Title: A Single-Arm, Open-Label, Phase II Clinical Trial Evaluating Anti-PD-1 Antibody SHR-1210 in Combination with Apatinib Mesylate in Treatment of Advanced Hepatocellular Carcinoma
Clinical trial registration number: NCT03463876
Version Date: 29 May, 2019

A SINGLE-ARM, OPEN-LABEL, PHASE II CLINICAL TRIAL EVALUATING ANTI-PD-1 ANTIBODY SHR-1210 IN COMBINATION WITH APATINIB MESYLATE IN TREATMENT OF ADVANCED HEPATOCELLULAR CARCINOMA

Protocol No.: SHR-1210-APTN-II-208-HCC

Trial Phase II

Products: Recombinant humanized anti-PD-1 monoclonal antibody for injection

Apatinib mesylate tablets

Study Director: [redacted]

[redacted]

Version: 3.0

Date: 29 May, 2019

Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

[redacted]

VERSION HISTORY/REVISION HISTORY

Document	Date	Reasons for Revisions and Summary of Changes
Initial version	25 December, 2017	Not Applicable
Version 1.1	*12 March, 2018*	*Corrected errors related to biomarker testing, revised any inconsistencies.*
Version 2.0	*01 September, 2018*	*Revised inclusion and exclusion criteria; revised dose modifications and management of immune-related adverse events; revised the duration of adverse event follow-up, and time windows for examinations after treatment; revised the SOP for SAE reporting*
Version 2.1	*15 September, 2018*	*Revised the duration of adverse event follow-up*
Version 3.0	*29 May, 2019*	*Added secondary endpoints as per mRECIST criteria; Added other biomarker testing; Added the reporting procedures for exploratory biomarker study; Added the collection of cirrhosis and history of alcoholism; Added an explanation for the expanded sample size; Added a detailed description of statistics; Corrected descriptive errors*

Sponsor Signature Page

I have read and confirmed this trial protocol (protocol no.: SHR-1210-APTN-II-208-HCC, version: 3.0, date: 29 May, 2019) I agree to fulfill my duties in accordance with Chinese laws, the Declaration of Helsinki, the Chinese GCP, as well as this study protocol.

Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

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

Lead Institution Signature Page

Signature of Principal Investigator

I will carefully execute the duties as an investigator in accordance with the Chinese GCP, and personally participate in or directly lead this clinical study. We have read and confirmed this protocol (protocol number: SHR-1210-APTN-II-208-HCC, version number: 3.0, version date: 29 May 2019). I agree to execute relevant duties in accordance with the laws of China, the Declaration of Helsinki, Chinese GCP and this clinical study protocol. In addition, I confirm that any measure is subject to approval by the Ethics Committee before implementation, unless they must be taken to protect the safety, rights and interests of subjects.

[redacted]

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

Trial Site Signature Page

Signature of Principal Investigator

I will carefully execute the duties as an investigator in accordance with the Chinese GCP, and personally participate in or directly lead this clinical study. We have read and confirmed this protocol (protocol number: SHR-1210-APTN-II-208-HCC, version number: 3.0, version date: 29 May 2019). I agree to execute relevant duties in accordance with the laws of China, the Declaration of Helsinki, Chinese GCP and this clinical study protocol. In addition, I confirm that any measure is subject to approval by the Ethics Committee before implementation, unless they must be taken to protect the safety, rights and interests of subjects.

Study Site:

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

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Synopsis

Title	A Single-Arm, Open-Label, Phase II Clinical Trial Evaluating Anti-PD-1 Antibody SHR-1210 in Combination with Apatinib Mesylate in Treatment of Advanced Hepatocellular Carcinoma
Protocol Number	SHR-1210-APTN-II-208-HCC
Version	3.0
Sponsor	Jiangsu Hengrui Pharmaceuticals Co., Ltd.
[redacted]	[redacted]
Participating Sites	Approximately 25 sites
Study Objectives	**Primary Objective** To evaluate objective response rate (ORR) of SHR-1210 in combination with apatinib mesylate in patients with advanced hepatocellular carcinoma **Secondary Objectives** To observe and evaluate the progression-free survival (PFS), duration of response (DOR), time to response (TTR), disease control rate (DCR), overall survival (OS), and 9-month/12-month survival rates of SHR-1210 in combination with apatinib mesylate in patients with advanced hepatocellular carcinoma. To evaluate the safety of SHR-1210 in combination with apatinib mesylate in patients with advanced hepatocellular carcinoma **Exploratory Objectives** • To explore the anti-HBV effects of SHR-1210 in combination with apatinib mesylate; • To explore the biomarkers for predicting response;
Study Endpoints	**Primary Endpoint** Objective response rate (ORR) as assessed by independent review committee (IRC) as per RECIST 1.1. **Secondary Endpoints** Efficacy: • Objective response rate as assessed by investigator as per RECIST 1.1; • Progression-free survival (PFS), as per RECIST 1.1; • Time to response (TTR); • Duration of response (DOR); • Disease control rate (DCR); • 9-month survival rate; • 12-month survival rate; • Overall survival (OS);

	ORR, PFS, DOR, and DCR as assessed by IRC as per mRECIST criteria. Safety: • Incidences and severities of adverse events (AEs) and serious adverse events (SAEs), laboratory abnormalities, as per NCI-CTCAE v4.03; • Incidence of AEs resulting in dose interruption and discontinuation; **Exploratory Endpoints:** • Serum HBV DNA levels and the rate of HBsAg loss; • The relationship between response and PD-L1 expression levels, the proportion of positive cells, and/or other biomarkers such as baseline tumor mutational burden (TMB); • The relationship between baseline alpha fetoprotein level and response; • The relationship between response and baseline levels of acyl-CoA: sterol O-acyltransferase 1 (SOAT1), Niemann–Pick C1 protein (NPC1), and transforming growth factor beta (TGF-β)
Study Population	Patients with advanced hepatocellular carcinoma who have no applicable radical therapy, are refractory to sorafenib, or are unwilling or unable to afford sorafenib
Study Design	This is a single-arm, open-label, multi-center Phase II clinical trial intended to observe and evaluate the efficacy and safety of anti-PD-1 antibody SHR-1210 in combination with apatinib mesylate in patients with advanced hepatocellular carcinoma. The study focuses on patients with advanced hepatocellular carcinoma who have no applicable radical therapy, are refractory to sorafenib, or are unwilling or unable to afford sorafenib The primary efficacy endpoint is objective response rate (ORR). Approximately 136 subjects with advanced hepatocellular carcinoma are planned to be enrolled, of which at least 80 subjects must be refractory to sorafenib. The number of patients refractory to sorafenib can be increased to 120. After a written informed consent is provided, eligible subjects will receive apatinib 250 mg p.o., q.d. + SHR-1210 200 mg I.V., q2W, in treatment cycles of 4 weeks. Treatment will continue until the criteria for treatment discontinuation (as specified in the protocol) is met. After discontinuation, subjects will continue safety follow-ups and survival follow-ups. Subjects who discontinue the treatment due to reasons other than disease progression/death will also be followed for disease progression after discontinuation. Safety visits are conducted prior to SHR-1210 administration on D1 and D15 in each treatment cycle. After treatment begins, response will be assessed once every 2 weeks for the first 12 cycles, and once every 3 weeks from Cycle 12 until the end of treatment, withdrawal of informed consent, or death. This study will also explore the anti-HBV efficacy of the combination therapy as well as biomarkers for predicting treatment response. Subjects who have abnormal HBV tests at baseline will undergo regular HBV titer and HBsAg tests during the study. Subjects who provide informed consent for biomarker sample collection will have their blood and tumor specimens collected at baseline and during the study, including possibly a baseline biopsy.

Investigational Drug	Recombinant humanized anti-PD-1 monoclonal antibody for injection (SHR-1210) (Manufacturer: Suzhou Suncadia Biopharmaceuticals Co., Ltd.) Apatinib mesylate tablets (Manufacturer: Jiangsu Hengrui Pharmaceuticals Co., Ltd.)
Regimen	Intravenous drip infusion of SHR-1210 (premedication not required) at a fixed dose of 200 mg, or 3 mg/kg for subjects weighing < 50 kg at baseline. The drug is administered over a period of 30 minutes (at least 20 minutes and no more than 60 minutes), once every 2 weeks in treatment cycles of 4 weeks for up to 2 years. Apatinib is administered orally once a day after meal, and will be continuously given in cycles of 4 weeks.
Inclusion Criteria	Subjects must meet all of the following criteria to be eligible for this study: 1. Subjects must participate voluntarily and sign the informed consent form; 2. Aged ≥ 18 years old, males and females; 3. Pathologically confirmed advanced hepatocellular carcinoma (unresectable or metastatic), with at least one measurable lesion that has not been treated locally (must be ≥ 10 mm in longest diameter by spiral CT or ≥ 15 mm in shortest diameter for enlarged lymph nodes, as per RECIST 1.1); 4. Child-Pugh score ≤ 6 (Child-Pugh Class A); 5. BCLC Stage B-C; 6. Refractory to sorafenib or lenvatinib (disease progression or unacceptable toxicity), or unwilling or unable to afford sorafenib; 7. Ability to swallow tablets; 8. ECOG PS of 0-1 (refer to Appendix I for ECOG criteria); 9. Expected survival ≥ 12 weeks; 10. Vital organ functions meet the following requirements (not including any use of blood components and cell growth factors within 14 days before the first dose): • Absolute neutrophil count ≥ 1.5×10^9/L; • Platelets ≥ 80×10^9/L; • Hemoglobin ≥ 90 g/L; • Serum albumin ≥ 28 g/L; • Thyroid stimulating hormone (TSH) ≤ 1×ULN (In case of abnormalities, FT3 and FT4 levels should be measured at the same time. If FT3 and FT4 levels are normal, the subject can be enrolled); • Bilirubin ≤ 1.5 × ULN (within 7 days prior to the first dose); • ALT and AST ≤ 3 × ULN (within 7 days prior to the first dose); • AKP ≤ 2.5 × ULN; • Serum creatinine ≤ 1.5 × ULN;

	11. For female patients of childbearing potential or female patients who are not sterilized by surgical operations, they need to use a medically approved contraceptive measure (such as an intra-uterine contraceptive device, contraceptive pills or condoms) during the study treatment period and within 3 months after the end of the study treatment; For female patients of childbearing potential who are not sterilized by surgical operations, they must have a negative serum or urine HCG test result within 72 h prior to study enrollment; and they must not be in the lactation period; For male patients with partners of childbearing potential, they should take effective contraceptive measures during the study period and within 3 months after the last dose of SHR-1210;
Exclusion Criteria	Subjects meeting any of the following are not eligible to participate in this study: 1. Subjects with any active autoimmune diseases or a history of autoimmune diseases (including but not limited to the following: autoimmune hepatitis, interstitial pneumonia, uveitis, enteritis, hepatitis, hypophysitis, vasculitis, nephritis, hyperthyroidism; adult subjects with vitiligo or completely relieved childhood asthma can be enrolled if they do not require any intervention; subjects with asthma requiring medical intervention with bronchodilators cannot be enrolled); 2. Subjects who are currently using immunosuppressants, or systemic hormonal therapy for immunosuppression (>10 mg/day of prednisone or an equivalent dose of other therapeutic hormones) and still use the above drugs within 2 weeks prior to enrollment; 3. ≥ 2 lines of systemic treatments; 4. Subjects who have experienced severe allergic reactions to other monoclonal antibodies; 5. Patients with known CNS metastasis or hepatic encephalopathy; 6. Patients with liver tumor burden greater than 50% of total liver in volume, or patients who have previously undergone liver transplantation; 7. Patients with symptomatic ascites requiring paracentesis or drainage or patients who have undergone ascites drainage within the past 3 months, except for those with asymptomatic ascites of a small amount; 8. Patients with hypertension which cannot be well controlled by antihypertensives (systolic pressure ≥ 140 mmHg or diastolic pressure ≥ 90 mmHg); 9. Uncontrolled cardiac diseases or symptoms, such as: (1) NYHA Class II or above heart failure, (2) unstable angina, (3) myocardial infarction within the past year, (4) clinically significant supraventricular or ventricular arrhythmia requiring treatment or intervention, or (5) QTc > 450 ms (males), or QTc > 470 ms (females); 10. Abnormal coagulation function (INR > 2.0, PT > 16 s), bleeding tendency or receiving thrombolytics or anticoagulant therapy. Prophylactic use of low-dose aspirin or low molecular weight heparin is allowed;

	11. Clinically significant bleeding symptoms or clear bleeding tendency within 3 months prior to enrollment, such as coughing > 2.5 mL of blood daily, gastrointestinal bleeding, esophageal varices with bleeding risks, hemorrhagic gastric ulcer, or vasculitis. In case of positive fecal occult blood at baseline, a re-examination is needed, and a gastroscopy is required if it is still positive. The subject will be excluded if the gastroscopy indicates severe esophageal varices (except for those where such conditions have been ruled out by gastroscopy within 3 months prior to enrollment); 12. Events of arterial/venous thrombosis within 6 months prior to enrollment, such as cerebrovascular accidents (including transient ischemic attacks, cerebral hemorrhage, cerebral infarction), deep vein thrombosis, and pulmonary embolism; 13. Known hereditary or acquired hemorrhage and thrombophilia (such as hemophilia, coagulopathy, thrombocytopenia, etc.); 14. The routine urinalysis indicates that urine protein is ≥ ++ and confirms that 24h urine protein is ≥ 1.0 g; 15. Patients who have previously received radiotherapy, chemotherapy, hormone therapy or surgery that is less than 4 weeks before the study after the end of such treatments (last dose); molecular targeted therapy (including oral targeted drugs in other clinical trials) is less than 5 drug half-lives from the first dose; or patients with adverse events caused by previous treatment (except for alopecia) that have not returned to ≤ CTCAE grade 1; 16. Patients with active infection, fever ≥ 38.5 °C of unknown causes within 7 days prior to administration, or WBC count > 15×10^9/L at baseline; 17. Patients with congenital or acquired immunodeficiency (such as HIV positive); 18. HBV DNA > 2000 IU/mL (or 10^4 copies/mL); or HCV RNA > 10^3 copies/mL; or HBsAg+ and anti-HCV antibody positive; 19. Patients with other malignancies currently or within the past 3 years (except for cured basal cell carcinoma and cervical carcinoma in situ); 20. Patients with bone metastasis who have received a palliative radiotherapy in an area of > 5% of bone marrow area within 4 weeks prior to the participation in this study; 21. Patients who have previously received other anti-PD-1 antibody therapies or other immunotherapies targeting PD-1/PD-L1, or have previously received apatinib treatments; 22. Patients who have received live vaccines within less than 4 weeks before the first dose or would probably receive during the study; 23. Patients with other potential factors that may affect the study results or result in the premature termination of the study as determined by the investigator, such as alcoholism, drug abuse, other serious diseases (including mental illness) requiring concomitant treatment, serious laboratory abnormalities, accompanied by family or social factors that could affect the safety of the patients.

Discontinuation Criteria	Subjects must withdraw from/terminate the treatment when any one of the following conditions occur: 1. Subject withdraws informed consent and requests to withdraw from the study; 2. Imaging examinations show disease progression; As per RECIST 1.1, a confirmation is required 4-6 weeks after the first documentation of disease progression (except those with rapid progression or significant clinical progression); Subjects with confirmed disease progression may continue the treatment if clinically stable (as assessed by the investigator) until further radiographic progression; Definition of stable clinical symptoms: a. no significant clinical symptoms or changes in laboratory test indicators; b. no changes in the performance status score (deterioration); c. non-tumor rapid progression and tumor progression not involving important organs/sites (e.g., spinal cord compression); 3. Accumulated use of SHR-1210 for 2 years (no radiographic progression). Subjects who achieve radiologically confirmed CR may consider discontinuation after 12 cycles of treatment; 4. Subjects showing unacceptable toxicity; 5. Subjects with poor compliance; 6. Subjects lost to follow-up or became pregnant; 7. Other reasons for which the investigator consider a withdrawal necessary.
Criteria for Study Termination	The termination criteria of this study include but are not limited to the following: 1. Discovery of unexpected, significant or unacceptable risks to the subjects; 2. Major errors in the protocol are found during the implementation of the trial; 3. The investigational drug/treatment is ineffective, or continuing the trial is meaningless; 4. Termination as determined by the sponsor due to a severe delay in enrollment or frequent protocol deviations.
Safety Evaluation	The severity of adverse events is determined according to the CTCAE v4.0.3 criteria. The adverse event record form should be filled out correctly during the trial, including the occurrence time, severity, relevance to the investigational drug, duration, actions taken and outcomes of the adverse events.
Efficacy Evaluation	The primary and secondary efficacy endpoints of SHR-1210 in combination with apatinib mesylate in patients with advanced hepatocellular carcinoma are evaluated as per RECIST 1.1 criteria; Baseline lesions should be checked once every 2 cycles during the first 12 treatment cycles (bone scan will be performed if bone progression is suspected or CR is confirmed), and then once every 3 cycles thereafter. Appropriate examination may also be performed if new lesions are suspected. The first documentation of PR/CR in a subject must be verified 4 weeks ± 7 days later.

Determination of Sample Size	This is a single-arm study with its primary efficacy endpoint being ORR. This study includes patients refractory to sorafenib and patients not treated with sorafenib. The sample size of the two groups is calculated based on the hypothetic conditions below. **Patients refractory to sorafenib** Assuming that the treatment efficacy is less than 10% for standard treatment and is 25% for PD-1 plus apatinib, and a two-sided alpha = 0.05, then a total of 64 subjects are required to provide a power of 90%. If the dropout rate is 20%, 80 subjects should be enrolled. The number of patients who failed sorafenib can be increased to 120 at late stages in the trial to better determine the efficacy and safety of the investigational drug in this population. **Patients not treated with sorafenib** Assuming that the treatment efficacy is less than 15% for standard treatment and is 30% for PD-1 plus apatinib, and a two-sided alpha = 0.05, then a total of 56 subjects are required so that the half-width of the 95% confidence interval of overall ORR does not exceed 12%.
Data Analysis/ Statistics	Trial results are mainly analyzed using descriptive statistics. Numerical data will be summarized in means, standard deviations, medians, maximums, and minimums. Categorical data will be summarized in frequencies (proportions), percentages, and confidence intervals. Statistical analysis will be performed using the SAS 9.4 or above. Safety analysis: Descriptive statistical analysis is primarily used to analyze the adverse events, serious adverse events and adverse reactions in each population (the adverse reactions are defined as adverse events that are "definitely related, possibly related, and not assessable" to the investigational drug). Laboratory test results describe the baseline and the worse on-treatment value. Efficacy analysis: Point estimates and 95% CI will be used for efficacy endpoints such as objective response rate (ORR) and disease control rate (DCR). The confidence intervals are estimated using the Clopper-Pearson method. PFS, DOR, OS, and 9-month and 12-month survival rates, as well as their respective 95% CIs will be estimated using the Kaplan-Meier method. TTR is described using mean, standard deviation, median, maximum, and minimum. Other analyses: Serum HBsAg and alpha-fetoprotein (AFP) levels are summarized descriptively; SHR-1210-related solid tumor markers, such as expression levels of PD-L1 or other biomarkers in tumor tissues, will also be analyzed using descriptive statistics. The relationship between response and baseline levels of acyl-CoA: sterol O-acyltransferase 1 (SOAT1), Niemann–Pick C1 protein (NPC1), and transforming growth factor beta (TGF-β) will be explored.

