	√	Including complete blood cell count and category (white blood cell, red blood cell, lymphocyte, monocyte, neutrophil, basophil, eosinophil, hemoglobin), platelet count. The test will be conducted within 72 hours prior to each administration.
Urinalysis	√	√	√	√	Including white blood cell, red blood cell, and urine protein. The test will be conducted within 72 hours prior to each administration. If urine protein is ≥ 2+, 24 hours urine protein quantification must be detected additionally.
Blood biochemistry	√	√	√	√	Including hepatic function (ALT, AST, TBIL, ALP), renal function (BUN or serum urea level), albumin, creatinine, amylase (lipase must be detected additionally if amylase is abnormal and clinically significant), blood glucose, and LDH. The test will be conducted within 72 hours prior to each administration.
Blood electrolytes	√	√	√	√	Including K^+, Na^+, Ca^{++}, Mg^{++}, Cl^-. The test will be conducted within 72 hours prior to each administration.
Coagulation function[4]	√				INR and/or PT (if INR cannot be collected, PT will be used as judgment basis). The test will start from Cycle 2, and will be finished at D1 of each cycle.
Alpha fetoprotein[4]	√				The teat will start from Cycle 2, and will be finished at D1 of each cycle.
Thyroid function[[4]	√				TSH, FT4 and FT3 will be detected on D1 of each cycle from Cycle 2.
Virology [4]	√				The teat will start from Cycle 2, and will be finished at D1 of each cycle. HBV-DNA (PCR) will be detected for those with HBV infection; HCV-RNA will be detected for those with HCV infection.

Items	Treatment period (One treatment cycle is 42 days)				Comment
	D1[3] (±3 days)	D15 (±3 days) (Group A)	D22 (±3 days) (Group B)	D29 (±3 days) (Group A)	
Efficacy assessments					
Tumor imaging evaluation	√				Tumor radiological evaluation must be performed in accordance with RECIST v1.1. The first imaging evaluation after initiation of treatment will be performed at week 8 (± 7 days). Once every 6 weeks afterwards, regardless of dose delay. Imagine evaluation will be performed once every 12 weeks (±14 days) for the subjects more than 12 months after the first dose of investigational drug, if tumor evaluation still needs to be continued. Including the enhanced CT scan at thorax, abdomen, pelvis and site of lesions. In case of allergy to the contrast agent for enhanced CT scan, thoracic plain CT scan + abdominal and pelvic MRI can be performed. Bone scan is only performed when clinically indicated.
Study treatment					
Intravenous infusion of SHR-1210	√	√	√	√	

3. End-of-Treatment and Follow-up Period

Items	End-of-Treatment[5]	Follow-up period		Comment
		Safety follow-up[6]	Survival follow-up[7]	
Child-Pugh score	√	√		
Safety assessments				
ECOG PS	√	√		
Physical examination	√	√		
Vital signs	√	√		Including blood pressure, heart rate, body temperature, and respiratory rate.

Items	End-of-Treatment[5]	Follow-up period		Comment
		Safety follow-up[6]	Survival follow-up[7]	
Concomitant medications/treatments	√	√		
Collection of AE	√	√		Including symptoms and signs.
Hematology	√	√		Including full blood count and classification, platelet count.
Urinalysis	√	√		If urine protein is ≥ 2+, 24 hours urine protein quantification must be detected additionally.
Blood biochemistry	√	√		Including hepatic function (ALT, AST, total bilirubin, ALP), renal function (BUN or serum urea level), albumin, creatinine, amylase (lipase must be detected additionally if amylase is abnormal and clinically significant), blood glucose, LDH.
Blood electrolytes	√	√		Including K^+, Na^+, Ca^{++}, Mg^{++}, Cl^-.
Coagulation function	√	√		INR and/or PT (if INR cannot be collected, PT will be used as judgment basis).
Alpha fetoprotein	√	√		
Thyroid function	√	√		TSH, FT4 and FT3 will be detected.
Virology	√	√		HBV-DNA will be detected for those with HBV infection; HCV-RNA will be detected for those with HCV infection.
Blood HCG test	√			Only for WOCBP
Efficacy assessments				
Tumor imaging evaluation	√	√	√	If the subject has no progression of disease when withdrawal from the study, the tumor still has to be evaluated once every 6 weeks according to RECIST v1.1, until progression of disease or start of subsequent anti-cancer therapy. Including the enhanced CT scan at thorax, abdomen, pelvis and site of lesions. In case of allergy to the contrast agent for enhanced CT scan, thoracic plain CT scan + abdominal and pelvic MRI can be performed. Bone scan is only performed when clinically indicated.

Items	End-of-Treatment[5]	Follow-up period		Comment
		Safety follow-up[6]	Survival follow-up[7]	
Others				
Survival information		√	√	
Subsequent anti-cancer therapy		√	√	

Note: [1] All the baseline data will be based on the value closest to the study dose.

[2] For the subjects who have failed screening and are enrolled during re-screening period, if the visit procedures completed at the initial screening, and meet the required time limit for this procedure prior to start dose of the investigational drug and meet the inclusion criteria, they do not need to repeat the procedure during the re-screening period.

[3] There's no ± 3 days window period for Day 1 of Cycle 1.

[4] Starting from Cycle 2, the test will be performed on D1 ± 3 of each cycle or at least once every 42 days, and more frequently when clinically indicated.

[5] End of Study Treatment/Withdrawal from Study: If these tests/procedures have been completed within 7 days after withdrawal from the study, no further repetition is required.

[6] Safety follow-up: until 90 days after last dose. During this period, one visit will be performed once every 30 days (± 7 days). The first (30 days after the last dose) and third (90 days after the last dose) safety visit after receiving drugs must be performed at the study center, the second visit (60 days after the last dose) is telephone visit, and only survival data, concomitant medication/therapy, AE need to be collected.

[7] Survival follow-up: The subjects will enter the survival follow-up period after the end of safety follow-up period. During this period, the subjects will be followed up by telephone once every 30 days (± 7 days) for collection of survival data and subsequent therapies.

ABBREVIATIONS AND DEFINITIONS

The following abbreviations and special terms will be used in the study protocol.

Abbreviation and specific terms	Definition
AE	Adverse event
AFP	Alpha fetoprotein
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Neutrophil count
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
B-ultrasonography	B-mode ultrasound examination
bFGF	Basic fibroblast growth factor
Ca	Calcium
Cl	Chlorine
Cr	Creatinine
CR	Complete response
CRC	Clinical research coordinator
CT	Computed tomography
CTLA-4	Cytotoxic T lymphocyte antigen 4
DCR	Disease control rate
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report form
EDC	Electronic data capture
GCP	Good Clinical Practice
FAS	Full analysis set
Hb	Hemoglobin
HCC	Hepatocellular carcinoma
INR	International normalized ratio
ITT	Intention-to-treat
i.v.	Intravenous injection
K	Potassium
Mg	Magnesium
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
Na	Sodium

Abbreviation and specific terms	Definition
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death protein-1
PFS	Progression-free survival
PI	Principal investigator
PLT	Platelets
PR	Partial response
PT	Prothrombin time
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RR	Response rate
SAE	Serious adverse event
SAS	Safety analysis set
SD	Stable disease
TTP	Time to progression
ULN	Upper limit of normal
WBC	White blood cell

1. STUDY BACKGROUND

1.1 Epidemiology and Current Treatment Status of Hepatocellular Carcinoma

Primary carcinoma of the liver is a common malignant tumor worldwide, with about 748,300 new cases per year according to the statistics in 2008, accounting for 6% of the new cases of all the cancers and ranking the fifth [1, 2]. Up to 695,900 persons die per year due to its very poor prognosis, thus it has become the third cause of cancer death. China is a high-risk area for liver carcinoma, the number of cases accounting for about 55% of the world, the number of deaths accounting for 50%; it is the second most common tumor follows lung cancer. The high incidence age is 35−45 years for liver carcinoma, male cases more than females, at the ratio of 2−5:1 for male to female. Male patients account for higher proportion in the area with higher incidence.

Hepatocellular carcinoma (HCC) is the most common type in primary carcinoma of liver and accounting for 90%. The main risk factors for HCC are infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, water pollution (blue-green algae toxins), alcoholism and aflatoxin. HCC mostly occurs based on hepatitis virus infection and liver cirrhosis, approximately 10−20 years after primary hepatic damage.

Most HCC are asymptomatic in the early stage, most patients have reached locally advanced stage or had distant metastasis when diagnosis. There is no standard therapeutic method for advanced HCC currently. Its clinical treatment is facing severe challenges. The survival time is usually 3–6 months in the patients with advanced HCC in our country, and no longer than one year worldwide, which is greatly related with the lack of effective systematic treatment in these patients. HCC is resistant to common chemotherapy, its therapeutic methods basically include surgery (hepatectomy, transplantation and palliative surgery), non-surgical therapy (local therapy, arterial chemoembolization, chemotherapy, radiotherapy, biotherapy and molecular targeted therapy) and other therapeutic methods (including participation in clinical studies).

1.2 Advances in the Treatment of Hepatocellular Carcinoma

1.2.1 Advances of targeted therapy in the treatment of hepatocellular carcinoma

In December 2007, sorafenib became the first drug approved by US FDA for the treatment of HCC, which is based on the result of significant survival benefits from SHARP trial, in which sorafenib increased progression-free survival (medians: 5.5 months and 2.8 months, respectively) by 73% and overall survival (medians: 10.7 months and 7.9 months, respectively) by 44% compared with placebo. Thus, it opened up a new era of targeted therapy for HCC. Sorafenib was approved for treatment of HCC in China in 2008, providing a new therapeutic option for numerous patients with HCC, however, its high cost (about 50,000 RMB per month for each patient) limits its further use.

In addition, a variety of multikinase inhibitors under development have been frustrated in the clinical study versus sorafenib: the phase III clinical trial of sunitinib (developed by Pfizer) versus sorafenib was terminated in advance in April 2010, because sunitinib did not improve the survival time compared with sorafenib, and the incidence of serious adverse events (SAE) in sunitinib group was higher than that in sorafenib group. The multikinase inhibitor ABT-869 (linifanib, developed by Abbott) has no advantage compared with sorafenib. The phase III clinical trial of ABT-869 was terminated according to the advice by the independent data monitoring committee. A clinical study with 731 patients showed that the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor erlotinib (Tarceva, developed by Roche) faced failure for no increase of additional benefit as compared with sorafenib. Brivanib is a tyrosine kinase inhibitor targeted VEGF receptor and basic fibroblast growth factor (bFGF, FGF-2) receptor, in the phase II clinical trial in patients with advanced HCC who are unsuitable for surgery, or have locally advanced or distant metastatic, the 6-month progression-free survival rate reached 18.2%, median progression-free survival was 2.7 months, median survival was 10 months, the adverse effects were mild and mainly included fatigue, hypertension and diarrhea. However, it encountered failure in the phase III non-inferiority clinical trial in comparison with sorafenib, its overall survival was not satisfactory.

In summary, no targeted drug is superior to sorafenib in the overall efficacy and safety in treatment of HCC.

1.3. Background of Immunotherapy

Tumor immunotherapy remains a hot spot in the field of tumor therapy for a long time, among which T-cell tumor immunotherapy lies in an essential position. Tumor immunotherapy is to take full advantage of and mobilize cytotoxic T-cell in the body, so as to kill tumors, which may be the most effective and safe way to treat cancer. However, tumor immunotherapy also has a huge obstacle, tumor escape, i.e. tumor cells can inhibit the immune system resulting in unlimited proliferation. There exists an extremely complicated relationship between the tumor immune escape mechanism and the body's immune response to tumor. In the early stage, tumor-specific cytotoxic T-cells are biologically active, but it loses its activity along with tumor growth at late stages. So, tumor immunotherapy is to maximize the patient's own immune response to tumors, not only to activate the original immune system response in the body, but also to maintain a longer and higher immune system response, which is the key in tumor immunotherapy.

Recently, with a deeper understanding of the molecular mechanism of the response to tumor cells, the study on the identification of signaling pathways that limit the antitumor immune response have been further clarified. Programmed cell death protein-1 (PD-1) pathway, one of the most important pathways responsible for the regulation of tumor-induced

immunosuppression, has been confirmed. PD-1 is a protein receptor expressed on the T-cell surface that was discovered in 1992, and be involved in the process of apoptosis. PD-1 belongs to the CD28 family, possessing 23% amino acid homology with cytotoxic T lymphocyte antigen (CTLA) 4, but it mainly expresses on activated T cells, B cells, and myeloid cells, which is different from that of CTLA. PD-1 has two ligands, PD-1 ligand (PD-L) 1 and PD-L2. PD-L1 mainly expresses on T cells, B cells, macrophages, and dendritic cells (DCs), and can be up-regulated in activated cells. Many human solid tumors express PD-L1, which is often associated with poor prognosis . The tumor-infiltrating lymphocytes in cancer patients typically express PD-1, with a damage to their antitumor function. Several antibodies that block PD-1 or PD-L1 have been shown to enhance T-cell function and facilitate tumor cell lysis in preclinical studies.

A number of multinational pharmaceutical companies are developing PD-1 monoclonal antibodies which block the binding of PD-L1 and PD-1, and improve the patient's own immune response to tumors as much as possible, so as to kill tumors . PD-1 monoclonal antibodies developed by BMS and Merck, are currently the most advanced PD-1 antibody drugs. In accordance with the results of the completed pivotal studies, BMS’s antibody nivolumab and Merck’s antibody pembrolizumab have been approved by FDA for multiple indications.

In July 2014, nivoluamb was approved by Japan's Ministry of Health and Welfare for treatment of advanced melanoma, and approved by FDA for treatment of melanoma (December 2014), non-small cell lung cancer (March 2015), renal cell carcinoma (November 2015), and classical Hodgkin's lymphoma (2016) .

Pembrolizumab was approved by FDA for treatment of advanced melanoma (September 2014) and non-small cell lung cancer (October 2015).

Except the above indications, the two companies are conducting large phase III studies for treatment of gastric cancer, bladder cancer, breast cancer, head and neck tumors and lymphoma, and are expected to bring new choices and shocks in the treatment of multiple tumors.

1.4 Background on Development of Anti-PD-1 Antibody SHR-1210

Hengrui obtained a series of anti-PD-1 antibodies in mouse using PD-1 recombinant protein as antigen through a large number of in vitro binding assays, in vitro ligand blocking experiments, T-cell proliferation assays, animal experiments and antibody-based drug assays. Precursor antibody was selected, and then humanized PD-1 monoclonal antibody was further synthesized by computer simulation of the mouse-derived antibody, among them, we focused on the development of the most active antibody SHR-1210. Since 2015, Hengrui has started phase 1 clinical trials in Australia and mainland China, and several studies are ongoing.

1.5 Preclinical Studies Result of SHR-1210

1.5.1 Drug name and physicochemical properties

[Generic name]: SHR-1210 for Injection

[English name]: SHR-1210 for injection

[Molecular weight]: about 146.3 kDa

1.5.2 Pharmacological class and mechanism of action

PD-1 is a protein receptor expressed on the T-cell surface that was discovered in 1992 and involved in the process of apoptosis. PD-1 belongs to the CD28 family, possessing 23% amino acid homology with CTLA-4, but it mainly expresses on activated T cells, B cells and myeloid cells, which is different from that of CTLA. PD-1 has two ligands, PD-L1 and PD-L2, respectively. PD-L1 is mainly expressed on T cells, B cells, macrophages and DCs, and can be up-regulated on activated cells. The expression of PD-L2 is relatively limited, mainly on antigen-presenting cells, such as activated macrophages and DCs.

