Title: A Phase II Clinical Study of PD-1 Antibody SHR-1210 in Combination with Apatinib Mesylate or Chemotherapy in the Treatment of Advanced Primary Liver Cancer or Extrahepatic Cholangiocarcinoma
Clinical trial registration number: NCT03092895
Version Date: 12 May., 2018

A Phase II Clinical Study of PD-1 Antibody SHR-1210 in Combination with Apatinib Mesylate or Chemotherapy in the Treatment of Advanced Primary Liver Cancer or Extrahepatic Cholangiocarcinoma

Protocol No.: **SHR-1210-APTN-II-203-PLC**

Version No. **2.0**

Version Date: **12 May, 2018**

[redacted] [redacted]

[redacted] [redacted]

Sponsor: **Jiangsu Hengrui Pharmaceuticals Co., Ltd.**

Version History/Revision History

Document	Version Date	Amendment Rationale and Summary of Changes
1.0	17 Feb., 2017	Not applicable
2.0	12 May 2018	Increased the number of subjects with extrahepatic cholangiocarcinoma in group B; added the study basis of immunotherapy combined with oxaliplatin plus gemcitabine chemotherapy in malignant bile duct tumors; adjusted the number of cases in group B due to changes in the study population; revised the section of statistics for group B; revised articles 3 and 5 of the inclusion criteria; added relevant contents of the investigational drug gemcitabine;

Sponsor's Signature Page

I have read and confirmed this study protocol (study no.: **SHR-1210-APTN-II-203-PLC**, version no.: 2.0, version date: 12 May 2018). I agree to fulfill my duties in accordance with Chinese laws, the Declaration of Helsinki, the Chinese GCP, and this study protocol.

Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Sponsor's Medical Director: _____ (print)

_____(signature)

Signature Date: _____

Telephone: _____

[redacted]

Principal Investigator's Signature Page (Coordinating Center)

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

Study Site: [redacted]

Principal Investigator:_____(print)

_____(signature)

Signature Date:_____

Telephone: _____

Address:_____

Postal Code:_____

Principal Investigator's Signature Page (Participating Center)

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

Study Site: _____

Principal Investigator:_____(print)

_____(signature)

Signature Date: _____

Telephone: _____

Address:_____

Postal Code: _____

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PROTOCOL SYNOPSIS

Study Title	A Phase II Clinical Study of PD-1 Antibody SHR-1210 in Combination with Apatinib Mesylate or Chemotherapy in the Treatment of Advanced Primary Liver Cancer or Extrahepatic Cholangiocarcinoma
Protocol No.	SHR-1210-APTN-II-203-PLC
Version No.	2.0
Sponsor	Jiangsu Hengrui Pharmaceuticals Co., Ltd.
[redacted]	[redacted]
[redacted]	[redacted]
Study Population	Patients with advanced primary liver cancer (PLC)/extrahepatic cholangiocarcinoma
Study Objective	Primary Objectives: • The safety and tolerability of PD-1 antibody SHR-1210 in combination with apatinib mesylate or the FOLFOX4 or GEMOX regimen in the treatment of advanced primary liver cancer or extrahepatic cholangiocarcinoma. Secondary Objectives: • To preliminarily observe the efficacy of PD-1 antibody SHR-1210 in combination with apatinib mesylate or the FOLFOX4 or GEMOX regimen in the treatment of advanced primary liver cancer or extrahepatic cholangiocarcinoma.
Study Endpoints	Primary Endpoints: • The incidence and severity of adverse events (AEs) and serious adverse events (SAEs) (per the NCI-CTCAE V4.03 criteria). Secondary Endpoints: (per the RECIST 1.1 criteria) • Objective response rate (ORR) • Duration of response (DoR) • Disease control rate (DCR) • Time to progression (TTP) • Overall survival (OS)

Study Design

This study is an open-label phase II study, and 152 patients with advanced primary liver cancer or extrahepatic cholangiocarcinoma are intended to be enrolled. Subjects will be enrolled into treatment group A or B based on whether they have received systemic treatment before.

Subjects in group A will receive treatment of SHR-1210 in combination with apatinib mesylate (APTN) for exploring the optimal dose first. The objective is to determine the optimal dose of SHR-1210 combined with APTN in patients with advanced primary liver cancer. After the determination of the optimal dose of the combined medication, the case extension stage was proceeded for collecting sufficient safety data of the combination of immunotherapy and targeted therapy.

Subjects in group B will receive treatment of SHR-1210 in combination with the FOLFOX4 or GEMOX regimen. The objective is to explore the safety and tolerability of the immunotherapy combined with systemic chemotherapy.

Subjects in group A will be given dose level 1 as the starting dose. The subjects will be enrolled in the group in sequence (see Table 1) from low dose to high dose to explore the optimal dose. The first cycle (28 days) of continuous medication is the tolerability observation period. After the tolerability observation period, if none of the 3 subjects experienced clinically significant toxicity, the next group of dose may be explored. If 1 of the 3 subjects developed clinically significant toxicity, another 3 subjects will be enrolled. If no clinically significant toxicity was observed in the later-enrolled 3 subjects, the next group of dose may be explored. If ≥ 1 of the 3 later-enrolled subjects developed clinically significant toxicity again, the dose exploration will be terminated. The dose prior to the current one is the tolerable dose.

Also, the Bayesian logistic regression model (BLRM) was used as an auxiliary analysis to help explore the probability of clinically significant toxicity at different doses.

Finally, the optimal dose level for case extension is determined through dose exploration, with 8-12 subjects enrolled, to collect sufficient safety data for the combination therapy. The dose levels for group A are as follows:

Dose Level	SHR-1210	Apatinib Mesylate (APTN)	Number of Enrolled Subjects
1	3 mg/kg Q2W	125 mg QD (once daily)	3-6
2	3 mg/kg Q2W	250 mg QD	3-6
3	3 mg/kg Q2W	375 mg QD	3-6
4	3 mg/kg Q2W	500 mg QD	3-6

A regimen will be selected by the investigator for the subjects in group B according to Table 2. Six (6) subjects are first enrolled to receive treatment at dose level 1. If the proportion of subjects showing clinically significant toxicity in the 6 subjects is < 0.33, some other 122 subjects will be enrolled to receive treatment at the same dose level. The dose levels for group B are as follows:

<table>
<tr><th>Dose Level</th><th>SHR-1210</th><th>FOLFOX4</th><th>Number of Enrolled Subjects</th></tr>
<tr><td rowspan="4">1</td><td rowspan="4">3 mg/kg Q2W</td><td>D1: Oxaliplatin (OXA) 85 mg/m^2 (2-h infusion) + levoleucovorin (LV) 200 mg/m^2 (2-h infusion), followed by fluorouracil 400 mg/m^2 (bolus injection), and fluorouracil 600 mg/m^2 (22-h infusion)
D2: Levoleucovorin (LV) 200 mg/m^2 (2-h infusion), followed by fluorouracil 400 mg/m^2 (bolus injection), and fluorouracil 600 mg/m^2 (22-h infusion)
Q2W</td><td rowspan="4">Approximately 122 subjects</td></tr>
<tr><td>GEMOX</td></tr>
<tr><td>D1: Gemcitabine 800 mg/m^2 (80-min infusion)
D2: Oxaliplatin (OXA) 85 mg/m^2 (2-h infusion)
Q2W</td></tr>
<tr><td colspan="3">During the study period, imaging tumor assessments are performed every 8 weeks (± 7 days) until disease progression or the subject's initiation of other anti-tumor treatments.</td></tr>
</table>

Screening Criteria

Inclusion Criteria:

1. Male and female subjects aged 18-70 years old.
2. Patients with histologically or cytologically confirmed advanced primary liver cancer or extrahepatic cholangiocarcinoma (only applicable to group B, including gallbladder cancer and common bile duct cancer) who are not suitable for surgery or local treatment, and have at least one measurable lesion (RECIST 1.1 criteria).
3. Group A: Patients who have previously undergone systemic therapy for advanced primary liver cancer, molecular targeted therapy (sorafenib, etc.) and/or systemic chemotherapy (monotherapy or combination therapy) but have failed or become intolerable;

   Group B: Patients who have not previously undergone systemic treatment (molecular targeted therapy or chemotherapy) of advanced primary liver cancer or extrahepatic cholangiocarcinoma.
4. There must have been at least a 2-week interval between the completion of previous anti-tumor treatment and the start of the investigational drug, or have reached the drug wash-out period (that is, 5 times the half-life of the drug), and treatment-related AE resolved to NCI-CTCAE Grade ≤ 1.
5. Subjects with primary liver cancer or a history of liver cirrhosis must meet the

Child-Pugh score: Class A and Class B (≤ 7 points).

6. ECOG PS: 0-1.
7. Expected survival ≥ 12 weeks.
8. Subjects with chronic HBV infection must have HBV-DNA < 500 IU/mL, and patients with positive HBsAg must receive antiviral treatment in accordance with the 2015 "Guidelines for the Prevention and Control of Chronic Hepatitis B". Patients with positive HCV-RNA must receive antiviral treatment in accordance with the 2015 "Guidelines for the Prevention and Control of Chronic Hepatitis C" and hepatic function tests must be within the normal range.
9. Major organs must function normally, meeting the following criteria:

   (1) Hematology: (no blood transfusion or use of hematopoietic stimulating factors within 14 days before screening)

   1) HB ≥ 90 g/L;
   2) ANC ≥ 1.5×10^9/L;
   3) PLT ≥ 80×10^9/L;

   (2) Biochemistry: (no blood transfusion or use of blood products within 14 days prior to screening)

   1) ALB ≥ 29 g/L;
   2) ALT and AST < 2.5 × ULN;
   3) TBIL ≤ 1.5 × ULN;
   4) Creatinine ≤ 1.5 × ULN;

   (3) Prothrombin time (PT) - International Normalized Ratio (INR) ≤ 2.3 or prothrombin time (PT) ≤ 6 seconds from normal
10. Female subjects of childbearing potential must have a negative serum or urine pregnancy results within 14 days prior to the start of the study treatment, and be willing to take effective contraceptive measures during the study period and within 60 days after the last dose of the investigational drug. Male subjects with partners of childbearing potential must have undergone surgical sterilization or agree to take effective contraceptive measures during the course of the study until 120 days after the last dose of the investigational drug.
11. Subjects must participate voluntarily, sign the informed consent form, have good compliance, and cooperate with follow-up visits.