End of Study	At 6 months after the first dose of the last subject, the primary and secondary endpoints of the study are statistically analyzed. All subjects will be followed up until 12 to 24 months after the first dose of the last subject, and supplemental analysis of the primary and secondary endpoints of the study will be performed after the follow-up. After the end of the study, if the subjects may continue to benefit from the investigational drug, the treatment can be continued until the criteria for discontinuation are met. The occurrence of SAEs will be collected and recorded during the treatment and after the last dose according to the protocol.
Study Duration	Anticipated enrollment of the first subject: March 2018 Anticipated enrollment of the last subject: December 2018 Anticipated study completion date: December 2019

Procedures of the Trial

Item	Screening Period		Treatment Period (28 days/cycle)				Post-Treatment		Survival Follow-Up
			Cycle 1		Cycles 2–26				
	Within 3 weeks before dosing	Within 1 week before dosing	Day 1	Day 15 (± 3 d)	Day 1 (± 3 d)	Day 15 (± 3 d)	End of Treatment/Withdrawal (+3d)	End of Treatment Visit (± 3 d)	Every 1 month (± 3 d)
Baseline Data									
Informed consent	×								
Demographics	×								
Tumor history	×								
Past medical history[1]									
Concomitant medication[2]	×	×	×						
History of alcoholism	×								
Laboratory Test									
Hematology[3]		×		×	×	×	×	×	
Blood biochemistry[4]		×		×	×	×	×	×	
Urinalysis[5]		×		×	×	×	×	×	
Routine stool test[6]		×		×	×		×		
Coagulation function test[7]		×		×	×		×		

Item	Screening Period		Treatment Period (28 days/cycle)				Post-Treatment		Survival Follow-Up
			Cycle 1		Cycles 2–26				
	Within 3 weeks before dosing	Within 1 week before dosing	Day 1	Day 15 (± 3 d)	Day 1 (± 3 d)	Day 15 (± 3 d)	End of Treatment/Withdrawal (+3d)	End of Treatment Visit (± 3 d)	Every 1 month (± 3 d)
Thyroid function test[8]	×				×		×		
Alpha-fetoprotein		×	× (D1 ± 7 d every 2nd cycle)				×		
Examination of hepatitis B and hepatitis C[9]	×		× (D1 ± 7 d every 2nd cycle)				×		
Pregnancy test[10]		×					×		
Myocardial zymogram[11]		×					×		
Pituitary adrenal axis test[12]	×								
HIV test	×								
Clinical Evaluation and Examination									
Adverse event[13]	From informed consent to 30 days after the last dose								
Vital signs[14]		×	×	×	×	×	×	×	
Physical examination[15]		×	×	×	×	×	×	×	
ECOG PS		×			×		×	×	
ECG[16]		×		×	×		×		
Echocardiography[17]		×					×		

Item	Screening Period		Treatment Period (28 days/cycle)				Post-Treatment		Survival Follow-Up
			Cycle 1		Cycles 2–26				
	Within 3 weeks before dosing	Within 1 week before dosing	Day 1	Day 15 (± 3 d)	Day 1 (± 3 d)	Day 15 (± 3 d)	End of Treatment/Withdrawal (+3d)	End of Treatment Visit (± 3 d)	Every 1 month (± 3 d)
Blood pressure monitoring[18]	×	×		×	×	×	×		
Investigational Drug									
Administration of SHR-1210[19]			×	×	×	×			
Apatinib administration[20]			**Oral administration once a day after meal**						
Apatinib dispensing/retrieval[21]			×		×		×		
Imaging Evaluation									
Imaging examination[22]	×		**Once every 2 cycles in the first 12 cycles of dosing, followed by once every 3 cycles**				×		
Follow-Ups After Discontinuation									
Time to progression[23]							Imaging evaluations are performed once every 3 months (± 7 d) until disease progression or start of new anti-tumor treatments (for subjects with non-radiological PD)		
Death[24]									×
Blood Sampling and Tumor Tissue Sampling									
Blood/tissue sampling for biomarkers[26]	×								

Notes:

[1] Tumor history/past medical history: tumor diagnosis, surgical history, interventional therapy, local ablation therapy, systemic treatment, radiation therapy, as well as past treatments of other conditions, history of cancers other than HCC.

[2] Concomitant medications and treatments received within 30 days prior to the first dose and during the study period should be recorded. Once a subject discontinues the investigational treatment, only concomitant medication or treatment for new or unresolved treatment-related adverse events are recorded, until 30 days after the last dose.

[3] Routine blood test: WBC, neutrophils, lymphocytes, RBC, hemoglobin, and platelets. Performed within 7 days prior to enrollment, on Day 15 of Cycle 1, Day 1 and 15 of subsequent cycles, at the end of study, and 30 days after the end of treatment.

[4] Blood biochemistry: total bilirubin, direct bilirubin, ALT, AST, AKP, γ-GT, total protein, albumin, urea/blood urea nitrogen, creatinine, uric acid, fasting blood glucose, TG, cholesterol, potassium, sodium, chlorine, calcium, phosphorus, blood lipase (only during the screening period and in case of subsequent abdominal pain, abdominal distension and other symptoms of suspected pancreatitis), blood amylase (only during the screening period and subsequent abdominal pain, abdominal distension and other symptoms of suspected pancreatitis). It is carried out within 7 days before enrollment, on Day 15 of Cycle 1, Day 1 and Day 15 of subsequent cycles, at the end of study, and 30 days after the treatment.

[5] Urinalysis: Urine protein, urine glucose, urine occult blood, urine red blood cells, and urine white blood cells. If 2 consecutive semi-quantitative tests show proteins of 2+, or a semi-quantitative test shows proteins > 2+, a quantitative 24-h urine protein test is required. Performed within 7 days before the enrollment, on Day 15 of Cycle 1, Day 1 and Day 15 of subsequent cycles, at the end of study, and 30 days after the treatment.

[6] Routine stool test: Patients with positive fecal occult blood must be retested. If fecal occult blood is confirmed, then a gastroscopy is performed. If fecal occult blood occurs during the course of the study, the subject should undergo a gastroscopy if deemed necessary by the investigator. Performed within 7 days before enrollment, on Day 15 of Cycle 1 and Day 1 of subsequent cycles, and at the end of study.

[7] Coagulation function: INR, APTT, PT, FIB; Performed within 7 days before enrollment, on Day 15 of Cycle 1 and Day 1 of subsequent cycles, and at the end of study.

[8] Thyroid function test: Including serum FT3, FT4 and TSH. Performed within 21 days before dosing, on Day 1 of Cycle 2, once every 3 cycles thereafter, and at the end of the study.

[9] Hepatitis B and C test: Subjects with abnormal hepatitis B markers should undergo quantitative tests of HBV DNA and HBsAg. Subjects with positive anti-hepatitis C virus (HCV) antibodies must be tested for HCV titer (HCV RNA). Subjects with abnormal baseline HBsAg must be tested for HBV DNA and HBsAg levels on D1 ±7 d every 2nd cycle and at the end of study.

[10] Pregnancy test: The urine pregnancy test shall be performed 72 h before the first dose in women of childbearing potential. If positive, a serum pregnancy test shall be performed. If necessary, a re-test can be performed for confirmation. By considering the subjects' condition, the test can be performed as needed and at the end of the study.

[11] Myocardial zymography: performed within 7 days prior to enrollment, when deemed necessary by the investigator, and at the end of treatment/upon withdrawal.

[12] Pituitary adrenal axis test: Including ACTH, cortisol, and follicle stimulating hormone, which shall be performed within 21 days before dosing during the screening period.

[13] Adverse events: Adverse events (AEs) should be recorded from signing the informed consent until at least 30 days after the last dose. SAE and irAE observed within 90 days after the last dose of SHR-1210 should be followed up. If the subjects start a new anti-tumor treatment, they should be followed-up until they start the tumor treatment (if the tumor treatment starts within 30 days after the last dose, the subjects should be followed-up until at least 30 days after the last dose; if the tumor treatment starts over 30 days after the last dose, the subjects should be followed-up until they start the new tumor treatment).

[14] Vital sign examination: Body temperature, pulse, respiratory rate, and blood pressure. Performed within 7 days before enrollment, on Day 1 and Day 15 of Cycle 1, Day 1 and Day 15 of subsequent cycles, at the end of study, and 30 days after treatment.

[15] Physical examination: Examination of major body systems (head and face, skin system, lymph nodes, eyes, ears, nose, throat, oral cavity, respiratory system, cardiovascular system, abdomen, urogenital system, musculoskeletal system, nervous system and mental state) is performed within 7 days before enrollment, on Day 1 and Day 15 of Cycle 1, Day 1 and Day 15 of subsequent cycles, at the end of study, and 30 days after the treatment.

Note: Except for baseline examinations, only abnormal findings are documented in the eCRF rather than the entire physical examination (although a comprehensive physical examination is still required).

[16] 12-Lead ECG: Performed within 7 days before enrollment, on Day 15 of Cycle 1 and Day 1 of subsequent cycles, and at the end of study. Abnormalities in ECG must be confirmed twice via additional ECG tests.

[17] Echocardiography: performed within 7 days prior to the enrollment and at the end of study, and when clinically significant abnormalities are found during the study.

[18] Blood pressure monitoring: The blood pressure measurement of subjects is performed by the investigator or study nurse during the screening period; during each blood pressure measurement, smoking and coffee are prohibited for 30 min before the measurement, and subjects should at least rest for 10 min, and the sitting position is taken during the measurement by placing the elbow at the same level as the heart. Each blood pressure measurement is taken on the same side of the body; during the trial, the blood pressure monitoring is performed by the subjects themselves and recorded in their diary card.

Blood pressure is detected at least 3 times a week in the first 2 cycles. If the blood pressure is abnormal, the measurement is carried out every day; If the blood pressure is normal, the blood pressure measurement is carried out twice a week after 2 cycles; In addition, the blood pressure is measured by the investigator or study nurse during each follow-up.

[19] SHR1210 administration: SHR-1210 is administered via intravenous infusion (without prophylactics) at a fixed dose of 200 mg within 30 min (not less than 20 min, no more than 60 min), once every 2 weeks. Each cycle contains 4 weeks and the longest dosing period is 2 years. After 12 cycles, the administration can be stopped if the imaging examination confirms the subjects as CR.

[20] Apatinib is administered orally once a day after meal, and will be continuously given in cycles of 4 weeks.

[21] Dispensation and return of apatinib. Apatinib is dispensed on Day 1 of Cycle 1. From Day 1 of Cycle 2, the return and dispensation of apatinib are done on Day 1 of each cycle. The remaining drugs are returned first to verify the dose actually taken before new investigational drugs are dispensed.

[22] Imaging examination: including CT or MRI of the chest, abdomen and pelvis, and enhanced MRI or CT of brain at screening to exclude brain metastasis. Tumor assessments performed within 3 weeks prior to treatment can be accepted as the baseline assessment. CT/MRI results prior to informed consent may be used for tumor assessments at screening if requirements are met. A bone scan is required if bone metastasis is suspected. A contrast-enhanced MRI or CT of the brain must be performed for those suspected of brain metastasis.

During the treatment period, the imaging examination should be performed under the same conditions as those of the baseline examination (layer thickness of the scan, use of contrast agent, etc.), and the baseline lesions should be checked every 2 cycles during the first 12 treatment cycles (bone scan will be performed if bone progression is suspected or CR is confirmed), and then once every 3 cycles thereafter. Appropriate examination may also be performed if new lesions are suspected. The first documentation of PR/CR in a subject must be verified 4 weeks ±7 days later. A confirmation is required 4-6 weeks after the first documentation of disease progression as per RECIST 1.1 (except those with rapid progression or significant clinical progression);

The window period for imaging examination schedule is ±7 days. Unscheduled imaging examinations can be perf ormed when progressive disease is suspected (such as worsening of symptoms).

[23] In addition to the progressive disease as evidenced by imaging, subjects who have ended the trial treatment for other reasons must be evaluated at the end of treatment if the imaging examination is not performed within 4 weeks prior to the end of the trial. At the same time, tumor efficacy is followed up every 3 months after the end of the trial until records confirm the progressive disease or initiation of new tumor treatments.

[24] Survival follow-up: After the trial treatment is discontinued, the survival status and subsequent anti-cancer treatment can be collected through clinical or telephone follow-ups every 1 month until death.

[25] 10 mL of blood, and paraffin-embedded tumor tissue specimens or fresh biopsy samples (size of a soybean) are collected. At least 10 slides are required, including 3-5 slides of 3-5 μm thickness for PD-L1, SOAT1, NPC1, and TGF-β testing, and 5-8 paraffin sections (paraffin blocks may be collected directly, without mounting onto slides) of 8-10μm thickness, otherwise fresh biopsy samples (pea-size) are required for testing biomarkers such as tumor mutational burden (TMB). See the laboratory manual for blood and tumor tissue sampling/sample collection, and disposal.

Abbreviations

Abbreviations and Terms	Full Name
ADA	Anti-drug antibody
ADRs	Adverse drug reactions
AE	Adverse event
AFP	A-fetoprotein
AKP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under curve
BP	Blood pressure
BUN	Blood urea nitrogen
B scan	B-mode ultrasound
Ca	Calcium
CFDA	China Food and Drug Administration
Cl	Chlorine
Cr	Creatinine
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DBIL	Direct bilirubin
DCR	Disease control rate
DOR	During of response
DLT	Dose limited toxicity
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data collection
FAS	Full analysis set
FIB	Fibrinogen
FDA	Food and Drug Administration
FT3	Free triiodothyronine

Abbreviations and Terms	Full Name
FT4	Free thyroxine
GCP	Good Clinical Practice
Glu	Glucose
Hb	Hemoglobin
HBV	Hepatitis B virus
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
irAE	Immune-related adverse event
INR	International Normalized Ratio
IRB	Institutional review board
ITT	Intend to treat
K	Potassium
LLN	Lower limits of normal
mPFS	Median progression-free survival
MRI	Magnetic Resonance Imaging
MTD	Maximum tolerated dose
Na	Sodium
NCCN	National Comprehensive Cancer Network
NCI-CTC	National cancer institute Common Terminology Criteria
NPC1	Niemann-Pick C1
ORR	Objective response rate
OS	Overall survival
P	Phosphorus
PD	Progressive disease
PD-1/PD-L1	Programmed death 1/programmed death ligand 1
PFS	Progression-Free-Survival
PK	Pharmacokinetics
PLT	Platelet
PPS	Per-Protocol Set
PR	Partial response
PT	Prothrombin time
QoL	Quality of life
RBC	Red blood cell
RO	Receptor occupancy
RECIST	Response evaluation criteria in solid tumors
SAE	Serious adverse event

Abbreviations and Terms	Full Name
SAS	
SD	Stable disease
SOAT1	Sterol O-acyltransferase 1
SOP	Standard Operation Procedure
SS	Safety analysis set
TB	Total bilirubin
TC	Total cholesterol
TCM	Traditional Chinese Medicine
TG	Triglyceride
TGF-β	Transforming growth factor-β
TP	Plasma total protein
TMB	Tumor mutant burden
TSH	Thyroid-stimulating hormone
TTR	Time to response
UA	Blood uric acid
UICC	Union for International Cancer Control
ULN	Upper limit of normal
WBC	White blood cell
γ-GT	γ-Glutamyltransferase

1. INTRODUCTION

1.1. Background

In recent years, significant progress has been made in cancer treatment, and small molecular targeted therapies inhibiting internal driving factors of tumor angiogenesis and cancer cell growth, as well as immunotherapies enhancing anti-cancer immunity of the patients, have been approved by regulatory agencies in many countries. With the deepening of the understanding of the body's immune system and the rapid development of biotechnology, the immunotherapy has become an important means of cancer treatment, and it is occupying an increasingly important position in the comprehensive treatment system of tumors.

Targeted therapy may result in significant clinical response for numerous types of tumors. However, the duration of response is short, and the initial responses are usually accompanied by tumor immune escape and clinical recurrence within a few months. In comparison, immunotherapy is also applicable to many types of cancers, and can provide a longer duration of response in some patients. Contrary to standard chemotherapy or targeted therapy which directly acts on the cancer cells, immunotherapy not only kills cancer cells directly, but more importantly, also enhances the immune response of the body by acting on the immune system and ultimately prolonging the survival of patient.

Programmed cell death protein 1, or PD-1, is a negative costimulatory molecule discovered in recent years. PD-1's ligands include PD-L1 and PD-L2, which can bind specifically to PD-1. Through high expression of PD-L1, cancer cells bind to the PD-1 molecules on T lymphocytes, which transmit a negative regulatory signal, resulting in the induction of apoptosis and immune incompetence of tumor antigen-specific T cells, allowing the cancer cells to evade immune monitoring and killing. PD-1 inhibitors are new immunotherapeutic drugs of interest.
By blocking the PD-1/PD-L1 signaling pathway, the anti-tumor activity of T lymphocytes is up-regulated, resulting in apoptosis of the cancer cells.

Since 2014, the U.S. Food and Drug Administration (FDA) has approved anti-PD-1 monoclonal antibodies, nivolumab from BMS and pembrolizumab from Merck for the treatment of patients with advanced melanoma, non-small cell lung cancer, renal cell carcinoma, head and neck cancer, Hodgkin's lymphoma, as well as HCC previously treated with sorafenib, including those with advanced disease, refractory to standard treatment, or without effective treatment options.
They are also used as first or second line treatment currently. In addition, due to its long-lasting efficacy and relatively mild adverse reactions, anti-PD-1 monoclonal antibodies have been studied in hundreds of clinical trials internationally for advanced solid tumors and malignant hematologic diseases, including monotherapy and combination therapy. Results have all shown better efficacy and longer survival compared to existing treatments.

On 23 Sept., 2017, the FDA approved nivolumab for the treatment of patients with HCC previously treated with sorafenib based on data from trial Checkmate-040, marking the beginning of the era of immunotherapy for HCC. This was a single-arm, dose-escalation and dose-expansion Phase I/II clinical trial in advanced HCC: a total of 262 subjects (48 in the dose-escalation stage and 214 in the dose-expansion stage) with or without chronic hepatitis were enrolled to evaluate the efficacy and safety of nivolumab.

In the dose-escalation stage, subjects received nivolumab 0.1-10 mg/kg one every 2 weeks. In the dose-expansion stage, subjects received nivolumab 3 mg/kg once every 2 weeks. The primary endpoints were safety and tolerability for the dose-escalation stage and ORR for the dose-expansion stage. Results showed that the nivolumab is safe and well-tolerated. The ORR was 15% in the dose-escalation stage and 20% in the dose-expansion stage. Most importantly, results showed that nivolumab is also effective in patients with Hepatitis B.

Subjects who had not received sorafenib had a 12-month survival of 73% using nivolumab as first-line treatment. Subjects previously treated with sorafenib had a 12-month survival of 58-60% with nivolumab.

Despite the unprecedented success of such therapies, it should not be overlooked that a considerable proportion of patients still do not respond to the therapy. From the current point of view, the combination therapy will be one of the inevitable trends in the future development of immunotherapy of tumors. How to carry out the combination therapy is a problem to be solved by the medical community.

There are currently a large number of Phase I/II clinical trials that combine targeted therapy with immunotherapy. The rationale supporting these combination therapies is that the combination of the two therapies combines different immunological and tumor biological mechanisms that enhance the anti-cancer activity; In addition, some evidence suggests that targeted therapies can enhance certain aspects of the "cancer-immune cycle" (such as tumor antigenicity, T cell initiation/transport/infiltration, etc.) to synergistically enhance the efficacy of the immunotherapy. In particular, targeted therapies targeting the mitogen-activated protein kinase (MAPK) and the vascular endothelial growth factor (VEGF) pathways, including drugs such as sunitinib, can have a direct impact on tumor cell growth and tumor angiogenesis, as well as on tumor antigenicity and intratumoral T cell infiltration. Their impact on the patient's immune response is beyond their role in tumor biology, providing a strong basis for the combination therapy.

Current combination therapies have largely focused on advanced melanoma, lung cancer, and renal cell carcinoma. Good clinical prospect is also seen in the treatment of liver cancer, ovarian cancer, colorectal cancer, head and neck cancer, and Hodgkin's lymphoma. Some key factors should be considered in the clinical development of combination therapies, such as optimizing dosing regimens, minimizing treatment-related toxicity, selecting appropriate endpoints to assess the efficacy, and so on.

This clinical trial involves recombinant humanized anti-PD-1 monoclonal antibody injection (SHR-1210), a new class 1 therapeutic biological product developed by Jiangsu Hengrui Pharmaceuticals Co., Ltd. that has not been marketed both in China and abroad. Preclinical trial data show that SHR-1210 has comparable *in vivo* efficacy and safety with those of similar drugs abroad. Since 2015, Jiangsu Hengrui Pharmaceuticals Co., Ltd. conducted Phase I/II clinical trials of several types of tumors in both Australia and China, and preliminarily validated the safety, tolerability and efficacy of SHR-1210 monotherapy in the treatment of advanced solid tumors. For details regarding SHR-1210, please refer to the SHR-1210 Investigator's Brochure provided by the sponsor.

This study also involves apatinib mesylate (trade name: Aitan), which was launched in 2014 by Jiangsu Hengrui Pharmaceuticals Co., Ltd. Apatinib is a small molecule targeted medicine that is a vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor. Apatinib exerts its anti-angiogenic effect mainly by inhibiting VEGFR. Preclinical studies have shown that it's superior to similar product in anti-tumor effect. In 2014, apatinib was approved for patients with refractory or relapsed advanced gastric adenocarcinoma or gastroesophageal junction adenocarcinoma who have previously been treated with at least 2 systemic chemotherapies.

The recommended dosage of apatinib mesylate in patients with refractory or relapsed advanced gastric adenocarcinoma or gastroesophageal junction adenocarcinoma previously treated with at least 2 systemic chemotherapies is 850 mg orally (p.o.) once daily (q.d.). The treatment is in cycles of 28 days (not including treatment interruption), and is continuously given until disease progression or unacceptable toxicity. Treatment can be interrupted (no more than 2 weeks) or the dose can be adjusted to 750 or 500 mg in case of Grade 3/4 hematologic or non-hematologic toxicities.

Primary hepatocellular carcinoma (HCC) is a typical hypervascular tumor. Its occurrence, development, metastasis, and invasion are all closely related to angiogenesis. A randomized, open-label, multi-center, Phase II clinical trial evaluating apatinib mesylate in advanced hepatocellular carcinoma was conducted from 2010 to 2013, led by the 81th Hospital of the Chinese People's Liberation Army. A total of 121 subjects received the medication. In the full analysis set, the median time to progression (mTTP) was 4.21 months and median overall survival (mOS) was 9.71 months in the 850 mg group. The mTTP was 3.32 months and mOS was 9.82 months in the 750 mg group. There were no statistically significant differences in mTTP and mOS between the 850 mg and 750 mg groups. The incidence of adverse reactions was 95.71% in the 850 mg group and 90.20% in the 750 mg group. The incidence of severe adverse reactions was 58.57% and 58.82%, respectively. The difference was not statistically significant. Therefore, 750 mg was the recommended dose for Phase III clinical trials due to its superior tolerability. The recommended dosing regimen is 750 mg, p.o., q.d., continuous administration in

cycles of 28 days (not including treatment interruption), until disease progression or unacceptable toxicity. Treatment can be interrupted (no more than 2 weeks) or the dose can be adjusted to 500 or 250 mg in case of Grade 3/4 hematologic or non-hematologic toxicities.