The humanized anti-PD-1 monoclonal antibody specifically binds to PD-1 and blocks the interaction of PD-1 with its ligand, allowing T-cell to recover immune respond against the tumor cells.

1.5.3 Pharmacodynamic studies

1.5.3.1 Affinity of antibody

We tested the binding affinity of antibody SHR-1210 to human, monkey, and mouse antigens. For the results see Table 1.

Table 1 The binding affinity of antibody SHR-1210 to human, monkey, and mouse PD1 antigens

Stationary phase	Mobile phase	Binding affinity (nM)
SHR-1210	Human PD1 antigen	6.9
SHR-1210	Mouse PD1 antigen	Very weak signals, no detectable binding
Monkey PD1 antigen (-hFc)	SHR-1210	4.1

The results showed that the affinity of antibody SHR-1210 to human and monkey PD1 antigens was very close, 6.9 nM and 4.1 nM, respectively, while no binding was detected to mouse PD1 antigen.

From the detection of the binding affinity of antibody SHR-1210 against human antigen PD-1, the affinity of SHR-1210 against antigen (human PD-1) was 3.0 nM, which was comparable to that of control antibodies Nivolumab and MK3475. For the results see Table 2.

Table 2 The binding affinity of antibody SHR-1210, Nivolumab and MK3475 to PD-1 antigen

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

1.5.3.2 Experiment on antibody SHR-1210 blocking the binding of PD-1/PD-L1

The experimental results (see Figure 1 and Figure 2) showed that the antibody SHR-1210, Nivolumab and Pembrolizumab were comparable in blocking the binding of PD-1 / PD-L1 in vitro. The blocking activity IC_{50} of the antibodies SHR-1210, Nivolumab and Pembrolizumab was 0.70 nM / 0.79 nM, 0.79 nM / 0.77 nM, respectively.

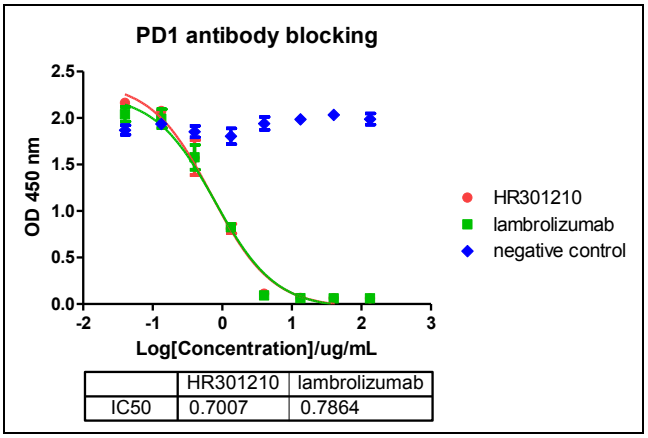


Figure 1 SHR-1210 and Pembrolizumab blocking the binding of PD-1 / PD-L1

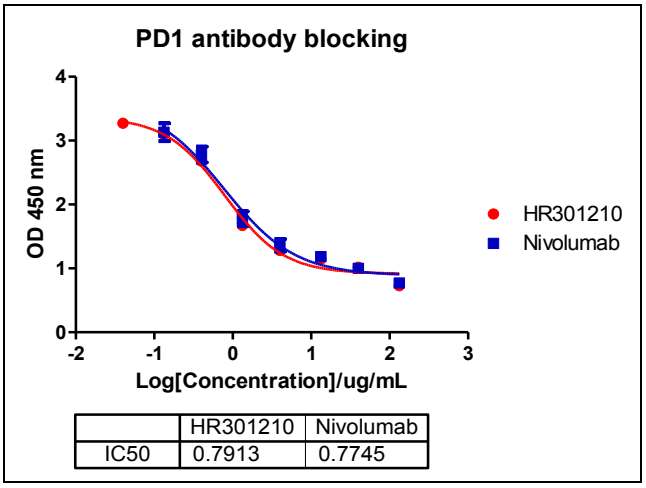


Figure 2 SHR-1210 and Nivolumab blocking the binding of PD-1 / PD-L1

1.5.4 Toxicology studies

Eight cynomolgus monkeys (half males and half females) were randomly divided into two groups in pre-clinical study of acute toxicity in cynomolgus monkeys. SHR1210 was intravenously injected at 200, 400 and 800 mg / kg for animals in Group 2 every other day in a dose-escalation manner. No changes in clinical signs, weight, food intake and blood clotting associated with SHR-1210 were observed. When dose ≥ 200mg / kg, lymphopenia was observed in male and female animals; when dose ≥ 400 mg / kg, increased serum globulin and decreased albumin were observed in male and female animals. For the range of the above changes was small, so it was not considered harmful. Maximum tolerated dose (MTD) of SHR-1210 ≥ 800 mg/kg.

In the completed pre-clinical study of acute toxicity in cynomolgus monkeys, male and female cynomolgus monkeys were well tolerated when SHR-1210 intravenously injected at 20, 50 and 100 mg / kg for 4 weeks (5 times) once a week. No changes in clinical signs associated with SHR-1210 were observed, including injection site irritation, or body weight, food consumption, body temperature, ECG, blood pressure, heart rate and respiratory parameters; No changes in B and T lymphocyte typing, cytokine, immunoglobulin and complement parameters were observed; No changes in organ weights, gross lesions and histopathological changes associated with SHR-1210 were observed.

1.5.5 Pharmacokinetic studies

Pharmacokinetic parameters of cynomolgus monkeys after single intravenous infusion of SHR-1210 are shown in Table 3 Pharmacokinetic parameters of cynomolgus monkeys after single intravenous infusion of SHR-1210 at different doses.

Table 3 Pharmacokinetic parameters of cynomolgus monkeys after single intravenous infusion of SHR-1210 at different doses

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

1.5.6 Clinical studies results

In 2015, Hengrui successfully carried out a phase 1 clinical trial in Australia, and achieved the expected clinical effect. Up to January 2016, 10 subjects had been enrolled, and 3 subjects had the first imaging data for 8 weeks. There was one case of PR in head and neck squamous carcinoma, two cases of SD in gastric/esophageal cancer and leiomyosarcoma of uterus. The domestic phase 1 clinical trials on SHR-1210 antibody, SHR-1210-101, SHR-1210-102 and SHR-1210-103, have also been conducted in multiple clinical centers in China and will provide more clinical data.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

To evaluate the efficacy and safety of anti-PD-1 antibody SHR-1210 in subjects with advanced hepatocellular carcinoma (HCC) who had received previous systematic treatment.

2.2 Primary Study Endpoints

1) Objective response rate (ORR)

2) 6-month overall survival rate (6-month OS rate)

2.3 Secondary Study Endpoints

1). Duration of response (DoR)

2). Disease control rate (DCR)

3). Safety of SHR-1210

4). Time to progression (TTP)

5). Progression-free survival (PFS)

6). Overall survival (OS)

2.4 Exploratory Study Endpoints

The relationship between PD-L1 expression level and efficacy.

3 STUDY PLAN

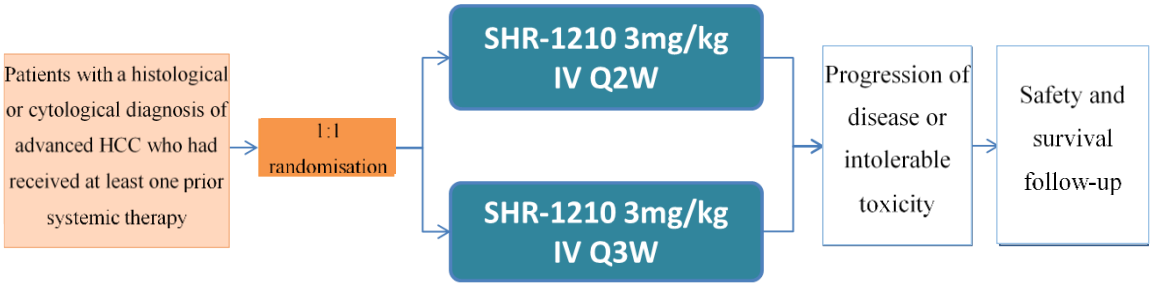
3.1 Study Design

The whole study project includes two parts, i.e., the first stage (phase II) and the second stage (phase III). The subjects enrolled should be patients with inoperable advanced hepatocellular carcinoma (HCC) who have received at least one systematic treatment.

The first stage: an open-label, randomized controlled phase II clinical study. Sixty subjects are planned to be enrolled initially in the study and 1:1 randomized into SHR-1210 3mg/kg, I.V, q2W (once every two weeks) or SHR-1210 3mg/kg, I.V, q3W (once every three weeks), on a 42-day cycle, until progression of disease, unacceptable toxicity, withdrawal of informed consent or the end of study, whichever comes first.

The study design of the phase II study is illustrated in In the phase II study, .

Figure 3 The schematic diagram for phase II study



In the phase II study, enrollment will be implemented on a continuous basis until approximately 220 subjects are randomized.

The second stage will not be included in the protocol temporarily, but using a separate protocol.

3.2. Study Procedures

3.2.1 Screening period

The screening period starts from the signing of informed consent form and ends with the start of dosing or screening failure.

Subjects must sign the informed consent form before performing any screening procedure specified in this study.

Unless otherwise noted, the following screening should be completed within 28 days prior to the first dose of investigational drug:

- Signing of informed consent form.
- Assignment of subject ID.
- Collection of medical history, including prior treatment history, current medical history, history of drug allergy, and concomitant diseases.
- Collection of adverse events and concomitant medications.
- Providing pathological specimens (if applicable). Pathological tissue samples are transported to a central laboratory for PD-L1 expression test.

- Tumor imaging evaluation according to RECIST v1.1.

The following information will be collected within 14 days prior to the first dose of investigational drug:

- Physical examination: height, weight, vital signs (performed after sitting still for 5 minutes): including temperature, blood pressure, heart rate, and respiratory rate.
- ECOG PS.
- Hematology, urinalysis, and fecal occult blood test.
- Blood biochemistry, including ALT, AST, total bilirubin (TBIL), ALP, LDH, albumin, urea nitrogen/serum urea, creatinine, blood glucose, amylase/lipase.
- Blood electrolyte: including potassium, sodium, chlorine, calcium, and magnesium.
- Coagulation parameters: PT or INR.
- Child-Pugh class.
- Serum pregnancy test (only for women of childbearing potential, within 72 hours before the first dose).
- Virology (including HBV, HCV, and HIV markers).
- Serum AFP test.
- Thyroid function (TSH, FT3, FT4).
- Color Doppler echocardiography (mainly observe LVEF).
- 12-Lead ECG (QTc interval time need to be noted, and QTc interval is calculated using Fridericia formula).

3.2.2 Treatment period

The treatment period starts from randomization, and the investigational drug must be given within 3 days after randomization.

A cycle is defined as 6 weeks. SHR-1210 3 mg/kg will be given i.v. drip over half an hour, no less than 20 minutes and no more than 60 minutes, including rinsing period, on D1, D15 and D29 of each cycle in Group A, and on D1 and D22 of each cycle in Group B. Physical examination and laboratory examinations will be conducted during treatment, AE and concomitant medications information will be collected.

The following evaluation will be completed within 72 hours prior to each administration of investigational drug in each cycle of therapy:

ECOG PS, physical examination (at least including heart, lungs, abdomen, skin), vital signs, hematology, urinalysis, blood biochemistry, and blood electrolytes examination. The investigational drug can be given only after investigators have reviewed the laboratory test results.

Since the second treatment cycles, the following assessment will be completed at D1 of each cycle:

Coagulation function, alpha fetoprotein, thyroid function (TSH, FT3, FT4), virology (HBV markers or HCV markers), and Child-Pugh class.

In accordance with RECIST v1.1, the initial tumor imaging evaluation is assessed at 8 weeks (± 7 days), and then every 6 weeks (± 7 days), with or without dosing. After 12 months of dosing (i.e., the first dose), if tumor assessment is still required, it should be performed every 12 weeks (± 14 days) until the disease progresses or end of the study (whichever happens later).

The subjects who are evaluated as progressive disease can continue to receive treatment if they meet the criteria defined in Section 3.2.4.

The treatment period will end and proceed to follow-up period when the subjects terminate the study (see Section 5.5).

Note: the specific study procedures during the treatment period are shown in the study flowcharts.

3.2.3 Follow-up period

Follow up period is initiated when the end-of-treatment decision is made.

Within 90 days after the last dose of investigational drug, follow-up visit will be performed once every 30 days (±7 days), the first and third follow-up must be face-to-face visit, and the required safety evaluation must be completed (see study flowchart), the second follow-up is telephone visit (only collect partial data).

After the end of the safety follow-up period, the subjects will enter survival follow-up period. Investigators must follow up subject's survival every 30 days (±7 days), until death, lost to follow-up, termination of study by the sponsor. Investigators can inquire the subject, his/her family members or local physician via phone, collect subject's survival information (death and reason of death) and data on other tumor therapies after the end of study treatment. The data on each survival follow-up needs to be recorded in detail in the original medical record.

Subjects who end study treatment for toxicity or other reasons with no radiological progression observed still need to receive radiological evaluation according to the same frequency, until progression of disease or start of other anti-cancer therapy, the radiological evidence on PD should be obtained from such subjects as much as possible.

The subject withdrawing from study treatment should also continue the safety follow-up and survival follow-up as required by protocol. Adverse effects of the investigational drug may occur after end of treatment; safety follow-up should be conducted as far as possible. Survival is one primary endpoint in this study, the study center should do their best to obtain the survival follow-up information.

3.2.4 Criteria for continuing treatment beyond progression

Some subjects receiving immunotherapy can still clinically benefit following radiological progression. After progression of disease as defined by RECIST v1.1, subjects meeting all of the following criteria may continue with the study treatment:

- Investigators judge continuation of study treatment meets the best benefit for the subject, and the subject does not need to start other anti-cancer therapy immediately;
- The subject can tolerate study treatment;
    - No obvious decrease in the physical performance, no obvious exacerbation in tumor related symptoms;
- The subject must sign the informed consent form before continuation of the study treatment. Possible risks, discomfort and other therapeutic choices will be described in the informed consent form;
    - The study treatment continued upon must be approved by the sponsor and principal investigator of the study.

The evaluation of clinical benefit must take clinical exacerbation, continued benefit from the treatment into consideration. It is advisable to discuss with the sponsor about the decision on post-progression continuation of treatment, as judged by investigators.

If a decision of continued study treatment is made following progression, the subject should be treated, evaluated and followed up as required in the protocol. Subjects who continue treatment after imaging progress need to assess the tumor and track each target lesion, non-target lesion, and new lesion according to protocol. The overall assessment is recorded as PD as long as the new lesion did not disappear.

If further progression occurs in the next tumor evaluation, the subject should be withdrawn from the study. The initial date of progression will be used for statistical analysis which including all progression data, regardless of the continuation of study treatment following progression.

If the subject terminates the treatment for systemic condition exacerbation and no objective evidence of disease progression is shown, the progression will be reported as systemic exacerbation. Every effort should be made to obtain the objective evidence on progression in these subjects after termination of the study (e.g., radiological confirmation).

Subjects withdrawn from study for unacceptable toxicity and haven't observed radiological progression still need to receive radiological assessment according to the original frequency, until disease progression or start of other anti-cancer therapy, the radiological evidence on PD should be obtained from such subjects as far as possible.