Exclusion Criteria:

1. Known fibrolamellar hepatocellular carcinoma; other uncured malignancies in the past (within 5 years) or concurrently. Except for localized tumors that have been cured, such as basal cell carcinoma, squamous cell carcinoma, superficial bladder cancer, prostate carcinoma in situ, cervical carcinoma in situ, and breast carcinoma in situ.
2. Current or past metastasis to the central nervous system.

3. Symptomatic ascites requiring therapeutic paracentesis or drainage, or with a Child-Pugh score > 2.
4. History of gastrointestinal bleeding within the past 6 months or a high risk of bleeding such as esophageal varices with bleeding risk, active ulcers, and persistent positive fecal occult blood.
5. Known hereditary or acquired hemorrhage and thrombophilia, such as hemophilia patients.
6. Abdominal fistula, gastrointestinal perforation, or abdominal abscess within 2 months prior to the study.
7. Grade II or higher myocardial ischemia or myocardial infarction, uncontrolled arrhythmias (including QTcF interval ≥ 450 ms in males and ≥ 470 ms in females) (QTc interval calculated using Fridericia's Formula).
8. NYHA Class III-IV cardiac insufficiency or LVEF (left ventricular ejection fraction) < 50% by echocardiography.
9. Hypertension uncontrolled by antihypertensives (systolic pressure > 140 mmHg or diastolic pressure > 90 mmHg).
10. Thromboembolism events that have occurred in the past 6 months, such as cerebrovascular events (including transient ischemia attacks) and pulmonary embolism.
11. Dysphagia, chronic diarrhea, or intestinal obstruction, which significantly affect drug intake and absorption.
12. History of hepatic encephalopathy.
13. Untreated active hepatitis (Hepatitis B: positive HBsAg with abnormal liver function and HBV-DNA ≥ 500 IU/ mL; Hepatitis C: positive HCV-RNA with abnormal liver function).
14. Infection with human immunodeficiency virus (HIV).
15. Subjects with active infection or unexplained fever (body temperature > 38.5 °C) during screening or prior to the first dose.
16. Received any vaccine treatment within 30 days prior to enrollment.
17. Patients planning to receive or previously received allogeneic organ or allogeneic bone marrow transplants, including liver transplant.
18. Subjects with previous or current pulmonary fibrosis, interstitial pneumonia, pneumoconiosis, radiation-induced pneumonitis, drug-induced pneumonitis, severe lung function impairment or other conditions that may interfere with the detection and management of suspected treatment-related pulmonary toxicities.
19. Urine protein ≥ 2+ and 24-h urine protein > 1.0 g as indicated by urinalysis.
20. Subjects with active, known, or suspected autoimmune diseases; subjects who are stable and do not require systemic immunosuppressive treatment may be enrolled.

	21. Subjects requiring systemic treatment with corticosteroids (> 10 mg/day of prednisone or equivalent) or other immunosuppressive medications within 14 days prior to the administration of the investigational drug; in the absence of active autoimmune disease, inhaled or topical use of corticosteroids and an equivalent dose to > 10 mg/day of prednisone for adrenal hormone replacement are permitted. 22. Received local treatment for liver within 4 weeks prior to participating in this study (including but not limited to surgery, radiation, hepatic artery embolization, TACE, hepatic arterial infusion, radiofrequency ablation, cryoablation, or percutaneous ethanol injection). 23. Palliative radiotherapy for symptomatic control of non-target lesions is permitted but must be completed at least 2 weeks prior to the start of the investigational drug, and no additional radiotherapy should be scheduled for the same lesion; radiation-induced adverse events that have not resolved to CTCAE grade ≤ 1; 24. Subjects who have previously received other PD-1 antibody treatment or other immunotherapies targeting PD-1/PD-L1. 25. Known history of severe allergies to any monoclonal antibodies, anti-angiogenesis targeted drugs, platinums, fluorouracils and other components of the investigational drug. 26. Requiring long-term anticoagulant therapy with warfarin or heparin; requiring long-term antiplatelet therapy (aspirin ≥ 300 mg/day, clopidogrel ≥ 75 mg/day). 27. Subjects with a known history of psychotropic substance abuse or drug abuse. 28. Pregnant or breastfeeding women. 29. Patients with any other potential factors that may result in the premature termination of the study as determined by the investigator, such as other serious illnesses or serious laboratory abnormalities or family or social factors that could affect the safety of the subject, or study data and sample collection
Method of Administration	Group A: SHR-1210, 3 mg/kg, I.V. on D1, once every 14 days; apatinib mesylate 125-500 mg orally, once daily (QD); Group B: SHR-1210, 3 mg/kg, I.V. on D1, once every 14 days; FOLFOX4, on D1-D2, once every 14 days. Or SHR-1210, 3 mg/kg, I.V. on D1, once every 14 days; GEMOX, on D1-D2, once every 14 days. The study treatment will continue until disease progression, intolerable toxicity, or subject withdrawal. Every 4-week is a treatment cycle.

Clinically Significant Toxicity	Any of the following toxicities that may or are definitely related to the investigational drug will be considered clinically significant toxicity: *Significant hepatotoxicity:* • ALT or AST > 10 × ULN for > 14 days; • ALT or AST > 15 × ULN regardless of the duration; • TBIL > 5 × ULN (> 8 × ULN for subjects with increased TBIL at baseline). *Significant hematological toxicity:* • Grade 3 treatment-related thrombocytopenia with bleeding; • Grade 3 treatment-related neutropenia with fever; • Grade 4 treatment-related neutropenia for > 5 days; • Grade 4 treatment-related thrombocytopenia. *Significant non-hematological toxicity:* • Grade 2 or above treatment-related eye pain or decreased vision that are not responsive to local treatment (not resolved to grade ≤ 1 within 14 days), and requiring systemic treatment; • Grade 3 or above treatment-related, non-skin AEs, except for the following: - Endocrine diseases that can be adequately controlled by replacement therapy; - Isolated laboratory abnormalities of no clinical significance; - Gastrointestinal AEs persistent for < 48 h; - Fatigue; - Fever persistent for < 72 h, without neutropenia or impairment of other organ functions; - Hypertension that can be controlled within the normal range after medication (systolic pressure ≤ 140 mmHg, diastolic pressure ≤ 80 mmHg) • Grade 4 treatment-related AEs, including laboratory abnormalities.
Criteria for Discontinuing the Study or Treatment	1. Subject withdraws informed consent and requests to withdraw from the study; 2. Imaging evaluations show disease progression, unless the subject meets the criteria for continuation of treatment beyond progression (see Section 3.2.4 for details); 3. Continuing the participation in the study is not in the best interests of the subject if still intolerable to the toxicity or due to adverse events, laboratory abnormalities, or concurrent diseases after dose modification per the investigator's judgment. 4. Other reasons for which the investigator considers a withdrawal necessary; 5. The subject becomes pregnant; 6. The study is terminated by the sponsor.

Statistical 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. All statistical analyses will be performed using SAS 9.2 or above. Safety Analysis: Subjects will be observed for any adverse event during the clinical trial, including clinical symptoms and abnormal vital signs, and laboratory abnormalities. The clinical manifestations, characteristics, severity, time of onset, duration, treatment, and prognosis will be recorded. In addition, the correlation of the adverse event with the investigational drug will be assessed. NCI-CTC AE (4.03) criteria will be used to evaluate drug safety. Efficacy Analysis: Point estimates of efficacy endpoints such as objective response rate (ORR) and disease control rate (DCR) are provided with 95% confidence interval. The median survival time, time to progression (TTP), duration of response (DoR), and corresponding 95% confidence intervals are calculated using the Kaplan-Meier method, and overall survival curves are plotted.
Study Period	Feb. 2017 to Mar. 2019

SCHEDULE OF ACTIVITIES

1. Procedures during Screening Period

Item	Screening Period (baseline[1], -28 days)	Note
Enrollment Assessment		
Signing of Informed Consent	√	Activities during the screening period must be carried out after the signing of the informed consent form. In this study, subjects who have failed the pre-treatment screening may be enrolled. The informed consent form should be re-signed and a new subject number should be given for re-enrollment.
Verification of inclusion/exclusion criteria	√	Evaluated during the screening period (including re-screening).
Demographics	√	
Medical History	√	Including past history, tumor history (initial diagnosis and treatments), and allergy history.
Child-Pugh Score	√	Performed within 14 days prior to the first dose.
Safety Assessments		
ECOG PS	√	Performed within 14 days prior to the first dose.
Physical Examination	√	Performed within 14 days prior to the first dose. Must include: height, weight, head and face, skin system, lymph nodes, eyes, ears, nose and throat, oral cavity, respiratory system, cardiovascular system, abdomen, urogenital system (when necessary), musculoskeletal system, nervous system, and mental state.
Vital Signs	√	Including blood pressure, heart rate, body temperature, and respiratory rate. Performed during screening visit.

Item	Screening Period (baseline[1], -28 days)	Note
Collecting information on concomitant medications/treatment	√	Including concomitant treatment within 28 days prior to the signing of informed consent form.
Collecting information on adverse events	√	Including symptoms, signs, complaints of discomfort, and abnormal laboratory results.
12-Lead ECG[2]	√	Performed within 14 days prior to the first dose. The QTc interval must be indicated, which was calculated by Fridericia's formula.
Echocardiography	√	Including LVEF assessment 14 days prior to the first dose.
Hematology	√	Including complete blood count with differential (white blood cells, red blood cells, lymphocytes, monocytes, neutrophils, basophils, and eosinophils), hemoglobin, and platelet count. Tested within 14 days prior to the first dose. If the screening tests were done within 72 h prior to the first dose, a retest was not required before the first dose.
Urinalysis	√	Including white blood cells, red blood cells, and urine protein. Tested within 14 days prior to the first dose. In case of a urine protein ≥ 2+ at screening, a 24-h urine protein quantitation should be added. If the screening tests were done within 72 h prior to the first dose, a retest was not required before the first dose.
Fecal occult blood	√	Tested within 14 days prior to the first dose.
Blood biochemistry	√	Including liver function measurements (ALT, AST, total bilirubin, ALP), renal function measurements (BUN or serum urea level, creatinine), albumin, amylase (a lipase test should be added in case of an abnormal amylase level), blood glucose, and LDH. Tested within 14 days prior to the first dose. If the screening tests were done within 72 h prior to the first dose, a retest was not required before the first dose.
Electrolytes	√	Including potassium, sodium, calcium, phosphorus, magnesium, and chlorine. Tested within 14 days prior to the first dose. If the screening tests were done within 72 h prior to the first dose, a retest was not required before the first dose.
Coagulation Function	√	International normalized ratio (INR) and/or prothrombin time (PT). Tested within 14 days prior to the first dose. If the screening tests were done within 72 h prior to the first dose, a retest was not required before the first dose.