A randomized (2:1), open-label, placebo-controlled, multi-center, Phase III clinical trial evaluating the efficacy and safety of apatinib as second-line treatment of advanced HCC is currently underway. Patients with advanced HCC who failed sorafenib or systemic chemotherapy or patients with relapse or unacceptable toxicity were recruited. As of December 2017, a total of 400 subjects were enrolled. Adverse events that have been observed include proteinuria, elevated blood pressure, thrombocytopenia, hand-and-foot syndrome, and elevated total bilirubin. For details regarding apatinib mesylate, please refer to the prescribing information for apatinib mesylate and the Investigator's Brochure provided by the sponsor.

Based on data from large-scale randomized, controlled trials described above, the maximum tolerated dose for apatinib mesylate monotherapy is 850 mg, q.d., and the minimum effective dose is 250 mg, q.d. Main adverse reactions include hand and foot skin reactions, hypertension, elevated transaminase, elevated bilirubin, decreased WBC, thrombocytopenia, diarrhea, esophagitis, nausea, and asthenia. Most were mild to moderate reactions. Since toxicity and efficacy may be compounded with combination therapy, 250 mg q.d. is selected as the dose for combination therapy. The dosing frequency for apatinib may be adjusted subsequently based on subject's tolerability and adverse reactions.

This study explores a new combination therapy, which is urgently needed in clinical practice, not only for laying a foundation for future studies, but also for exploring biomarkers related to cancer immunity. Therefore, it has important scientific significance and clinical value.

1.2. Scientific Basis

Primary liver cancer is a common cancer in China. It currently ranks the 4th among common malignant tumors and the 3rd among causes of cancer deaths, and heavily threatens the lives and health of Chinese people. Primary liver cancer mainly includes hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC), and a mixed HCC-ICC type. These three types differ a great deal in pathogenesis, biological behavior, histological morphology, treatments, and prognosis. HCC accounts for more than 85-90% of all liver cancers.

Treatment regimens for advanced HCC is very limited. Sorafenib is the only first-line medicine approved by the FDA and NMPA for the treatment of advanced HCC. When compared to placebo, sorafenib can effectively prolong the time to progression and overall survival in patients with advanced HCC. However, the overall treatment efficacy of sorafenib against HCC is unsatisfactory. Many studies have shown that the objective response rate (ORR) is < 10% and mOS is < 10 months when sorafenib is used as first-line treatment for advanced liver cancer. An effective treatment for advanced HCC is urgently needed.

1.2.1. Rationale

An earlier study involving SHR-1210 in combination with apatinib in advanced HCC (results yet to be published) found that a fixed dose of SHR-1210 200 mg plus apatinib 250 mg orally q.d. was a tolerated dose. As of 25 Dec., 2017, a total of 14 patients with advanced HCC were enrolled to receive a fixed dose of SHR-1210 200 mg plus apatinib 125 mg or 250 mg, p.o., q.d. In the 4 subjects receiving SHR-1210 200 mg plus apatinib 125 mg, 2 had an increased dose of apatinib to 250 mg q.d. during the treatment period. The other 10 subjects received SHR-1210 200 mg plus apatinib 250 mg.

All subjects were HBV-positive, and 11 of the 14 subjects had previously failed sorafenib. A total of 13 subjects completed at least 1 efficacy evaluation after enrollment. There were 7 cases of partial response (PR) and 5 cases of stable disease (SD). The 6-week disease control rate was over 90%. Most subjects continued to benefit from the treatment, and the median duration of treatment was more than 7 months.

Other than the efficacy in advanced HCC, the tolerability and preliminary efficacy of SHR-1210 plus apatinib in non-squamous and squamous cell lung cancer were also explored. Initial results showed that SHR-1210 plus apatinib is also safe and well-tolerated in patients with lung cancer, and the combination therapy is superior to anti-PD-1 antibody monotherapy.

Multiple studies have demonstrated the safety, tolerability, and preliminary efficacy of SHR-1210 plus apatinib, suggesting that the combination therapy is superior to anti-PD-1 antibody monotherapy.

1.2.2. Basis for development

Sorafenib is the first-line treatment for advanced HCC. Sorafenib achieved an ORR of 3.3-8.3%, a TTP of 2.8-3.6 months, and an OS of ~10 months when used as first-line monotherapy for advanced HCC in the Asians, with limited efficacy.

There is yet a widely accepted standard for treating HCC in patients who failed sorafenib. Anti-PD-1 antibodies demonstrated significant preliminary efficacy against HCC in patients who failed sorafenib. Nivolumab achieved an ORR of 14% when used as second-line treatment for HCC in the Caucasian population. Regorafenib achieved an ORR of 11% in patients with advanced HCC who had disease progression despite sorafenib treatment (excluding those intolerant of sorafenib). However, these clinical trials mostly enrolled Caucasians, most of which were HCV-positive. Stratified analysis of data from previous studies showed that HBV infection is a poorer prognostic factor than HCV infection, and ~90% of all Chinese patients with liver cancer are HBV-positive.

An effective treatment for Chinese patients with HCC is urgently needed. The tolerability and safety of SHR-1210 plus apatinib have been adequately studied. Its preliminary efficacy in HCC patients refractory to sorafenib is significant. Further exploration of this treatment against advanced HCC is well supported.

1.2.3. Rationale of regimen

Numerous studies in various cancers such as non-squamous and non-small cell lung cancer, HCC, ICC, and gastric adenocarcinoma have demonstrated that: A fixed-dose of SHR-1210 200 mg plus apatinib 250 mg p.o., q.d., is a tolerated dose. Apatinib 250 mg is superior to 125 mg in terms of efficacy when combined with SHR-1210. Apatinib 250 mg is better tolerated than 375 mg when combined with SHR-1210. In a Phase II study involving SHR-1210 plus apatinib in non-squamous, non-small cell lung cancer, SHR-1210 plus apatinib 375 mg resulted in experiencing Grade 3 rash in multiple subjects and treatment interruption due to adverse events in multiple subjects during the tolerability observation. In a Phase II study involving SHR-1210 plus apatinib in advanced primary liver cancer (patients with HCC and ICC were enrolled), multiple subjects experienced Grade 3 thrombocytopenia after receiving SHR-1210 plus apatinib 375 mg.

Therefore, a fixed dose of SHR-1210 200 mg q2w plus apatinib 250 mg p.o., q.d., is selected for this study. The efficacy and safety of this combination are studied in patients with advanced HCC refractory to sorafenib or patients unwilling or unable to afford sorafenib.

1.3. Potential Risks and Benefits

1.3.1. Known potential risks

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

As of 25 Aug., 2017, among all subjects who have received SHR-1210, 214 (34.3%) reported skin toxicity event hemangioma (which has not been reported for other anti-PD-1 IgG4 antibodies). Among subjects who experienced hemangioma, 6 underwent surgery and/or were hospitalized for long-term clinical observation. Therefore, hemangioma in these subjects were considered as SAEs. All hemangiomas were reported as Grade ≤ 2. The hemangiomas resolved after discontinuation of SHR-1210.

In SHR-1210 studies conducted in Australia and China, 7 (1.1%) subjects reported pneumonitis SAEs and 3 (0.5%) reported interstitial lung disease SAEs.

Other immune-related AEs frequently reported for other anti-PD-1 antibodies are considered to be class effects and are also observed in SHR-1210 clinical studies. These included AST elevation (73 subjects, 11.7%), ALT elevation (58 subjects, 9.3%), rash (57 subjects, 9.1%; preferred terms include rash, rash macular, rash maculo-papular, rash erythematous, rash pustular,

and rash pruritic), diarrhea (44 subjects, 7.1%), hypothyroidism (37 subjects, 5.9%), and hyperthyroidism (8 subjects, 1.3%). These events are considered to be related to the investigational drug due to their high incidence and consistency with safety outcomes of other anti-PD-1 antibodies. Note that only 1 case of diarrhea was reported as an SAE. There was no colitis reported as an SAE. Therefore, many diarrhea events may not be immune-related, but may be caused by underlying conditions. In addition, many patients with AST and ALT elevations were with liver cancer. Among the 659 subjects enrolled in SHR-1210 studies in China, nearly a quarter were patients with primary liver cancer.

Analyses showed that the investigator-assessed immune-mediated adverse events assessed where SHR-1210 could not be ruled out as a potential cause were prominently skin toxicities (such as rash or hemangioma of skin). Most immune-related adverse events were Grades I-II.

The above data was compared with adverse reactions reported for other approved anti-PD-1 antibodies - nivolumab from BMS and pembrolizumab from Merck. The incidence and severity were both lower. Overall, the adverse reactions are expected to be similar to those of nivolumab and pembrolizumab.

Recommended management of common side effects and protocol-specified dose modifications have been established for this study, so that subjects may continue to receive SHR-1210 treatment, given that subjects will benefit clinically.

Overall, anti-PD-1 antibodies as monotherapy are superior to traditional chemotherapy and targeted therapy in terms of adverse reactions. When compared to chemotherapy, the combination treatment demonstrated an increase in incidence of fatigue, nausea, rash, and alopecia, but is well tolerated. Immune-related adverse reactions still require special interest, including immune-related interstitial lung disease, rash, thyroiditis, as well as those with lower incidence (≤ 1%) such as vitiligo, colitis, nephritis, hepatitis, uveitis, adrenal insufficiency, and nerve palsy. These immune-related adverse reactions were mostly mild and manageable. Very few were SAEs or potentially life-threatening. By established procedures for toxicity management, the majority of immune-mediated adverse events can be adequately controlled.

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

A tumor biopsy may be required for subjects in this study in order to obtain tumor tissues (after obtaining informed consent). This is required for determining PD-L1 expression level and other biomarkers for predicting treatment response, and can generally be completed successfully. However, due to health status of subjects, individual differences, and certain unpredictable factors, anaphylactic shock due to anesthesia, local pain, local infection, local bleeding, and local nerve injury may occur, or severe occult diseases may be induced. Also, pathological examinations for malignant tumors may not be completed with the tissue obtained from one biopsy. Thus, biopsies may be repeated when necessary.

Medical examinations performed during the course of the study may also bring potential risks to the subjects. Frequent imaging tumor assessments may expose subjects to low-dose radiation more frequently. However, since advanced or metastatic non-small cell lung cancer usually progresses rapidly, frequent imaging tumor assessments are necessary to determine whether the subject has disease progression.

1.3.2. Known potential benefits

In summary, existing treatments pose limited efficacy against advanced HCC. Less than 10% of all patients achieve response from first-line treatment with sorafenib. Also, a large number of patients are unable to afford the medication due to the high spending on sorafenib. Preliminary clinical results of nivolumab and SHR-1210 in advanced liver cancer showed that anti-PD-1 is effective in advanced liver cancer. The ORR of anti-PD-1 antibodies in patients with advanced HCC who failed sorafenib reached approximately 14%, which is superior to current treatments. SHR-1210 plus apatinib also achieved favorable preliminary results in the treatment of advanced HCC. Participating in this study and receiving study treatment may bring about clinical benefits for patients with advanced HCC, providing an effective treatment option for these patients.

2. OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary objective

- To evaluate objective response rate (ORR) of SHR-1210 in combination with apatinib mesylate in patients with advanced hepatocellular carcinoma

2.1.2. Secondary objectives

- To observe and evaluate the progression-free survival (PFS), duration of response (DOR), time to response (TTR), disease control rate (DCR), overall survival (OS), and 9-month/12-month survival rates of SHR-1210 in combination with apatinib mesylate in patients with advanced hepatocellular carcinoma;

- To determine the safety of SHR-1210 in combination with apatinib mesylate in patients with advanced hepatocellular carcinoma.

2.1.3. Exploratory objectives

- To explore the anti-HBV effects of SHR-1210 in combination with apatinib;
- To explore the biomarkers for predicting response;

2.2. Study Endpoints

2.2.1. Primary endpoint

- Objective response rate (ORR) as assessed by independent review committee (IRC) as per RECIST 1.1.

2.2.2. Secondary endpoints

Efficacy:

- Objective response rate as assessed by investigator as per RECIST 1.1;
- Progression-free survival (PFS)
- Time to response
- Duration of response
- Disease control rate (DCR)
- 9-month overall survival rate (9-month OS%)
- 12-month overall survival rate (12-month OS%)
- Overall survival
- ORR, PFS, DOR, and DCR as assessed by IRC as per mRECIST criteria.

Safety:

- Incidences and severities of adverse events (AEs) and serious adverse events (SAEs), laboratory abnormalities, as per NCI-CTCAE v4.03;
- Incidence of AEs resulting in dose interruption and discontinuation;

2.2.3. Exploratory endpoints

- Serum HBV DNA levels and the rate of HBsAg loss;
- The relationship between response and PD-L1 expression levels, the proportion of positive cells, and/or other biomarkers such as baseline tumor mutational burden (TMB);

- The relationship between baseline alpha fetoprotein level and response;
- The relationship between response and baseline levels of acyl-CoA: sterol O-acyltransferase 1 (SOAT1), Niemann–Pick C1 protein (NPC1), and transforming growth factor beta (TGF-β);

3. STUDY DESIGN

3.1. Overall Design

This is a single-arm, open-label, multi-center Phase II clinical trial intended to observe and evaluate the efficacy and safety of anti-PD-1 antibody SHR-1210 in combination with apatinib mesylate in patients with advanced hepatocellular carcinoma.

The study focuses on patients with advanced hepatocellular carcinoma who have no applicable radical therapy, are refractory to sorafenib, or are unwilling or unable to afford sorafenib.

The primary efficacy endpoint is ORR. Approximately 136 patients are planned to be enrolled, of which 80 patients must be refractory to sorafenib, and the other 56 subjects must have not been treated with sorafenib. The number of patients refractory to sorafenib can be increased to 120.

After being fully informed and providing a written informed consent, eligible subjects will receive apatinib 250 mg p.o., q.d. + SHR-1210 200 mg I.V., q2W, in treatment cycles of 4 weeks. Treatment will continue until the criteria for treatment discontinuation (as specified in the protocol) is met. After discontinuation, subjects will continue safety follow-ups and survival follow-ups. Subjects who discontinue the treatment due to reasons other than disease progression/death will also be followed for disease progression after discontinuation.

Safety visits are conducted prior to SHR-1210 administration on D1 and D15 in each treatment cycle. After treatment begins, response will be assessed once every 2 weeks for the first 12 cycles, and once every 3 weeks from Cycle 12 until the end of treatment, withdrawal of informed consent, or death.

This study will also explore the anti-HBV efficacy of the combination therapy as well as biomarkers for predicting response. Subjects who have abnormal HBV tests at baseline will undergo regular HBV titer and HBsAg tests during the study. Subjects who provide informed consent for biomarker sample collection will have their blood and tumor specimens collected at baseline and during the study, including possibly a baseline biopsy.

3.2. Reducing Bias

3.2.1. Enrollment/randomization/blinding

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

3.2.2. Blinding

Not applicable.

3.2.3. Unblinding

Not applicable.

4. SELECTION AND WITHDRAWAL OF SUBJECTS

4.1. Inclusion Criteria

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

1. Subjects must participate voluntarily and sign the informed consent form;
2. Aged ≥ 18 years old, males and females;
3. Pathologically confirmed advanced hepatocellular carcinoma (unresectable or metastatic), with at least one measurable lesion that has not been treated locally (must be ≥ 10 mm in longest diameter by spiral CT or ≥ 15 mm in shortest diameter for enlarged lymph nodes, as per RECIST 1.1);
4. Child-Pugh score ≤ 6 (Child-Pugh Class A);
5. BCLC Stage B-C;
6. Refractory to sorafenib or lenvatinib (disease progression or unacceptable toxicity), or unwilling or unable to afford sorafenib;
7. Ability to swallow tablets;
8. ECOG PS of 0-1 (refer to Appendix I for ECOG criteria);
9. Expected survival ≥ 12 weeks;
10. Vital organ functions meet the following requirements (not including any use of blood components and cell growth factors within 14 days before the first dose):
    - Absolute neutrophil count ≥ 1.5×10^9/L;
    - Platelets ≥ 80×10^9/L;
    - Hemoglobin ≥ 90 g/L;
    - Serum albumin ≥ 28 g/L;
    - Thyroid stimulating hormone (TSH) ≤ 1×ULN (In case of abnormalities, FT3 and FT4 levels should be measured at the same time. If FT3 and FT4 levels are normal, the subject can be enrolled);

- Bilirubin ≤ 1.5 × ULN (within 7 days prior to the first dose);
- ALT and AST ≤ 3 × ULN (within 7 days prior to the first dose);
- AKP ≤ 2.5 × ULN;
- Serum creatinine ≤ 1.5 × ULN;

11. For female patients of childbearing potential or female patients who are not sterilized by surgical operations, they need to use a medically approved contraceptive measure (such as an intra-uterine contraceptive device, contraceptive pills or condoms) during the study treatment period and within 3 months after the end of the study treatment; For female patients of childbearing potential who are not sterilized by surgical operations, they must have a negative serum or urine HCG test result within 72 h prior to study enrollment; and they must not be in the lactation period; For male patients with partners of childbearing potential, they should take effective contraceptive measures during the study period and within 3 months after the last dose of SHR-1210;

4.2. Exclusion Criteria

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

1. Subjects with any active autoimmune diseases or a history of autoimmune diseases (including but not limited to the following: autoimmune hepatitis, interstitial pneumonia, uveitis, enteritis, hepatitis, hypophysitis, vasculitis, nephritis, hyperthyroidism; adult subjects with vitiligo or completely relieved childhood asthma can be enrolled if they do not require any intervention; subjects with asthma requiring medical intervention with bronchodilators cannot be enrolled);
2. Subjects who are currently using immunosuppressants, or systemic hormonal therapy for immunosuppression (>10 mg/day of prednisone or an equivalent dose of other therapeutic hormones) and still use the above drugs within 2 weeks prior to enrollment;
3. ≥ 2 lines of systemic treatments;
4. Subjects who have experienced severe allergic reactions to other monoclonal antibodies;
5. Patients with known CNS metastasis or hepatic encephalopathy;
6. Patients with liver tumor burden greater than 50% of total liver in volume, or patients who have previously undergone liver transplantation;
7. Patients with symptomatic ascites requiring paracentesis or drainage or patients who have undergone ascites drainage within the past 3 months, except for those with asymptomatic ascites of a small amount;

8. Patients with hypertension which cannot be well controlled by antihypertensives (systolic pressure ≥ 140 mmHg or diastolic pressure ≥ 90 mmHg);
9. Uncontrolled cardiac diseases or symptoms, such as: (1) NYHA Class II or above heart failure, (2) unstable angina, (3) myocardial infarction within the past year, (4) clinically significant supraventricular or ventricular arrhythmia requiring treatment or intervention, or (5) QTc > 450 ms (males), or QTc > 470 ms (females);
10. Abnormal coagulation function (INR > 2.0, PT > 16 s), bleeding tendency or receiving thrombolytics or anticoagulant therapy. Prophylactic use of low-dose aspirin or low molecular weight heparin is allowed;
11. Clinically significant bleeding symptoms or clear bleeding tendency within 3 months prior to enrollment, such as coughing > 2.5 mL of blood daily, gastrointestinal bleeding, esophageal varices with bleeding risks, hemorrhagic gastric ulcer, or vasculitis. In case of positive fecal occult blood at baseline, a re-examination is needed, and a gastroscopy is required if it is still positive. The subject will be excluded if the gastroscopy indicates severe esophageal varices (except for those where such conditions have been ruled out by gastroscopy within 3 months prior to enrollment);
12. Events of arterial/venous thrombosis within 6 months prior to enrollment, such as cerebrovascular accidents (including transient ischemic attacks, cerebral hemorrhage, cerebral infarction), deep vein thrombosis, and pulmonary embolism;
13. Known hereditary or acquired hemorrhage and thrombophilia (such as hemophilia, coagulopathy, thrombocytopenia, etc.);
14. The routine urinalysis indicates that urine protein is ≥ ++ and confirms that 24h urine protein is ≥ 1.0 g;
15. Patients who have previously received radiotherapy, chemotherapy, hormone therapy or surgery that is less than 4 weeks before the study after the end of such treatments (last dose); molecular targeted therapy (including oral targeted drugs in other clinical trials) is less than 5 drug half-lives from the first dose; or patients with adverse events caused by previous treatment (except for alopecia) that have not returned to ≤ CTCAE grade 1;
16. Patients with active infection, fever ≥ 38.5 °C of unknown causes within 7 days prior to administration, or WBC count > 15×10^9/L at baseline;
17. Patients with congenital or acquired immunodeficiency (such as HIV positive);
18. HBV DNA > 2000 IU/mL (or 10^4 copies/mL); or HCV RNA > 10^3 copies/mL; or HBsAg+ and anti-HCV antibody positive;

19. Patients with other malignancies currently or within the past 3 years (except for cured basal cell carcinoma and cervical carcinoma in situ);
20. Patients with bone metastasis who have received a palliative radiotherapy in an area of > 5% of bone marrow area within 4 weeks prior to the participation in this study;
21. Patients who have previously received other anti-PD-1 antibody therapies or other immunotherapies targeting PD-1/PD-L1, or have previously received apatinib treatments;
22. Patients who have received live vaccines within less than 4 weeks before the first dose or would probably receive during the study;
23. Patients with other potential factors that may affect the study results or result in the premature termination of the study as determined by the investigator, such as alcoholism, drug abuse, other serious diseases (including mental illness) requiring concomitant treatment, serious laboratory abnormalities, accompanied by family or social factors that could affect the safety of the patients.