4. RANDOMIZATION AND BLINDING

Eligible subjects will be randomized at a 1:1 ratio to receive SHR-1210 3 mg/kg as q2w or q3w. No drug number will be produced in this period.

5 SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Inclusion Criteria

1. Age: 18 years old or older; male or female;
2. Had a histological or cytological diagnosis of advanced HCC, not amenable for surgical or local therapy, and having at least one measurable lesion (≥ 10 mm in long axis when assessed by spiral CT scan or ≥15 mm in short axis for malignant lymph nodes as per RECIST v1.1);
3. Failure of or intolerant to at least one systematic treatment for HCC: 1) the previous systematic treatment must be chemotherapy or sorafenib; 2) if not, the patient must be adequately informed by the treating physician that current therapeutic options include sorafenib and chemotherapy and need to refuse these options, which is recorded by investigator in a written form;
    a. Failure of treatment is defined as disease progression during treatment or recurrence after the end of treatment (the systematic chemotherapy must be ≥ 1 cycle, duration of sorafenib treatment must be ≥ 14 day)
    b. Intolerance to chemotherapy is defined as ≥ Grade 4 hematological toxicity or ≥ Grade 3 non-hematological toxicity or ≥ Grade 2 cardiac, hepatic or renal impairment during treatment;
    c. Intolerance to sorafenib is defined as: continuation or recurrence of CTCAE Grade 2 treatment-related adverse event (AE) after sufficient supportive treatment according to local standard, and dose interruption for at least 7 days and reduction of one dose level (until 400 mg qd); continuation or recurrence of CTCAE ≥ Grade 3 treatment-related adverse event after sufficient supportive treatment according to institutional standard, or dose interruption for at least 7 days and reduction of one dose level (until 400 mg qd);

4. The end of previous systematic treatment was ≥ 2 weeks from the start of the study (at least reaching drug elution period, i.e., 5 times of drug half-life) and treatment related AE recovered to NCI-CTCAE ≤ Grade 1 (except Grade 2 alopecia);
5. Child-Pugh scores of grade A and the better part of grade B (≤7);
6. ECOG PS: 0–1;
7. With a life expectancy of ≥ 12 weeks;
8. Subjects with chronic hepatitis B (HBV) infection: HBV- deoxyribonucleic acid (DNA) must be < 500 IU/ml; and the patients with positive hepatitis B surface antigen must receive antiviral therapy according to the treatment guideline; the patients with positive hepatitis C (HCV) must receive antiviral therapy according to the treatment guideline and have ≤ CTCAE Grade 1 elevated hepatic function;
9. Have adequate main organ function, which meets the following criterion:
   (1) Hematology Complete blood cell count: (no blood transfusion, no use of granulocyte colony-stimulating factor (G-CSF), no use of drug correction within 14 days prior to screening)
      d. Hemoglobin (HB) ≥ 90 g/L
      e. Absolute neutrophil count (ANC) ≥ 1.5×10^9/L
      f. Platelet count (PLT) ≥ 60×10^9 /L
   (2) Blood biochemistry: (no infusion of albumin (ALB) within 14 days)
      e. ALB ≥ 29 g/L
      f. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 5 × ULN
      g. Total bilirubin (TBIL) ≤ 1.5 × ULN
      h. Creatinine ≤ 1.5 × ULN
   (3) Pro-thrombin time (PT)- International normalized ratio (INR) ≤ 2.3 or PT ≤ 6 seconds exceeding the range of normal control;
   (4) Urine protein < 2+ or 24 hours urine protein quantification < 1.0 g;
10. Women of childbearing potential must receive serum pregnancy test within 72 hours prior to start dose of investigational drug, and have negative result, willing to use at least two highly effective contraceptive methods during the trial and 60 days after the last dose of

investigational drug (about 5 drug half-lives + menstrual cycle). The male subjects whose partner are women of childbearing potential should use at least two highly effective contraceptive methods during the trial and 120 days after the last dose of investigational drug (about 5 drug half-lives + sperm emptying cycle);

11. The subjects are voluntary to participate in the study, signing the informed consent form, with good compliance and willingness to cooperate with follow-up.

5.2 Exclusion Criteria

1. Known hepatocholangiocarcinoma, mixed cell carcinoma, and lamellar cell carcinoma; other active malignant tumor except HCC within 5 years or simultaneously. Cured localized tumor, for example, basal cell carcinoma of skin, squamous cell carcinoma of skin, superficial bladder cancer, carcinoma in situ of prostate, carcinoma in situ of cervix, breast cancer in situ may be enrolled;
2. Be ready for or previously received organ or bone marrow transplantation;
3. Ascites with clinical symptoms, i.e., requiring therapeutic abdominal puncture or drainage, or Child-Pugh score > 2;
4. History of gastrointestinal hemorrhage within 6 months prior to the start of study treatment or clear tendency of gastrointestinal hemorrhage, for example, esophageal varices with hemorrhagic risk, locally active peptic ulcer, persistent fecal occult blood (+);
5. Abdominal fistula, gastrointestinal perforation or abdominal abscess within 28 days prior to the start of study treatment;
6. Previous or current presence of metastases to central nervous system;
7. Grade 2 or higher myocardial ischemia, myocardial infarction, or poorly controlled arrhythmia (including QTc interval ≥ 450 ms for man and ≥ 470 ms for woman) (QTc interval is calculated using Fridericia formula);
8. Grade III−IV myocardial insufficiency in accordance with New York Heart Association (NYHA) criteria or color Doppler echocardiography: LVEF (left ventricular ejection fraction) < 50%;
9. History of hepatic encephalopathy;
10. Untreated active hepatitis (hepatitis B: HBsAg positive and HBV-DNA ≥ 500 IU/mL; hepatitis C: HCV-RNA positive and obviously abnormal hepatic function); combined hepatitis B and hepatitis C co-infection;
11. Human immunodeficiency virus (HIV) infection;

12. Previous and current history of pulmonary fibrosis, interstitial pneumonia, pneumoconiosis, radiation pneumonitis, treatment-related pneumonia, serious pulmonary impairment that may interfere with the detection and management of suspected treatment-related pulmonary toxicity;
13. Known active or suspected autoimmune disease. Subjects who have stable disease state and do not require systemic immunosuppressive therapy can be enrolled;
14. Within 14 days prior to any dose of the investigational drug, use of corticosteroid (prednisone at the therapeutic dose of >10 mg/day) or other immunosuppressant for systematic treatment. With no active autoimmune disease, inhaled or local use of steroids and adrenaline equivalent to > 10 mg/day prednisone therapeutic dose are allowed for replacement;
15. Use of any local therapy for the hepatic lesion (including but not limited to surgery, radiotherapy, hepatic artery embolism, TACE, hepatic artery perfusion, radiofrequency ablation, cryoablation or percutaneous ethanol injection) within 4 weeks prior to participation in the study;
16. Palliative radiotherapy to control symptoms is allowed, and must be completed at least 2 weeks prior to the start of study treatment, and no additional radiotherapy for the same lesion is planned; radiotherapy induced adverse events haven't recovered to ≤ CTCAE Grade 1;
17. Patients may receive other anti-cancer therapies during the study, such as chemotherapy, targeted therapy, or radiation therapy; previous treatment with other anti–PD-1 antibodies or other immunotherapy against PD-1/PD-L1;
18. Known history of serious allergy to any monoclonal antibody;
19. Pregnant or breastfeeding women;
20. Known to have a history of psychiatric substance abuse or drug abuse; Patients who have stopped drinking can be enrolled;
21. Other factors that may affect the study results or lead to forced termination of the study early as judged by investigators, such as other serious diseases, with serious laboratory examination abnormalities which may affect patient's safety, or with family or social factors, which may affect the collection of trial data and samples.
22. Patients who have participated in "the randomized, double-blind, parallel-controlled, multicenter, phase III clinical study on apatinib sulfonate tablets as the second line therapy for advanced hepatocellular carcinoma" previously and been randomized to any medication cannot be enrolled before the primary study endpoint is reached in this study.

5.3 Concomitant Medications and Treatments

All treatments and drugs used within 1 month prior to signing the informed consent form and in the course of the study should be recorded in the eCRF strictly in accordance with the GCP guideline. If adverse events occur, the subject should be closely observed, as well as given active symptomatic treatment if necessary, and the drug used shall be recorded and specified in the eCRF.

5.3.1 Drugs and therapies prohibited during the study

Subjects are prohibited from using modern traditional Chinese medicines that have been approved by the NMPA (including but not limited to Delisheng Injection, Kanglaite Injection, Aidi Injection, Huaier Granule and Ganfule Tablet) and immunomodulators (including but not limited to interferon, interleukin-2, thymosin, etc.) during the study.

During the treatment period of this study, subjects are not allowed to receive any local therapies against liver lesion and targeted lesion, and other systemic anti-cancer therapies, such as chemotherapy, molecular targeted therapy, hormone therapy, immunotherapies, traditional Chinese medicine therapy (as mentioned above) and radiotherapy.

Subjects are not allowed to receive other immunosuppressive therapy simultaneously during the treatment period of this study (except management on the treatment-related AE).

Investigational drugs for cancer treatment

5.3.2 Permitted concomitant medications and treatments during the study

1. Antiviral treatment

Subjects infected with HBV and HCV must receive antiviral therapy according to local standards, and the antiviral therapy is recommended as below:

Subjects with HBV infection can continue the original antiviral therapy if HBV-DNA is positive and they have started antiviral therapy and achieved satisfactory control of virus (HBV-DNA < 500 IU/mL) prior to inclusion in the study; the drug must be replaced by Entecavir if the virus is not satisfactorily controlled, and subjects can be enrolled when HBV-DNA is < 500 IU/mL; subjects with newly discovered HBV infection in screening period can start Entecavir therapy immediately and can be enrolled when HBV-DNA is < 500 IU/mL.

Subjects with HCV infection, if HCV-RNA is positive, subjects must receive antiviral therapy in accordance with the local standard guideline on diagnosis and treatment of hepatitis C.

2. Steroids

Local use of steroids is allowed, for example, topically external use, eye, nasal cavity, intra-joint and inhalation; corticosteroids for epinephrine replacement therapy are allowed; corticosteroids for treatment of adverse reactions are allowed; transient use of steroids for prevention and treatment of allergic reactions (prevention of allergy to contrast agent, or treatment of other allergic reactions) is allowed.

3. Vaccines

Vaccines for preventing infectious disease are allowed, for example, pneumonia or influenza vaccines. It must be discussed with the sponsor before using other vaccines.

4. Other systemic therapies

During the treatment period, subjects should be given the best supportive treatment. The original hormone replacement therapy is allowed. Bisphosphonate for treatment of bone metastasis is permitted.

5. Palliative local treatment

Palliative therapy for local lesions causing obvious symptoms is allowed, for example, bone pain; local radiotherapies or surgery can be considered, however, the following conditions must be met:

Progression of disease must be judged by investigators for subjects who need local therapy due to deterioration of symptoms during the study;

Subjects with disease progression must meet the criteria for treatment beyond progression (see Section 3.2.4);

The lesions for local therapy cannot be target lesions.

It is advisable to discuss with the sponsor prior to the start of palliative local therapy. The content of palliative therapy should be recorded carefully in eCRF and medical record, including the date, site of treatment, therapeutic method and dosage, adverse reactions, and so on.

5.4 Criteria for Re-screening of Subjects

Rescreening is allowed in this study, i.e., subjects who have entered screening process but do not meet randomization criteria, and have not been randomized or treated, can be re-enrolled. They must sign the informed consent form again, and obtain a new subject number at the time of re-screening.

5.5 Criteria for Subjects' Withdrawal from the Study or Termination of Study Treatment

Subjects must terminate study treatment when any of the following conditions occurs:

1. Subject withdraws informed consent and requires to withdraw from the study.
2. Medical imaging examination shows progression of disease, unless the subject meets the criteria on post-progression continuation of therapy (see Section 3.2.4);
3. Occurrence of clinical adverse events, abnormal laboratory examination or co-morbidities occur, when continued participation in the study is judged by investigators as violating the subject's optimal benefit;
4. Other reasons for inability to continue study treatment, as considered by investigators, for example, loss of the ability to express wills freely for custody or isolation;
5. Pregnancy in female subject occurs during the study;
6. Termination of study by sponsor.

5.6 Criteria for Termination of Study Treatment

The criteria for study termination are as follows:

(1) Criteria for terminating treatment at study site:

If the sponsor discovers a serious or persistent non-compliance with the protocol and other trial procedures in study sites, the sponsor will have the right to suspend the trial conducting at the study site. In this case, the sponsor will immediately inform the investigator and the regulatory authorities of the termination information. The investigator must immediately report this termination information to the ethics committee and provide corresponding reasons.

If the investigators terminate or suspend the trial in study site, they must inform subjects immediately and report the written decision to the sponsor and the regulatory authority, as required by regulations, and state the reason. The investigator should also report promptly to the ethics committee and the clinical trial institution, and state the reason.

(2) Criteria for terminating the entire study:

The study can be terminated or interrupted prematurely if the reason is sufficient. If the study is terminated or interrupted in advance, the sponsor shall provide a written notice which records the reasons for early termination or interruption to investigators, the National Medical Products Administration and relevant departments. The principal investigator should notify the ethics committee and the sponsor immediately, and provide relevant reasons.

The reasons for premature termination or interruption of the study may include (but not limited):

- Discovery of unexpected, significant or unacceptable risk;
- Major mistakes in the protocol are found during the trial;
- Ineffective investigational drug/trial therapy, or meaningless to continue the study;
- The enrollment of subjects is seriously prolonged or having frequent protocol deviation, which makes it extremely difficult in completing the study.

5.7 Subject ID

Subjects will be assigned a unique number in the study with five digits:

- The first 2 digits = Site number.
- The last 3 digits = Subject number in the same site. The subjects will be numbered in accordance with the sequence in which the subjects sign the informed consent form, for example: 001, 002, 003, etc.

6 STUDY TREATMENT

6.1 Information of Investigational Drug

Investigational drug: SHR-1210 for injection

Manufacturer: Shanghai Hengrui Pharmaceutical Co., Ltd., Suzhou Shengdia Biological Medicine Co., Ltd.

Dosage form: lyophilized powder

Specification: tentatively set as 200 mg and packed in 20 ml vials. The batch number is provided in the drug inspection report in detail;

Administration: intravenous infusion;

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

Storage: Stored in sealed, protected from light, stored in a medical refrigerator at 2–8℃, must not be frozen.

6.2 Drug Dispensation

Management, dispensation and return of the investigational drugs in this study will be performed by a special person, investigators must make sure all the investigational drugs are only used for the subjects in this clinical trial, the dosage and administration method should be in accordance with the protocol, the residual investigational drugs will be returned to the sponsor and must not be transferred to any non-clinical trial participant.

The investigational drugs are stored in a medical refrigerator at 2–8 °C. When the drug is dispensed to the study site, a drug receipt form must be signed by two persons in duplicate, one for clinical study site and the other for sponsor. At the end of the study, the remaining drugs and empty boxes will be returned, and the two sides need to sign a drug return form. The dispensation and return of each drug shall be recorded on a specific record sheet in time.

Monitors are responsible for monitoring supply, use, storage of the investigational drugs and treatment of the remaining drugs.

6.3 Drug Storage and Management

In accordance with the requirement of the GCP, the investigational drugs are uniformly stored, dispensed and returned by the participating study site. The investigational drugs should be sealed and protected from light, stored in a medical refrigerator at 2−8 °C, and must not be frozen.