Item	Screening Period (baseline[1], -28 days)	Note
Alpha-Fetoprotein	√	Tested within 14 days prior to the first dose.
Thyroid function	√	Including TSH, FT3, and FT4. Tested within 14 days prior to the first dose.
Virological Examination	√	Including HIV-Ab, HBV and HCV infection tests. HBV testing requirements: HBsAg is tested at screening to determine the presence of HBV infection. If positive, HBsAg (quantitative), HBsAb (qualitative), HBcAb (qualitative), HBeAg (qualitative), HBeAb (qualitative) and HBV-DNA (qualitative, and if positive, quantitatively) are tested. Requirements for HCV testing: HCV-Ab is tested at screening to determine the presence of HCV infection. If positive, HCV-RNA will be tested (qualitative, and if positive, quantitatively). Performed within 14 days prior to the first dose.
Blood or urine HCG test	√	For women of childbearing potential (WOCBP) only. Must be tested within 14 days prior to the first dose.
Efficacy Assessment		
Tumor imaging assessment	√	Baseline imaging assessment must be performed as per the RECIST 1.1 criteria, including enhanced CT scans of the chest, abdomen, pelvis, and lesions. If subject was allergic to the contrast agents used in enhanced CT, non-enhanced chest CT and abdominal and pelvic MRI scans were done. Brain MRI or enhanced CT scan. Bone scans were only performed when clinically indicated, and must be within 42 days prior to the first dose. If routine tumor imaging assessment was performed prior to the signing of informed consent form, as long as the CT or MRI scan was done within 28 days prior to the first dose, a repeat CT or MRI during the screening period was not required.

2. Procedures during Treatment Period

Item	Treatment Period (28 days/cycle)		Note
	D1[3] (± 3 days)	D15 (± 3 days)	
Child-Pugh score	√		Completed on D1 of each cycle.
Safety Assessments			
ECOG PS	√	√	Conducted before dosing on the day of each visit.
Physical Examination	√	√	Conducted before dosing on the day of each visit, must include: body weight, skin system, respiratory system, cardiovascular system, and abdomen.
Vital Signs	√	√	Including blood pressure, heart rate, body temperature, and respiratory rate. Conducted before dosing on the day of each visit (after sitting for 5 min).
Collecting information on concomitant medications/treatment	√	√	
Collecting information on adverse events	√	√	Including symptoms, signs, complaints of discomfort, and abnormal laboratory results.
12-Lead ECG	√	√	Conducted within 72 h before dosing of each visit. The QTc interval must be indicated, which was calculated by Fridericia's formula.
Echocardiography			This is performed according to local standard practice when clinically indicated.
Hematology	√	√	Including complete blood count with differential (white blood cells, red blood cells, lymphocytes, monocytes, neutrophils, basophils, and eosinophils), hemoglobin, and platelet count. Tested within 72 h before dosing of each visit.
Urinalysis	√	√	Including white blood cells, red blood cells, and urine protein. Tested within 72 h before dosing of each visit. In case of a urine protein ≥ 2+, a 24-h urine protein test should be added.

Item	Treatment Period (28 days/cycle)		Note
	D1[3] (± 3 days)	D15 (± 3 days)	
Blood Biochemistry	√	√	Including liver function measurements (ALT, AST, total bilirubin, ALP), renal function measurements (BUN or serum urea level, creatinine), albumin, amylase (a lipase test should be added in case of an abnormal amylase level), blood glucose, and LDH. Tested within 72 h before dosing of each visit.
Electrolytes	√	√	Including potassium, sodium, calcium, phosphorus, magnesium, and chlorine. Tested within 72 h before dosing of each visit.
Coagulation Function	√		International normalized ratio (INR) and/or prothrombin time (PT). Tested on D1 of each cycle starting from cycle 2.
Alpha-Fetoprotein	√		Tested on D1 of each cycle starting from cycle 2.
Thyroid Function	√		Completed on D1 of each cycle starting from Cycle 2. Including: TSH, FT4, and FT3.
Virological examination	√		Completed on D1 of each cycle starting from Cycle 2. Including: HBV-DNA qualitative + quantitative assay (quantitative assay using PCR). HCV-RNA qualitative + quantitative assay (quantitative assay using PCR).
EFFICACY ASSESSMENT			
Tumor imaging assessment	√		Tumor imaging assessments must be performed as per the RECIST 1.1 criteria. Once every 8 weeks (± 7 days), regardless of any medication delays. Including enhanced CT scans of the chest, abdomen, pelvis, and lesions. If subject was allergic to the contrast agents used in enhanced CT, non-enhanced chest CT and abdominal and pelvic MRI scans were done. Brain MRI or enhanced CT and bone scans were performed only when clinically indicated.
Study Treatment			
Injection of SHR-1210	√	√	
Apatinib Mesylate	√	√	Only applicable to the subjects in group A. Orally administered daily starting from D1 of cycle 1.
FOLFOX4/GEOX Chemotherapy	√	√	Only applicable to the subjects in group B.

Item	Treatment Period (28 days/cycle)		Note
	D1[3] (± 3 days)	D15 (± 3 days)	
Distribution, Validation, and Recovery of Subject Diary Card	√	√	Only applicable to the subjects in group A administered with apatinib mesylate.

3. End of Treatment and Follow-Up Period

Item	End of treatment [4]	Follow-Up Period		Note
		Safety follow-up [5]	Survival follow-up [6]	
Child-Pugh score	√	√		
Safety Assessments				
ECOG PS	√	√		
Physical Examination	√	√		
Vital Signs	√	√		Including blood pressure, heart rate, body temperature, and respiratory rate (after sitting for 5 min).
Collecting information on concomitant medications/ treatment	√	√		
Collecting information on	√	√		Including symptoms, signs, complaints of discomfort, and abnormal laboratory results.

Item	End of treatment [4]	Follow-Up Period		Note
		Safety follow-up [5]	Survival follow-up [6]	
adverse events				
12-Lead ECG	√	√		The QTc interval must be indicated, which was calculated by Fridericia's formula.
Echocardiography	√			
Hematology	√	√		Including complete blood count with differential, platelet count, and hemoglobin.
Urinalysis	√	√		In case of a urine protein ≥ 2+, a 24-h urine protein test should be added.
Blood Biochemistry	√	√		Including liver function measurements (ALT, AST, total bilirubin, ALP), renal function measurements (BUN or serum urea level, creatinine), albumin, amylase (a lipase test should be added in case of an abnormal amylase level), blood glucose, and LDH.
Electrolytes	√	√		Including potassium, sodium, calcium, phosphorus, magnesium, and chlorine.
Coagulation Function	√	√		International normalized ratio (INR) and/or prothrombin time (PT).
Alpha-Fetoprotein	√	√		
Thyroid Function	√	√		TSH, FT4, and FT3.
Virological examination	√	√		Including: HBV-DNA qualitative + quantitative assay (quantitative assay using PCR). HCV-RNA qualitative + quantitative assay (quantitative assay using PCR).
Blood or urine HCG test	√			For women of childbearing potential (WOCBP) only.

Item	End of treatment [4]	Follow-Up Period		Note
		Safety follow-up [5]	Survival follow-up [6]	
EFFICACY ASSESSMENT				
Tumor imaging assessment	√	√	√	If the subject did not have tumor progression when withdrawing from the study treatment, tumor assessments were still required every 8 weeks (± 7 days) as per the RECIST 1.1 criteria until disease progression or initiation of new anti-tumor treatment. Including enhanced CT scans of the chest, abdomen, pelvis, and lesions. If subject was allergic to the contrast agents used in enhanced CT, non-enhanced chest CT and abdominal and pelvic MRI scans were done. Brain MRI or enhanced CT and bone scans were performed only when clinically indicated.
Others				
Survival information		√	√	
Subsequent anti-tumor treatment		√	√	

Note:

[1] Baseline measurements obtained closest to the first dose were used.

[2] Fridericia's formula: QTcF = QT/(RR^0.33), where RR is the standardized heart rate value, obtained by dividing 60 by the heart rate.

[3] There was no ±3-day window for Day 1 of Cycle 1.

[4] End of treatment/withdrawal: These examinations/procedures were not repeated if they were completed within 7 days from withdrawal.

[5] Safety follow-up period: 90 days after the last dose. During this period, follow-up visits were conducted once every 30 days (± 7 days). The first safety follow-up (30 days after the last dose) and the third safety follow-up (90 days after the last dose) must be conducted at the study site. The safety follow-up in between (60 days after the last dose) was a telephone interview, and only survival information, concomitant medications/treatments, and adverse events were collected.

[6] Survival follow-up period: the survival follow-up period started after the end of the safety follow-up period. During this period, a telephone follow-up was conducted every 30 days (±7 days) to collect information about subject survival and about subsequent treatments.