4.3. Withdrawal or Discontinuation

4.3.1. Discontinuation criteria

Subjects must withdraw from/terminate the treatment when any one of the following conditions occur:

1. Subject withdraws informed consent and requests to withdraw from the study;
2. Imaging examinations show disease progression;

As per RECIST 1.1, a confirmation is required 4-6 weeks after the first documentation of disease progression (except those with rapid progression or significant clinical progression);

Subjects with confirmed disease progression may continue the treatment if clinically stable (as assessed by the investigator) until further radiographic progression;

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

3. Accumulated use of SHR-1210 for 2 years (no radiographic progression). Subjects who achieve radiologically confirmed CR may consider discontinuation after 12 cycles of treatment;
4. Subjects showing unacceptable toxicity;

5. Subjects with poor compliance;
6. Subjects lost to follow-up or became pregnant;
7. Other reasons for which the investigator consider a withdrawal necessary.

Notes: Subjects with radiologically confirmed PD may continue the investigational treatment after providing informed consent for continuation after PD, if they are judged able to benefit from the investigational drug by the investigator. The treatment may continue until another radiographic PD or they can no longer benefit from the treatment. Subjects who continue the medication after PD will undergo periodic visits and efficacy evaluations according to the visit procedures specified in the protocol.

Subjects who agree to continue the treatment after PD should be fully informed of possible alternative treatments, potential risks of continuation, etc.

4.3.2. Procedures for withdrawal or discontinuation

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

Survival status should still be followed even if the subject refuses to visit the study site, unless the subject withdraws consent to provide further information or consent to be further contacted. In such case, no study assessment is performed, nor any data are collected. The sponsor can retain and continue to use all data collected before withdrawal of informed consent, unless the subject requests a retraction of collected data.

4.4. Study Termination or Suspension

The termination criteria of this study include but are not limited to the following:

1. Discovery of unexpected, significant or unacceptable risks to the subjects;
2. Major errors in the protocol are found during the implementation of the trial;
3. The investigational drug/treatment is ineffective, or continuing the trial is meaningless;
4. Termination as determined by the sponsor due to a severe delay in enrollment or frequent protocol deviations.

4.5. Definition of Study Completion

The study is completed at 6 months after the first dose of the last subject, and the primary and secondary endpoints of the study are statistically analyzed.

All subjects will be followed up until 12 to 24 months after the dosing of the last subject, and supplemental analysis of the primary and secondary endpoints of the study will be performed after the follow-up.

After the end of the study, if the subjects may continue to benefit from the investigational drug, the treatment can be continued until the criteria for discontinuation are met. The occurrence of SAEs will be collected and recorded during the treatment and after the last dose according to the protocol.

5. STUDY MEDICATION

5.1. Description of the Investigational Drug and Control Drugs

5.1.1. Access to drugs

The investigational drugs are uniformly packaged, tested and provided by the sponsor (see corresponding test report).

Concomitant medications and prophylactics for adverse events are not investigational drugs and are not provided by the sponsor. Such drugs are all marketed products and are purchased and stored by the study site based on the package insert or outlined product properties.

5.1.2. Dosage form, appearance, packaging, and label

Investigational Drug 1: SHR-1210 for injection

Manufacturer: Suzhou Suncadia Biopharmaceuticals Co., Ltd.

Dosage form: lyophilized powder

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

Batch no.: see label

Route of administration: intravenous drip infusion

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

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

Investigational Drug 2: Apatinib mesylate tablets

Manufacturer: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Dosage Form: Tablet

Strength: 250 mg/tablet

Batch no.: see label

Route of administration: oral

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

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

Specification and packaging of SHR-1210: 200 mg/20 mL vial, one vial per box, and 20 boxes per carton.

The labeling of the investigational drug follows relevant guidelines in Good Clinical Practice (GCP). The contents of the label include but are not limited to: clinical approval number, name of study, name of drug, drug number, specifications, manufacturing batch number, expiry date, route of administration and dose, and storage conditions. "For Clinical Use Only" should also be noted on the label.

Label of the investigational drug (for illustrative purposes only; refer to the actual product label):

Clinical Study of Anti-PD-1 Antibody SHR-1210 in Combination with Apatinib Mesylate in Treatment of Advanced Hepatocellular Carcinoma
For clinical study only

Product Name: SHR-1210 for injection
Clinical Study No.: SHR-1210-APTN-II-208-HCC
Clinical Trial Approval No.: 2016L01455
Indication: Advanced carcinoma hepatocellular
Specification: Lyophilized powder for injection, 200 mg/vial
Administration: Prepare according to the product manual. For intravenous injections only.
Drug No._____

Storage: Store at 2-8 °C away from light, Batch No.: Validity period: Till DD/MM/YY

Manufacturer: Suzhou Suncadia Biopharmaceuticals Co., Ltd.

Specification of apatinib: 250 mg/tablet

Label of apatinib (for illustrative purposes only; refer to the actual product label):

Clinical Study of Anti-PD-1 Antibody SHR-1210 in Combination with Apatinib Mesylate in Treatment of Advanced Hepatocellular Carcinoma
For clinical study only

Product Name: Apatinib mesylate tablets
Clinical Study No.: SHR-1210-APTN-II-208-HCC
Clinical Trial Approval No.: 2014L00877
Indication: Advanced carcinoma hepatocellular
Specification: Tablets, 0.25 g × 10 tablets/tray × 3 trays/box
Administration: Oral, 30 minutes after meal, once daily.
Drug No._____

Storage: Store below 25 °C away from light, Batch No.: Validity period: Till DD/MM/YY

Manufacturer: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

5.1.3. Storage and stability of drugs

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

The investigational drugs should be stored in its original container and match with the label. For inconsistence of the storage conditions on the label with those in other materials (such as product manual), the storage conditions on the label should be followed.

Daily maximum and minimum temperatures of all storage zones must be measured and recorded by the study site (such as freezer, refrigerator or room temperature). The period of recording starts from receiving and lasts until the end of the study. Even if a continuous monitoring system is employed, a written log must be kept to ensure a correct record of storage temperature. The temperature monitoring and storage devices (such as refrigerator) should be regularly inspected to ensure proper operation.

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

Investigational drugs that are affected by temperature deviations must be temporarily quarantined until approved by the sponsor for further use, and such case is not considered a protocol deviation. The use of affected investigational drugs without the approval of the sponsor is considered a protocol deviation. The sponsor will provide a detailed procedure on reporting temperature deviations to the study site.

5.1.4. Preparation

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

Refer to the product manual of SHR-1210 for the mixing method, concentration of the solution, and route of administration. Since this product does not contain any preservatives with antimicrobial activity or bacteriostatic agents, care must be taken to ensure that the preparations are sterile.

The overall storage period (total duration in the refrigerator and room temperature storage) from the preparation of SHR-1210 to administration should not exceed 24 hours. Please refer to the product manual for details on storage of prepared medication at room temperature/under light and in the refrigerator.

Expired or remaining preparations must be disposed.

5.1.5. Administration

SHR-1210 is an intravenous injection drug that must be administered by qualified or experienced trial staff in the outpatient department or ward of the study center. Administration is not permitted outside the study center.

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

SHR-1210 is infused intravenously over a period of 30 minutes (no less than 20 minutes and no more than 60 minutes, including the flushing of the infusion line). Do no administer by intravenous bolus or rapid bolus injection.

The intravenous drip infusions are performed through a medical infusion bag using an infusion set with an in-line filter (0.2 μM).

Do not use this infusion line to administer other drugs before and after infusion.

Apatinib mesylate is an oral tablet. The investigator prescribes the medicine and the subjects shall take the medicine orally after meal at home. Refer to the dosing regimen for details.

5.1.6. Considerations for special administration devices

Intravenous infusion bags, diluent and infusion tubing with micron filter (i.e., 0.2/1.2 μm; please refer to the product manual for details of all required filters) should be prepared at the study site.

5.2. Regimen

SHR-1210 is administered via intravenous infusion (without prophylactics) at a fixed dose of 200 mg (or 3 mg/kg for subjects weighing < 50 kg at baseline) within 30 min (not less than 20 min, no more than 60 min), once every 2 weeks. Each cycle contains 4 weeks and the longest dosing period is 2 years.

During the study, SHR-1210 is administered once every 2 weeks. The dosing window is ± 3 days from the scheduled dosing time. A SHR-1210 dose delayed by more than 3 days can be skipped, and the dosing is resumed at the next scheduled time point.

One apatinib tablet (250 mg) is administered orally once a day after meal, and the medication will be continued in cycles of 4 weeks.

Definition of after meal: dosing within 30 min after the end of a meal.

The subjects continue to use the investigational drugs until the criteria for discontinuation specified in the protocol are met.

5.3. Dose Modifications

The dose of the investigational drugs may be modified according to the toxic side effects of the investigational drugs. The options of dose modification include: dose interruption, dose reduction, change in route of administration, and discontinuation.

In this study, SHR-1210 treatment may be interrupted for up to 12 weeks;

In addition to treatment interruption, the dosage of SHR-1210 can be reduced to 3 mg/kg, q2w, for subjects with a body weight of less than 50 kg during the treatment.

Dose modifications caused by apatinib-related toxicity include: dose interruption, modification of method of administration (first modification: 5 days of drug administration followed by 2 days of dose interruption; re-modification: 7 day of drug administration followed by 7 day of dose interruption), and dose termination. A changed route of administration for apatinib shall never be resumed for the subject.

If apatinib-related AE occurs during the study, such as hypertension, proteinuria, or hand-and-foot syndrome, apatinib may be interrupted, and can be resumed, administered in a modified route, or discontinued accordingly when the toxicity resolves. Subjects may continue SHR-1210 as monotherapy if apatinib treatment is discontinued.

For immune-related toxicity occurring during the trial, such as immune-related pneumonia, hepatitis and colitis, the dosing of SHR-1210 and apatinib should be interrupted as appropriate. The dosing can be resumed when the toxicity returns to Grade ≤ 1 or baseline levels (for subjects with abnormal laboratory measurements such as ALT/AST and TBIL at baseline). The dosing of SHR-1210 should be resumed first. The dosing of apatinib can be resumed when no significant abnormality is observed within 7 to 14 days after SHR-1210 administration. The route of subsequent administration of apatinib should be modified.

During the study, in case of ≥ Grade 3 immune-related pneumonia, ≥ Grade 3 elevation in TBIL (recurrent), Grade 4 elevation in ALT/AST (recurrent), other Grade 4 immune-related toxicities (except for hypothyroidism), Grade 4 injection reactions, or the interruption of SHR-1210 administration for more than 12 weeks due to immune-related toxicity but the toxicity can still not return to ≤ Grade 1 or baseline levels (subjects with baseline abnormality), the administration of SHR-1210 should be terminated permanently.

After discontinuation of SHR-1210 treatment, subjects may continue to receive apatinib monotherapy after toxicity recovery if the investigator judges that the subjects can benefit from the apatinib monotherapy, until an event meeting the criteria for discontinuation as specified in the protocol occurs.

If Grade 3 or higher capillary endothelial proliferation occurs during the study, no dose adjustments are required for apatinib, but SHR-1210 should be interrupted until the toxicity returns to Grade ≤ 2.

If signs/symptoms or laboratory abnormalities are observed, symptomatic treatment should be provided immediately. Refer to the following recommendations for dose modifications:

Table 1. Dose modifications

Treatment-related toxicity		Grade	Whether to suspend		Criteria for resuming	Dose modifications for apatinib	Criteria for discontinuation
			SHR-1210	Apatinib			
SHR-1210- and apatinib-related toxicities	Hematological toxicity	Grade 1 to 2	No	No	—	—	—
		Grade 3	No	Yes (except for lymphocyte count decreased)	Toxicity returns to Grade ≤ 2	Resume at original dose Change the route of apatinib administration if Grade 3 hematologic toxicities recur	—
		Grade 4	Yes	Yes	Toxicity returns to Grade ≤ 2	First onset: treat for 5 days and hold for 2 days; Second onset: treat for 7 days and hold for 7 days;	Discontinue apatinib if Grade 3 or higher hematologic toxicities recur after two modifications
	Immune-related pneumonia	Grade 2	Yes	No	Toxicity returns to Grade ≤ 1	First onset: Resume at original dose Second onset: treat for 5 days and hold for 2 days; Third onset: treat for 7 days and hold for 7 days;	Discontinue SHR-1210 treatment after > 12 weeks of interruption without return to Grade ≤ 1;

Treatment-related toxicity		Grade	Whether to suspend		Criteria for resuming	Dose modifications for apatinib	Criteria for discontinuation
			SHR-1210	Apatinib			
	ALT or AST elevation	Normal baseline: Grade 2 Grade 1 at baseline: Grade 3	Yes (does not return to Grade ≤ 1 after hepatoprotective treatment)	Yes	Toxicity returns to Grade ≤ 1	First onset: Resume at original dose Second onset: treat for 5 days and hold for 2 days; Third onset: treat for 7 days and hold for 7 days;	1. Discontinue SHR-1210 treatment after > 12 weeks of interruption without return to Grade ≤ 1; 2. Discontinue SHR-1210 treatment if Grade 4 ALT/AST elevation recurs
		Normal baseline: Grade ≥ 3 Grade 1 at baseline: Grade 4	Yes	Yes	Toxicity returns to Grade ≤ 1	First onset: treat for 5 days and hold for 2 days; Second onset: treat for 7 days and hold for 7 days;	
	TBIL elevation	Grade 2	Yes	Yes	Toxicity returns to Grade ≤ 1	First onset: Resume at original dose Second onset: treat for 5 days and hold for 2 days; Third onset: treat for 7 days and hold for 7 days;	1. Discontinue SHR-1210 treatment after > 12 weeks of interruption without return to Grade ≤ 1; 2. Discontinue SHR-1210 treatment if Grade ≥ 3 TBIL elevation recurs
		Grade ≥ 3	Yes	Yes	Toxicity returns to Grade ≤ 1	First onset: treat for 5 days and hold for 2 days; Second onset: treat for 7 days and hold for 7 days;	

Treatment-related toxicity		Grade	Whether to suspend		Criteria for resuming	Dose modifications for apatinib	Criteria for discontinuation
			SHR-1210	Apatinib			
	Other non-hematological toxicities	Grade 1	No	No	—	—	—
		Grade 2 (lasts for ≥ 7 d)	Yes	Yes	Toxicity returns to Grade ≤ 1	Resume at original dose	Discontinue SHR-1210 treatment after > 12 weeks of interruption without return to Grade ≤ 1;
		Grade 3	Yes	Yes	Toxicity returns to Grade ≤ 1	First onset: treat for 5 days and hold for 2 days; Second onset: treat for 7 days and hold for 7 days;	
SHR-1210-related toxicity	Capillary hemangioma	Grade 3	Yes	No	Toxicity returns to Grade ≤ 2	Resume at original dose	Discontinue SHR-1210 treatment after > 12 weeks of interruption without return to Grade ≤ 1;
Apatinib-related toxicities	Hypertension	Grade 3 (after corrective treatment)	No	Yes	Toxicity returns to Grade ≤ 1	First onset: Resume at original dose Second onset of Grade 3 hypertension: treat with apatinib for 5 days and hold for 2 days; Third onset of Grade 3 hypertension: treat with apatinib for 7 days and hold for 7 days;	Discontinue apatinib treatment if Grade 3 hypertension recurs after 2 modifications

Treatment-related toxicity		Grade	Whether to suspend		Criteria for resuming	Dose modifications for apatinib	Criteria for discontinuation
			SHR-1210	Apatinib			
		Hypertensive crisis	Yes	Yes	Toxicity returns to Grade ≤ 1	Permanently discontinue apatinib treatment	Discontinue apatinib treatment
	Proteinuria (without significant increase in blood creatinine)	Grade 3 (24 h protein urine quantification)	No	Yes	Toxicity returns to Grade ≤ 2	Treat with apatinib for 5 days and hold for 2 days; Second onset of Grade 3 proteinuria: treat with apatinib for 7 days and hold for 7 days;	Discontinue apatinib treatment if Grade 3 proteinuria recurs after 2 modifications
	Hand-and-foot syndrome	Grade 3	No	Yes	Toxicity returns to Grade ≤ 1	Treat with apatinib for 5 days and hold for 2 days; Second onset of Grade 3 hand-and-foot syndrome: treat with apatinib for 7 days and hold for 7 days;	Discontinue apatinib treatment if Grade 3 hand-and-foot syndrome recurs after 2 modifications
	Headache	Grade 2 headache lasting ≥ 7 d despite symptomatic treatment, or Grade 3 headache	No	Yes	Toxicity returns to Grade ≤ 1	Treat with apatinib for 5 days and hold for 2 days; Second onset: treat with apatinib for 7 days and hold for 7 days;	Discontinue apatinib treatment if the event recurs after 2 modifications

The investigator may consider suspend the treatment for subjects who experience persistent and significant toxicities despite symptomatic treatment, including persistent Grade 2 or higher non-hematologic toxicities (except for asymptomatic Grade 2 hypertension) lasting 2 weeks or longer, and abnormal laboratory findings (except <2g/24h proteinuria). After the toxicity resolves, route of subsequent apatinib administration should be adjusted accordingly.

In the course of the study and based on the above regulations for dose modification, the investigator may modify the dose appropriately by comprehensively considering the drug-related toxicity in the subjects (if a subject experiences multiple Grade 2 drug-related toxicity and shows poor tolerance to the drugs, the route of apatinib administration can be adjusted after treatment interruption and toxicity recovery).

During the trial, if a subject has fever (>38 °C) and needs to use medications for corrective treatment, or in case of obvious wheezing, polypnoea, or symptoms of suffocation, the administration of SHR-1210 is skipped for the current or next scheduled time of SHR-1210 administration before the symptoms are recovered. After the symptoms are relieved and become stable for more than 7 days, the subjects are given SHR-1210 according to the subsequent dosing schedule. The possibility of pneumonia should be eliminated by imaging examinations before drug administration if necessary.

Once hypertensive crisis, cerebral hemorrhage, Grade ≥ II pulmonary hemorrhage, other Grade ≥ III hemorrhage, arterial thrombosis, or Grade IV venous thrombosis occurs during the trial, leukoencephalopathy syndrome, gastrointestinal perforation, the administration of apatinib should be discontinued, the administration of SHR-1210 should be interrupted and active symptomatic treatment should be given. The resumption of SHR-1210 treatment will depend on the toxicity recovery.

5.4. Drug Management, Dispensing and Retrieval

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

The investigational drug must be stored according to the label. The study site must sign the drug receipt forms in duplicate upon arrival of drugs, one for the study site and one for the sponsor. If there is a need for collecting remaining drugs and empty boxes at the end of the study, a drug retrieval form will also be signed by both parties. The dispensing and retrieval of every dose should be recorded on designated record forms in a timely manner.

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

Used investigational drugs will be disposed in a unified manner by the Sponsor after returning, or by the study site upon authorization. Before authorization, the monitor must confirm the disposal procedure and related specifications of the study site, and ensure that a disposal certificate can be provided after disposal.

5.5. Concomitant Therapies

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

All concomitant medications and treatments within 30 days prior to the start of study treatment and during the study must be documented in the eCRF in strict accordance with the GCP.

Once a subject discontinues the investigational treatment, only concomitant medication or treatment for new or unresolved treatment-related adverse events are recorded, until at least 30 days after the last dose.

5.5.1. Other anti-tumor/cancer or investigational drugs

Other anti-tumor treatments are not permitted when the subject is receiving treatment with the investigational drugs.

Not permitted anti-tumor traditional Chinese medicine concurrently: Huatan Huisheng tablets, *Brucea javanica* oil soft capsules, Mandarin melon berry syrup, cantharidin, cinobufotalin, bufotoxin, Kang'ai Injection, Kanglaite, *Sarcandra glabra* injection, Aidi injection, Awei huapi

cream, Kangaiping pills, Fukang capsules, Xiaoaiping, Pingxiao capsules, Pingxiao tablets, Shendan Sanjie capsules, Ankangxin capsules, Boshengaining, Zedoary turmeric oil and glucose injection, Kanglixin capsules, Cidan capsules, GFL tablets, Huaier granule, Delisheng injection, and other traditional Chinese medicine (TCM) preparations with "anti-tumor" effect described in the package insert.