SHR-1210 is not permitted to be used in the treatment outside of this study.

6.4 Disposal of Remaining Drugs

Investigators should record the date and dose of the drug administered for each subject. The total amount of investigational drugs is 110% of the designed amount, and the residual investigational drugs will be returned to the sponsor regularly for destruction after being counted. If the remaining drugs should be destroyed at study sites, the written certification of the destruction of residual investigational drugs needs to be obtained and stored as well.

6.5 Dose Regimen

The subjects randomized to Group A will receive SHR-1210 3 mg/kg intravenous infusion over 30 minutes (no less than 20 minutes and no more than 60 minutes, including a wash-out period) once every two weeks. The subjects randomized to Group B will receive the same dose once every three weeks.

The interval between two doses cannot be less than 12 days for once every two weeks. The interval between two doses cannot be less than 18 days for once every three weeks.

6.6 Common Recommendations on Safety Management

6.6.1 Infusion reaction

As SHR-1210 is a fully humanized monoclonal antibody, the possibility of infusion or allergic reaction is low, and preventive medication is not needed prior to infusion. Allergic reaction is most likely to occur within 24 hours after infusion. Once the allergic reactions occur, the infusion should be slowed down or interrupted based on the condition, and clinical supportive treatment is needed, and after that, the preventive medication should be given prior to the subsequent doses.

The allergic reactions are possibly characterized by fever, intolerance of cold, chills, headache, rash, pruritus, joint pain, low or high blood pressure, or bronchospasm. All the Grade 3 or 4 infusion reactions should be reported to the sponsor within 24 hours, and reported as SAE in case of meeting the criteria for SAE. See detailed reporting method in Section 9.2.

Response to allergic reactions should be based on the medical practice and guidelines of the study site. The following is the recommendations for the treatment of infusion reaction for reference.

Table 4 Recommendations on management of immune related adverse reactions

CTCAE Grade	Clinical symptoms	Clinical treatments	SHR-1210 treatment
Grade 1	Mild transient reactions	Bedside monitor, close monitoring till recovery. Preventive medication is recommended prior to the infusion afterwards: Diphenhydramine 50 mg, or equivalent and/or Acetaminophen 325–1000 mg, administered at least 30 minutes before the infusion of SHR-1210.	Continue.
Grade 2	Moderate reaction requiring treatment or dose interruption that can be rapidly relieved after symptomatic treatment (e.g., antihistamine drugs, non-steroid anti-inflammatory drugs, anaesthetics, bronchodilator, intravenous infusion, etc.)	Normal saline i.v. infusion, Diphenhydramine 50 mg i.v. or equivalent and/or Acetaminophen 325–1000 mg; bedside observation, close monitoring till recovery. Corticosteroid or bronchodilator can be considered if clinically required; The dose of investigational drug administered will be recorded in the source documents; Preventive medications are recommended prior to the infusion afterwards: Diphenhydramine 50 mg, or equivalent and/or Acetaminophen 325–1000 mg, administered at least 30 minutes before the infusion of SHR-1210. Cortisol (equivalent to 25 mg hydrocortisone), can be used if necessary.	Interrupted temporarily. Resuming the medication after symptoms disappear at 50% of the initial infusion rate. If there is no complication within 30 minutes, increase to the original 100% infusion rate. Closely monitor. If relapse, the current dose of SHR-1210 cannot be given again.
Grade ≥ 3	Grade 3: serious reaction, no rapid relief after treatment and/or dose interruption; or relapse after remission; sequela occurred requiring hospitalization. Grade 4: life threatening	The infusion of SHR-1210 shall be immediately discontinued; And normal saline i.v. infusion should be started. • Bronchodilator, 0.2–1 mg 1:1000 epinephrine solution (s.c.) , or 0.1–0.25 mg 1:10000 epinephrine solution (i.v.), and/or diphenhydramine 50 mg combined with methylprednisolone 100 mg or equivalent drugs (i.v.) is/are recommended;	Discontinued permanently.

CTCAE Grade	Clinical symptoms	Clinical treatments	SHR-1210 treatment
		• Comply with guidelines for allergic reactions of the study site; Bedside monitor, close monitoring, till recovery.	

6.6.2 Principles of management for immune-related adverse events

In overall principle, according to the severity of adverse reaction, interruption of SHR-1210 is taken as the main measure, resumption of SHR-1210 can be considered when the severity of adverse event has recovered to Grade 1 or below, and SHR-1210 should be discontinued permanently when serious Grade 3 or life-threatening Grade 4 adverse events occur.

Management of immune-related adverse events should base on the medical practice of the study site and the guidelines. The following provides the recommendations on management of immune-related adverse events (see Table 5), for reference. Recommended treatment procedures for common immune-related adverse events are detailed in Appendix 4.

Table 5 Recommendations on management of immune-related adverse events

CTCAE Grade	Clinical Treatment*	SHR-1210 Treatment
Grade 1 (Mild)	Close observation; symptomatic and supportive treatment.	Continue
Grade 2 (moderate)	Close monitoring; Symptomatic and supportive treatment; Local or systemic steroids treatment, 0.5–1 mg/kg/day, Prednisone or equivalent drugs.	Interrupted temporarily, resume the medication when adverse reactions ≤ Grade 1; Resuming the medication, except cutaneous and endocrine disorders.
Grade 3 (severe)	Hospitalization is recommended; 1–2 mg/kg/day, prednisone or equivalent drugs (i.v. or p.o.); If failed after steroids treatment for 3–5 days, consider addition of other immunosuppressants; Specialized consultation is recommended.	Interrupted temporarily; dose resumption must comprehensively consider risk/benefit ratio and be decided after discussion.
Grade 4 (life threatening)	Intravenous 1–2 mg/kg Methylprednisolone; If failed after steroids treatment for 3–5 days, consider addition of other immunosuppressants; Specialized consultation is recommended.	Discontinued permanently.

（S. Champiat, O. Lambotte, E. Barreau, er al. Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper. Annals of Oncology 27: 559–574, 2016）

7 DOSE ADJUSTMENT AND SAFETY MANAGEMENT

7.1 Dose Level and Regimen

The dose level in trial is 3 mg/kg, q2w or q3w, intravenously infusion over 30 minutes (no less than 20 minutes and no more than 60 minutes, including a wash-out period), until progression of disease, unacceptable toxicity, withdrawal of informed consent or the end of study, whichever comes first.

The administration interval cannot be less than 12 days at the frequency of once every two weeks. The administration interval cannot be less than 18 days at the frequency of once every three weeks. Dosing 3 days post the intended date of administration will be considered as delayed dose. The subsequent time of administration will be calculated on the actual date of the previous dose.

7.2 Dose Modification

7.2.1 Criteria for dose modification

Dose modification is not allowed.

7.2.2 Criteria for dose delay

The dose should be delayed if the following conditions occur:

- Any ≥ Grade 2 treatment-related non-cutaneous AE, except Grade 2 treatment-related fatigue or laboratory abnormalities;
- Any Grade 3 treatment-related cutaneous AE;
- Any Grade 3 treatment-related laboratory abnormalities, except Grade 3 abnormal amylase or lipase unrelated with the symptoms and clinical manifestations of pancreatitis;
- The administration will be delayed if the following AST or ALT abnormalities occurs:
  - AST and ALT at baseline are within normal range, and Grade 2 treatment-related adverse events occur ;
  - AST or ALT at baseline elevates no greater than Grade 1, and Grade 3 treatment-related adverse events occur;
  - AST or ALT at baseline elevates no greater than Grade 2, and treatment-related elevated AST or ALT reaches > 2 times the baseline or either AST or ALT reaches > 8×ULN (whichever is lower).

- The administration needs to be delayed for any AE, laboratory examination abnormalities or complications, as judged by investigators;

Subjects who need delayed dose should be monitored every week, and the frequency of monitoring can be increased when clinically indicated. It is recommended to monitor liver function every three days, until the highest value of AST or ALT starts to decrease. When meeting the criteria for resumption of medication (see Section 7.2.3), the investigational drug can be resumed.

Tumor evaluation still needs to proceed for all the subjects as required in the protocol, regardless of dose delay.

7.2.3 Criteria for dose resumption

When treatment-related AEs recover to ≤ Grade 1 or baseline level, the dose can be resumed, except the following:

- The therapy can be resumed for the subjects with Grade 2 fatigue that has not been recovered;
- The therapy can be continued for Grade 2 cutaneous AE;
- For subjects with AST, ALT or TBIL Grade 1 elevation at baseline who delay SHR-1210 for reasons other than treatment-related hepatic AE, the therapy can be resumed in the presence of AST, ALT or TBIL Grade 2 elevations;
- For subjects who delay the dose for treatment-related AST, ALT or TBIL elevation, when these parameters are recovered to baseline CTCAE Grade or normal (see Section 7.2.4) and have not reached the criteria for permanent discontinuation of the treatment, the investigational drugs can be resumed;
- In the case that the treatment-related endocrine disorder can be sufficiently controlled only with hormone replacement at physiological dose, the treatment can be resumed.

The study medication is allowed to be delayed for up to 6 weeks, as calculated from the last dose. If the subject still does not reach the criteria for dose resumption after delay for 6 weeks, the study treatment need to be discontinued permanently, except the exceptions mentioned in Section 7.2.4. The guideline on management of adverse reactions is seen in Appendix 4 in detail.

7.2.4 Criteria for permanent treatment discontinuation

The study medication must be discontinued permanently when the following conditions occur:

- Any Grade 2 treatment-related uveitis, ophthalmodynia, and blurred vision, that has no response to local therapy and is not recovered to Grade 1 after delayed dose; or the above AE requiring systemic therapy.

- Any Grade 3 treatment-related non-cutaneous AE, lasting for > 7 days, except the following:
  - When any Grade 3 treatment-related uveitis, pneumonia, bronchospasm, hypersensitivity, or infusion reaction occurs, the study treatment must be terminated;
  - In case the Grade 3 treatment-related endocrine disorder can be sufficiently controlled only with hormone replacement therapy at physiological dose, the treatment does not need to be terminated;
  - The treatment does not need to be terminated for Grade 3 treatment-related laboratory abnormality, however, the study medication must be terminated for Grade 3 thrombocytopenia > 7 days or related with hemorrhage.
- Hepatotoxicity meeting the following:
  - AST or ALT > 10 times of ULN for over two weeks;
  - ALT or AST > 15 × ULN;
  - TBIL > 8 times of ULN for subjects with elevated TBIL at baseline, > 5 times of ULN for subjects with normal TBIL at baseline;
- Any Grade 4 treatment-related AE or abnormal laboratory examination, except the following:
  - Grade 4 granulocyte decrease lasts less than 7 days;
  - Grade 4 lymphopenia or leukopenia;
  - Isolated Grade 4 elevated amylase or lipase, without symptoms or clinical manifestations of pancreatitis. The sponsor needs to be informed in case of Grade 4 elevated amylase or lipase occurs;
  - Isolated Grade 4 electrolyte imbalance/abnormality without clinical sequela that could be corrected through supplement/appropriate management within 72 hours after occurrence;
  - Grade 4 treatment-related endocrine disorder that can be sufficiently controlled only with hormone replacement therapy at physiological dose, the treatment does not need to be terminated.

- The study treatment must be terminated in case dose delay > 6 weeks is required, except the following:
  - After the use of cortisol for management of treatment-related AEs, the study medication is allowed to be delayed for > 6 weeks due to the need for dose tapering. Discussion with the sponsor must be made before resuming the dose. During the dose delay, the tumor assessment should continue as required by the protocol. Safety visits and laboratory tests should also be performed at the original frequency (at least once every 6 weeks, window period ± 7 days) or more frequently when clinically indicated;
  - The dose delay for > 6 weeks due to non-related reasons must be discussed with the sponsor prior to resuming administration. During dose delay, the tumor evaluation should still proceed as required in the protocol. Safety visits and laboratory examinations should also be performed at the original frequency (at least once every 6 weeks, window period ± 7 days), or more frequently when clinically indicated;
- Clinical AE, laboratory abnormality, or complications may bring major risk to subjects who continue taking the study medication, as judged by investigators.
- Progression of disease evaluated by investigators in accordance with RECIST v1.1 (unless the subject meets the criteria in Section 3.2.4).

Even though the study medication is terminated, subjects must continue to perform tumor evaluation as required in the protocol.

7.3 Safety Management of Immuno-Oncology Drugs

7.3.1 Rules for safety management of immuno-oncology drugs

The AEs induced by Immuno-Oncology (I-O) drugs vary from other types of anti-cancer drugs, the severity and duration are special. SHR-1210 belongs to this type of drugs, thus it is required to achieve early identification and management of the AE induced by it, in order to reduce the incidence of serious toxicities. The investigator may refer to the rules for safety management of similar products in overseas markets to facilitate evaluation and management of I-O treatment-related AEs occurring in the following systems:

- Gastrointestinal tract
- Lung
- liver

- Endocrine
- Skin

Rules for safety management are provided in Appendix 4 in detail.

7.3.2 Rules for management on hepatic adverse events

Below are suggestions on management of hepatic AEs during the treatment period of this study:

- The criteria on dose delay resulted from hepatic AE are listed in Appendix 4. If the dose is delayed for 3−5 days and AST or ALT level is not improved but even exacerbated, cortisol, i.e., methylprednisolone 0.5−2 mg/kg/day or equivalent oral drugs will be given.
- In case of AST or ALT > 8 times of ULN, cortisol, i.e., methylprednisolone 0.5−2 mg/kg/day or equivalent oral drug will be given immediately.
- The sponsor must be informed within 24 hours when cortisol treatment starts. At the same time, a gastroenterology consultation is advised.
- If AST or ALT level is not improved but even exacerbated 3−5 days after the start of corticosteroids treatment, it must be discussed with the sponsor, and other immunosuppressants may need to be added, such as mycophenolate 1g BID.
- Once AST or ALT is decreased by CTCAE Grade, the dose can be decreased gradually in no less than one month.

The study medication can be resumed when AST or ALT is recovered to baseline level, unless the criteria on permanent discontinuation is reached.

8 EFFICACY EVALUATION

8.1 Primary Endpoints and Observation Method

1) 6-month survival rate (6-month OS%): defined as the percentage of non-death cases in the evaluable subjects from the start of the trial to 6 months.
2) Objective response rate (ORR):

   Defined as objective tumor response evaluated based on RECIST v1.1, including CR and PR cases.

   Definition of evaluable population: all the subjects meeting the following criteria, i.e., having received at least one dose of SHR-1210 treatment and at least one tumor evaluation after the start of study treatment. If the efficacy reaches CR or PR, subjects must receive repeated test for confirmation in no less than 4 weeks (28 days) after the first evaluation.

8.2 Secondary Endpoints and Observation Method

1). Duration of response (DoR): defined as the time from the date of first record of objective response (CR or PR) to the first occurrence of progression or death.

2). Time to progression (TTP): defined as the time from the date of randomization to any documented radiological tumor progression.

3). Disease control rate (DCR): defined as the percentage of subjects with CR, PR and SD (≥ 6 weeks) in the evaluable population.

4). Progression-free survival (PFS): defined as the time from randomization to any documented radiological tumor progression or death.

5). Overall survival (OS): defined as the time from randomization to death from any cause.

8.3 Independent Tumor Imaging Evaluation

In order to provide objective, neutral and reproducible efficacy data except investigators' evaluation, the 3rd-party Independent Radiology Review Committee (IRC) will be set up for tumor response evaluation in this study.