ABBREVIATIONS AND DEFINITIONS

Abbreviations and Special Terms	Definitions
AE	Adverse event
AFP	Alpha-Fetoprotein
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APTN	Apatinib mesylate
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BLRM	Bayesian logistic regression model
BUN	Blood urea nitrogen
B-Scan	B-mode ultrasound
CIV	Continuous intravenous infusion
CR	Complete response
CT	Computed tomography
DCR	Disease control rate
DoR	Duration of response
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
eCRF	Electronic case report form
GCP	Good Clinical Practice
FAS	Full analysis set
FT3	Free triiodothyonine
FT4	Free thyroxine
Glu	Glucose
Hb	Hemoglobin
HCC	Hepatocellular carcinoma
HSF	Hand-and-Foot Syndrome
INR	International normalized ratio
ITT	Intention to Treat
LDH	Lactate dehydrogenase
I.V.	Intravenous injection
LV	Levoleucovorin

Abbreviations and Special Terms	Definitions
LVEF	Left ventricular ejection fraction
MRI	Magnetic resonance imaging
NCI-CTC	National Cancer Institute Common Toxicity Criteria
NHYA	New York Heart Association
OB	Occult blood
ORR	Objective response rate
OS	Overall survival
OXA	Oxaliplatin
PD	Progressive disease
PFS	Progression free survival
PI	Principal Investigator
PLC	Primary liver cancer
PLT	Platelet
PO	Oral administration
PR	Partial response
PT	Prothrombin time
QD	Quaque die
Q2W	Once every 2 weeks
RECIST	Response evaluation criteria in solid tumors
RTKs	Receptor tyrosine kinase
SAE	Serious adverse event
SAS	Safety analysis set
SD	Stable disease
TBIL	Total bilirubin
TSH	Thyroid stimulating hormone
TTP	Time to progression
ULN	Upper limit of normal
WBC	White blood cell
WOCBP	Women of childbearing potential
5-Fu	5-fluorouracil

1 BACKGROUND

1.1 Epidemiology and Current Treatment Status of Liver Cancer

Primary hepatocellular carcinoma ranked fifth among common malignant tumors in the world in 2012, with about 782,500 new cases, accounting for 6% of all new cancer cases. Due to the poor prognosis of this disease, it is responsible for up to 745,500 deaths per year, hence making it the third leading cause of cancer deaths [1]. China has a high incidence of liver cancer. In 2016, statistics showed there were approximately 466,100 new cases per year, accounting for 10.8% of all new cancer cases, ranking fourth. The annual number of deaths from liver cancer was 422,100, second only to lung cancer and gastric cancer in tumor-related deaths, ranking third [2]. Liver cancer is more prevalent in men than in women, with male-to-female ratio of 2.8:1, and is most common in the age group of 45-59 years old. A higher proportion of male patients has been observed in areas with higher incidence [2].

Primary liver cancer mainly includes different pathological types such as hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC) and mixed hepatocellular carcinoma-intrahepatic cholangiocarcinoma. HCC is the most common type of primary liver cancer, accounting for 90% of patients with primary liver cancer [3]. The main risk factors are infection with hepatitis B and C virus and non-alcoholic fatty liver; in addition, rare causes include hereditary hemochromatosis, α-antitrypsin deficiency, and autoimmune hepatitis [3]. HCC occurs mostly in patients with hepatitis and liver cirrhosis, at approximately 10-20 years after primary hepatic damage.

Most early-stage liver cancers are asymptomatic, and majority of the patients have reached a locally advanced stage or distant metastasis at the time of diagnosis, with clinical treatment facing severe challenges. The survival times of patients with advanced primary liver cancer in China fall within the range of 3-6 months, and the longest survival time among patients worldwide is not more than 1 year [4]. The overall 5-year survival rate of liver cancer is 5-6%. The treatment challenge mainly comes from the high heterogeneity of the disease, the diversified etiology, and the different diagnostic and treatment standards. Patients are also often accompanied by impaired liver function. Thus, the treatment is more complicated and the efficacy thereof varies [5-7].

Due to its insensitivity to conventional chemotherapy, liver cancer is usually treated through surgical operations (hepatectomy, liver transplantation, and palliative treatment), non-surgical approaches (locoregional treatment, arterial chemoembolization, chemotherapy, radiotherapy, biological therapy, and molecular targeted therapy), and other therapies (including participation

in clinical studies). The treatment method is usually selected according to the stage of the disease, the extent of tumor invasion, and the physical status of the patient, while in patients with liver cancer, the liver function status should also be considered. Approximately 90% of patients with liver cancer also have liver cirrhosis, which should be treated at the same time as tumor treatment.

1.2 Research Developments in Targeted Therapies for Liver Cancer

In December 2007, sorafenib became the first FDA-approved drug for the treatment of HCC. Sorafenib is a multi-target tyrosine kinase inhibitor. Its approval was based on the results of its remarkable benefits in terms of survival as demonstrated in the SHARP and Oriental trials. The SHARP study was a randomized phase III study in the western population. Sorafenib, in comparison with the placebo, the progression-free survival (median of 5.5 months and 2.8 months, respectively) was increased by 73% and the overall survival (median of 10.7 months and 7.9 months, respectively) was increased by 44%. Oriential, another randomized phase III study conducted in Asian populations with a study design similar to those of SHARP, also yielded the same results, with the overall survival increased by 2.3 months (median OS of 6.5 months and 4.2 months, respectively) [8, 9].

In 2008, sorafenib was approved in China for the treatment of HCC, hence offering a new treatment option to numerous liver cancer patients in China.

Several multi-kinase inhibitors have suffered setbacks in head-to-head comparisons with sorafenib. The phase III clinical trial of sunitinib (Pfizer) in patients with advanced liver cancer was terminated prematurely in April 2010 due to the failure of sunitinib to improve survival in comparison to sorafenib, and the incidence of serious adverse events (SAEs) was higher in the sunitinib group than in the sorafenib group [10]. The multi-kinase inhibitor ABT-869 (Linifanib) developed by Abbott had also failed to demonstrate any advantages over sorafenib. As such, the phase III clinical trial of ABT-869 was terminated based on the recommendation of the independent data monitoring committee (IDMC) [11]. A study involving 731 patients showed that Roche's Tarceva (erlotinib), an epidermal growth factor receptor tyrosine kinase inhibitor, also failed to provide additional benefits, as compared with sorafenib [12]. Brivanib is a tyrosine kinase inhibitor targeting VEGF receptor and basic fibroblast growth factor (bFGF, FGF-2) receptor. The phase II trial of brivanib in patients with unresectable, locally advanced or distant metastatic liver cancer showed that 6-month PFS reached 18.2%, median PFS was 2.7 months, and median survival was 10 months, with relatively mild side effects, mainly including fatigue, hypertension, and diarrhea [13]. However, brivanib failed in the comparison with sorafenib in the phase III non-inferiority clinical trial, because the overall survival for brivanib treatment was not superior to sorafenib [14]. Even the main exploration in the population after sorafenib treatment

cannot demonstrate the superiority of other targeted drugs relative to the best supportive treatment in terms of overall survival. The primary endpoints of 2 phase III studies of brivanib and everolimus in patients with advanced HCC who failed or were intolerant after sorafenib treatment were not reached, with a median OS of 9.4 months vs. 8.2 months (HR 0.89, P = 0.33) [15] and 7.6 months vs. 7.3 months (HR 1.05) [16] compared with the best supportive treatment.

In summary, sorafenib remains the most superior targeted drug in terms of overall efficacy and safety in the treatment of HCC. The median survival of sorafenib in patients with advanced HCC was not more one year, and new treatments that improve patients' survival were still expected clinically.

1.3 Background of Immunotherapy in Liver Cancer

Contrary to chemotherapy or molecular targeted therapy that directly acts on cancer cells, tumor immunomodulatory therapy 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. Molecular 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 resistance and clinical recurrence within a few months. Tumor immunomodulatory therapy can be applied to a various types of tumors, and can also produce a long-lasting response in some patients.

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

Programmed death-1 (PD-1) is a protein receptor expressed on the surface of T cells discovered in 1992 and is involved in the process of cell apoptosis. PD-1 is a member of the CD28 family and has a 23% consistency in amino acid sequence with cytotoxic T lymphocyte antigen 4 (CTLA-4). However, its expression is different from CTLA. It is primarily expressed by

activated T cells, B cells, and myeloid cells. PD-1 has two ligands, PD-L1 and PD-L2. PD-L1 is primarily expressed on T cells, B cells, macrophages, and dendritic cells (DCs), and is up-regulated on activated cells. Many human solid tumors have expression of the PD-1 ligand (PD-L1), which is often associated with a poor prognosis. Tumor-infiltrating lymphocytes in patients with cancers usually express PD-1 and their anti-tumor function is impaired. Pre-clinical trials of several antibodies that block PD-1 or PD-L1 have proven that they can enhance T-cell function and promote tumor cell lysis.

A number of pharmaceutical companies are currently developing monoclonal antibodies targeting PD-1. By blocking the binding of PD-L1/PD-1, these monoclonal antibodies maximize a patient's own immune response against the tumor, thereby achieving the purpose of killing tumor cells. BMS and Merck's PD-1 monoclonal antibodies are currently the most advanced PD-1 antibody drugs. Based on the results of key studies that have been completed, the FDA has approved nivolumab from BMS and pembrolizumab from Merk for multiple indications: nivoluamb has been approved by the FDA for the treatment of melanoma, non-small cell lung cancer, renal cell carcinoma, Hodgkin lymphoma, and squamous cell carcinoma on the head and neck; pembrolizumab has been approved by the FDA for the treatment of advanced melanoma, non-small cell lung cancer, and squamous cell carcinoma in the head and neck.

Currently, multiple antibody drugs against PD-1 are undergoing clinical study in advanced hepatocellular carcinoma. A phase I/II study of nivolumab in the treatment of patients with advanced hepatocellular carcinoma (HCC) was reported at the ASCO meeting in 2015. The preliminary results of the dose escalation part of the study were announced. Fourty-seven (47) patients with HCC were enrolled; among them, 51% were not accompanied with viral infection, 25.5% had HCV coinfection, 23.4% had HBV coinfection, and 98% had Child-Pugh score of class A; 75% received systemic therapy; 68% received previous treatment with sorafenib. The patients received nivolumab at different doses (0.1-10 mg/kg, once every 2 weeks). The results showed that nivolumab was safe and tolerable. Only one patient withdrew from treatment due to treatment-related hepatitis. The incidence of Grade 3 increased transaminase was not high, with 11% of patients experienced Grade 3 AST elevation and 9% of patients experienced Grade 3 ALT elevation. Among the 42 evaluable patients, 8 patients (19%) showed objective response (CR + PR, RECIST 1.1), and 6 patients had a duration of response of more than 12 months (2 patients with CR discontinued the medication). The one-year overall survival rate was 62%. In patients with HCV coinfection, transient reduction of HCV-RNA in some patients was observed. The preliminary results of this study suggested that the immune checkpoint inhibitor PD-1 antibody was safe and tolerable in the treatment of advanced HCC, and it was also very safe in patients with hepatitis B or hepatitis C infection. The preliminary efficacy results were