Palliative radiation is permitted for the treatment of painful bone lesions, provided that these lesions existed prior to enrollment and the investigator must clearly specify that the palliative radiation does not indicate progression of disease. Patients can receive bisphosphonate for the treatment of bone metastases. If systemic or local analgesia is not effective in controlling painful lesions of bone metastases, a small area of palliative radiotherapy (the area of the radiotherapy must be <5% of the bone marrow region, and the percent bone marrow in human skeleton is shown in the figure of **Appendix III**) is allowed.

Palliative treatment for lesions outside the lungs and liver is allowed during the trial (when the treatment of the subjects is needed to improve symptoms upon the onset of PD), and the treatments include the treatments for the chest and ascites. During the treatment, the subjects should suspend the administration of the investigational drugs until the end of the recovery period of palliative treatment.

5.5.2. Supportive care

Palliative and supportive care for disease-related symptoms will be based on the investigator's judgment and relevant guidelines. The best oral anti-viral drug for the treatment of hepatitis B is permitted during the study, but interferon is prohibited.

Subjects should be given optimal supportive care during the treatment. Comorbidities and various adverse reactions, especially immune-related adverse reactions, should be actively treated.

5.5.3. Immunologic agents

The concurrent use of thymalfasin, interferon, interleukin-2 and other immunologic agents is not allowed.

5.5.4. Drugs that may have drug-drug interactions with apatinib

In vitro studies have shown that apatinib is prominently metabolized by the liver P450 enzyme CYP3A4. Apatinib has a strong inhibitory effect on CYP3A4 and CYP2C9, and has a moderate inhibitory effect on CYP2C19. CYP3A4 inducers (dexamethasone, carbamazepine, rifampicin, and phenobarbital) should be used with caution during the treatment. Strong CYP3A4 inhibitors (ketoconazole, itraconazole, erythromycin, and clarithromycin) are prohibited.

CYP3A4 substrates prohibited during the trial (drugs with narrow safety windows and may cause serious adverse reactions when their metabolism is affected) include but are not limited to:

- Hypoglycemic agents: tolbutamide, chlorpropamide
- Ergot derivatives: dihydroergotamine, ergometrine, ergotamine, methyl ergometrine (potential risk of ergot poisoning, including severe vasospasm leading to peripheral and cerebral ischemia)
- Antipsychotic: pimozide (can potentially increase the risk of prolonged QT interval)
- Antiarrhythmics: amiodarone (prohibited within 6 months prior to enrollment), bepridil, flecainide, lidocaine, mexiletine, quinidine, propafenone
- Immunomodulators: cyclosporine, tacrolimus, sirolimus (potentially increase the risk of nephrotoxicity and neurotoxicity)
- Miscellaneous: quetiapine, risperidone, clozapine, tomoxetine hydrochloride

If warfarin is used for anticoagulation during the trial, a reduced dose should be considered with its use being monitored closely, and the use of the investigational drugs should be discontinued if necessary.

5.5.5. Drugs that prolong the QT interval of the heart:

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

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

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

5.5.6. Surgery or palliative radiotherapy

Any surgery or palliative radiotherapy conducted during the study period must be reasonable and necessary. The interval between the treatment and drug must not affect the recovery of the wound as much as possible and the investigation on hemorrhage of unknown cause. Investigational drugs should be interrupted 7 days before surgery or palliative radiation, during premedication, and at least 7 days after surgery/radiation. Resumption in subjects who undergo surgery depends on the clinical assessment of wound healing and postoperative recovery.

6. STUDY PROCEDURES

Before the study commences, the subjects must read and sign the current informed consent form approved by the ethics committee (EC). All examinations and trial procedures will be carried out according to the time schedule of the study procedures, and will not be affected by the duration of drug interruption. However, it is allowed to change within the window period of test items due to holidays, weekends or other administrative reasons.

6.1. Screening Period (D-21–D-1)

Unless otherwise stated, the following screening procedures must be completed within 21 days prior to the first dose:

[Informed consent] A written informed consent of subject must be obtained before any procedures of the clinical trial are carried out.

[Demographics] gender, date of birth, ethnicity, height, and weight;

[Tumor history]

(1) Tumor diagnosis: clinical diagnosis prior to enrollment, date of first pathological confirmation, first pathological diagnosis, pathological grade, presence of extrahepatic metastasis, presence of vascular invasion, clinical staging, presence of liver cirrhosis;

(2) History of surgery: the surgical history of primary lesions (name, date), and the surgical history of metastatic lesions (name, date);

(3) History of intervention: name of intervention, date, use of chemotherapy, name of chemotherapeutic agent;

(4) Local ablation therapy: name of the ablation therapy, date;

(5) History of systemic treatment: name of targeted therapy, start date, end date, best response, outcome. For an outcome of PD for targeted therapy, the date and nature of PD (progression of target lesion or progression of non-target lesion or new lesion); for an outcome of intolerated targeted therapy, the specific adverse event should be documented;

(6) History of radiotherapy: name of radiotherapy, date, dose, site (total body/local); seed implantation (name, date);

[Past medical history] Name of disease, date of diagnosis, name of medication, persistence, history of cancers other than HCC.

[Concomitant medication] Concomitant medications and treatments received within 30 days prior to the first dose and during the study period should be recorded. Once a subject discontinues the investigational treatment, only concomitant medication or treatment for new or unresolved treatment-related adverse events are recorded, until at least 30 days after the last dose. If a new anti-tumor therapy starts within 30 days, only concomitant medications for treatment-related adverse events are documented.

[History of alcoholism]

[Thyroid function] FT3, FT4, and TSH;

[Examination of the pituitary adrenal axis] Including ACTH, cortisol, and follicle stimulating hormone;

[HIV test] HIV antibody test;

[Hepatitis B and C tests] Hepatitis B markers: for abnormal test results, the subject should undergo quantitative tests of HBV DNA and HBsAg; then HBV DNA titer and HBsAg levels should be determined. Hepatitis C antibodies (anti-HCV): Subjects with positive anti-HCV antibodies must be tested for HCV RNA titer. Subjects with abnormal baseline HBsAg must be tested for HBV DNA and HBsAg levels on D1 ± 7 d every 2nd cycle and at the end of study.

[Alpha-fetoprotein] Alpha-fetoprotein assay;

[Adverse events] Adverse events (AEs) should be recorded from signing the informed consent until at least 30 days after the last dose and should be followed-up until the AEs are resolved or stabilized. SAE and irAE observed within 90 days after the last dose of SHR-1210 should be followed up. If the subjects start a new anti-tumor treatment, they should be followed-up until they start the tumor treatment (if the tumor treatment starts within 30 days after the last dose, the subjects should be followed-up until at least 30 days after the last dose; if the tumor treatment starts over 30 days after the last dose, the subjects should be followed-up until they start the new tumor treatment).

[Imaging examination] Including enhanced CT or MRI of the chest, abdomen and pelvis, and enhanced MRI or CT of brain at screening. Tumor assessments performed within 3 weeks prior to treatment can be accepted as the baseline assessment. CT/MRI results prior to informed consent may be used for tumor assessments at screening if requirements are met. A bone scan is required if bone metastasis is suspected.

[Biomarker collection/harvest] The existing paraffin-embedded tumor tissue specimens or fresh biopsy samples (size of a soybean) are collected. At least 10 slides are required, including 3-5 slides of 3-5 μm thickness for PD-L1, SOAT1, NPC1, and TGF-β testing, and 5-8 paraffin sections (paraffin blocks may be collected directly, without mounting onto slides) of 8-10 μm thickness, otherwise fresh biopsy samples (size of a soybean) are required for testing biomarkers such as tumor mutational burden (TMB). See the laboratory manual for tumor tissue sampling/sample collection, and disposal.

Unless otherwise stated, the following screening procedures must be completed within 7 days prior to the first dose:

[Blood routine test] White blood cell count (WBC), absolute neutrophil count (ANC), lymphocyte count (LYM), red blood cell count (RBC), hemoglobin (Hb), and platelet count (PLT);

[Routine urinalysis] Urine protein, urine glucose, urinary occult blood, urinary RBC; urinary WBC; If 2 consecutive semi-quantitative tests show proteins of 2+, a quantitative 24-h urine protein test is required.

[Stool routine] Subjects with positive fecal occult blood must be retested. If fecal occult blood is confirmed, then a gastroscopy is performed.

[Blood biochemistry] Total bilirubin, direct bilirubin, ALT, AST, AKP, γ-GT, total protein, albumin, urea/blood urea nitrogen, creatinine, uric acid, fasting blood glucose, triglycerides, cholesterol, potassium, sodium, chlorine, calcium, phosphorus, blood lipase (only checked in the screening period and in case of subsequent abdominal pain, abdominal distension and other symptoms of suspected pancreatitis), blood amylase (only checked in the screening period and subsequent abdominal pain, abdominal distension and other symptoms of suspected pancreatitis);

[Coagulation function] Including INR, APTT, PT, and FIB;

[Myocardial zymography]

[Pregnancy test] The urine pregnancy test shall be performed 72 h before the first dose in women of childbearing age. If positive, a serum pregnancy test shall be performed. If necessary, a re-test can be performed for confirmation;

[Vital signs] Body temperature, heart rate, respiratory rate, blood pressure.

[Blood pressure monitoring] The blood pressure measurement of subjects is performed by the investigator or study nurse during the screening period; during each blood pressure measurement, smoking and coffee are prohibited within 30 min before the measurement, and subjects should at least rest for 10 min. The sitting position is taken during the measurement by placing the elbow at the same level as the heart. Each blood pressure measurement is taken on the same side of the body;

[Physical examination] General conditions, head and face, skin, lymph nodes, eyes (sclera, pupils), ears, nose, throat, mouth, respiratory system, cardiovascular system, abdomen (including liver and spleen), reproductive and urinary systems, musculoskeletal system, nervous system, and mental state. Note: Comprehensive physical examinations must be performed during the study, but only abnormal findings need to be documented in the eCRF. Repeated documentation is not required if there is no change from baseline.

[ECOG PS] See Appendix I;

[12-lead ECG] Two additional ECGs or other investigations may be added as determined by the investigator if results are abnormal.

[Echocardiography]

[Blood sampling for biomarkers] A 10-mL blood sample is collected from the subjects at baseline, and processed and shipped according to the laboratory manual.

The inclusion and exclusion criteria are verified again. Subjects must meet all inclusion criteria and must not meet any of the exclusion criteria before they can be included in the study.

6.2. Trial Period

D1 of Cycle 1 [Vital signs] [Physical examinations and weight measurement] [Intravenous drip of SHR-1210] [Dispensation of apatinib] [Administration of apatinib]

Within 24 h after the first dose of SHR-1210, the subjects should be closely monitored for acute allergic reactions. If an acute allergic reaction occurs, it should be treated according to the medical practice of the hospital and relevant guidelines.

In order to improve the compliance of the subjects and ensure that apatinib is taken after breakfast every day, only SHR-1210 is administered on D1 of Cycle 1 while the oral administration of apatinib is started on D2 after breakfast, and will be continuously given in cycles of 4 weeks.

D15 of Cycle 1 [Hematology] [Blood biochemistry] [Urinalysis] [Stool routine] [Coagulation function] [Vital signs] [Physical examination and weight measurement] [ECG] [Intravenous drip of SHR-1210] [Adverse events] [Concomitant medication]

D1 of subsequent cycles [Routine blood test] [Biochemistry] [Routine urinalysis] [Routine stool test] [Coagulation] [Vital signs] [Physical examinations and weight measurement] [ECOG PS] [ECG] [SHR-1210 IV drip infusion] [Adverse events] [Concomitant medication] [Retrieval/dispensing of apatinib]

D15 of subsequent cycles: [Hematology] [Blood biochemistry] [Urinalysis] [Vital signs] [Physical examination and weight measurement] [Intravenous drip of SHR-1210] [Adverse events] [Concomitant medication]

A window period of ±3 d is set and the intravenous administration of SHR-1210 should be carried out after the evaluation of examinations and tests specified in the flowchart is completed.

[Imaging evaluation] During the treatment period, the imaging examination should be performed under the same conditions as those of the baseline examination (layer thickness of the scan, use of contrast agent, etc.), and the baseline lesions should be checked every 2 cycles during the first 12 treatment cycles (bone scan will be performed if bone progression is suspected or CR is confirmed), and then once every 3 cycles thereafter. Appropriate examination may also be performed if new lesions are suspected. The first documentation of PR/CR in a subject must be verified 4 weeks ± 7 days later. A radiological confirmation is required 4-6 weeks after the first documentation of disease progression as per RECIST 1.1 (except those with rapid progression or significant clinical progression);

The window period for imaging examination schedule is ± 7 days. Unscheduled imaging examinations can be performed when progressive disease is suspected (such as worsening of symptoms).

[Thyroid function test] On D1 ± 7 d of Cycle 2, then on D1 ± 7 d of every 3rd cycles subsequently;

[Alpha-fetoprotein] On D1 ± 7 d every 2nd cycle;

[HBV DNA and HBsAg quantitative tests] Perform on D1 ± 7 d of every 2nd cycle during the study for those with abnormal HBsAg at baseline;

[Blood pressure monitoring] During the treatment period, blood pressure is monitored by the subject and documented in the patient's daily log. Blood pressure should be measured at least 3 times per week during the first 2 cycles. For subjects with abnormal blood pressure, the blood pressure should be measured daily; otherwise, the blood pressure should be measured at least 2 times per week after Cycle 2. The investigator or study nurse will also measure the blood pressure at each visit;

6.3. End of Treatment/Withdrawal

The treatment shall be discontinued if events specified in "Section 4.3.1. Criteria for Discontinuation" occur. At the end of the study treatment or upon withdrawal from the study (a window period of ±3 d), if a subject has not undergone examinations within 14 days prior to the end of the study, the subject should undergo the following examinations:

[Hematology] [Blood biochemistry] [Urinalysis] [Stool routine] [Coagulation function] [Pregnancy test] [Thyroid function test] [Alpha-fetoprotein] [HBV DNA and HBsAg quantitative tests] [Myocardial zymogram] [Vital signs] [Physical examination] [ECOG PS] [ECG] [Echocardiography] [Blood pressure monitoring] [Adverse events] [Concomitant medication] [Return of apatinib]

If a subject has not undergone imaging examinations within 4 weeks prior to the end of the study, the subject should undergo an imaging examination for response assessment at the end of the study treatment or upon withdrawal from the study (a window period of ±3 d). For subjects with PD demonstrated by non-imaging evidence (intolerability, other conditions), a tumor evaluation is carried out every 3 months until PD, death, or the initiation of other anti-tumor treatments.

6.4. Follow-up

30 days after discontinuation/end of treatment (30 days ± 3 d after the last dose)

[Vital signs] [Physical examination] [ECOG PS] [Routine blood test] [Routine urinalysis] [Biochemistry] [Adverse events] [Concomitant medication]

Adverse events should be followed-up until at least 30 days after the last dose. SAE and irAE observed within 90 days after the last dose of SHR-1210 should be followed up. If the subjects start a new anti-tumor treatment, they should be followed-up until they start the tumor treatment (if the tumor treatment starts within 30 days after the last dose, the subjects should be followed-up until at least 30 days after the last dose; if the tumor treatment starts over 30 days after the last dose, the subjects should be followed-up until they start the new tumor treatment).

[Survival follow-up] After the trial treatment is discontinued, the survival status and subsequent anti-cancer treatment can be collected through clinical or telephone follow-ups every 1 months until death.

7. EVALUATIONS

7.1. Efficacy Evaluation

7.1.1. Efficacy indicators

The primary efficacy endpoint for this study is the objective response rate (ORR) as assessed by independent review committee (IRC) as per RECIST 1.1.

Objective response rate (ORR): The proportion of subjects with a best overall response (BOR) of complete response (CR) or partial response (PR) as per RECIST 1.1 criteria.

CR and PR must be verified at least 4 weeks ± 7 days after their first presence.

Best overall response refers to the best response assessed by the IRC, or the best response from the date of first dose to the first documentation of progression as per RECIST 1.1 or to the start of a new anti-tumor treatment (whichever comes first).

For subjects without documented progression or new anti-tumor treatment, the best overall response will be determined on the basis of all efficacy assessments.

For subjects who continue SHR-1210 treatment beyond progression, the best overall response should be based on the efficacy assessment at the time of first documented progression as per RECIST 1.1.

Secondary efficacy endpoints include:

- Objective response rate as assessed by the investigator as per RECIST 1.1;
- Progression-free survival (PFS): The period of time from the date of first dose to the date of the first recorded tumor progression (according to RECIST v1.1 criteria, regardless of whether treatment is continued) or death of any cause (whichever comes first).

When determining PFS, clinical exacerbations without definite evidence of disease progression (as per RECIST 1.1) is not considered progression. For subjects who die without any prior reports of progression, the date of death is considered the date of progression. Subjects without disease progression or death will be censored on the date of their last evaluable tumor assessment. Subjects without tumor assessments during the study or death will be censored on their date of first dose. Subjects who discontinue the treatment for reasons other than disease progression (no subsequent tumor assessments) will be censored on the date of their last evaluable tumor assessment. Subjects without disease progression before starting a new anti-tumor therapy will be censored on the date of their last evaluable tumor assessment prior to the start of new anti-tumor therapy.

- Time to objective response (TTR) is defined as the period of time from the date of first dose to the first documented tumor response (as per RECIST 1.1).
- Duration of response (DOR) is defined as the period of time from the first documented tumor response (as per RECIST 1.1) to the first documented objective progression (as per RECIST 1.1) or death of any cause. Subjects without disease progression or death will be censored on the date of their last evaluable tumor assessment. Subjects who start a new anti-tumor therapy (not including treatment for non-target bone lesions or palliative radiation) without previously reported progression will be censored on the date of their last tumor assessment prior to the start of new anti-tumor therapy.
- 9-month survival rate: defined as the rate the subjects survive for more than 9 months from the date of the first dose;
- 12-month survival rate: defined as the rate the subjects survive for more than 12 months from the date of the first dose;
- Overall Survival (OS): defined as the time between the start of randomization and the death of the subject caused by any reasons. For subjects who are alive at the last follow-up, their OS will be censored at the last follow-up time. For subjects who are lost to follow-up, their OS will be censored at the last confirmed survival time before lost to follow-up. The OS of censored subjects is defined as the time from the first dose to censoring.
- ORR, PFS, DOR, and DCR as assessed by IRC as per mRECIST criteria.

7.1.2. Efficacy evaluation

To evaluate the primary and secondary efficacy endpoints of SHR-1210 in combination with apatinib mesylate in patients with advanced hepatocellular carcinoma as per RECIST v1.1 (Appendix II).

Baseline lesions will be assessed once every 2 cycles during the first 12 treatment cycles (bone scan will be performed if bone progression is suspected or CR is confirmed) and then once every 3 cycles thereafter. Tumor assessments are not affected by treatment discontinuation or delay. Tumor assessments may also be performed if new lesions are suspected. The first PR/CR must be confirmed after 4 weeks ± 7 days. As per RECIST 1.1, imaging confirmation is required 4-6 weeks after the first documentation of disease progression (except those with rapid progression or significant clinical progression).

For the record and assessment of survival, the subjects will be followed up by telephone for survival once every month after leaving the group until death, lost to follow-up, withdrawal of informed consent, or termination of the study by Hengrui.

Assessments of tumor response include all known or suspected lesions.

Radiographic examination includes CT or MRI scans of the chest, abdomen, or pelvis. Brain CT or MRI is performed for subjects with known or suspected brain metastasis, while bone scan is performed for subjects with known or suspected bone metastasis **(See 7.1 Imaging Examinations for details)**.

If discontinuation is indicated by deterioration of overall health in absence of objective evidence of disease progression, such event shall be reported as symptomatic deterioration.

If a subject has not undergone imaging examinations within 4 weeks prior to the end of the study, the subject should undergo an imaging examination for response assessment at the end of the study treatment or upon withdrawal from the study. For subjects with PD demonstrated by non-imaging evidence (intolerability, other conditions), a tumor evaluation is carried out every 3 months until PD, death, or the initiation of other anti-tumor treatments.

Secondary efficacy endpoints in this study include ORR, PFS, DOR, and DCR assessed by the Independent Review Committee (IRC) in accordance with the mRECIST criteria.[7]

7.2. Safety Evaluation

7.2.1. Adverse events

The incidence and severity of adverse events (AE) and serious adverse events (SAE) will be assessed according to NCI-CTCAE V4.03.

Incidence of treatment interruption and discontinuation due to AEs.

AEs that occur during the study, including signs and symptoms at screening, will be recorded in the eCRF. Treatment interruption and reduction as well as other modifications will be documented in the eCRF.

7.2.2. Laboratory safety evaluation

All laboratory abnormalities that are clinically significant or meet the definition of an AE/SAE should be recorded in the eCRF:

Investigators are recommended to use clinical terms rather than laboratory terms (such as anemia instead of hemoglobin decreased) in reports.