All the images (including unscheduled scan, possibly including bone scan or brain scan) obtained from each center will be centrally reviewed by IRC, and tumor evaluation will be performed in accordance with RECIST v1.1. The central evaluated data will be used for analysis of ORR, TTP, DoR and DCR. The clinical decisions related with response evaluation will be based on investigator's evaluation.

The detailed procedures and standard for central evaluation will be defined in the additional "Radiology Manual for Study Center".

9. SAFETY EVALUATION

The safety evaluation of investigational drug includes vital signs, laboratory parameters, AE, SAE, treatment-related AE and SAE, which will be evaluated according to NCI-CTC AE v4.03 criteria.

9.1 Adverse Events

9.1.1 Definition of AE

AE is defined as adverse medical event that occurs after the subject who receives a drug in clinical trial, but do not necessarily have a causal relationship with the treatment. Any AE from the signature of informed consent form to 90 days after the last dose will be collected. AE can be any undesirable and unexpected symptom, sign, laboratory abnormal or disease, including at least the following conditions:

1) Aggravation of existing (prior to enrollment of clinical trial) medical condition/disease (including exacerbation of symptoms, signs, abnormal laboratories);
2) Any new occurrence of AE: any adverse medical condition newly occurs (including symptom, signs, newly diagnosed diseases);
3) Abnormal laboratory test or result of clinical significance.

The investigators should carefully record any AE occurs in the subjects, including: description of adverse event and relevant symptoms, time of onset, severity, causality with investigational drug, duration, actions taken, final outcomes and prognosis.

9.1.2 Judgment standard on severity of AE

Refer to NCI-CTC AE v4.03 grading criteria for AE related drugs. If any AE is unlisted in NCI-CTC AE v4.03, refer to the following criteria:

Grade	Clinical description of severity
1	Mild; without clinical symptoms or mild clinical symptoms; only with clinical or laboratory abnormalities; no treatment is required.
2	Moderate, requiring minimal, local or non-invasive treatment; age-appropriate limits activities of daily living (ADL); involving tools refer to cooking, shopping, calls and counting money, etc.
3	Severe conditions or serious medical symptoms but not life-threatening; leading to hospitalization or hospitalization prolonged; leading to disability; limited in self-care ADL. Daily self-care includes bathing, dressing, undressing, eating, going to the bathroom, medication, and so on, non-bedridden.
4	Life-threatening, emergency treatment is required.
5	Leading to death.

9.1.3 Judgment standard on causality assessment

Collection of AE starts from the signing of informed consent form to 90 days after the last dose of investigational drug, records are collected regardless of whether the event is related to the investigational drug, whether the subject is assigned to the experimental arm, or even whether the drug is used or not. Any discomfort or abnormal change in objective laboratory tests during the treatment should be recorded accurately, and the severity, duration, actions taken and outcome of the AE should be recorded. The study doctor should determine the relationship between AE and investigational drug, such as whether the occurrence of AE has relationship with a reasonable medication order, the properties of investigational drug, toxicological and pharmacological effects of investigational drug, subjects' use of other concomitant drugs, subjects' underlying diseases, medical history, family history and provocative and re-provocative reactions, etc. The causality between AE and investigational drug will be assessed using the following 5 categories: "definitely related", "possibly related", "unlikely related", "not related", and "unassessable". Among them, AEs with a causality of "definitely related", "possibly related", "unlikely related" and "unassessable" will be listed as adverse drug reactions.

9.1.4 Follow-up of AE

An AE will be followed up until it is resolved, returns to the baseline level or ≤ Grade 1, or reaches a stable state, or until other reasonable time points (e.g., lost to follow-up, death).

9.2 Serious Adverse Event (SAE)

9.2.1 Definition of SAE

Serious adverse events (SAE) is defined as the medical events that require hospitalization or prolonged hospitalization, disability, limiting working ability, life-threatening or death, and leading to congenital malformation during the clinical trial. Including the following medical events:

- Events leading to death;
- Life-threatening events (defined as the subject has a risk of immediate death);
- Events requiring hospitalization or prolonged hospitalization;
- Events that result in persistent or severe disability/dysfunction/limiting working ability;
- Congenital abnormalities or birth defect;
- Other significant medical events (defined as the event threatens the safety of the subject, or requires intervention measures for the prevention of any of the above conditions).

9.2.2 Disease progression

Disease progression is defined as the exacerbation of the subject caused by indications of the investigational drug, including radiological progression and progression of clinical symptom and sign. New metastases relative to the primary tumor and the progression of the original metastases are both considered to be progressive disease. Events that are life-threatening, requiring initial or prolonged hospitalization due to symptoms and signs of disease progression, which can lead to permanent or severe disability/dysfunction/limiting work ability, congenital abnormalities or birth defects are not reported as SAEs in expedition. Death caused by symptoms and signs of disease progression is reported as SAE.

9.2.3 Hepatic enzyme abnormalities

Hepatic enzyme abnormalities with abnormal values in AST and/or ALT and meet the laboratory abnormalities in the following table should be reported as SAE. Additional follow-up of subjects will be required until the hepatic enzyme returns to the baseline level.

Baseline period	Normal (AST, ALT, and TBIL)		Abnormal (AST, ALT, or TBIL, any of them)	
Treatment period	ALT ≥ 3× ULN	AST ≥ 3× ULN	ALT ≥ 8× ULN	AST ≥ 8× ULN
	Meeting one of the above two criteria, with TBIL ≥ 2× ULN and alkaline phosphatase ≤ 2×ULN with no hemolysis		Meeting one of the above two criteria, with TBIL ≥ 3×ULN or increase ≥ 1× baseline value	

9.2.4 Other anti-cancer therapy

The record of AE starts from the signing of informed consent form until 90 days after the last dose of investigational drug. SAEs occurring within 90 days after the last dose also need to be reported even if the subject has started to use other anti-cancer drugs.

9.2.5 Hospitalization

AEs that result in hospitalization or prolonged hospitalization should be considered as SAEs. Any initial hospitalization meets the criteria.

Hospitalization does not include the following situations:

- Rehabilitation facilities
- Nursing homes
- Routine emergency room admissions
- Surgeries at the same day (as outpatient/same day/ambulatory procedures)

Hospitalization or prolongation of hospitalization which are unrelated to the exacerbation of AEs will not be considered as SAEs. For example,

- Admission for treatment of a preexisting condition without the development of new adverse events or worsening of the preexisting condition (e.g., for check of persistent pre-trial laboratory test abnormality);
- Administrative admission (e.g., for yearly physical exam);
- Hospitalization as per the trial protocol during the study (e.g., as required by the protocol);
- Elective admission not associated with the aggravation of adverse events (e.g., elective surgery);

- Predefined treatments or surgical procedures should be documented throughout the study program and/or in the baseline data of individual subject.

- A subject is hospitalized due to only use of blood products.

Diagnostic or therapeutic invasive (e.g., operation) and non-invasive procedures should not be reported as AE, but if the disease condition leading to the operation, it should be reported as long as it conforms to the definition of AE, e.g., acute appendicitis during the AE reporting period should be reported as AE; therefore, the appendectomy should be recorded as the treatment of AE.

9.2.6 Reporting procedures of SAE

The reporting of SAEs starts from the signing of informed consent form to 90 days (inclusive the 90th day) after the last dose of investigational drug. In case of SAE, regardless of first report or follow-up report, the investigators must fill in the "serious adverse event report form" immediately, sign and date it, report it to the sponsor within 24 hours after learning of it, and report it to relevant organizations in time as required by regulations.

The sponsor's email to receive SAE report in this study: hengrui_drug_safety@shhrp.com

The SAEs occurring 90 days after the last dose of investigational drug will generally not be reported, unless it is suspected to be related to the investigational drug. The detailed record content of SAE should include symptoms, severity, and causality with investigational drug, time of onset, time of treatment, actions taken, follow-up time and method as well as outcome. If the investigator considers that an SAE is not related to investigational drug while potentially related to the study conditions (e.g., termination of the original treatment or complications during the trial), the relationship should be described in detail in the narrative section of SAE report form.

If there is a change in the severity of an ongoing serious adverse event or its relationship with the investigational drug, follow-up reports should be submitted immediately. If misinformation is considered to be present in the previously reported SAE, it can be corrected, withdraw or degraded in the follow-up report, and reported in accordance with the SAE reporting procedure.

9.2.7 Follow-up of SAE

An SAE should be followed up until it is resolved, returns to the baseline level ≤ Grade 1, or reaches a stable state, or until other reasonable time points (e.g., lost to follow-up, death).

9.3 Pregnancy

If a female subject is pregnant during the clinical study, the subject will be withdrawn from the group, investigators should fill in "Pregnancy Report/Follow-up Form in Hengrui Clinical Study", and report to the sponsor within 24 hours after investigator awareness.

If the partner of male subject becomes pregnant during the clinical study, the subject can continue the clinical trial, investigators should fill in "Pregnancy Report/Follow-up Form in Hengrui Clinical Study", and report to the sponsor within 24 hours after investigator awareness.

The investigator should follow up the pregnancy result, until one month after delivery, and will report the result to sponsor.

If the outcome of pregnancy is stillbirth, spontaneous abortion, or fetal malformations, it should be considered as an SAE and be reported in accordance with SAE reporting requirements.

If an SAE occurs during pregnancy, the investigator is required to complete the "Serious Adverse Event Report Form" and report this SAE according to the reporting procedures.

9.4 AEs of Special Interest

For the AE of special interest specified in the clinical study protocol, investigators need to fill in the "Adverse Event of Special Interest Report Form in Hengrui Clinical Study" within 24 hours after awareness, and report to the sponsor.

If it is SAE at the same time, please also fill in "Serious Adverse Event Report Form" and report to the relevant department in accordance with SAE procedure.

- ≥ Grade 3 infusion reaction
- ≥ Grade 2 diarrhea/colitis, uveitis, or interstitial pneumonia
- ≥ Grade 3 other immune-associated adverse events
- Any possible event of abnormal hepatic enzyme (see Section 9.2.3, whilst lacking other related causes, for example, progression of disease, acute viral hepatitis, cholestasis, concomitant medication, pre-existing hepatopathy, etc.)
- Grade 4 increased amylase or lipase

9.5 Emergency Unblinding

Not applicable.

10 DATA MANAGEMENT

10.1 Material Collection and Data Management

Electronic case report form (eCRF) will be used for collection and management of the study data in this study.

10.1.1 Collection of data

eCRF is used for acquisition of study data in this study; the electronic data collection (EDC) system will be provided by Jiangsu Hengrui Pharmaceuticals Co., Ltd. to study institutions. The company's staff will train on EDC system for the designated personnel at the study institutions. The personnel at the study institutions can login EDC system only after the training. PI or specialized person for data entry (qualified investigator and/or CRC) should enter the data into

EDC system in accordance with the requirement for visit procedure and the guideline on filling in eCRF. The system logic verification program will check the completeness and logicality of the clinical trial data entered in EDC system, and generate error message for the problem data, allowing PI, investigator or CRC to modify or explain the data. After the database is locked, investigators will receive one CD-ROM or hard copy of the data, for archival at the study institution.

10.1.2 Data management and quality control

In order to ensure the clinical data are true and reliable, improve the quality of clinical data, clinical monitors will review the completeness, consistency and accuracy of the trial data in clinical database in accordance with monitoring plan during the trial, and discuss with the study staff on the problem data, and the study staff should make supplement or correction when necessary. The clinical monitor or data management professionals will propose their queries on the questionable data to PI, investigator or CRC in a form of electronic query table, PI, investigator or CRC must respond to the queries and make correction or explanation to the problem data, the query can be proposed for multiple times until the problem data are solved, if necessary. The person in charge of medical affairs, drug safety affairs and data management professionals will conduct consistency comparison for SAE on a regular basis.

At the end of the trial, the data management professionals and medical staff will do the final quality control of all the data in the database, summarize all the protocol deviations and violations appeared in the trial, and convene data verification meeting. After the data in the database meet the requirement for quality, the database will be locked, the data management professionals will export data for analysis by statistical department.

10.1.3 Data review and monitoring of study institution

At the initiation of the trial, the representatives from Jiangsu Hengrui Pharmaceuticals Co., Ltd. will introduce the protocol and eCRF together with investigators and working staff at the first visit to study institutions or in the investigator’s meeting. During the trial, the monitor will visit study centers on a regular basis, check the completeness of record and accuracy of the content on eCRF, compliance with the protocol and Good Clinical Practice, progress in enrollment, and make sure the investigational drug is stored, dispensed and counted in accordance with the provisions. During these visits, the key study staff must be able to assist the monitors.

Investigators must keep the original documents of each subject participating in the trial, including the study medical records and visit records (hospitalization or outpatient medical record), which include demographic parameters and medical information, laboratory data, ECG and results of any other examination or evaluation. All the information on eCRF must be sourced from the original document in the subject’s archives. Investigators also have to keep the informed consent forms signed by subjects.

Investigators must confirm all the relevant original documents can be monitored, so as to verify the consistency with that on eCRF. The monitoring standard by Jiangsu Hengrui Pharmaceuticals Co., Ltd. requires a 100% monitoring for study-related original documents, including but not limited to informed consent form signed by the subject, compliance with inclusion/exclusion criteria, visit record, AE/SAE record, and all the data required for evaluation of the main efficacy and safety parameters. Any information on subject's identity in the original documents will not be disclosed.

11 DATA ANALYSIS AND STATISTICAL METHODS

The detailed summary of the data collected in this study and the statistical analysis method will be recorded in the statistical analysis plan (SAP), and will be finalized and put on record by the sponsor. If any change to the study protocol is judged by the sponsor or the principal investigator to have an impact on the statistical analysis plan, the SAP needed to be re-modified so as to keep consistency with the study protocol.

11.1 Determination of Sample Size

This is a single-arm, open-label phase II study to observe the objective response rate (ORR) and survival rate at 6 months simultaneously.

Referring to the study results on similar products, assuming the ORR is 15% for SHR-1210 in treatment of target population of this study, and the lower limit of 95% confidential interval of ORR obtained from this study is >7%, it can be considered as effective. 154 subjects need to be enrolled to obtain 90% power at a one-sided significance level of 0.025. Further assuming evaluable cases accounting for 80% of the enrolled subjects, 194 subjects are required to be enrolled.

Assuming the survival rate at 6 months is 80% for SHR-1210 in treatment of target population, and the lower limit of 95% confidential interval is >70%, this therapy can be considered to have advantage in efficacy. 200 subjects need to be enrolled to obtain 90% power at a one-sided significance level of 0.025. Considering the drop-out rate of 10%, a total of 220 subjects are required to be enrolled.

Therefore, the planned sample size of this study is 220.

11.2 Analysis Populations

Full analysis set (FAS): an analysis set determined in accordance with intention-to-treat principle. All the subjects who are randomized and have documented at least one dose of investigational drug will be included in this analysis set. The full analysis set is the primary efficacy analysis set.

Per protocol set (PPS): one subset of full analysis set. The subjects with protocol violation which has important influence on efficacy will be excluded from this set. The list of subjects who are included or excluded from PPS needs to be determined through review by the sponsor and investigators prior to lock of database.

Safety analysis set (SS): all the subjects who are randomized and have documented at least one dose of investigational drug will be included in the safety analysis set.

PD-L1 analysis set: PD-L1 expression analysis set of this trial comprise of all the subjects who have been randomized and enrolled and have received at least one dose of the investigational drug, and have provided tumor biopsy samples.