encouraging [17]. At the 2016 ASCO annual meeting, the interim analysis data, as the subsequent extension of the study in 214 patients with HCC, was announced. All the enrolled patients had Child-Pugh score of class A. Among them, 66% had previously received sorafenib treatment. The numbers of patients with HCV infection, HBV infection, and non-viral infection were 51, 51, and 112, respectively. Nivolumab was given at 3 mg/kg, once every 2 weeks. As of the analysis (15 Mar., 2016), the median number of administrations was 10, and 8 patients withdrew from treatment due to treatment-related toxicity. Elevated transaminase was the most common laboratory abnormality. The incidences of elevated ALT and AST were 7% and 6%, respectively, of which 3% and 4%, respectively, were of Grade 3-4. Most were asymptomatic and more common in patients with HCV infection. The tumor objective response rate (ORR) was 16% (35/214). The ORR in patients with PD-L1 expression of ≥ 1% and < 1% was 19% (5/26) and 20% (20/102), respectively. The majority (29/35) of tumor objective response was observed within 3 months at the start of treatment, and the majority response (30/35) continued. The 6- and 9-month OS rates were 82.5% and 70.8%, respectively. Viral reactions were observed in some patients with viral infections (6% of patients with HBV infection showed HBsAg quantitative decrease, and 20% of patients with HCV infection experienced HCV-RNA transient decrease) [18]. At the ESMO meeting in October 2016 and the ASCO GI meeting in January 2017, the updated follow-up results of the study were further reported. A total of 262 patients in the dose-escalation group and subsequent extension group received treatment, with 48 in the dose-escalation group and 214 in the subsequent extension group. Asian patients accounted for 45%. Patients treated with sorafenib accounted for 67%. The safety results showed that the incidence of Grade 3/4 treatment-emergent adverse events was 19%, and the incidence rates of Grade 3/4 elevated ALT and elevated AST were 5% and 3%, respectively. The efficacy results showed, in the extension group, that the ORR was 20%, the median duration of response (DoR) was 9.9 months, the 9-month OS rate was 74%, and the median OS was 13.2 months. Nivolumab was safe and controllable in the treatment of advanced HCC and showed long duration of response and long-term survival benefits. Its efficacy was not associated with whether accompanied with HBV/HCV infection, whether treated with sorafenib, and the expression status of PD-L1 [19, 20].

A global phase III study of nivolumab vs. sorafenib in the first-line treatment of patients with advanced HCC is currently underway, the results of which are worth looking forward to [21].

1.4 Study Basis of Combined Immunotherapy in Hepatobiliary Malignancies

1.4.1 Application of immunotherapy combined with targeted therapy in tumor treatment

Tumor immunotherapy has received more and more attention and affirmation. The duration of response of this therapy is long in patients, and the incidence and severity of adverse drug reactions are low. However, no or late responses to this therapy exist in a large number of patients, causing a considerable number of patients to abandon the treatment due to early disease progression. On the other hand, although tumor-targeted therapy results in responses in the early stage of treatment, but the duration of response is short and drug resistance is prone to appear. Combining the respective characteristics of the above two therapies, tumor immunotherapy combined with targeted therapy has a good development prospect. It not only improves the response rate but also result in sustained clinical benefits [22, 23]. In addition, studies have shown that small molecule targeted drugs can induce tumor cell death. Dead tumor cells can release tumor autoantigens, which are taken up by antigen-presenting cells and presented to tumor-specific T lymphocytes. PD-1 antibody inhibits the PD-1/PD-L1 signaling pathway by binding to PD-1 on T lymphocytes, thereby activating the specific killing effect of T lymphocytes on tumor cells. In addition, the release of tumor autoantigens caused by targeted therapy reduces attacks of T lymphocytes on non-tumor antigens, thereby reducing immunotherapy-related adverse drug reactions [24]. This provides a strong basis for tumor immunotherapy combined with targeted therapy.

At present, some clinical trials of the combination of targeted therapy and immunotherapy are being actively carried out. For example, Merck's Keynote-022 study (NCT02130466) aims to study the safety and efficacy of PD-1 monoclonal antibody, pembrolizumab, combined with trametinib and dabrafenib in patients with advanced melanoma. Merck's Keynote-426 study (NCT02853331) is a study on the efficacy and safety of pembrolizumab combined with axitinib vs. sunitinib monotherapy in renal cancer. The preliminary study results showed that the objective response rate (ORR) was 40%-50% [25], showing a good response rate. Therefore, the combination of immunotherapy and targeted therapy will be one of the inevitable trends in tumor treatment in the future. How to carry out the combination medication is a problem that needs to be solved by the medical community.

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. Phase I clinical studies have been conducted by Hengrui in Australia and China since 2015. Several clinical studies are currently underway.

This study also involves apatinib mesylate (trade name: Aitan), which was launched in 2014 by Jiangsu Hengrui Pharmaceuticals Co., Ltd. Apatinib mesylate is a small molecule targeted drug, which is a vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor. It exerts its anti-angiogenic effect mainly by inhibiting VEGFR. Preclinical studies have shown that it is superior to similar product in anti-tumor effect. In 2014, apatinib mesylate 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 completed phase II clinical trial of apatinib mesylate in the treatment of advanced HCC showed good efficacy (mTTP of the 850 mg group and 750 mg group was 4.2 months and 3.3 months, respectively; and mOS of the 850 mg group and 750 mg group was 9.7 months and 9.8 months, respectively). Currently, a randomized (2:1), double-blind, placebo-controlled, multi-center phase III clinical trial evaluating the efficacy and safety of apatinib mesylate as second-line treatment of advanced HCC is underway. Patients with advanced HCC who failed sorafenib or systemic chemotherapy, had relapse, or intolerant to sorafenib were recruited.

This study intends to use drugs that target the VEGF-VEGFR signaling pathway combined with PD-1 monoclonal antibody in the treatment of advanced liver cancer as an exploratory study, aiming to provide guidance and experience for new combination therapies urgently needed in clinical practice, and laying a foundation for subsequent studies. Thus, it has important significance in scientific studies and clinical value.

1.4.2 Study basis of immunotherapy combined with oxaliplatin chemotherapy in liver cancer

Oxaliplatin (OXA) is a third-generation platinum anti-tumor drug. In addition to its cytotoxic effect on DNA, several studies in recent years have shown that the anti-tumor activity of OXA is more related to its immune effect [26, 27]. The immunological mechanism of OXA's anti-tumor effect mainly includes its ability to induce immunogenic cell death (ICD), regulate the STAT signal pathway, and regulate the immune microenvironment of tumor [26-33].

Since OXA has an immunomodulatory effect against tumors, it may produce synergistic anti-tumor activity when combined with immunotherapy drugs [26, 27]. Current researches on immunotherapy focus on the development of immune checkpoint inhibitors, the main targets being T cell surface receptors CTLA-4 and PD-1. The expression level of these receptors can regulate the proliferation and activation of T cells [26]. Platinum enhances the effect of immune checkpoint inhibitors by inducing ICD production, enhancing the sensitivity of tumor cells to cytotoxic lymphocyte (CTL) lysis, and stimulating the proliferation of T cells. Recently, data of multiple clinical studies have shown that the effect of platinum combined with anti-PD-1 monoclonal antibody exhibited good anti-tumor effects [34, 35].

In recent years, many progresses have been made in systemic chemotherapies for HCC. A prospective, randomized, controlled, international multicenter phase III clinical study (EACH study) [36] compared the efficacy and safety of the FOLFOX4 regimen containing OXA with doxorubicin monotherapy in the treatment of Asian patients with advanced HCC. The results showed that the PFS, OS, and RR of the FOLFOX4 group were better than those of the doxorubicin group (PFS: 2.93 months vs. 1.77 months; OS: 6.40 months vs. 4.9 months; RR: 8.15% vs. 2.67%). Further analyses showed that [37]: In the main target population, i.e., Chinese patients, the mOS of the FOLFOX4 group vs. the doxorubicin group was prolonged (5.9 months vs. 4.3 months, P = 0.0281); also, the mPFS, RR and DCR showed significant superiority (2.4 months vs. 1.7 months, 8.6% vs. 1.4%, and 44.0% vs. 30.8%, respectively); the OS and PFS benefits of patients in the FOLFOX4 group remained consistent in each subgroup. The EACH study showed that the OXA-based FOLFOX4 regimen is effective and safe for the treatment of patients with HCC in the Asia-Pacific region, especially in China. Based on the above study results and other clinical observation data, in 2013, the China Food and Drug Administration (now National Medical Products Administration, or NMPA) approved the indication of systemic chemotherapy with OXA for the treatment of advanced HCC [38]. Also, the "Guideline for the Diagnosis and Treatment for HCC" formulated by the Chinese Ministry of Health (now National Health Commission) also listed the OXA-based FOLFOX4 regimen as a first-line treatment for advanced HCC [39]. In view of the results of the large-scale phase III study of OXA in HCC, the approval of the NMPA, and the recommendations of the Chinese guidelines, the immunotherapy of immune checkpoint inhibitors combined with OXA-based systemic chemotherapy can hopefully improve clinical outcomes for patients with advanced liver cancer.

Therefore, this study intends to carry out an exploratory study on FOLFOX4 regimen combined with PD-1 monoclonal antibody SHR-1210 in the treatment of advanced primary liver cancer simultaneously. It is expected to provide guidance and experience for the new combination of immunotherapy and chemotherapy in the future as well as effectively improve the anti-tumor efficacy of monotherapy while minimizing the toxic side effects as much as possible, and ultimately bringing better survival benefits for patients.

1.4.3 Study basis of immunotherapy combined with oxaliplatin chemotherapy in bile duct malignancies

Malignant tumors of the bile duct originate from epithelia of intrahepatic and extrahepatic bile ducts or of the gallbladder, including cholangiocarcinoma and gallbladder cancer, of which gallbladder cancer is more common, accounting for approximately 2/3. Cholangiocarcinoma consists of intrahepatic cholangiocarcinoma (20-25%), hilar cholangiocarcinoma (50-60%), and

distal cholangiocarcinoma (20-25%) according to anatomical location. Malignant tumors of the bile duct are not common in clinical practice, accounting for approximately 2% of all malignant tumors and ranking fifth among malignant tumors of the gastrointestinal tract. The etiology is not yet clear, and may be related to high-risk factors such as chronic inflammation of the bile duct, cholelithiasis, ulcerative colitis, cystic malformation of the bile duct, sclerosing cholangitis, K-ras mutation, liver flukes, and hepatitis B. Malignant tumors of the bile duct have high malignancy, poor prognosis, and insidious onset, most of which are advanced at the time of diagnosis [40-42].