7.2.3. Vital signs, physical examination, and body weight measurement

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

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

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

7.3. Biomarker Evaluation

The following biomarkers are planned to be evaluated in this study:

- Serum HBV DNA levels and the rate of HBsAg loss;
- The relationship between PD-L1 expression levels, proportion of positive cells, and/or other biomarkers such as tumor mutation burden (TMB) at baseline, and response in tumor tissue and/or peripheral blood samples collected at baseline;
- The relationship between baseline alpha fetoprotein level and response;
- Acyl-CoA at baseline: The relationship between the expression levels of cholesterol acyltransferase-1 (SOAT1), type C Niemann-Pick disease type 1 (NPC1), and transforming growth factor-β (TGF-β) and treatment response.

The results of the exploratory biomarker study will be reported separately and will not be included in the clinical study report.

The results from the exploratory biomarker study may be combined and analyzed with biomarker data from other studies of the investigational drug to formulate a hypothesis which will be further validated in future studies.

8. REPORTING OF ADVERSE EVENTS

8.1. Adverse Events (AEs)

8.1.1. Definition of AEs

An AE is any adverse medical occurrence in a study subject, which does not necessarily have a causal relationship with the trial intervention. Adverse advents will be collected from the signing of the informed consent form until at least 30 days after the last dose. SAEs and irAEs observed within 90 days after the last dose of SHR-1210 should be followed up and collected. If the subjects start a new anti-tumor treatment, they should be followed-up until they start the tumor treatment (if the tumor treatment is started within 30 days after the last dose, the subjects should be followed-up until at least 30 days after the last dose; if the tumor treatment is started more than 30 days after the last dose, the subjects should be followed-up until they start the new tumor treatment). AEs can include any unfavorable and unexpected symptoms, signs, laboratory abnormalities or diseases, etc., including the following:

1) Worsening of pre-existing (prior to enrollment) medical conditions/diseases (including symptoms, signs, and laboratory abnormalities);
2) Any new AE: Any new adverse medical conditions (including symptoms, signs, and newly diagnosed diseases);
3) Abnormal clinically significant laboratory values or results that are not caused by concomitant diseases.

Any AEs should be recorded in details, including: the name of the AE and description of all relevant symptoms, onset time, severity, causes, correlation with the investigational drug, duration, measures taken, and final results and outcomes.

8.1.2. AE severity grading criteria

Please refer to NCI CTCAE 4.03 for grading standards. Refer to the following criteria for AEs not listed in NCI CTCAE 4.03:

Table 2. AE severity grading criteria

Grade	Clinical Description of Severity
1	Mild; no or mild clinical symptoms; only clinical or laboratory abnormalities; no intervention required
2	Moderate; minor, local, or non-invasive interventions required; age-appropriate limitations in activities of daily living (ADL) suing tools, e.g. cooking, shopping, making phone call, counting money, etc.;
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization; disability; limited self-care ADL. Self-care ADL includes: bathing, dressing, undressing, eating, using the toilet, taking medications, etc.
4	Life-threatening consequences; urgent intervention indicated
5	Fatal

8.1.3. Determination of the relationship between AEs and the investigational drug

The potential relationship between the AE and the investigational drug was assessed with 5 grades of causality: definitely related, possibly related, unlikely related, not related and indeterminable. "Definitely related", "possibly related", and "not assessable" events are included as adverse drug reactions. The incidence of AEs is calculated with the sum of these three categories as the numerator and the number of subjects for safety evaluation as the denominator.

8.2. Serious Adverse Events (SAEs)

8.2.1. Definition of SAEs

An SAE is a medical occurrence during the clinical trial that results in hospitalization, prolonged hospitalization, disability, incapacity, life threat or death, or congenital malformation, etc. The following unexpected medical events are included:

- Events leading to death;
- Life-threatening events (defined as the risk of immediate death at the time of the event);
- Events leading to hospitalization or prolonged hospitalization;
- Events that could result in permanent or serious disability/incapacity/impairment of work ability;
- Congenital anomalies or birth defects;
- **Other important medical events** (refers to events that may not be immediately life-threatening, result in death or hospitalization, but based on reasonable medical and scientific judgment, may jeopardize the subject or may require intervention (medical or surgical) to prevent of the serious consequences listed in the definition above). Examples of these events include but are not limited: allergic bronchospasm requiring intensive treatment in an emergency room or at home, hematological cachexia or convulsions no requiring hospitalization, potential drug-induced hepatic injury, suspected transmission of pathogens (e.g., pathogenic or non-pathogenic) via the investigational drug, pregnancy, drug overdose, and secondary neoplasm, etc.

8.2.2. Hospitalization

AEs that lead to hospitalization or prolonged hospitalization during clinical trials should be considered SAEs. Hospitalization does not include: rehabilitation centers, nursing homes, routine ER admission, same-day surgery (such as outpatient/same-day/ambulatory surgery). Inpatient or prolonged hospitalization unrelated to worsening of AEs is not an SAE. For example:

- hospitalization due to existing disease without occurrence of new AEs or worsening of the existing disease (e.g., in order to examine the laboratory abnormalities that have persisted since before the trial);
- hospitalization for management reasons (e.g., annual routine physical examination);
- hospitalization during the clinical trial as specified in the study protocol (e.g., operations as required by the protocol);
- elective hospitalization unrelated to worsening of AEs (e.g., elective surgery);
- scheduled treatment or surgery that should be recorded throughout the trial protocol and/or the baseline data of subjects;
- hospitalization for blood use only.

Diagnostic or therapeutic invasive procedures (e.g. surgery), and non-invasive procedures should not be reported as AEs. However, when conditions resulting in such operations and meeting the definition of AE shall be reported accordingly. For example, acute appendicitis during the AE reporting period should be reported as an AE, and the resulting appendectomy should be recorded as the treatment for the AE.

8.2.3. Progressive disease (PD)

A PD is defined as the deterioration of the patient's conditions caused by the primary tumor that the investigational drug is targeting, including radiological progressions and progressions in clinical symptoms and signs. New metastases relative to the primary tumor, or progression of the previous metastases, are recognized as PD. Life-threatening conditions, hospitalization or prolonged hospitalization arising from disease progression, or events resulting in permanent or severe disability/incapacity/impairment of work ability, are not reported as SAE. Death caused by the symptoms and signs of PD is reported as an SAE on an expedited basis.

8.2.4. Hepatic enzyme abnormalities

Abnormal AST and/or ALT levels that meet the laboratory abnormalities in the table below should be reported as SAEs, which are judged to be due to PD after comprehensive assessment by the investigator and should not be reported as SAEs. The investigator is required to enhance the follow-up of the subjects, who are followed up until their levels of hepatic enzymes become normal or reach the baseline levels.

Table 3. Abnormal hepatic enzymes reported as SAEs

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

8.2.5. Other anti-tumor treatments

SAEs should be recorded from the signing of the informed consent form until 90 days after the last dose of the investigational drug. If the subjects start a new anti-tumor treatment, they should be followed-up until they start the tumor treatment (if the tumor treatment is started within 30 days after the last dose, the subjects should be followed-up until at least 30 days after the last dose of SHR-1210; if the tumor treatment is started more than 30 days after the last dose, the subjects should be followed-up until they start the new tumor treatment). Death that occurs within the SAE reporting period after study treatment is completed should be reported regardless of whether the patient received other treatment.

8.2.6. SAE reporting system

In the event of an SAE, whether it was the first report or a follow-up report, the investigator must have completed the "NMPA Serious Adverse Event Report Form" immediately, with a signature and date. It must have been reported to the relevant regulatory authorities, the sponsor, and the ethics committee within 24 hours of knowing of the event.

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

SAEs that occur after the safety follow-up period are generally not reported unless suspected to be related to the investigational drug. The symptoms, severity, relevance to the investigational drug, time of occurrence, treatment duration, measures taken, time and method of follow-up, and outcome were recorded in detail in the SAE report. If the investigator believes that an SAE is not related to the investigational drug but potentially related to the study conditions (e.g., termination of the original treatment, or complications during the trial), this relationship should be detailed in the description section of the "SAE Report Form". If the intensity of an occurrent SAE or its relationship to the investigational drug changes, a follow-up report should be submitted immediately. If an error is found in a previously reported SAE, such an SAE may be revised, revoked, or downgraded in follow-up reports and reported in accordance with the SAE reporting procedure. If the intensity of an occurrent SAE or its relationship to the investigational drug changes, a follow-up report should be submitted immediately.

8.2.7. Follow-up of AEs/SAEs

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

During each visit, the investigator should ask about the situation of AE/SAEs that occur after the last visit and provide follow-up information in a timely manner based on the sponsor's query request.

8.3. Pregnancy

During the study, if a female subject becomes pregnant, she must be excluded from the study. The investigator must report to the sponsor within 24 hours of knowing the event and fill out the "Pregnancy Report/Follow-up Form for Hengrui Clinical Studies".

During the study, if a partner of a male subject becomes pregnant, the subject can continue in the study. The investigator must report to the sponsor within 24 hours of knowing the event and fill out the "Pregnancy Report/Follow-up Form for Hengrui Clinical Studies".

The investigator must continuously monitor on the outcome of the pregnancy until the 1 month after delivery, and report the outcome to the sponsor.

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

If the subject also experiences an SAE during the pregnancy, the "NMPA SAE Report Form" should also be filled out and reported according to the procedures of SAE reporting.

8.4. AEs of Special Interest

When an AE of special interest specified in the trial protocol occurs, the investigator must fill out the "Report of Adverse Event of Special Interest for Hengrui Clinical Studies" and report to the sponsor within 24 hours of event awareness. If an AE of special interest is also an SAE, the "NMPA Serious Adverse Event Report Form" must also be completed.

- ≥ Grade 3 infusion reaction
- ≥ Grade 2 diarrhea/colitis, uveitis, interstitial pneumonia
- Other ≥ Grade 3 immune-related AEs
- Any possible hepatic enzyme abnormalities (see 8.2.3, lacking other related causes of the abnormalities at the same time, e.g., PD, acute viral hepatitis, cholestasis, concomitant medication, previous concomitant liver disease, etc.)
- Grade 4 amylase or lipase elevation

When an AE of special interest specified in the trial protocol occurs, the investigator must fill out the "Report of Adverse Event of Special Interest for Hengrui Clinical Studies" and report to the sponsor within 24 hours of event awareness.

If an AE of special interest is also an SAE, the "NMPA Serious Adverse Event Report Form" must also be completed.

8.5. Infusion Reactions

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

In general, no administration of prophylactics before the infusion of SHR-1210 is required. Based on published relevant information, an allergic reaction/event is most likely to occur within 24 h after infusion. If an allergic reaction/event occurs, the infusion should be slowed or interrupted according to the situation, and a supportive treatment should be given. In addition, prophylactics should be given before further administration. Possible allergic reactions include fever, chills, shiver, headache, rash, pruritus, joint pain, hypotension/hypertension, or bronchospasm. All Grade 3 or 4 infusion reactions should be reported in accordance with SAE procedures.

9. MANAGEMENT OF ADVERSE EVENTS

9.1. Immune-Related Adverse Events (irAEs)

Immune-related adverse events (irAEs) are clinically significant side effects that are consistent with the immunological mechanisms of the investigational drugs. irAEs require further serological, immunological and pathological (biopsy) data to support its diagnosis. Also, tumors, infections, metabolism, toxins, or other pathogenic factors must be ruled out.

Management principles for immune-related adverse events (see Annex IV for details):

The treatment of irAEs should be based on the medical practice and guidelines of the study site. The treatment recommendations for irAEs are as follows. The details are shown in Annex IV for reference.

Subjects using hormones should pay attention to calcium and vitamin D3 supplement, acid suppression, and protection of gastric mucosa.

- **Immune-related pneumonitis**

In the clinical study of SHR-1210, the monitoring of signs and symptoms of immune-related pneumonitis, such as cough and chest discomfort, in the subjects will be strengthened.
A high-dose hormone therapy will be given to subjects with a Grade 2 and above event confirmed by chest CT. Subjects with a Grade 2 event can interrupt SHR-1210 and be treated, but subjects with a Grade 3 or 4 event should permanently discontinue SHR-1210. Consultation with the Department of Respiration is recommended.

For specific operations, refer to the followings:

Grade 2 event: 1 mg/kg/day of methylprednisolone or equivalent given via intravenous or oral administration. The changes in CT should be closely monitored. After the event recovers to Grade 1, oral administration of 0.5 mg/kg/day of prednisone is continued for 2 weeks, then the dose of prednisone is reduced by 5 mg/week until drug discontinuation.

Grade 3 event: 2-4 mg/kg/day of methylprednisolone or equivalent given via intravenous injection. The changes in CT should be closely monitored. After the event recovers to Grade 1, the dose of methylprednisolone is reduced by 50% every 3 days. Oral administration of 0.5 mg/kg/day of prednisone is continued for 2 weeks, then the dose of prednisone is reduced by 5 mg/week until drug discontinuation.

If the hormone therapy does not improve or deteriorate the condition after 3-5 days, a combination therapy with immunosuppressants can be used for the treatment after discussion with the sponsor.

- **Immune-related hepatitis**

In the clinical study of SHR-1210, the monitoring of signs and symptoms of immune-related hepatitis, such as liver discomfort and transaminase abnormal, in the subjects will be strengthened. A high-dose hormone therapy will be given to subjects with a Grade 2 and above event. For specific operations, refer to the followings:

Grade 2 event: 0.5-1 mg/kg/day of methylprednisolone or equivalent given via intravenous or oral administration. The changes in liver function indicators should be closely monitored. After the event recovers to Grade 1, the dose of hormone is slowly reduced in a period no less than 1 month.

Grade 3 event: 1-2 mg/kg/day of methylprednisolone or equivalent given via intravenous or oral administration. The changes in liver function indicators should be closely monitored. After the hepatitis recovers to Grade 1, the dose of hormone is slowly reduced in a period no less than 1 month.

If the hormone therapy does not improve or deteriorate the condition after 3-5 days, a combination therapy with immunosuppressants can be used for the treatment after discussion with the sponsor.

- **Immune-related enteritis**

In the clinical study of SHR-1210, the monitoring of signs and symptoms of immune-related enteritis, such as abdominal pain, diarrhea, and hematochezia, in the subjects will be strengthened. A high-dose hormone therapy will be given to subjects with a Grade 2 and above event. Subjects with a Grade 2 event can interrupt SHR-1210 and be treated, but subjects with a Grade 3 or 4 event should permanently discontinue SHR-1210.

- **Immune-related thyroid dysfunction**

Thyroid dysfunction can occur at any time during the study. Therefore, in the clinical study of SHR-1210, the thyroid functions of the subjects will be regularly examined to closely monitor the clinical symptoms of thyroid dysfunction. After the occurrence of immune-related hyperthyroidism, the subject should be given a high dose of cortisone/prednisone. Hormone replacement therapy is used for the treatment of hypothyroidism, but glucocorticoids are not applicable.

In the clinical study of SHR-1210, the monitoring of signs and symptoms of immune-related thyroid dysfunction in the subjects will be strengthened. A high-dose hormone therapy will be given to patients with Grade 3 or higher hyperthyroidism. Patients with Grade 4 event should permanently discontinue SHR-1210. Treatment discontinuation of SHR-1210 is not required for patients with Grade ≥ 2 hypothyroidism.

- **Immune-related nephritis and renal failure**

In the clinical study of SHR-1210, the monitoring of signs and symptoms of immune-related nephritis in the subjects will be strengthened. A high-dose hormone therapy will be given to subjects with a Grade 2 and above event. Subjects with a Grade 2 or 3 event can interrupt SHR-1210 and be treated, but subjects with a Grade 4 event should permanently discontinue SHR-1210.

- **Immune-related hypophysitis**

In the clinical study of SHR-1210, the monitoring of signs and symptoms of immune-related hypophysitis in the subjects will be strengthened. A high-dose hormone therapy will be given to subjects with a Grade 2 and above event. Subjects with a Grade 2 or 3 event can interrupt SHR-1210 and be treated, but subjects with a Grade 4 event should permanently discontinue SHR-1210.

- **Other immune-related adverse reactions**

In principle, interruption of SHR-1210 is preferred based on the severity of the adverse reaction. The study treatment can be considered to resume when AE returns to Grade ≤ 1. The study treatment should be permanently discontinued if severe (Grade 3) or life-threatening (Grade 4) adverse reactions occur.

9.2. Infusion Reactions

Since SHR-1210 is a fully humanized monoclonal antibody, the possibility of infusion reactions is small, and no pre-dose prophylactics are required. If an infusion reaction occurs, the infusion should be slowed or interrupted according to the situation, and a supportive treatment should be given. In addition, prophylactics should be given before further administration. Signs and symptoms of acute infusion reactions (including cytokine release syndrome, angioedema, anaphylactic shock, and allergic reaction, refer to the terms and criteria in NCI CTCAE v4.03) usually occur during or after the infusion and disappear within 24 h after infusion. The signs and symptoms include: allergic reaction/hypersensitivity reaction (including drug-induced fever), coughing, chills, rigor, dizziness, headache, fatigue (weakness, somnolence), rash/peeling skin, pruritus/itching, arthralgia, myalgia, hypotension/hypertension, nausea, vomiting, diaphoresis, tachycardia, cancer pain, urticaria, dyspnea (shortness of breath), or bronchospasms. All Grade 3 or 4 infusion reactions should be reported to the sponsor within 24 h. An infusion reaction meeting the criteria of an SAE should be reported as an SAE.

Management of allergic reactions should be based on the medical practice and guidelines of the study site. The treatment recommendations for infusion reactions are as follows for reference.

Table 4. Treatment recommendations for infusion reactions

CTCAE Grade	Clinical Symptoms	Clinical Management	SHR-1210 Treatment
Grade 1 (Mild)	Mild and transient reactions;	Bedside observation and close monitoring until recovery. (Pre-dose prophylactics are recommended for subsequent administrations: 50 mg of diphenhydramine or equivalent, and/or 325-1000 mg of acetaminophen, at least 30 min before the administration of SHR-1210)	Continuation
Grade 2 (Moderate)	Moderate reactions requiring treatment or interruption; rapidly resolve after symptomatic treatment (such as antihistamines, non-steroidal antiphlogistics, anesthetics, bronchodilators, intravenous fluids, etc.)	Intravenous administration of normal saline: 50 mg of diphenhydramine IV or equivalent and/or 325-1000 mg of acetaminophen; Bedside observation and close monitoring until recovery. Corticosteroids or bronchodilators can be considered based on clinical needs; The amount of investigational drug infused should be recorded in the original medical record; Pre-dose prophylactics are recommended for subsequent administrations: 50 mg of diphenhydramine or equivalent and/or 325-1000 mg of acetaminophen can be given at least 30 min before the administration of SHR-1210. Use corticosteroids (equivalent to 25 mg of hydrocortisone) when necessary.	Interruption. Re-administer at 50% of the initial rate after symptoms resolve. If no reaction occurs within 30 minutes, restore the original infusion rate (100%). Closely monitor. If the symptoms recur, the current SHR-1210 should be discontinued.
Grade ≥ 3 (Severe)	Grade 3: Severe reaction without rapid recovery upon treatment and/or interruption; or symptoms recur after alleviation; or the subject develops sequelae that requires hospitalization. Grade 4 (Life-threatening)	Immediately discontinue SHR-1210; Intravenous administer normal saline. • Bronchodilators are recommended: subcutaneous injection of 0.2-1 mg of 1:1000 adrenaline solution or slow intravenous injection of 0.1-0.25 mg of 1:10000 adrenaline solution, and/or 50 mg of diphenhydramine plus 100 mg methylprednisolone or equivalent by intravenous injection if necessary; • Based on the study site's guidelines for treating allergic reactions; Bedside observation and close monitoring until recovery.	Permanent discontinuation.

9.3. Symptomatic Treatment for Apatinib-Related Adverse Reactions

1) Hand-and-foot syndrome (HFS)

HFS is s skin toxicity with palmar-plantar dysaesthesia or acral erythema and manifests especially in areas under pressure or force. It may occur in patients with tumor during chemotherapy or molecular targeted therapy. HFSR is characterized by numbness, dysesthesia, paraesthesia, tingling, no pain or pain, skin swelling, or erythema, desquamation, chapping, scleroma-like blisters, and severe pain.

HFS grading:

Grade 1: numbness/dysesthesia/paraesthesia, painless swelling or erythema of the hands and/or feet and/or discomforts that does not affect normal activities.

Grade 2: painful erythema and swelling of the hands and/or feet and/or discomforts affecting patients' activities of daily living.

Grade 3: wet desquamation, ulcers, blisters, or severe pain of hands and/or feet and/or severe discomforts that causes the patients to be unable to work or perform activities of daily living. Intense pain and loss of skin function, relatively rare.

Symptomatic treatment and management of HFS:

Some necessary symptomatic and supportive treatments must be taken, including: strengthen skin care, keep skin clean, and avoid secondary infections; avoid pressure or friction; use moisturizers or lubricants, topically use lotions or lubricants containing urea and corticosteroids; topically use antifungal or antibiotic treatment if necessary.

Note: If a HFS of Grade 3 or above occurs for more than 3 consecutive times with an aggravating trend, the subject should discontinue the study treatment and withdraw from the clinical study.