11.3 Statistical Analysis

11.3.1 General analysis

Unless otherwise specified, the continuous variables in this study will be summarized with mean, standard deviation, median, maximum and minimum; the categorical variables will be summarized with frequency and percentage; Kaplan-Meier method will be used to estimate the survival rate and plot survival curve for time-event data.

11.3.2 Efficacy analysis

The tumor evaluation will be performed by the investigators based on RECIST v1.1. This evaluation data will be based on following responding parameters: complete response (CR), partial response (PR), stable disease (SD), progression of disease (PD), and not evaluable (NE). All the efficacy analysis will be based on the full-analysis set.

The survival distribution of OS will be estimated based on Kaplan-Meier (KM) method, median OS and two-sided 95% confidential interval will be calculated. In addition, KM method will be used to estimate the probability of survival at different time points (at month 6/9/12), and the corresponding 95% confidential interval will be calculated. Moreover, the subgroup analysis of OS will be performed by the predefined factors, the analytical method will be based on the aforementioned method.

The survival distribution of time to progression (TTP) will be estimated based on Kaplan-Meier (KM) method, median TTP and two-sided 95% confidential interval will be calculated.

The survival distribution of progression-free survival (PFS) will be estimated based on Kaplan-Meier (KM) method, median PFS and two-sided 95% confidential interval will be calculated. Objective response rate (ORR) and disease control rate (DCR): Clopper-Pearson method will be used to calculate the 95% confidential interval of overall percentage.

11.3.3 Safety analysis

Analysis of adverse events will be based on the safety analysis set. The data for analysis will include but not limited to the calculation of the incidence of adverse reactions by group; incidences and frequencies of adverse reactions by system; calculation of the percentage and detailed listing of a variety of adverse events, and the specific analysis will be presented in the statistical analysis plan.

Number of "normal to abnormal" or "exacerbation of abnormal" laboratory parameters, ECG, physical examinations and the abnormality conversion rate after the trial, the number of abnormal laboratory parameters, ECG, physical examinations and the clinical explanation would be presented.

11.3.4 Exploratory analyses

PD-L1 expression will be analyzed using descriptive statistics. PD-L1 analysis set is the analysis data set.

12 INFORMED CONSENT AND ETHICS

12.1 Informed Consent

The clinical research physician must fulfill the obligation of full disclosure to the subjects, and explain to subjects that they are voluntary to participate in the clinical trial, and have the right to withdraw from the trial without discrimination and retaliation at any time during the trial, their medical treatment and benefits would not be affected at all and they could still continue other treatment. The subjects must be made aware that the participation in the trial and the personal data in the trial are kept confidential. The property, objective, expected possible benefit and possible risks and inconvenience of the trial are also needed to be informed to the subjects, the available other therapies, rights and obligations for subjects in compliance with the Helsinki Declaration should be informed to the subjects, allowing subjects to have adequate time to consider whether they are willing to participate in the trial and sign the informed consent form.

12.2 Ethical Principles

This trial protocol needs to be approved by the hospital ethics committee prior to its conduct with written approval. The study protocol, amendments, informed consent form and other relevant documents, e.g., recruitment advertisement, should be provided to the ethics committee. This study shall be conducted strictly in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) and relevant regulations issued by NMPA. Prior to the start of the trial, the approval from the ethics committee must be obtained, the study could be initiated then.

The sponsor and investigator must not amend this study protocol unilaterally without mutual agreement. Only limited to eliminate the direct and immediate injury to subjects, investigators can change or deviate from the study protocol prior to approval by the ethics committee/institutional review board. At the same time, all the deviations or changes made, their reasons, and the recommended amendment to the protocol should be submitted to the ethics committee/institutional review board for review as soon as possible, and communicate with the sponsor. Investigators must explain and record any deviation from the protocol.

During the clinical study, any amendment made to the study protocol should be submitted to the ethics committee, corresponding amendment should also be made to other study documents when necessary and submitted and/or approved as required by the ethics committee. Investigators are responsible for periodic submission of the in-trial report to the ethics committee in accordance with relevant requirement, and should inform the ethics committee that the trial has ended after the end of trial.

12.3 Regulatory Considerations

SHR-1210 for injection, innovatively developed and submitted for approval by Jiangsu Hengrui Pharmaceuticals Co., Ltd., has been approved by NMPA, and given the clinical trial approval for national Class I new drugs. Now, the nationwide, multi-center, phase II/III clinical trial on SHR-1210 for injection in the subjects with advanced hepatocellular carcinoma who had received systematic treatment previously is conducted in accordance with Drug Registration Regulation and GCP, led and organized by National Drug Clinical Research Institute of the 81st Hospital of PLA (Nanjing).

12.4 Security Measures of Subject Information

Every effort will be made to protect subject's personal privacy during the study. Subject's name and other personal privacy information must not be included in the study related documents, study report, publications and any other public materials, unless required by the law. Collection, transmission, process and maintenance of subject's information will be in accordance with the provisions in relevant laws and regulations, so as to protect subject's personal data from disclosure.

13 QUALITY CONTROL AND QUALITY ASSURANCE

- The clinical trial institution must be the base of drug clinical trials determined by NMPA with clinical study conditions;
- The study staff must be the qualified persons who have been trained on clinical trials, and conduct their work under the guidance of highly specialized personnel.

- The clinical ward must be in accordance with the standardized requirement before the trial, so as to ensure complete rescue equipment;
- The dose will be given by healthcare professionals, intake of the drug will be carefully understood, so as to ensure subject's compliance;
- Each study center must conduct it strictly in accordance with the study protocol and fill in the eCRF truthfully;
- The monitor should follow the standard operating procedure to supervise the conduct of the clinical trial, confirm proper and complete record and report of all the data, accurate filling of all the eCRFs and consistency with the original data, and ensure the trial is conducted in accordance with the protocol;
- Once SAE occurs, the sponsor must inform each study unit promptly, the study needs to be discontinued temporarily if necessary;
- Each center participating in the trial should receive the audit from the sponsor and Food and Drug Administrations, it is particularly important for the investigators and relevant staff to provide convenience and time for the monitoring and audit.

14 PUBLICATION OF STUDY RESULTS

Hengrui does not restrict the investigators to publish any information collected or produced, despite whether this result favors for the investigational drug. However, in order to make sure no unintentional leakage of the confidential information or unprotected invention, the investigators must give an opportunity for sponsor to review any proposed publication or publication in other forms in advance prior to submission or publication of the documents. If the study is one part of one multi-center study, the investigators need to agree on the first publication of the comprehensive results from all the study centers. However, if the manuscript of the comprehensive analysis has not been submitted for publication within 12 months after completion or termination of the study at all the study sites, investigators can request independent publication of the results in accordance with other requirement in this section.

15 SCHEDULE OF THE TRIAL

Expected Oct. 2016 to May 2018 (primary endpoint analysis)

16 PROTOCOL COMPLIANCE

Investigators will guarantee that every effort will be made to avoid violations from the protocol. Investigators cannot contact with Jiangsu Hengrui Pharmaceuticals Co., Ltd. to request approval of the violation from the protocol at any time, as no any authorized violation of the protocol shall

be allowed. If investigators consider some deviation from the protocol can improve the implementation of the trial, amendment to the protocol must be considered, however, it can be conducted only when the amendment is agreed by Jiangsu Hengrui Pharmaceuticals Co., Ltd. and approved by the medical ethics committee. All the major violations from the protocol will be recorded and reported on the clinical trial report.

17 STUDY SITE AND PARTICIPATING PERSONNEL

17.1 Leading Site

Name: the 81st Hospital of PLA

Address: No. 34, Yanggongjing 34, Qinhuai District, Nanjing, Jiangsu

Study Team Leader: Shukui Qin, Professor

17.2 Sponsor

Name of sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Sponsor's person responsible for the project: See signature page

Address: No. 7 Kunlunshan Road, Economic and Technological Development Zone, Lianyungang City, Jiangsu Province

Telephone: See signature page

E-mail: See signature page

17.3 Other Study Participating Personnel

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Annex 1 Response Evaluation Criteria in Solid Tumors RECIST Version 1.1

1 Measurability of Tumor at Baseline Level

1.1 Definition

At baseline level, tumor lesions/lymph nodes can be divided as measurable and non-measurable according to the definitions below:

Measurable Lesions

Tumor lesions: at least one diameter that could be precisely measured (recorded as maximum diameter), its minimum length is as below:

- 10 mm for CT scan (thickness of CT scan is no more than 5 mm)
- 10 mm for clinical routine instrument (tumor lesion that could not be accurately measured by diameter-measuring instrument should be recorded as non-measurable)
- 20 mm for chest X-ray
- Malignant lymph nodes: pathologically enlarged and measurable, and short axis ≥ 15 mm for single lymph node in CT scan (thickness of CT scan recommended no more than 5 mm). Only the short axis is measured and followed up at baseline and during follow-up.

Non-measurable Lesions

All the other lesions, including small lesions (maximum diameter < 10 mm or short axis of pathological lymph node ≥ 10 mm and < 15 mm) and non-measurable lesions. Non-measurable lesions include: meningeal disease, ascites, pleural or pericardial effusion, inflammatory breast cancer, skin/pulmonary cancerous lymphatic inflammation, abdominal mass that cannot be diagnosed and followed up by radiology, as well as cystic lesion.

Special Considerations on the Measurement of Lesions

Osseous lesion, cystic lesion and the lesion previously given topical therapy needed to be specially noted:

Osseous lesion:

- Bone scan, PET scan or plain X-ray are inappropriate for measurement of osseous lesions, however, they can be used for confirmation of the presence or disappearance of osseous lesions;
- If the osteolytic lesion or mixed osteolytic/osteogenic lesion with determined soft tissue component could be evaluated with tomographic imaging technique, such as CT or MRI, when the soft tissue component meets the above definition on measurability, these lesions can be regarded as measurable lesion;

- Osteoblastic lesions belong to non-measurable lesions.

Cystic lesions:

- The lesions meeting the definition of radiologically simple cyst should not be considered as malignant foci as they are simple cysts in terms of the definition; they are neither measurable lesions nor the non-measurable lesions.
- Cystic metastatic lesions that meet the above definition on measurability can be considered as measurable lesions. However, if non-cystic lesions are present in the same patient, the non-cystic lesions should be preferably selected as the target lesion.

Lesions treated topically:

- The lesions located at the site once radiated or treated with other topical therapies are generally considered as non-measurable lesions, unless clear progression occurred in these lesions. The study protocol should describe the conditions for these lesions to become measurable lesions in detail.

1.2 Description of Measurement Method

Measurement of Lesions

Measurement of all the tumors is recorded in meter in the clinical evaluation. All the baseline evaluations in terms of the size of tumor foci should be completed as close as possible to the start of treatment, and must be completed within 28 days (4 weeks) prior to the start of treatment.

Methods of Evaluation

Baseline evaluation and subsequent measurements of a lesion should be carried out by the same techniques and methods. All the lesions must be radiologically evaluated except those that cannot be radiologically evaluated but only be evaluated with clinical examinations.

Clinical lesion: only the superficial clinical lesions with diameter ≥ 10 mm measured could be considered as measurable lesions (e.g., cutaneous nodule). For patients with cutaneous lesions, it is advised to use the color image containing one ruler to measure the size of lesion for documentation. When the lesion is evaluated with radiology and clinical examination simultaneously, the radiological evaluation should be used as much as possible as it is more objective and can be reviewed repeatedly at the end of the study.

Chest X-ray: when the progression of tumor is used as the important endpoint, chest CT should be used preferably, as it is more sensitive than X-ray, in particular for new lesions. Breast X-ray are only suitable when the lesion measured has a clear border and pulmonary ventilation is patent.

CT, MRI: CT is currently the best reproducible method for evaluation of efficacy. The definition of measurability in this guideline is based on the thickness of CT scan ≤ 5 mm. If the thickness of CT scan is more than 5 mm, the measurable lesion should be at least 2 times of the thickness. MRI could also be accepted in some circumstances (e.g., systemic scan).

Ultrasound: ultrasound should not be used as one method for measurement of the size of lesion. Ultrasonography is not reproducible due to its dependency on the operation, thus could not ensure the technical and measurement consistency between different measurements. If one new lesion is found in ultrasound during the trial, CT or MRI should be used for confirmation. If the exposure to the radiation from CT scan is considered, alternative MRI can be used.

Endoscopic and laparoscopic examination: these techniques are not recommended for the objective evaluation of tumors, however, these methods can be used for confirmation of CR when biopsy specimen is obtained, and for confirmation of recurrence in the trial while recurrence after CR or surgical resection are taken as the study endpoint.

Tumor marker: tumor marker cannot be used independently to evaluate the objective response of tumors. However, if the marker level exceeds the upper limit of normal at baseline, it must return to the normal level when it is used to evaluate complete response. As the tumor marker varies for disease, it is needed to be considered when including this measurement criterion in the protocol. The specific criteria on CA-125 response (recurrent ovarian cancer) and PSA response (recurrent prostate cancer) have been published. The criteria on CA-125 progression have been established by the international organization of gynecological cancers, i.e., it will be added in the evaluation criteria on the objective response of tumors in the 1st-line therapy for ovarian cancer.

Cytological /histological technology: in the specific situations specified in the protocol, these techniques can be used to differentiate PR and CR (e.g., residual benign tumor tissue is usually present in the lesions of germline cell tumors). When exudation is possibly one potential side effect of one therapy (e.g., Taxanes or angiogenesis inhibitor), and the measurable lesion met the criteria on response or stable disease; cytological technique could be used to differentiate response (or stable disease) and progression of disease when tumor related exudation occurred or became exacerbated during the treatment.

2 Tumor Response Evaluation

2.1 Evaluation of Target Lesions

Complete response (CR): all target lesions disappear, and the minimum diameter of all pathological lymph nodes must decrease to < 10 mm (including target nodes and non-target nodes).

Partial response (PR): The sum of diameter of target lesion decreases by at least 30% from the baseline level.

Progressive disease (PD): The sum of diameter of all measurable target lesions increases by at least 20% over the minimum value of such sum or over the baseline measured value (whichever is smaller), and the absolute value of such sum should increase by at least 5 mm. Or there are one or more new lesions.

Stable disease (SD): The target lesion does not decrease in a degree of PR or increase by an intensity of PD, but changes in the intensity between PR and PD (the minimum sum of diameter is used as reference).

2.2 Considerations on Target Lesion Evaluation

Lymph node: Even when the lymph node of target lesion decreases to less than 10 mm, the corresponding actual value of minimum diameter should be recorded at each examination (same as dissection plane at baseline examination). That means if lymph node is considered as target lesion, the lesion cannot be regarded as complete disappearance despite meeting the requirements of CR, because the minimum diameter of normal lymph node is defined as < 10 mm. In eCRF or other record ways, the lesion of target lymph node should be recorded in specific position: in case of CR, the minimum diameter of all lymph nodes should be <10 mm; and in case of PR, SD and PD, the actual measured value of minimum diameter of target lymph node will be included into the sum of diameter of target lesion.