The recommended chemotherapy regimen for advanced patients is the two-drug combination regimen based on gemcitabine or fluorouracil. Commonly used regimens include: gemcitabine + cisplatin, gemcitabine + carboplatin, gemcitabine + oxaliplatin, capecitabine + oxaliplatin, capecitabine + cisplatin, and fluorouracil + cisplatin. In multiple phase II studies, the response rates were 9-40% and the median survivals were 5-13 months. In UKABC-02, the only phase III study with positive results in bile duct malignancies, gemcitabine combined with cisplatin vs. gemcitabine monotherapy in the treatment of 410 patients with advanced or metastatic cholangiocarcinoma, gallbladder cancer, or ampullary cancer showed a median OS of 11.7 months and 8.1 months, and a PFS of 8 months and 5 months, respectively [43-45].

The chemotherapy regimen based on gemcitabine is the recommended treatment regimen for advanced biliary tract tumors. Among them, the GEMOX regimen combined with oxaliplatin has been used in multiple single-arm phase II studies and randomized controlled phase II studies, showing good activity and safety characteristics. In consideration of the proven efficacy of gemcitabine in biliary tract tumors and the possible immunomodulatory effect of oxaliplatin, the GEMOX regimen combined with PD-1 monoclonal antibody SHR-1210 is selected for this study to treat patients with advanced cholangiocarcinoma and is expected to improve the treatment efficacy in such a refractory population [46-48].

1.5 Scientific Basis

1.5.1 Preclinical study results of SHR-1210

1.5.1.1 Product name and physicochemical properties

[Generic Name]: SHR-1210 Injection

[English Name]: SHR-1210 Injection

[Molecular Weight]: approx. 146.3 kDa

1.5.1.2 Pharmacology and mechanism of action

Programmed death-1 (PD-1) is a protein receptor expressed on the surface of T cells discovered in 1992 and is involved in the process of cell apoptosis. PD-1 is a member of the CD28 family and has a 23% consistency in amino acid sequence with cytotoxic T lymphocyte antigen 4 (CTLA-4). However, its expression is different from that of CTLA-4. It is primarily expressed by activated T cells, B cells, and myeloid cells. PD-1 has two ligands, PD-L1 and PD-L2. PD-L1 is primarily expressed on T cells, B cells, macrophages, and dendritic cells (DCs), and is up-regulated on activated cells. In contrast, the expression of PD-L2 is mainly restricted to antigen presenting cells, such as activated macrophages and dendritic cells. Humanized anti-PD-1 monoclonal antibody can specifically bind to PD-1, blocking the interaction between PD-1 and its ligands, and restore T cell immune response to tumor cells.

1.5.1.3 Pharmacodynamic studies

1) Antibody affinity

The binding affinity of antibody SHR-1210 to human, monkey, and rat antigens was assayed. The results are shown in Table 1.

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

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

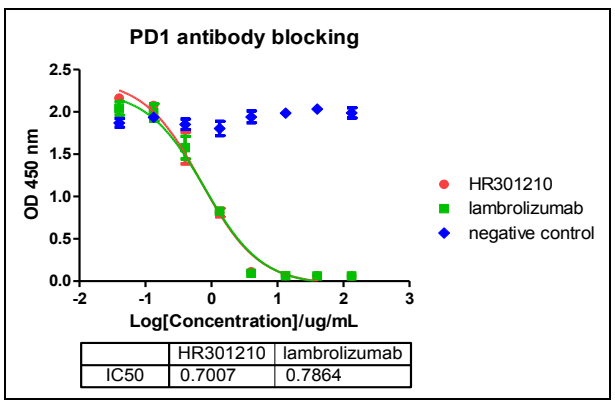
Results from affinity assays showed that the affinity of SHR-1210 to human and monkey PD-1 antigens were quite close at 6.9 nM and 4.1 nM, respectively, but no binding was detected with rat PD-1 antigens. Results from the binding affinity assay involving SHR-1210 and human PD-1 antigen showed that the binding affinity of SHR-1210 to human PD-1 antigen was 3.0 nM, which was similar to those of the control antibodies nivolumab and MK3475. The results are shown in Table 2.

Table 2. Binding affinity of SHR-1210, nivolumab, and MK3475 to PD-1 antigens.

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

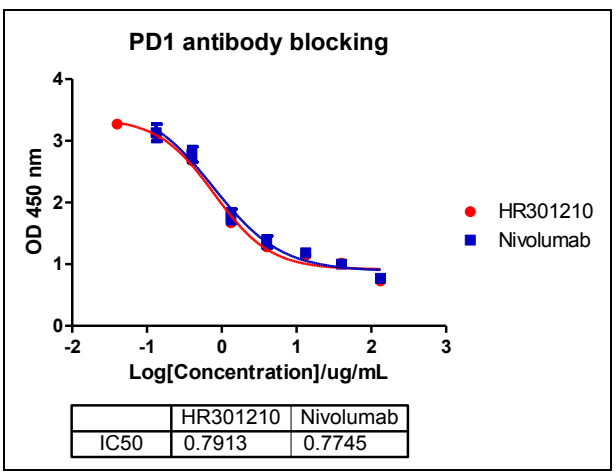
2) Inhibition of PD-1/PD-L1 binding by SHR-1210

The experimental results (see Figure 1 and Figure 2) showed that the *in vitro* activity of SHR-1210 in blocking the binding of PD-1/PD-L1 was comparable to that of nivolumab and pembrolizumab. The IC50 of inhibition activities of SHR-1210 antibody, nivolumab, and pembrolizumab was 0.70 nM/0.79 nM and 0.79 nM/0.77 nM, respectively.



	HR301210	lambrolizumab
IC50	0.7007	0.7864

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



	HR301210	Nivolumab
IC50	0.7913	0.7745

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

1.5.1.4 Toxicology studies

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

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

1.5.1.5 Pharmacokinetic studies

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

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

Dose (mg/kg)	Gender	$T_{1/2}$ (hr)	T_{max} (hr)	C_{max} (μg/mL)	AUC_{last} (hr•μg/mL)	Vz (mL/kg)	Cl (mL/hr/kg)	MRT_{last} (hr)
1	Female	76.06 ± 32.93	0.83 ± 0.29	31.16 ± 11.25	1716.12 ± 453	54.09 ± 14.85	0.57 ± 0.17	80.95 ± 18.58
	Male	91.72 ± 25.26	0.83 ± 0.29	35.96 ± 13.09	2359.7 ± 684.07	55.15 ± 20.51	0.37 ± 0.06	102.23 ± 38.56
	Overall	83.89 ± 27.62	0.83 ± 0.26	33.56 ± 11.23	2037.91 ± 627.32	54.62 ± 16.02	0.47 ± 0.15	91.59 ± 29.47
3	Female	92.95 ± 22.60	0.83 ± 0.29	81.09 ± 12.66	6896.79 ± 1673.36	40.75 ± 12.66	0.44 ± 0.11	120.92 ± 49.96
	Male	113.54 ± 8.26	1.67 ± 0.58	71.65 ± 10.85	6380.24 ± 2062.85	47.05 ± 27.05	0.47 ± 0.12	127.10 ± 59.24
	Overall	103.25 ± 18.94	1.25 ± 0.61	76.37 ± 11.74	6638.51 ± 1703.60	43.91 ± 19.21	0.46 ± 0.11	124.01 ± 49.13
10	Female	169.70 ± 38.96	2.17 ± 1.76	217.46 ± 20.22	31357.28 ± 9338.28	41.24 ± 24.76	0.33 ± 0.1	179.68 ± 73.6
	Male	128.94 ± 35.93	0.67 ± 0.29	251.88 ± 6.49	26779.98 ± 7205.43	30.9 ± 30.2	0.31 ± 0.05	113.25 ± 44.39
	Overall	149.32 ± 40.28	1.42 ± 1.39	234.67 ± 23.15	29068.63 ± 7869.83	36.07 ± 25.34	0.32 ± 0.07	146.46 ± 65.42

1.5.2 Progress in the clinical studies of SHR-1210

After SHR-1210 was approved for clinical trials in 2016, three phase I clinical studies have been carried out in China, all of which were studies on the safety and tolerability in patients with advanced solid tumors. As of 28 Feb., 2018, a total of 258 patients with advanced solid tumors who failed standard treatment were included in the 3 phase I studies. The safety was summarized and analyzed as follows:

All 258 subjects (100.0%) had at least one AE. AEs with an incidence of ≥ 10% mainly included: Skin and subcutaneous tissue diseases: skin capillary hyperplasia (81.8%), pruritus (22.5%), rash (16.3%); abnormal liver function: aspartate aminotransferase increased (22.1%), alanine aminotransferase increased (19.0%), bilirubin conjugated increased (17.8%), blood bilirubin increased (13.2%); hematological toxicity: anemia (29.5 %), white blood cell count decreased (17.1%), neutrophil count decreased (10.5%); systemic symptoms: asthenia (38.4%), fever (22.1%); gastrointestinal AEs: nausea (12.0%), diarrhea (11.6%); respiratory, thoracic, and mediastinal disorders: cough (21.3%), upper respiratory tract infection (10.9%); metabolism and nutrition disorders: hypoproteinemia (22.1%), blood sodium decreased (18.2%), appetite decreased (12.0%); renal and urinary disorders: proteinuria (22.5%); endocrine disorders: hypothyroidism (20.9%). A total of 98 subjects (38.0%) experienced at least one Grade 3 or higher AE. Grade 3 or higher AEs with an incidence of ≥ 2% mainly included anemia (7.0%), lung infection (6.6%), blood sodium decreased (4.3%), bilirubin conjugated increased (3.9%), tumor progression (3.5%), death (3.1%), aspartate aminotransferase increased (2.7%), alanine aminotransferase increased (2.3%), and blood bilirubin increased (2.3%).