2) Hypertension

Patients should be strictly screened according to blood pressure requirements in the inclusion and exclusion criteria prior to enrollment. Patients with hypertension can control the blood pressure by adjusting the dose of or adding new antihypertensive drugs before administering the investigational drug. The blood pressure must be under 140/90 mmHg (average of 2 blood pressure measurements taken at least 24 h apart) before randomization.

Monitoring and handling of such hypertension: Blood pressure should be monitored at least 3 times a week during the first 2 cycles of the targeted pharmacological treatment.

Since anti-VEGF/VEGFR targeted drugs can decrease the synthesis of NO and ultimately activate the renin-angiotensin-aldosterone system to cause hypertension, angiotensin converting enzyme (ACE) inhibitors (such as captopril, enalapril, benazepril, and cilazapril) are preferred for antihypertensive therapy. For some patients who are allergic or intolerant to ACE inhibitors, angiotensin II receptor blockers (ARB, such as losartan, valsartan, irbesartan and telmisartan) can be used for treatment. In addition to lowering the blood pressure, ARB is also beneficial for alleviating proteinuria. ACE inhibitors can be used in patients with chronic kidney diseases, proteinuria and metabolic syndrome; dihydropyridine calcium ion antagonists are suitable for elderly patients.

When subjects develop hypertension or aggravated hypertension during drug administration, the following measures should be used: 1) adjust the study drugs according to the protocol (see table below); 2) start the administration of antihypertensive drugs or adjust the dose of antihypertensive drugs.

Antihypertensive drugs recommended for the trial: 1) angiotensin converting enzyme inhibitor (ACEI); 2) angiotensin II receptor blocker (ARB); 3) dihydropyridine calcium channel blocker; 4) β-receptor blocker.

Diuretic antihypertensive drugs are not recommended. Antihypertensive drugs with an inhibitory effect on CYP3A4, such as nicardipine, diltiazem and verapamil, are prohibited during the administration period of the investigational drug. For those with hypertensive crisis, the application of apatinib should be terminated.

3) Hemorrhage

Symptomatic treatment should be actively given for gastrointestinal hemorrhage, including fecal occult blood (++) and above, hematemesis or bloody stool. Patients with upper gastrointestinal hemorrhage should be fasted and given acid suppression, gastric mucosal protection, hemostasis (transamin, reptilase, etc.), as well as octreotide if necessary; patients with lower gastrointestinal hemorrhage should be given hemostasis, blood transfusion and supportive care, etc.; for those whose bleeding cannot be controlled, assistance from the surgery department should be requested immediately.

Patients with hemoptysis should be given hemostasis, blood transfusion and supportive care, etc.; for those whose bleeding cannot be controlled, assistance from the surgery department should be requested.

Note: Patients with cerebral hemorrhage, Grade II or higher pulmonary hemorrhage, and Grade III or higher hemorrhage should stop the study treatment immediately, undergo symptomatic treatment, terminate apatinib administration, and discontinue SHR-1210 administration. Consider whether to resume SHR-1210 as appropriate after symptoms resolve or disappear.

4) Proteinuria

All subjects should be closely monitored for proteinuria throughout the entire treatment period, especially for those with a history of hypertension. For those with a urine protein result of ++ to +++ in 2 consecutive tests, a 24-h urine protein assay is required. For those with urine protein of ++++ and above, a 24-h urine protein assay is required.

Note: In case of nephrotic syndrome, the subject should discontinue the treatment permanently and withdraw from this clinical study.

5) Thrombosis

If any arterial thrombosis (such as cerebral ischemia, stroke, angina pectoris, myocardial infarction, etc.) occurs, the subject should discontinue the treatment immediately and withdraw from the study. In case of any symptomatic IV venous thrombosis, the subject should discontinue the treatment and withdraw from the study.

Once the symptoms are observed, symptomatic treatment, surgery, or anticoagulants shall be immediately given.

6) Fatigue and weakness

Fatigue and weakness are common tumor-related clinical symptoms, the cause of which might be electrolyte disturbance, abnormal liver function, abnormal cardiac function, etc. Also, fatigue and weakness are common adverse reactions of targeted anti-angiogenic drugs, such as sunitinib, pazopanib, and sorafenib. Clinical reports show that targeted anti-angiogenic drugs may increase the incidence of fatigue and weakness through hypothyroidism.

In previously completed clinical trial of apatinib, subjects in the test group showed a higher incidence of fatigue and weakness than those in the control group, and the mechanism behind the increased incidence of fatigue and weakness caused by apatinib is yet unidentified.

Therefore, close attention should be paid when a patient shows and reports Grade II or higher fatigue and weakness. In the case of Grade III or higher fatigue and weakness, the patient should be admitted to the hospital immediately for detailed examinations to exclude possible reasons such as electrolyte disturbance, abnormal liver function, cardiac dysfunction (ECG, echocardiography), and abnormal hormone levels (adrenal hormones, thyroid hormones).
A symptomatic treatment should be given and the dose should be interrupted or modified according to the principle of dose modification.

7) Abdominal pain

Abdominal pain is not uncommon in the treatment with apatinib, which are mostly a concomitant symptom of tumor. Also, gastrointestinal perforation occasionally occurs in clinical trials of apatinib and other anti-angiogenic drugs. For subjects with abdominal pain, the investigator should be cautious of potential gastrointestinal perforation. Upon the observation of gastrointestinal perforation, the drug should be discontinued immediately, and the subject should withdraw from the trial and be given an active symptomatic treatment.

8) Interstitial pulmonary fibrosis

The clinical physicians should fully understand the conditions of subjects and be familiar with the drugs that may lead to pulmonary toxicity. The clinical symptoms and changes in chest X-ray or CT are closely monitored. Once cough, chest tightness, labored breathing, dyspnea, and hemoptysis of unknown causes, the drug should be discontinued as soon as other causes (such as infection and heart failure) are ruled out. Alveolar lavage fluid analysis and surgical lung biopsy are important means to diagnose interstitial lung disease. Currently, no therapy yields a satisfactory result against pulmonary fibrosis, and correction of hypoxemia and timely administration of corticosteroids are recommended following "Guidelines for Diagnosis and Treatment of Idiopathic Pulmonary (Interstitial) Fibrosis" issued by the Chinese Medical Association Respiratory Diseases Branch.

Note: Consult specialists when necessary.

10. INDEPENDENT IMAGING EVALUATION

On-site imaging review will be performed at each study site, and the Independent Review Committee (IRC) will perform central review on the primary efficacy endpoint of ORR.

Imaging assessments will be performed by an experienced and qualified study physician designated by each study site. All the imaging data related to efficacy assessment should be archived on CD and sent by each study site to the Independent Review Committee for evaluation at regular intervals.

Independent imaging assessment will be performed blindly by two independent radiologists. In the event of disagreement between these 2 independent radiologists, a third radiologist will make the final judgment. See the "Independent Review Committee Charter" for details.

Treatment response will be evaluated by independent radiologists in accordance with the RECIST 1.1 and mRECIST criteria.

11. DATA ANALYSIS/STATISTICS

Data analysis will not be performed by study sites (data from all participating sites will be combined).

Screen failure subjects (those who signed the informed consent form but did not receive any treatment) and the reasons for screen failures will be included in the statistical analysis.
In addition, these subjects will be reported in a separate list.

11.1. Sample Size

This is a single-arm study with its primary efficacy endpoint being ORR. This study includes patients refractory to sorafenib and patients not treated with sorafenib. The sample size of these two groups is calculated based on the hypothetic conditions below.

Subjects refractory to sorafenib

Assuming that the treatment efficacy is less than 10% for standard treatment and is 25% for PD-1 plus apatinib, and a two-sided alpha = 0.05, then a total of 64 patients are required to provide a power of 90%. If the dropout rate is 20%, 80 subjects should be enrolled.

The number of patients who failed sorafenib can be increased to 120 at late stages in the trial to better determine the efficacy and safety of the investigational drug in this population.

Subjects not treated with sorafenib

Assuming that the treatment efficacy is less than 15% for standard treatment and is 30% for SHR-1210 plus apatinib, and a two-sided alpha = 0.05, then a total of 56 subjects are required so that the half-width of the 95% confidence interval of overall ORR does not exceed 12%.

11.2. Statistical Hypothesis and Discriminatory Rules

The hypothesis for population refractory to sorafenib are as follows:

Null hypothesis: ORR = 10%

Alternative hypothesis: ORR ≠ 10%

Efficacy is established for PD-1 antibody SHR-1210 plus apatinib in patients with advanced HCC refractory to sorafenib if the lower limit of the 95% CI of ORR is greater than 10%.

11.3. Statistical Analysis Plan

Statistical analysis for data collected in this study will be documented in the Statistical Analysis Plan (SAP) which will be finalized and filed by the sponsor. If there are any changes to the study protocol that are deemed significant by the sponsor or principal investigator to the statistical analysis, the SAP will be revised accordingly to conform to the study protocol. Relevant content in this SAP that is relevant to the protocol may be revised. However, if revised content involves the main and/or key factors of the protocol, such as the definition of primary endpoints or their analysis, such content in the protocol will be revised.

11.4. Analysis Population

- Full analysis set: including all enrolled subjects who have received at least one study dose.
- Safety analysis set: including all enrolled patients who have received at least one dose of the investigational drug and have safety data after the dose. This dataset is used for safety analysis.

11.5. Statistical Methods

11.5.1. Basic Methods

Trial results are mainly analyzed using descriptive statistics. Numerical data will be summarized in means, standard deviations, medians, maximums, and minimums. Categorical data will be summarized in frequencies (proportions), percentages, and confidence intervals.

Statistical analysis will be performed using the SAS 9.4 or above.

11.5.2. Baseline characteristics

The mean, standard deviation, median, maximum, and minimum of quantitative data such as age, height, and weight are calculated, and the frequency and percentage of qualitative data such as gender and ECOG PS are listed.

11.5.3. Efficacy Endpoint Analysis

Point estimates and 95% CI will be used for efficacy endpoints such as objective response rate (ORR) and disease control rate (DCR). The confidence intervals are estimated using the Clopper-Pearson method.

PFS, DOR, OS, and 9-month and 12-month survival rates, as well as their respective 95% CIs will be estimated using the Kaplan-Meier method. The two-sided 95% CI of the median PFS, DOR, and OS will be estimated using Brookmeyer-Crowley method. For the two-sided 95% CI of 9-month and 12-month overall survival rates, the 95% CI after log-log transformation is calculated using the normal approximation method followed by inverse transformation. TTR is described using mean, standard deviation, median, maximum, and minimum.

11.5.4. Safety Analysis

Descriptive statistical analysis is primarily used to analyze the AEs, CTCAE Grade ≥ 3, serious adverse events and adverse reactions, ≥ Grade 3 adverse reactions, and AEs leading to dose modification in each population (the adverse reactions are defined as adverse events that are "definitely related, possibly related, and not assessable" to the investigational drug). Laboratory test results describe the baseline and the worse on-treatment value.

Besides, irAEs, including immune-related pneumonitis, immune-related enteritis, immune-related thyroid dysfunction, immune-related nephritis and renal failure, and immune-related hypophysitis, will be categorized and summarized using above summary analysis of AEs.

11.5.5. Exploratory Analysis

Serum HBsAg and alpha-fetoprotein (AFP) levels are summarized descriptively;

SHR-1210-related biomarkers, such as PD-L1 in tumor tissue or TMB in tumor tissue and plasma will be summarized using descriptive statistics.

Acyl-CoA at baseline: The relationship between the expression levels of SOAT1, NPC1, and TGF-β and treatment response will also be summarized using descriptive statistics.

The results of the exploratory biomarker study will be reported separately (except for the results of descriptive statistical analysis) and will not be included in the clinical study report.

The results from the exploratory biomarker study may be combined and analyzed with biomarker data from other studies of the investigational drug to formulate a hypothesis which will be further validated in future studies.

12. DATA MANAGEMENT METHOD

12.1. Data Recording

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

Hengrui will notify the investigator when these study records are no longer needed.

If the investigator withdraws from the study (e.g., change of positions, retirement), the records should be transferred to designated personnel recognized by both parties (such as another investigator or IRB). Hengrui must be notified in writing for these types of transfers.

12.1.1. Documentation of the Original Medical Records

Original medical records should be retained in their entirety as the source documents.
The investigator is responsible for filling out and keeping the original medical records. Medical records should be neat and legible so the sponsor's monitor can verify data with the eCRF during each inspection.

12.1.2. eCRF Entry

Clinical trial data are collected using the HRTAU EDC system.

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

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

Modifications: The system instructions must be followed when correcting the eCRF data as needed, and the reason for data correction must be recorded.

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

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

12.1.3. eCRF Review

The investigator must complete, review, and submit the eCRF within 10 working days after the end of each subject's treatment course. The investigator should promptly respond to queries raised by the monitor, data manager, and medical reviewer. After data cleaning is completed, the investigator will sign the completed eCRF for verification.

12.2. Data Monitoring and Auditing

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

To confirm that the study protocol is adhered to; the records on CRF is correct, and complete and consistent with the original medical records and laboratory test results, and whether there are errors or omissions in the data. The monitor must check the content in eCRF against the source documents one by one, ensuring that the data in eCRF are consistent with the original source. This process is also known as source data verification (SDV).

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

12.3. Data Management

12.3.1. EDC Database Establishment

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

12.3.2. Data Entry and Verification

After the investigator completes and submits eCRF, the monitor, data manager, and medical reviewer should review the data. Questions during the review are submitted to the investigator in the form of queries. After data cleaning is completed, the investigator should sign the completed eCRF for verification.

12.3.3. Database Locking

After SDV is completed by the CRA, the study director, sponsor, statistician, and data administrator must jointly perform the final quality control of all data in the database, summarize all protocol deviations and violations, and hold the data verification meeting to determine the analysis dataset to which each subject belongs (including FAS, PPS, and SS), the judgment of missing values, and the handling of outliers. The database will be locked after quality requirements have been met. The data manager will export the data to the statistics department for data analysis.

12.3.4. Data Archiving

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

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

13. SOURCE DATA AND DOCUMENTS

According to ICH E6, relevant regulations, and requirements for subject's personal information protection of the study sites, each study site must properly keep all the treatment and scientific records related to this study. As a part of the study that Jiangsu Hengrui Pharmaceuticals Co., Ltd. sponsors or participates in, each study site must allow the authorized representative of Jiangsu Hengrui Pharmaceuticals Co., Ltd. and regulatory authorities to inspect the clinical records (which may be copied if permissible by law) for quality review, audit, and evaluations of safety, study progress, and data validity.

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

14. QUALITY ASSURANCE AND QUALITY CONTROL

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

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

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

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

The drug regulatory authorities, Institutional Review Board (IRB)/Independent Ethics Committee (IEC), sponsor's monitor and/or auditor may carry out systemic inspection of study-related activities or documents to assess whether the study is implemented based on the study protocol, SOPs, and relevant regulations and whether the study data is recorded in a prompt, truthful, accurate, and complete manner.

The audit will be conducted by research personnel that are not directly involved in the clinical trial.

15. REGULATORY ETHICS, INFORMED CONSENT, AND SUBJECT PROTECTION

15.1. Regulatory Considerations

According to the corresponding regulatory requirements in China, an application should be submitted to the NMPA before starting a new drug trial and the clinical trial can only be carried out after an approval is obtained.

The clinical approval number for SHR-1210 preparation is 2016L01455 and the clinical approval number for apatinib preparation is 2014L00877.

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

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

15.2. Ethical Standards

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

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

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

15.3. Independent Ethics Committee

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

15.4. Informed Consent

15.4.1. ICFs and other written information for subjects

Jiangsu Hengrui Pharmaceuticals Co., Ltd. will provide a suitable sample of the ICF to the investigator, including all the contents required by ICH, GCP, and regulatory authorities. The ICF sample will adhere to the ethical principles mentioned in the "Declaration of Helsinki".

The ICF sample will describe the investigational drugs and study process in detail and fully explain the risks of the study to the subjects. Written ICFs must be obtained before the administration of the investigational drugs.

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

The ICF should state that the identity of the subjects must be remained confidential, but the medical representative of Jiangsu Hengrui Pharmaceuticals Co., Ltd. and regulatory authorities are allowed to access the information.

15.4.2. Informed consent process and records

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

15.5. Confidentiality of Subject Information

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

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

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

Subject's study data that are collected for statistical analysis and scientific reports will be uploaded and kept in the HRTAU EDC system, which should not include the subject's contact information and identification information. Instead, individual subjects and their study data will be given a unique study identification number. The study data entry and study management system used by the research personnel at the study sites are all confidential and password-protected.

After subject's consent and local IRB approval are obtained, de-identified biological samples (this study only involves venous blood samples and paraffin blocks or slides of tumor tissue sent to the central laboratory for biomarker testing) will be stored in the central laboratory, and the data will be shared between the sponsor and various study sites for the same purpose. These samples can only be used for biomarker testing, and the subject privacy will be protected during the entire process.

After subject's consent and local IRB approval are obtained, the de-identified imaging information used for independent imaging evaluation will be kept in an independent image evaluation committee and the subject privacy will be protected during this entire process.

During the study, subjects have the right to withdraw the informed consent to use their biological samples or data in the future. However, subjects are no longer allowed to withdraw the informed consent for preserving their biological samples or data once the study has ended.

Study data and/or samples can be accessed from the central laboratory once the study has ended.

16. PUBLISHING OF STUDY RESULTS

The ownership of the study results belongs to both the PI and Hengrui. Hengrui does not limit the publication of any collected or generated data by the investigator, regardless of whether the results are beneficial to the investigational drug. The investigator must promise that no data relevant to the study and/or study results should be published on journals and academic or commercial conferences without written permission from Hengrui, and also understand that Hengrui will not disapprove the publication without reasons.

However, the investigator should inform the Hengrui in advance to review any proposed publication or other forms of release before submission or publication to prevent unintentional leakage of confidential information or unprotected inventions. The investigator should provide Hengrui with the manuscript, abstract, or full text of all planned publications (posters, invited lectures, or guest lectures) at least 30 days prior to the submission for publication or other forms of release. Hengrui will check the content according to the laws and regulations and intellectual property. To protect the intellectual property, especially before the acquisition of patent, the investigator should agree to delay or cancel the publication. Before open publication, Hengrui can require the investigator to delete any previously unpublished confidential information.

The investigator is not allowed to mention Hengrui in their promotional materials or publications before obtaining written agreement from Hengrui. In the meantime, sponsors are not allowed to use the investigator's name in promotional materials or publications before obtaining written agreement from the investigator and/or collaborator.

17. CLINICAL TRIAL PROGRESS

Anticipated enrollment of the first subject: March 2018

Anticipated enrollment of the last subject: December 2018

Anticipated study completion date: June 2019

18. REFERENCES

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Appendix 1 Performance Status (ECOG)

(Eastern Cooperative Oncology Group)

Score	Description
0	Asymptomatic, fully active, able to carry on all performance without restriction.
1	Symptomatic, restricted in physically strenuous activity but ambulatory and able to carry out physical activities of a light or sedentary nature, e.g., light house work, office work.
2	Symptomatic, ambulatory and capable of all self-care but unable to carry out any physical activities; up and about more than 50% of waking hours (confined to bed < 50% of waking hours).
3	Symptomatic, capable of only limited self-care; confined to bed or chair more than 50% of waking hours, but not totally confined to bed.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.
5	Death.

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Appendix 2 Response Evaluation Criteria in Solid Tumors (RECIST v1.1)

Response Evaluation Criteria in Solid Tumors Version **1.1** (Excerpt)

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

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

1 Background

Omitted

2 Purpose

Omitted

3 Measurability of tumor at baseline

3.1 Definitions

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

3.1.1 Measurable Lesions

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

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

3.1.2 Non-Measurable Lesions

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

3.1.3 Special Considerations Regarding Lesion Measurability

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

Bone lesions:

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

Cystic lesions:

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

Lesions with prior local treatment:

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

3.2 Method of Measurement

3.2.1 Measurements of Lesions

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

3.2.2 Method of Evaluation

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

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

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

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

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

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

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

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

4 Tumor Response Assessment

4.1 Assessment of Overall Tumor Burden and Measurable Lesions

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

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

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

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

Lymph nodes merit special mention since they are normal tissues which may be visible by imaging even if not involved by tumor metastasis. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes needs to be measured at baseline. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by tumor metastasis. Nodule size is normally reported as two dimensions in the plane in which

the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smallest of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. Nodes with short axis ≥ 10 mm but < 15 mm should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

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

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

4.3 Response Criteria

4.3.1 Evaluation of Target Lesions

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

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

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

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

4.3.2 Precautions for Target Lesion Assessment

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if complete response criteria

are met, since a normal lymph node is defined as having a short axis of < 10 mm. CRFs or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

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

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

4.3.3 Evaluation of Non-Target Lesions

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

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

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

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

4.3.4 Special Notes on Assessment of Progression of Non-Target Lesions

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

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

4.3.5 New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of radiographically detected lesions; however, the finding of a new lesion should

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

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

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

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

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

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

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

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

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

4.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the trial until the end of trial taking into account any necessary requirement for confirmation. On occasion a response may not be documented until after the end of treatment so protocols should be clear if

post-treatment assessments are to be considered in the evaluation of best overall response. Protocols must specify how any new treatment introduced before progression will affect best response evaluation. The patient's best overall response evaluation will depend on the findings of both target and non-target diseases and will also take into consideration the characteristics of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to determine either one is the best overall response.