Target lesion too small to be measured: In clinical study, for all lesions recorded at baseline (including nodular or non-nodular lesion), the actual measured value should be recorded again at the subsequent assessment even if the lesion is very small (e.g., 2 mm). However, the lesion may sometimes be so small that the image of CT scanning is so obscure that it is very difficult to determine a definite value even by the radiologists, and then such lesion may be reported as too small to be measured. In this case, it is very important to record a value in eCRF. If the radiologists think that the lesion may disappear, such lesion should also be recorded as 0 mm. If the lesion exists really but is too obscure to be measured accurately, the default value can be regarded as 5 mm. (note: such case is improbable to appear in the lymph nodes, because they are generally of measurable dimension under the normal conditions or they are often wrapped with fat tissue just like those in the retro peritoneum. However, if the accurate examination is impossible just as mentioned above, the default value can also be regarded as 5 mm). The default value of 5 mm is obtained from the cutting depth of CT scanning, but does not change with such depth. Since the same measured value is improbable to reappear, this default value is offered so as to reduce the risk for wrong assessment. However, to be reaffirmed, if the radiologists cannot offer a precise value for size of lesion, the actual value should be recorded even if the diameter of lesion is less than 5 mm.

When the non-nodular lesion is split into fragment, the maximum diameter of each separated part is added up as the sum of diameter of lesion. Likewise, the merged lesion is first distinguished through the plane between each merged part, and then the maximum diameter of each merged part is calculated; but if the merging is too tight to be split, the overall maximum diameter of merged lesion should be regarded as maximum diameter of lesion.

2.3 Evaluation of Non-target Lesions

The criteria of response are defined as follows for the tumor of non-target lesion. If some non-target lesions are actually measurable but need not be measured, only a qualitative assessment needs to be made at the time point stipulated in the protocol.

Complete response (CR): All non-target lesions disappear, and the level of tumor marker becomes normal. All lymph nodes are of non-pathological dimension (minimum diameter < 10 mm).

Non-complete Response or non-progressive Disease-Persistence: 1 or more non-target lesion(s) and/or maintenance tumor marker level above normal limits.

Progressive disease (PD): a definite progress appears in the existing non-target lesion. Note: PD is also regarded if there is one or more new lesion.

2.4 Special Precautions for Evaluation of Non-target Lesion Progression

Supplementary explanation for defining the progression of non-target lesion: For measurable non-target lesions, a definite progress can be judged on the basis of non-target lesion only when the non-target lesion has deteriorated in an overall intensity necessary for treatment termination, even if the target lesion is assessed as SD or PR. However, the ordinary increase in the dimension of one or more non-target lesions is often insufficient to reach the criteria of PD. Therefore, when the target lesion is assessed as SD or PR, it is nearly very rare to judge overall progression only according to the change of non-target lesion

When all non-target lesions are unmeasurable, such condition will appear in some Phase III studies if the necessary existence of measurable lesion is not stipulated in the inclusion criteria, and the overall assessment is still made by referring to the above-mentioned criteria because there are unmeasurable data of lesions in this case. Since the deterioration of non-target lesions is difficult to assess (as defined, all non-target lesions should be really unmeasurable), a definite progress is judged according to the non-target lesion and an effective examination method should be established for assessment if the change of non-target lesion increases the overall load of disease in an intensity equivalent to the PD of target lesion. e.g. the increase in tumor load is equivalent to the additional increase of 73% in volume (i.e. equivalent to an increase of 20% in the diameter of measurable lesion); the peritoneal exudates change from trace to massive, with a change in the lesion of lymph duct from localized to extensive (or enough to change the

therapeutic method as described in the protocol); or pleural exudates change from trace to massive, with a spreading of involved lymph from original position to distal position (or necessary to change the therapeutic method as described in the protocol). In case of definite progress, PD should be overall judged for this patient at that time point. The objective assessment criteria had better be established for unmeasurable lesion (note: the added criteria should be reliable).

2.5 New Lesions

Since the emergence of new malignant lesions predicts a PD, it is very important to make some assessment of such new lesions. At present, there are no concrete criteria for imaging examination of lesions, but a new lesion can be found only in a definite way. E.g., PD shall not be based on the difference in imaging technique, the change in imaging morphology or the lesions other than tumor (e.g. some so-called new bone lesions are only the cure of original lesions or the recurrence of original lesions). When the baseline lesion is judged as PR or CR, such treatment is very important, e.g., the necrosis in one liver lesion may be judged as new cystic lesion in the CT report, which does not actually appear.

If a lesion is found during the follow-up but not found at the baseline examination, a new lesion should be identified, and PD is indicated. E.g., when a metastatic lesion is found at skull CT or MRI in the patients with visceral lesion found at baseline examination, such intracranial metastatic lesion is regarded as the basis for PD even though the skull examination is not made at baseline examination.

If a new lesion is not definite for some reasons (e.g., due to small dimension), a further treatment and follow-up evaluation should be made to determine whether this lesion is new. If a new lesion is verified through the repeated examination, the time of PD should be calculated by starting from the time of its preliminary finding.

For FDG-PET assessment of lesions, an additional examination is generally required for supplementary confirmation, and it is rational to evaluate the conditions of progress by combining the results of FDG-PET examination and supplementary CT examination (especially for new suspicious disease). A new lesion can be definitely judged through the FDG-PET examination according to the following criteria:

The results of baseline FDG-PET examination are negative but the results of subsequent FDG-PET examination are positive at follow-up, indicating a PD;

The baseline FDG-PET examination is not made and the results of subsequent FDG-PET examination are positive;

The new lesion is shown by the positive results of FDG-PET examination at follow-up, which consists with the results of CT examination, verifying a PD.

If the new lesion indicated by the positive results of FDG-PET examination at follow-up is not confirmed by the results of CT examination, CT examination should be made again for confirmation (if such new lesion is confirmed, the time of PD should be calculated by starting from the time of abnormal finding at previous FDG-PET examination).

If the lesion indicated by the positive results of FDG-PET examination at follow-up does not consist with that confirmed by the results of CT examination and the imaging showed no progression of such lesion, PD is not judged.

2.6 Explanation for Absence of Evaluation or Non-evaluation

If the imaging or examination of lesions cannot be made at a specific time point, this patient is judged as unevaluable at this time point. If only some lesions are evaluated at an evaluation, this patient is generally judged as unevaluable at this time point, unless the lesions of missing evaluation are verified through some evidences as no influence on the evaluation of efficacy response at a specified time point.

2.7 Special Hints for Efficacy Evaluation

When the nodular lesion is included into overall assessment of target lesion and this node is shrunk to normal size (< 10 mm), there should still be scanning report on the size of lesions. To avoid overestimation of the condition reflected on the basis of node size, the measurement results will be recorded, even though the node is normal. Just as mentioned above, for the patients judged as CR, 0 is not recorded in the eCRF.

If it is required to confirm response during trial, optimal efficacy evaluation will be complicated by repeated “immeasurable” time points. The analytical plan of study should specify that: while judging the efficacy, such missing data/evaluation can be clearly explained. E.g., in most studies, the response of PR-NE-PR in a certain patient can reflect that the efficacy is confirmed.

When the treatment has to be terminated after the overall deterioration of health conditions but not verified disease progression through the objective evidence, a symptomatic progress should be reported. Even after the termination of treatment, the conditions of objective progress should also be assessed as far as possible. The symptomatic deterioration is not the assessment description of objective response, but the reason for termination of treatment. The conditions of objective response in such patients will be assessed through the conditions of target and non-target lesions as stipulated in attached Table 1−3.

In special case, an early progress, early death and unevaluable condition can be judged, which should be definitely described in each protocol (according to the interval and cycle of treatment).

In some cases, it is very difficult to distinguish the localized lesions from normal tissues. When complete response is judged on the basis of such definition, a biopsy is recommended to be performed before the localized lesion is judged as CR. When a lesion fibrosis or scar formation is considered according to the abnormal results of imaging examination on localized lesions in some patients, FDG-PET is used as assessment criteria similar to biopsy for confirming the efficacy of CR. In this case, the application of FDG-PET should be described prospectively in the protocol, which is supported through the report on the specialty medical literatures for such conditions. However, to be noteworthy, a false positive result of CR judgment can be caused by the limitation of FDG-PET and biopsy (including their resolution and sensitivity).

Table 1 Time Point Response-Patients with Target Lesions (Including Non-target Lesions or Not)

Target lesion	Non-target lesion	New lesions	Overall response
CR	CR	None	CR
CR	Non CR/non PD	None	PR
CR	Unevaluable	None	PR
PR	Non-progress or incomplete assessment	None	PR
SD	Non-progress or incomplete assessment	None	SD
Incomplete assessment	Non-progress	None	NE
PD Any conditions Any conditions	Any conditions PD Any conditions	Y or N Y or N Yes	PD PD PD

Note: CR=complete response, PR=partial response, SD=stable disease, PD=progressive disease, NE= non-evaluable.

Table 2 Time Point Response-Patients with Only Non-target Lesions

Non-target lesion	New lesions	Overall response
CR	None	CR
Non-CR or non-PD	None	Non CR/Non PD
Incomplete assessment	None	Unevaluable
Indefinite PD	Y or N	PD
Any conditions	Yes	PD

Note: For the non-target lesions, “non-CR or non-PD” means an efficacy superior to SD. Since SD becomes more and more as endpoint index of efficacy evaluation, the efficacy of non-CR or non-PD is stipulated when the conditions of no measurable lesions are not specified.

In case of indefinite progress finding (e.g., very small uncertain new lesions and cystic degeneration or necrotic lesion of original lesions), the treatment can continue until the next assessment of efficacy. If PD is verified at the next assessment, the date of progression should be the date of previous suspicious progression.

Table 3 Best Overall Response for Which It Is Required to Confirm CR and PR

Overall response at the first time point	Overall response at the subsequent time points	Best overall response
CR	CR	CR
CR	PR	SD, PD, or PRa
CR	SD	If SD lasts for a sufficient time, SD is judged; otherwise PD is judged
CR	PD	If SD lasts for a sufficient time, SD is judged; otherwise PD is judged
CR	NE	If SD lasts for a sufficient time, SD is judged; otherwise NE is judged
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	If SD lasts for a sufficient time, SD is judged; otherwise PD is judged
PR	NE	If SD lasts for a sufficient time, SD is judged; otherwise NE is judged
NE	NE	NE

Note: CR is complete response, PR is partial response, SD is stable disease, PD is progressive disease, and NE is non-evaluable. Superscript “a”: If actual CR occurs at the first time point, then for any disease occurs at subsequent time points, its response evaluation is PD at subsequent time points (as the disease occurs again after CR), even though the response evaluation of the patient meets the PR criteria. The best response depends on whether SD appears within the minimum treatment interval. However, although CR is judged at the first time point, a small lesion sometimes seems to still appear under the scanning at the subsequent time points; and therefore, the efficacy at the first time point is actually judged as PR but not as CR. In this case, PR (but not CR) should be judged at the first time point, and PR is considered as the best response.

2.8 Confirmation of Efficacy Evaluation/Response Period

Efficacy Confirmation

In the non-randomized clinical study with tumor response as primary study endpoint, the efficacy of PR and CR should be confirmed to ensure that the efficacy is not caused by error in evaluation. However, in the studies with SD or PD as primary study endpoint, the efficacy should not be confirmed again, because such efficacy confirmation is useless for explaining the study results. In case of SD, at least one measurement complies with the SD criteria specified in the protocol at the minimum time interval (generally not less than 6−8 weeks) after start of the trial.

Duration of response

The overall duration of response is calculated as time duration from first conformance with the criteria of CR or PR (whichever is earlier) to first actual recording with recurrence or progression of disease (the minimum measured value recorded in the studies will be used as reference for the calculation of PD). The overall response time is the period from the time when the measurement first meets the CR criteria to the time when disease or progressive disease is first recorded.

Duration of stable disease

The duration of SD is calculated as time duration from start of treatment to PD (or from randomization in the randomized trial), with the minimum sum in the trial as reference value (and the sum of baseline level will be used as reference for the calculation of PD, if it is the minimum). The clinical relevance during stable disease varies in different studies and for different diseases. If, in a certain trial, the proportion of patients maintaining the minimum stable disease time is used as research endpoint, then the protocol shall describe particularly the minimum time interval between two measurements in the definition of SD.

Notes: The response period, the stable disease period and PFS are impacted by follow-up frequency after baseline evaluation. This guideline is not applicable to define the standard frequency of follow-up. The frequency of follow-up should be determined by various factors, including type/stage of disease, treatment cycle and standard specifications. However, if a comparison needs to be made between studies, the limitation in the accuracy of these measurement endpoints should be considered.

2.9 PFS/TTP

PFS or TTP is used as the primary endpoint in many trials for advanced tumors. If all the patients are required to have measurable lesions in the protocol, evaluation of progression will be relatively simple. More and more trials allow patients with or without measurable lesions to be enrolled. In such circumstance, the clinical finding of progression of disease must be described

carefully and clearly for patients without measurable lesions. As the date of progression often has a deviation in its determination, the time point for observation should be the same for each test group.

Annex 2 Child-Pugh Classification on Hepatic Function

Indicators	Score		
	1	2	3
Hepatic encephalopathy	None	Grade 1−2	Grade 3−4
Ascites	None	Mild	Moderate and above
Prolonged prothrombin time or INR	1−3 seconds	4−6 seconds	> 6 seconds
	< 1.7	1.7−2.3	> 2.3
Total bilirubin (μmol/L)	< 34	34−51	> 51
Serum albumin (g/L)	> 35	28−35	< 28

Note: 5−6 for Grade A; 7−9 for Grade B and 10−15 for Grade C;

Grade A and the better part of Grade B (i.e., score 7) can be enrolled.

Annex 3 Criteria for ECOG Performance Status

ECOG PS	Standard
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 housework, office work
2	Being capable of free walking and self-care, but loss of working ability, can get up for activities in no less than half time of a day.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Loss of self-care. Totally confined to bed or chair
5	Death

Annex 4 Recommended Rules for Management of Immune-related Adverse Events

1. Rules for management of gastrointestinal adverse event

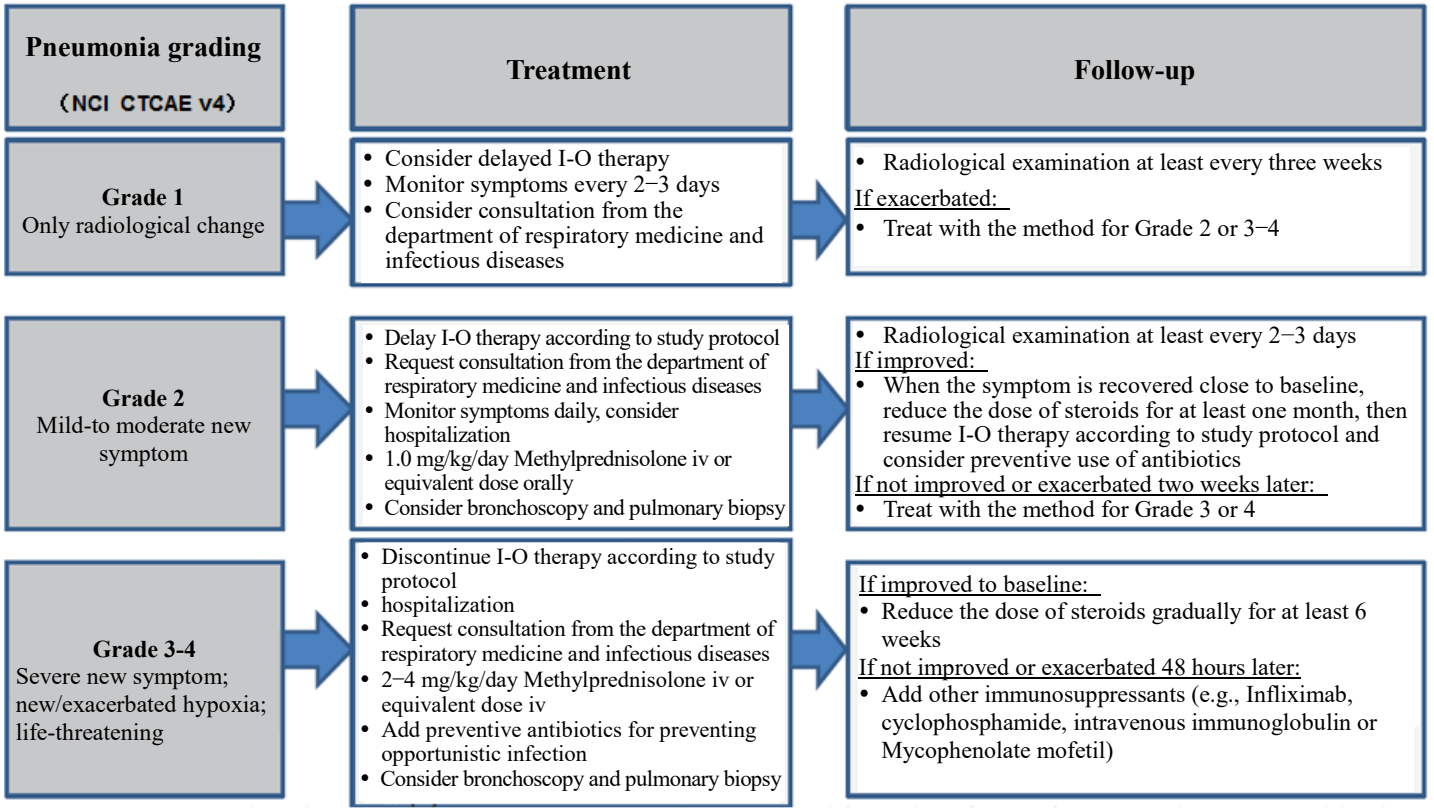
Non-inflammatory etiology should be excluded. Opioids/anesthetic may cover the symptom of perforation. Infliximab cannot be used in case of perforation/sepsis.