Of the 258 subjects, 256 (99.2%) experienced at least one treatment-related AE. Treatment-related AEs with an incidence of ≥ 10% mainly included: Skin and subcutaneous tissue diseases: skin capillary hyperplasia (81.8%), pruritus (22.1%), rash (16.3%); systemic symptoms: asthenia (37.6%), fever (20.9%); abnormal liver function: aspartate aminotransferase increased (21.7%), alanine aminotransferase increased (18.6%), bilirubin conjugated increased (16.7%), blood bilirubin increased (12.0%); hematological toxicity: anemia (27.5%), white blood cell count decreased (14.7%); gastrointestinal disorders: diarrhea (11.2%), nausea (10.5%); respiratory, thoracic, and mediastinal disorders: cough (19.0%), upper respiratory tract infection (10.1%); metabolism and nutrition disorders: hypoalbuminemia (19.4%), blood sodium decreased (14.3%); renal and urinary disorders: proteinuria (22.1) %); endocrine disorders: hypothyroidism (19.8%). A total of 82 subjects (31.8%) experienced at least one Grade 3 or higher drug-related AE. Grade 3 or higher treatment-related AEs with an incidence of ≥ 2% mainly included anemia (6.2%), lung infection (5.8%), bilirubin conjugated increased (3.9%),

blood sodium decreased (3.5%), death (3.1%), aspartate aminotransferase increased (2.7%), alanine aminotransferase increased (2.3%), and blood bilirubin increased (2.3%).

Of the 258 subjects, Grade 3 or higher AEs with an incidence of ≥ 2% mainly included anemia (7.0%), lung infection (6.6%), blood sodium decreased (4.3%), bilirubin conjugated increased (3.9%), tumor progression (3.5%), death (3.1%), aspartate aminotransferase increased (2.7%), alanine aminotransferase increased (2.3%), and blood bilirubin increased (2.3%).

In general, in patients with advanced solid tumors, AEs of SHR-1210 other than skin capillary hyperplasia were similar to those of similar drugs on the market. Skin capillary hyperplasia mostly occurred within 1-2 months after the start of medication. The earlier ones appeared within a few days after the medication while the later ones appeared approximately 5 months after the medication. It mainly occurred on the trunk or limbs. Most (99.5%) were Grade 1-2 as per CTCAE, with only one subject reported as Grade 3. The subject was hospitalized due to surgical resection and was assessed as a Grade 3 AE. No patient discontinued medication due to this AE. A small number of subjects with bleeding symptoms received local symptomatic treatment. The symptoms gradually disappeared after the interruption of SHR-1210 treatment. Overall, SHR-1210 has good safety and tolerability. See the investigator's manual for more safety information.

1.5.3 Phase II clinical study results of apatinib mesylate in the treatment of advanced liver cancer

A randomized, open-label, multi-center phase II clinical trial evaluating apatinib mesylate in advanced HCC was conducted from 2010 to 2013 by the 81st Hospital of the Chinese People's Liberation Army and other sites. A total of 121 subjects were enrolled in this study. The trial involved two treatment groups: the 850 mg group and the 750 mg group. Primary endpoint: TTP; secondary endpoints: OS, ORR, DCR, AFP, QoL, and safety. Efficacy results showed that in the FAS (ITT population), mTTP values in the 850 mg and 750 mg groups were 4.2 and 3.3 months, and mOS values were 9.7 and 9.8 months, respectively. ORRs were 8.6% and 0.0%, and DCRs were 48.6% and 37.3%, respectively. See Table 4 for the comparison of efficacy results of the subjects in the two groups.

Table 4. Comparison of efficacy results of the subjects in the two groups (FAS).

Group	mTTP (month)	mOS (month)	ORR (%)	DCR (%)
850 mg	4.2	9.7	8.6	48.6
750 mg	3.3	9.8	0.0	37.3

Safety results: The incidences of AEs in the 850 mg and 750 mg groups were 98.6% and 94.1%, respectively; the incidences of severe AEs (NCI CTCAE Grade III-V) were 67.1% and 72.6%, respectively. The incidences of adverse drug reactions in the 850 mg and 750 mg groups were 95.7% and 90.2%, respectively; the incidences of severe adverse reactions (NCI CTCAE Grade III-V) were 58.6% and 58.8%, respectively. The incidences of SAEs were 18.6% and 23.5%, respectively; and the incidences of serious ADRs were 4.3% and 5.9%, respectively. See Table 5 for the comparison of incidences of adverse events and adverse drug reactions of the subjects in the two groups .

Table 5. Comparison of incidences of adverse events and adverse drug reactions of the subjects in the two groups (SS).

	Group	Yes	None	Total	Incidence (%)	Inter-group comparison P
Adverse event (n)	850 mg group	69	1	70	98.57	0.3090
	750 mg group	48	3	51	94.12	
Grade III-V Adverse Events (n)	850 mg group	47	23	70	67.14	0.5551
	750 mg group	37	14	51	72.55	
Adverse drug reaction (n)	850 mg group	67	3	70	95.71	0.2790
	750 mg group	46	5	51	90.20	
Grade III-V Adverse Drug Reactions (n)	850 mg group	41	29	70	58.57	1.0000
	750 mg group	30	21	51	58.82	
Serious adverse event (n)	850 mg group	13	57	70	18.57	0.5060
	750 mg group	12	39	51	23.53	
Serious adverse drug reaction (n)	850 mg group	3	67	70	4.29	0.6960
	750 mg group	3	48	51	5.88	

Common adverse events (incidence ≥ 10%) mainly included: transaminases increased, hypertension, proteinuria, hand-and-foot syndrome, etc., most of which were mild to moderate, and all were controllable. Refer to Table 6 for details:

Table 6. Common AEs (incidence ≥ 10%) in both groups.

Adverse event	Group	Total	Adverse event n (%)	Grade III-V Adverse Events n (%)
Transaminases increased	850 mg	70	44 (62.9)	8 (11.4)
	750 mg	51	25 (49.0)	7 (13.7)
Bilirubin increased	850 mg	70	44 (62.9)	8 (11.4)
	750 mg	51	24 (47.1)	8 (15.7)
Hypertension	850 mg	70	36 (51.4)	3 (4.3)
	750 mg	51	25 (49.0)	7 (13.7)
Proteinuria	850 mg	70	33 (47.1)	1 (1.4)
	750 mg	51	24 (47.1)	2 (3.9)
Gamma-Glutamyltransferase increased	850 mg	70	30 (42.9)	13 (18.6)
	750 mg	51	6 (31.4)	5 (9.8)
Hand-and-Foot syndrome	850 mg	70	29 (41.4)	4 (5.7)
	750 mg	51	15 (29.4)	4 (7.8)
Platelet count decreased	850 mg	70	27 (38.6)	6 (8.6)
	750 mg	51	23 (45.1)	7 (13.7)
White blood cell count decreased	850 mg	70	21 (30.0)	3 (4.3)
	750 mg	51	17 (33.3)	2 (3.9)
Lactate dehydrogenase increased	850 mg	70	19 (27.1)	2 (2.9)
	750 mg	51	6 (11.8)	2 (3.9)
Neutrophil count decreased	850 mg	70	18 (25.7)	4 (5.7)
	750 mg	51	16 (31.4)	3 (5.9)
Abdominal pain	850 mg	70	18 (25.7)	4 (5.7)
	750 mg	51	7 (13.7)	0 (0.0)
Asthenia	850 mg	70	17 (24.3)	3 (4.3)
	750 mg	51	9 (17.7)	2 (3.9)

The 850 mg and 750 mg groups had comparable efficacy. In terms of safety, the types and incidence of AEs and adverse drug reactions observed in both groups were also similar.

1.5.4 Phase III clinical study results of apatinib mesylate in the treatment of advanced liver cancer

A randomized (2:1), double-blind, placebo-controlled, multi-center, phase III clinical trial evaluating the efficacy and safety of apatinib mesylate 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 31 Oct., 2017, a total of 400 subjects were enrolled, including 7 randomized patients who have not received the medication and 393 patients who took at least one dose of medication. Adverse events that have been observed included proteinuria, blood pressure increased, thrombocytopenia, aspartate aminotransferase increased, hand-and-foot syndrome, total bilirubin increased, asthenia, diarrhea, leukopenia, neutropenia, headache/dizziness, alanine aminotransferase increased, vomiting, direct bilirubin increased, abdominal pain, decreased appetite, nausea, and glutamyltransferase increased.

1.5.5 Experimental report on the efficacy of SHR-1210 combined with apatinib mesylate in human PD-1 transgenic mice

With human PD-1 transgenic mice as the test subject, the efficacy of the combination of PD-1 antibody SHR1210 and VEGFR-2 compound apatinib on C57 human PD-1 transgenic mice with mouse colon cancer cell MC-38 (PD-L1) xenograft transfered with PD-L1 gene. In the experiment, antibody SHR1210 was injected intraperitoneally, Q2D × 7. Compound apatinib was administered through oral gavage, QD × 14. On day 21 of observation, the tumor inhibition rate of SHR1210 (3 mg/kg) reached 20.40%, the tumor inhibition rate of apatinib (200 mg/kg) monotherapy group reached 35.67%; The tumor inhibition rate of the combination of SHR1210 (3 mg/kg) + apatinib (200 mg/kg) reached 63.07% (significantly different from the HIgG control group), and the other monotherapy groups showed no significant difference from the HIgG control group. See Table 7 and Figure 3 for details.

Table 7. Efficacy of medication with the antibody and the compound on xenograft in MC38 (PD-L1) tumor-bearing mice.