4.4.1 Time Point Response

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

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

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

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

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

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

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

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

4.4.2 Missing Assessments and Inevaluable Designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable at that time point. If only a subset of lesion measurements is made at an evaluation, usually the case is also considered not evaluable at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) has/have no effect on the assigned time point response. This would be most likely to happen in the case of PD.
For example, if a patient has 3 lesions that sum to 50 mm at baseline but only 2 lesions are evaluable with a sum of 80 mm at subsequent follow-ups, the patient will be evaluated as having progressive disease, regardless of the impact of the missing lesion.

4.4.3 Best Overall Response: All Time Points

The best overall response is determined once all the data for the patient are known.

Best response determination in trials where confirmation of complete or partial response is not required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD in evaluation at Cycle 1, PR at Cycle 2, and PD at the last cycle has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time calculated from baseline. If the minimum time is not met when SD is otherwise the best overall response, the patient's best overall response depends on the subsequent assessments. For example, a patient who has SD at Cycle 1, PD at Cycle 2 and does not meet minimum duration for SD, will have a best overall response of PD. The same patient lost to follow-up after the first SD assessment would be considered not evaluable.

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

Table 3. Best overall response confirmed for CR and PR

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

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

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

4.4.4 Special Notes on Response Assessment

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

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

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

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

In some circumstances it may be difficult to distinguish residual lesions from normal tissues. When the evaluation of complete response depends upon this definition, it is recommended that the local lesion be investigated before assigning a status of complete response. FDG-PET may be used to confirm a response to a CR in a manner similar to a biopsy in cases where a residual

radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

4.5 Frequency of Tumor Re-Evaluation

Frequency of tumor re-evaluation during treatment should be protocol-specific and consistent with the type and schedule of treatment. However, in the Phase II trials where the beneficial effect of treatment is not known, follow-ups for every 6-8 weeks (timed to coincide with the end of a cycle) is reasonable. Interval adjustments could be justified in specific regimens or circumstances. The protocol should specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumor type under study) and how often evaluations are repeated. Normally, all target and non-target sites are evaluated at each assessment. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when CR is identified in target disease or when progression in bone is suspected.

After the treatment, the need for tumor re-evaluations depends on whether the trial has as made the response rate or the time to an event (progression/death) an endpoint. If time to an event (e.g., TTP/DFS[1]/PFS) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomized comparative trials in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6-8 weeks on treatment or every 3-4 months after treatment) and should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment.

4.6 Response Evaluation/Confirmation of Response Duration

4.6.1 Confirmation

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, i.e., in

randomized trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

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

4.6.2 Duration of Overall Response

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

4.6.3 Duration of Stable Disease

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

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

4.7 PFS/TTP

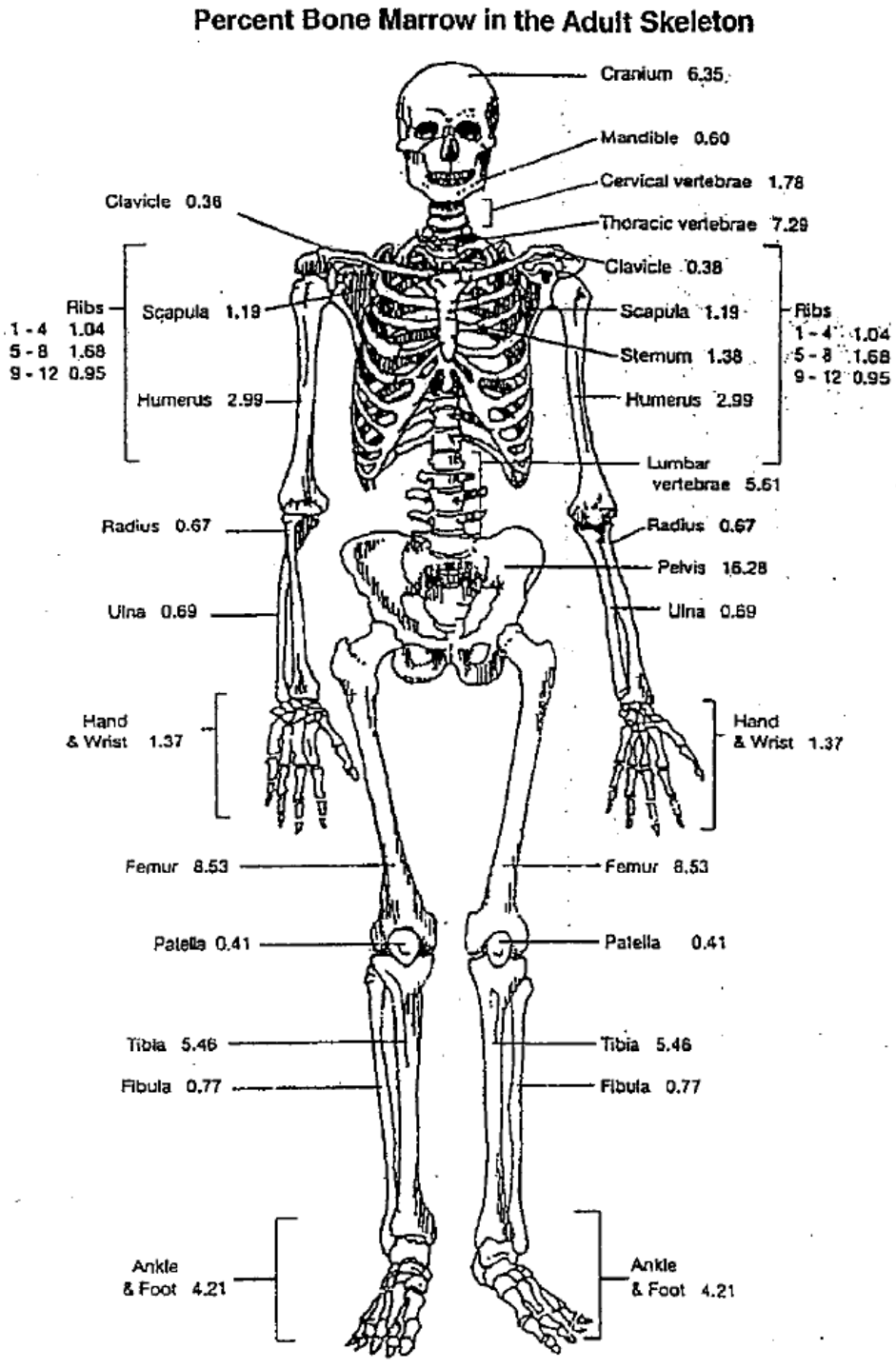
4.7.1 Phase II clinical trials

This guideline is focused primarily on the use of objective response as study endpoints for phase II trials. In some circumstances, response rate may not be the optimal method to assess the potential anti-cancer activity of new agents/regimens. In such cases PFS/PPF at landmark time points, might be considered appropriate alternatives to provide an initial signal of biologic effect of new agents. It is clear, however, that in an uncontrolled trial, these measures are subject to

criticism since an apparently promising observation may be related to biological factors such as patient selection and not the impact of the intervention. Thus, phase II screening trials utilizing these endpoints are best designed with a randomized control. Exceptions may exist where the behavior patterns of certain cancers are so consistent (and usually consistently poor), that a non-randomized trial is justifiable. However, in these cases it will be essential to document with care the basis for estimating the expected PFS or PPF[2] in the absence of a treatment effect.

[2] Proportion of progress-free

Appendix 3 Percent Bone Marrow Content in Human Skeleton



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

Appendix 4 Management Principles for irAEs

1. Management Principles for Gastrointestinal AEs

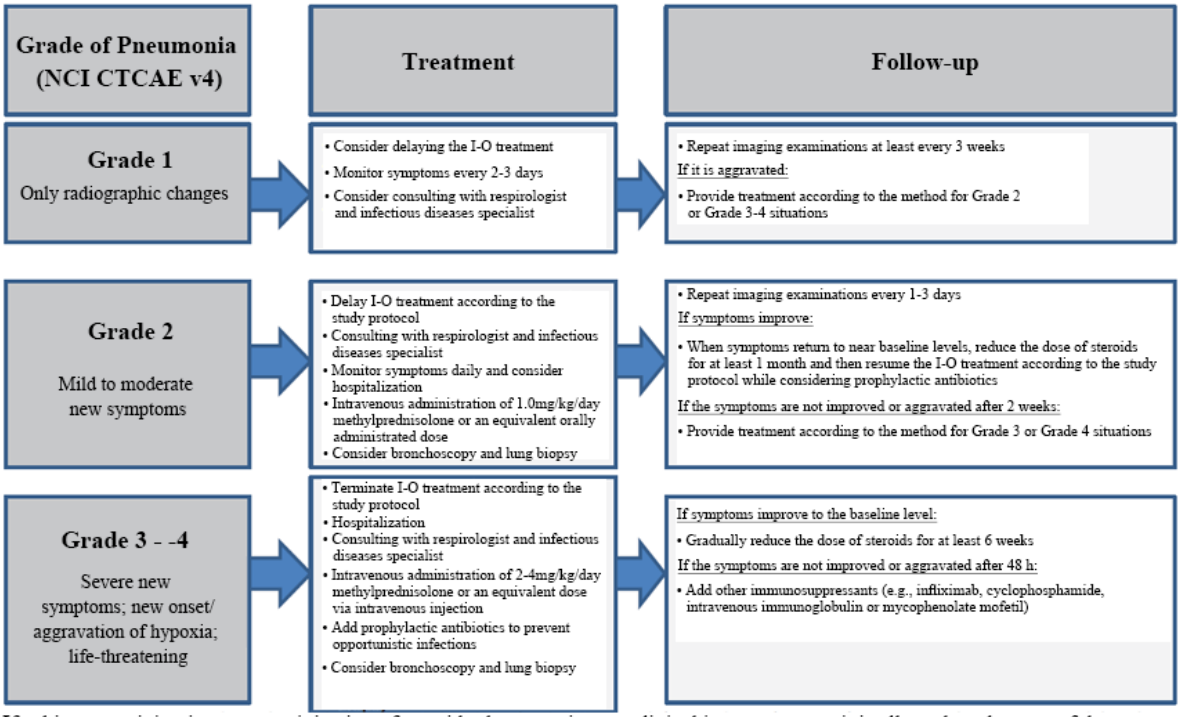
Non-inflammatory causes of disease should be excluded.
Opioids/anesthetics may mask the symptoms of perforation.
Do not use infliximab in the case of perforation/sepsis.

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

If subjects receiving intravenous injection of steroids show continuous clinical improvements, it is allowed, at the start of dose tapering or earlier, to switch to oral administration of corticosteroids (such as prednisone) at equivalent dose. When switching to oral corticosteroids with an equivalent dose, it should be considered that the bioavailability of oral corticosteroids is relatively low.

2. Management Principles for Pulmonary AEs

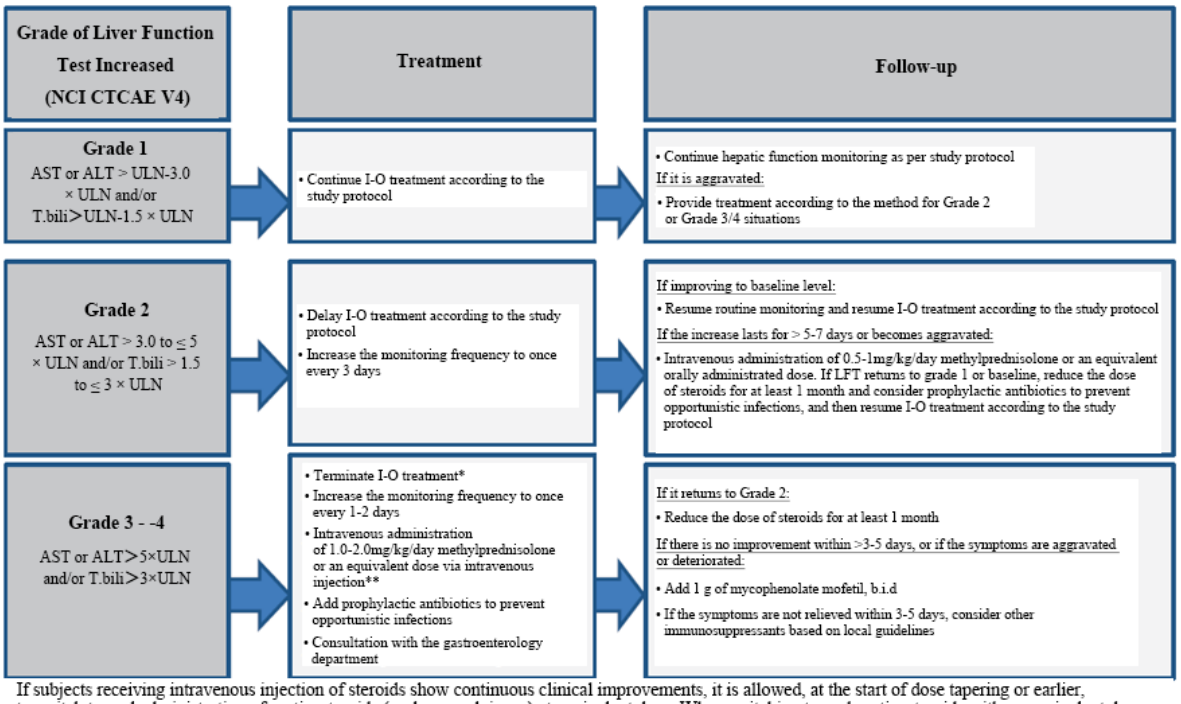
Non-inflammatory causes of disease should be excluded. If it is due to a non-inflammatory cause, a symptomatic treatment should be given while the I-O therapy should be continued. Imaging evaluation and consultations with the respiratory department should be performed.



If subjects receiving intravenous injection of steroids show continuous clinical improvements, it is allowed, at the start of dose tapering or earlier, to switch to oral administration of corticosteroids (such as prednisone) at equivalent dose. When switching to oral corticosteroids with an equivalent dose, it should be considered that the bioavailability of oral corticosteroids is relatively low.

3. Management Principles for Hepatic AEs

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



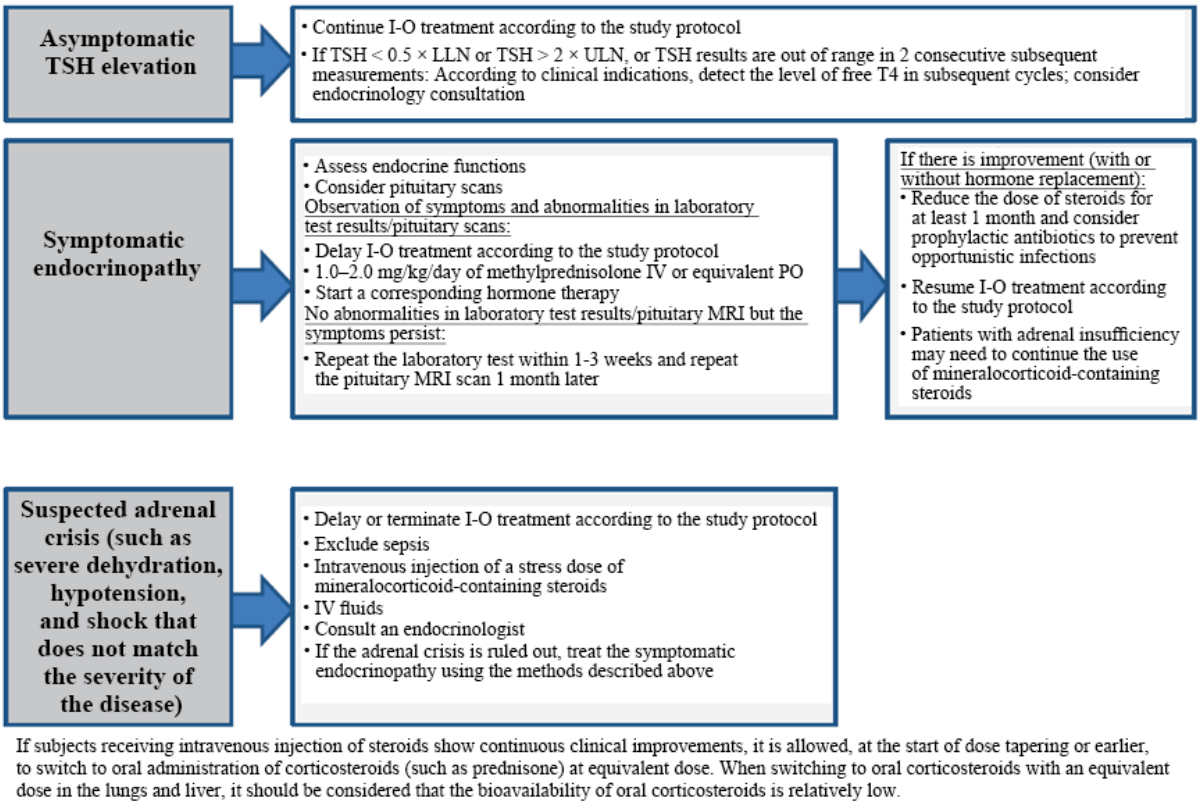
If subjects receiving intravenous injection of steroids show continuous clinical improvements, it is allowed, at the start of dose tapering or earlier, to switch to oral administration of corticosteroids (such as prednisone) at equivalent dose. When switching to oral corticosteroids with an equivalent dose, it should be considered that the bioavailability of oral corticosteroids is relatively low.

***If AST/ALT ≤ 8×ULN and T.bili ≤ 5×ULN, the I-O treatment can be delayed rather than discontinued.**

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

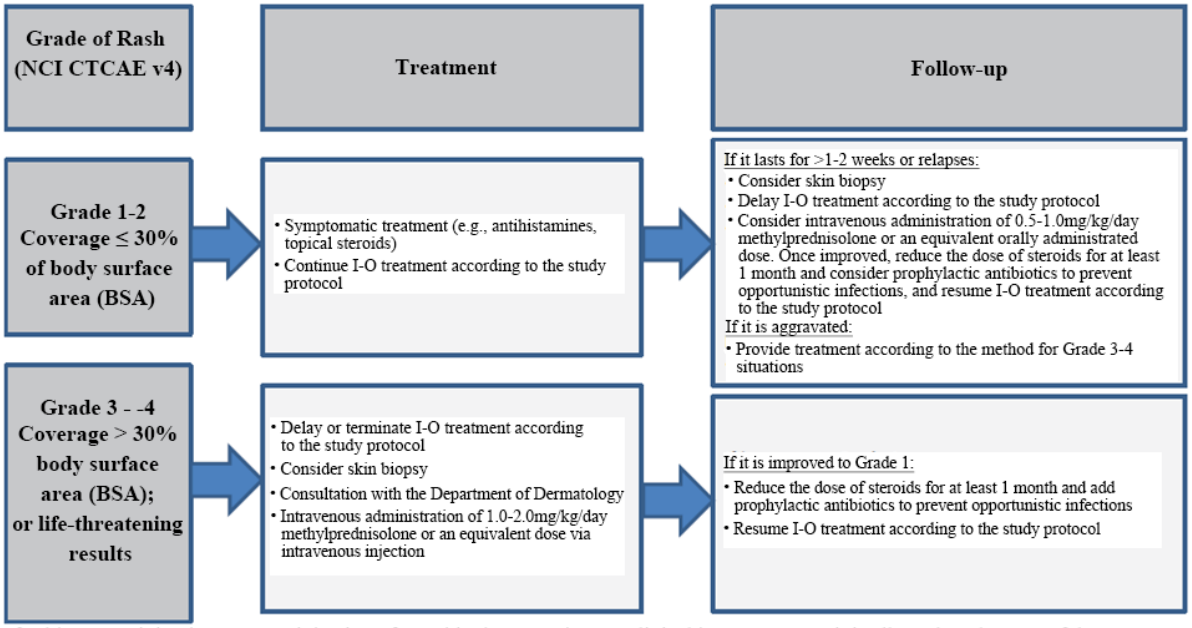
4. Management Principles for Endocrine AEs

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



If subjects receiving intravenous injection of steroids show continuous clinical improvements, it is allowed, at the start of dose tapering or earlier, to switch to oral administration of corticosteroids (such as prednisone) at equivalent dose. When switching to oral corticosteroids with an equivalent dose in the lungs and liver, it should be considered that the bioavailability of oral corticosteroids is relatively low.

5. Management Principles for Skin AEs



If subjects receiving intravenous injection of steroids show continuous clinical improvements, it is allowed, at the start of dose tapering or earlier, to switch to oral administration of corticosteroids (such as prednisone) at equivalent dose. When switching to oral corticosteroids with an equivalent dose in the lungs and liver, it should be considered that the bioavailability of oral corticosteroids is relatively low.

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

(2008). Sorafenib in Advanced Hepatocellular Carcinoma. The New England Journal of Medicine *n engl j med 359;4 www.nejm.org july 24, 2008*.