Diarrhea/colitis Grade (NCI CTCAE v4)	Treatment	Follow-up
Grade 1 Diarrhea: defecation frequency < 4 times/day beyond baseline Colitis: no symptom	• Continue I-O therapy according to the study protocol • Symptomatic treatment	• Close monitoring of symptoms exacerbated • Educate patients to report immediately in case of exacerbation If exacerbated: • Treat with the method for Grade 2 or 3/4
Grade 2 Diarrhea: defecation frequency 4−6 times/day beyond baseline; requiring intravenous infusion < 24 hours; no effect on daily living Colitis: abdominal pain; hematochezia	• Delay I-O therapy according to the study protocol • Symptomatic treatment	If improved to Grade 1: • Resume I-O therapy according to study protocol If lasting for > 5−7 days or recurrence: • 0.5−1.0 mg/kg/day Methylprednisolone iv or equivalent dose orally • When the symptom is improved to Grade 1, reduce dose of steroids for at least one month, and consider preventive use of antibiotics for
Grade 3-4 Diarrhea (Grade 3): defecation frequency ≥ 7 times/day beyond baseline; fecal incontinence; requiring intravenous infusion ≥ 24 hours; affect daily life Colitis (Grade 3): severe abdominal pain; indicative of medical intervention; peritoneal sign Grade 4: life-threatening, perforation	• Stop I-O therapy according to the study protocol • 1.0−2.0 mg/kg/day Methylprednisolone iv or equivalent dose iv drip • Addition of preventive antibiotics for prevention of opportunistic infection • Endoscopy of lower digestive tract considered	If improved: • Continue steroid treatment until recovery to Grade 1, then gradually reduce the dose of steroids for at least one month If lasting for > 3−5 days or recurrence post improvement: • Add Infliximab 5 mg/kg (in case of no contraindications). Note: Infliximab cannot be used in case of perforation or sepsis.

Once continuous clinical improvement is observed, the patients receiving intravenous steroids can switch to equivalent dose of oral corticosteroid (e.g., prednisone) at the same time or earlier than the dose is reduced gradually. When switching to the equivalent dose of oral corticosteroid, low bioavailability of oral corticosteroid should be considered.

2. Rules for management of pulmonary adverse events

Non-inflammatory etiology should be excluded. Symptomatic treatment should be given and I-O therapy should be continued in case of non-inflammatory etiology. Radiological evaluation will be performed and a consultation from the department of respiratory will be requested.



Once continuous clinical improvement is observed, the patients receiving intravenous steroids can switch to equivalent dose of oral corticosteroid (e.g., Prednisone) at the same time or earlier than the dose is reduced gradually. When switching to the equivalent dose of oral corticosteroid, low bioavailability of oral corticosteroid should be considered.

3. Rules for management of hepatic adverse events

Non-inflammatory etiology should be excluded. Symptomatic treatment should be given and I-O therapy should be continued in case of non-inflammatory etiology. Radiological evaluation will be considered to exclude obstruction/progression of tumor.

Elevated hepatic function Grade (NCI CTCAE v4)	Treatment	Follow-up
Grade 1 AST or ALT > ULN-3.0×ULN and/or T.bili >ULN-1.5×ULN	• Continue I-O therapy according to study protocol	• Continue monitoring of hepatic function according to study protocol If exacerbated: • Treat with the method for Grade 2 or 3/4
Grade 2 AST or ALT > 3.0 to ≤ 5×ULN and/or T.bili > 1.5 to ≤ 3×ULN	• Delay I-O therapy according to study protocol • Increase monitoring frequency to once every three days	If returned to baseline: • Resume routine monitoring, and I-O therapy according to study protocol If elevated for > 5−7 days or exacerbated: • 0.5−1 mg/kg/day Methylprednisolone iv or equivalent dose orally, if LFT is recovered to Grade 1 or baseline, reduce the dose of steroids for at least one month, use antibiotics for prevention of opportunistic infection, then resume I-O therapy according to study protocol
Grade 3-4 AST or ALT > 5×ULN and/or T.bili > 3×ULN	• Discontinue I-O therapy* • Increase monitoring frequency to once every 1−2 days • 1.0−2.0 mg/kg/day Methylprednisolone iv or equivalent dose iv • Add preventive antibiotics for prevention of opportunistic infection • Request a consultation from the department of gastroenterology	If returned to Grade 2: • Reduce the dose of steroids for at least one month If not improved, exacerbated or rebound > 3−5 days: • Add Mycophenolate mofetil 1g bid • If not relieved within 3−5 days, consider other immunosuppressants according to local guideline

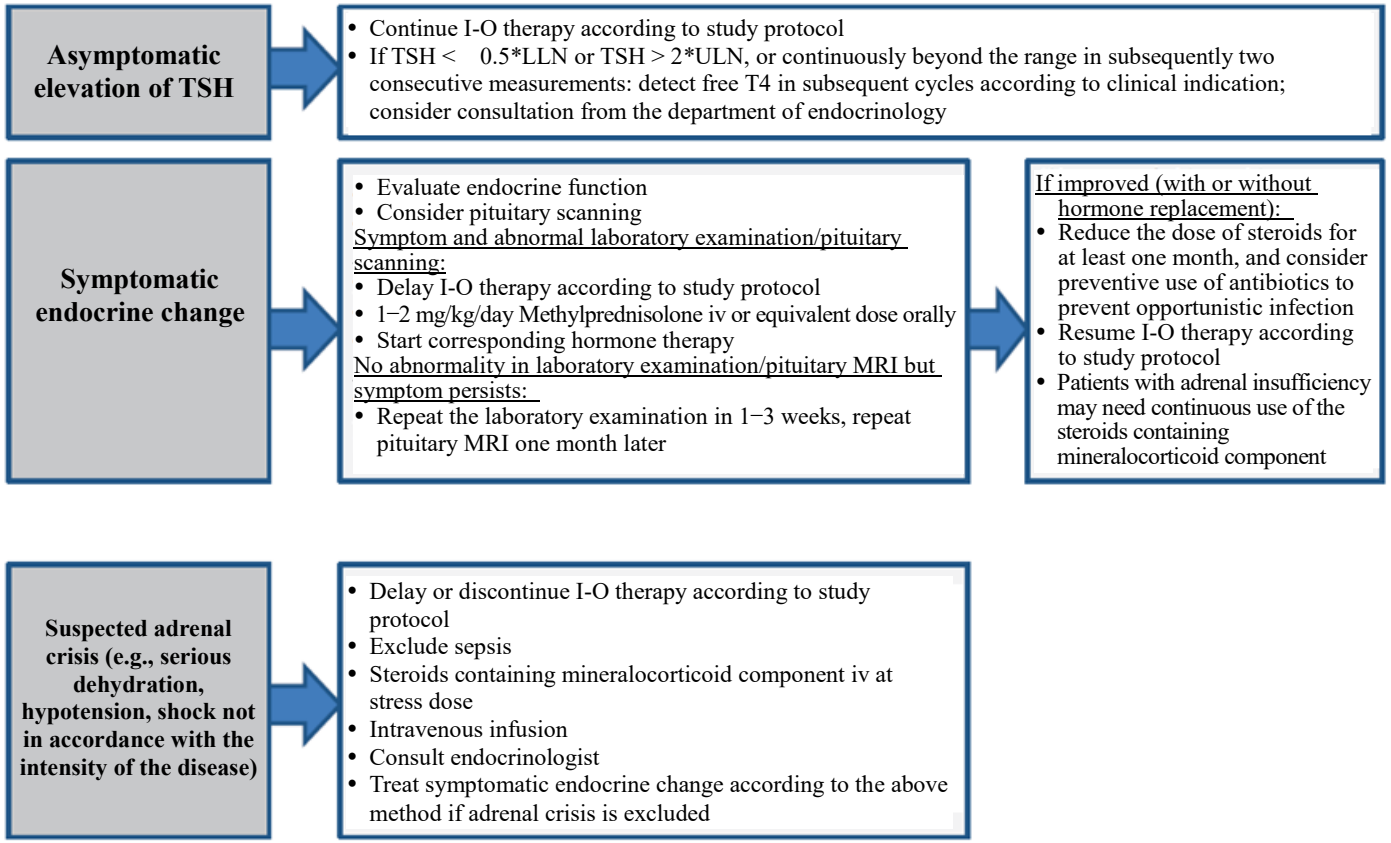
Once continuous clinical improvement is observed, the patients receiving intravenous steroids can switch to equivalent dose of oral corticosteroid (e.g., Prednisone) at the same time or earlier than the dose is reduced gradually. When switching to the equivalent dose of oral corticosteroid, low bioavailability of oral corticosteroid should be considered.

*In case of AST/ALT ≤ 8×ULN and T.bili ≤ 5×ULN, I-O therapy can be delayed rather than discontinued.

**For Grade 4 hepatitis, the recommended initial dose of Methylprednisolone iv drip is 2 mg/kg/day.

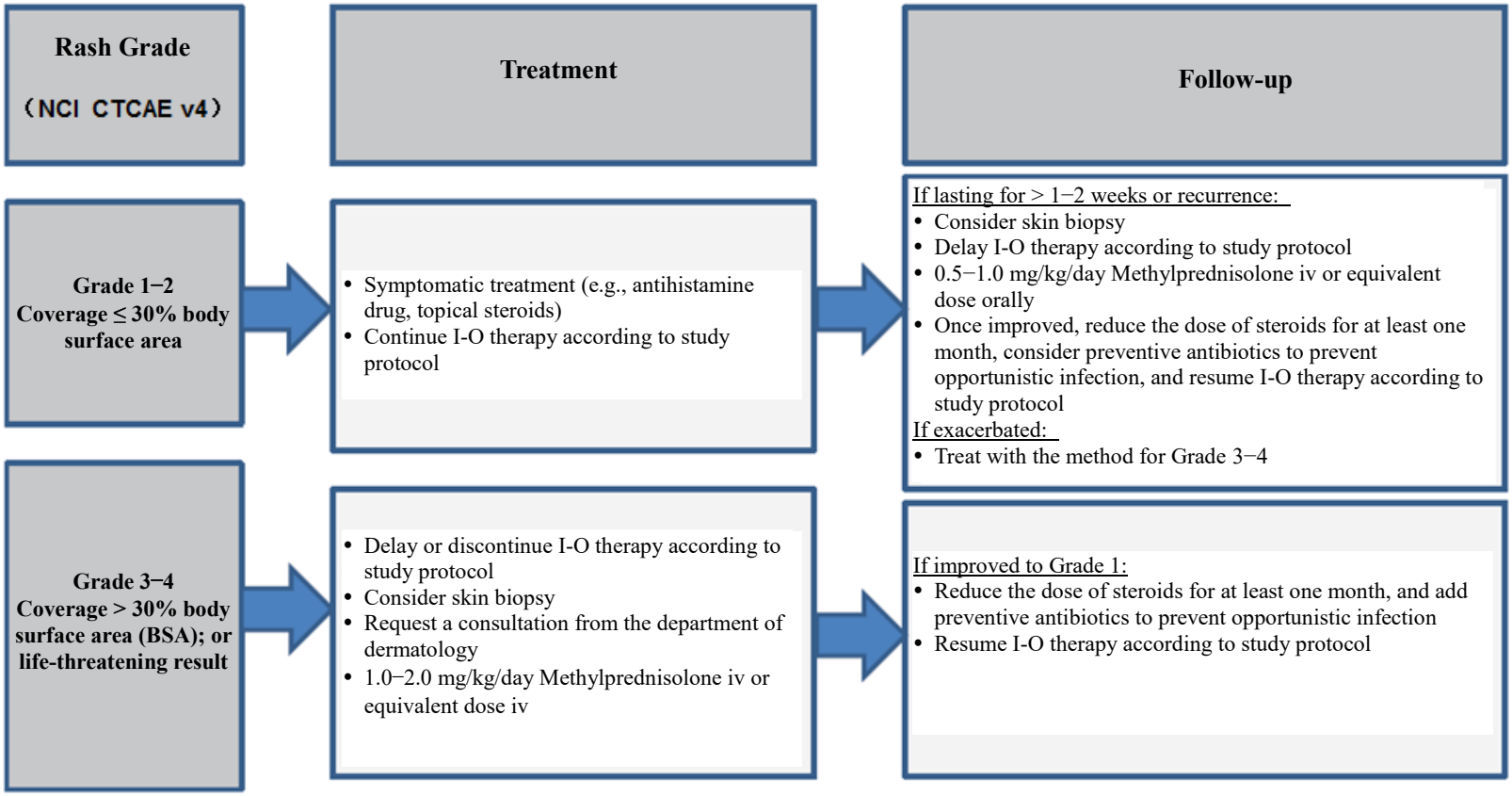
4. Rules for management of endocrine adverse event

Non-inflammatory etiology should be excluded. Symptomatic treatment should be given and I-O therapy should be continued in case of non-inflammatory etiology. Perimetry, consultation from the department of endocrinology and radiological examination will be considered.



Once continuous clinical improvement is observed, the patients receiving intravenous steroids can switch to equivalent dose of oral corticosteroid (e.g., Prednisone) at the same time or earlier than the dose is reduced gradually. When switching to the equivalent dose of oral corticosteroid, low bioavailability of oral corticosteroid should be considered.

5. Rules for management of cutaneous adverse events



Once continuous clinical improvement is observed, the patients receiving intravenous steroids can switch to equivalent dose of oral corticosteroid (e.g., Prednisone) at the same time or earlier than the dose is reduced gradually. When switching to the equivalent dose of oral corticosteroid, low bioavailability of oral corticosteroid should be considered.

(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.)