Group	Administration	Route	Average Tumor Volume (mm^3)		Relative Tumor Volume		Relative Tumor Volume		Tumor Inhibition Rate%	p (vs blank)	Number of Animals per Group
			D0	SEM	D21	SEM	D21	SEM			
HIgG(3mg/kg)	Q2D*7	ip	141.46	13.23	1,983.55	292.09	14.41	2.07	-	-	8
SHR1210(3mg/kg)	Q2D*7	ip	141.40	12.68	1,652.93	309.61	11.47	2.49	20.40%	0.379164	8
SHR1210(3mpk)+Apatinib(200mg/kg)	Q2D*7/QD(14D)	ip/po	146.11	11.69	771.98	73.42	5.32	0.73	63.07%**	0.001007	8
Apatinib(200mg/kg)	QD(14D)	po	139.70	7.59	1,263.86	206.54	9.27	1.58	35.67%	0.068923	8

**: $p < 0.01$, vs. blank

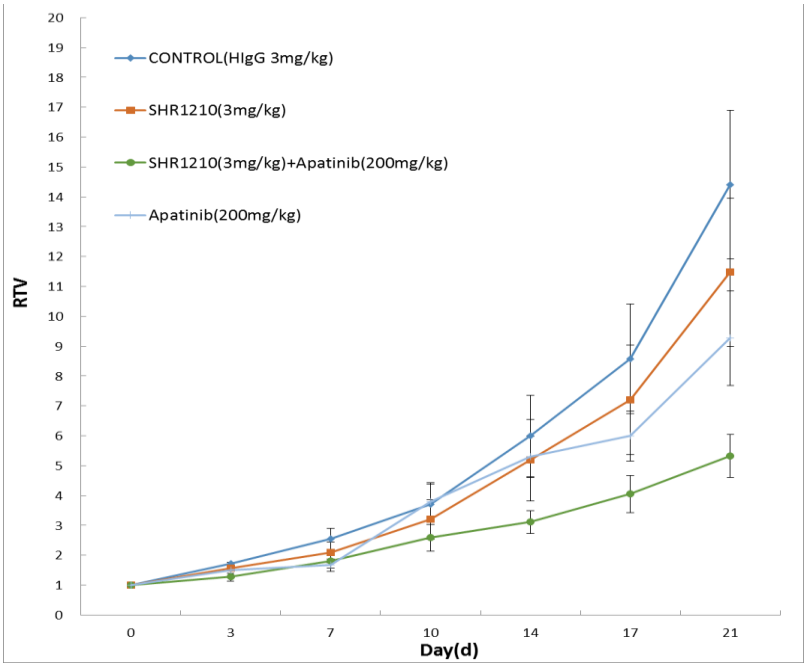


Figure 3. Effects of medication with the antibody and the compound on the relative volume of xenograft in MC38 (PD-L1) tumor-bearing mice.

The experimental results showed that the efficacy of the combination of SHR1210 (3 mg/kg) + apatinib (200 mg/kg) was superior to that of SHR1210 and apatinib monotherapy (Table 7, Figure 3, and Figure 4). The weight of the mice in each treatment group was normal, indicating that the drug had no significant toxic adverse effects. See Figure 6 for details.

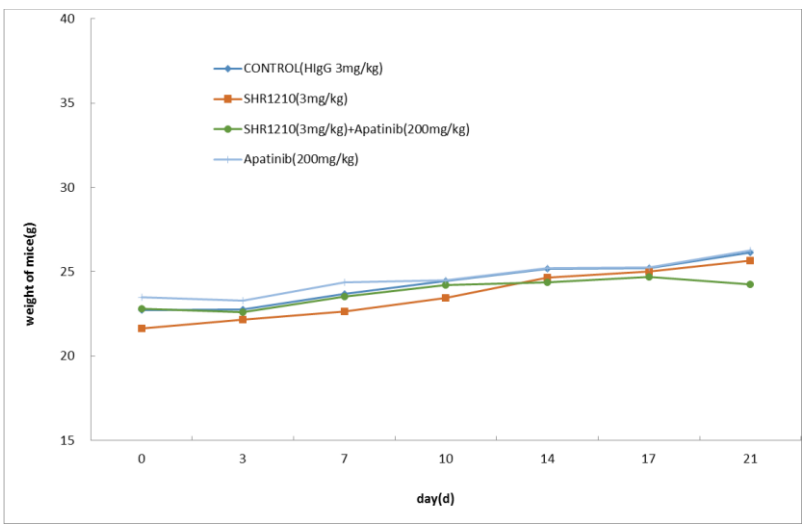
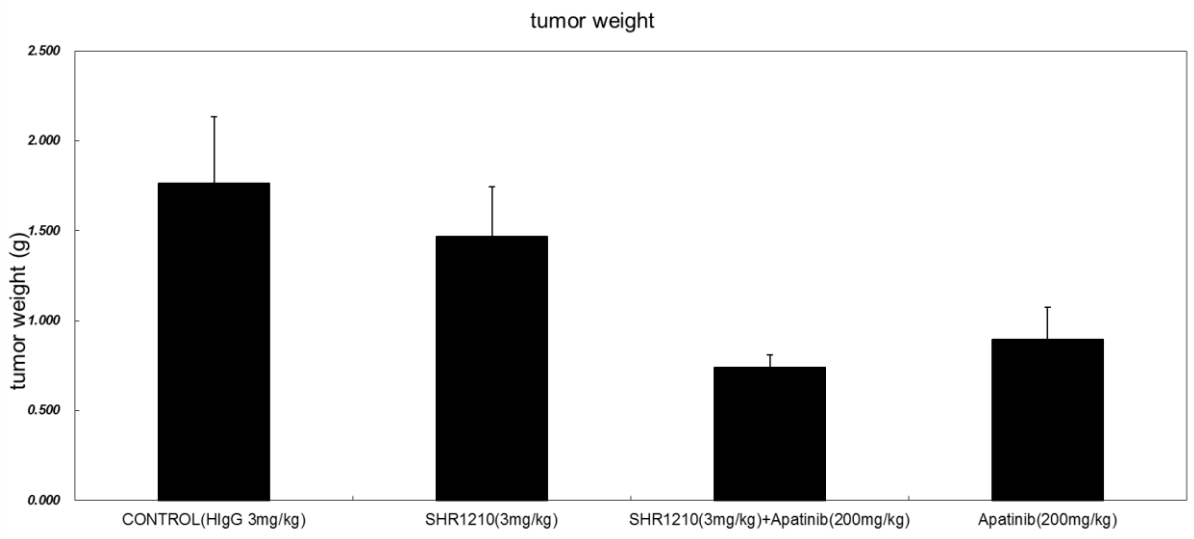


Figure 5. Efficacy of medication with the antibody and the compound on xenograft in MC38 (PD-L1) tumor-bearing mice - tumor weight.



*: $p < 0.05$, vs. blank

Figure 6. Effects of medication with the antibody and the compound on the weight of xengraft in MC38 (PD-L1) tumor-bearing mice.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary objectives

- To observe and evaluate the safety and tolerability of PD-1 antibody SHR-1210 in combination with apatinib mesylate or the FOLFOX4 regimen or GEMOX regimen in the treatment of advanced primary liver cancer or extrahepatic cholangiocarcinoma.

2.1.2 Secondary objectives

- To preliminary observe the efficacy of PD-1 antibody SHR-1210 in combination with apatinib mesylate or the FOLFOX4 regimen or GEMOX regimen in the treatment of advanced primary liver cancer or extrahepatic cholangiocarcinoma.

2.2 Study Endpoints

2.2.1 Primary endpoints (per the NCI-CTCAE V4.03 criteria)

- The incidence and severity of adverse events (AEs) and serious adverse events (SAEs), including laboratory tests, vital signs, physical examinations, ECOG PS, and electrocardiography.

2.2.2 Secondary endpoints (per the RECIST 1.1 criteria)

- Objective response rate (ORR)
- Duration of response (DoR)
- Time to progression (TTP)
- Refers to the time from the start of treatment to any documentation of radiologic tumor progression.
- Disease control rate (DCR)
- Overall survival (OS): Refers to the time from the start of treatment to death due to any cause.

3 STUDY DESIGN

3.1 Study Design

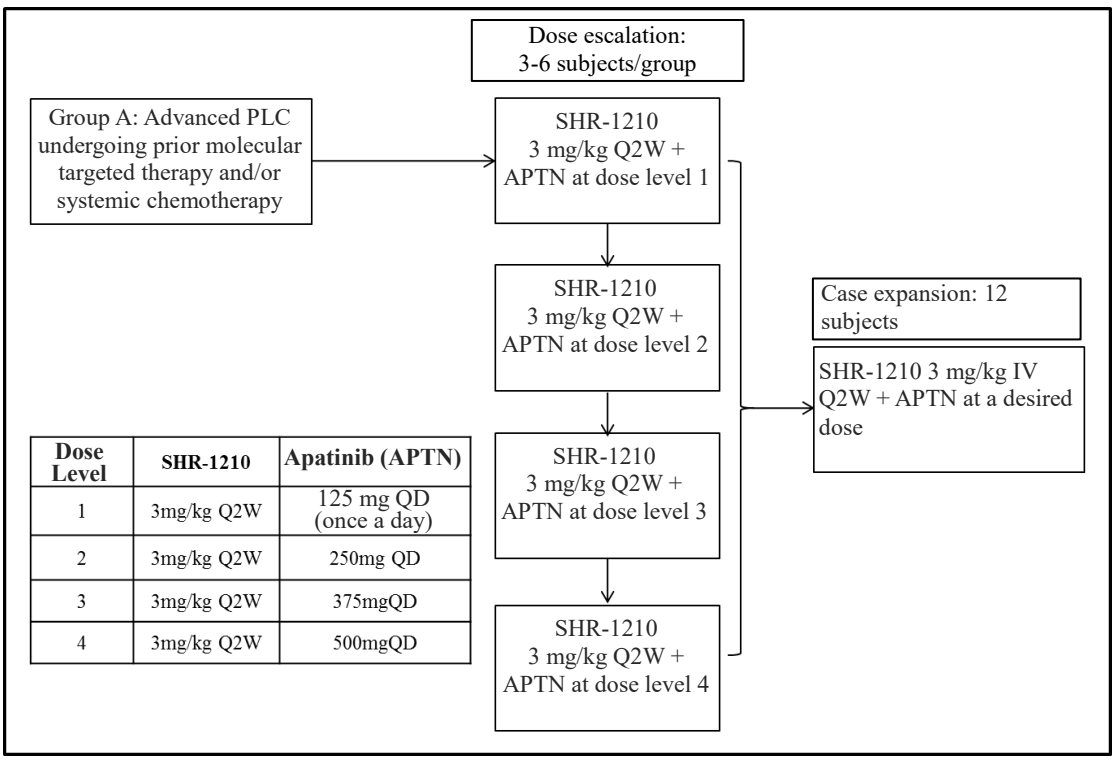
This study is an open-label phase II study, and 152 patients with advanced primary liver cancer or extrahepatic cholangiocarcinoma are intended to be enrolled. Subjects will be enrolled into treatment group A or B based on whether they have received systemic treatment for advanced liver cancer or extrahepatic cholangiocarcinoma.

Subjects in group A will receive treatment of SHR-1210 in combination with apatinib mesylate (APTN) for exploring the optimal dose first. The objective is to determine the optimal dose of SHR-1210 combined with apatinib mesylate in patients with advanced primary liver cancer and extrahepatic cholangiocarcinoma. After the determination of the optimal dose of the combined medication, the case extension stage was proceeded for collecting sufficient safety data of the combination of immunotherapy and targeted therapy.

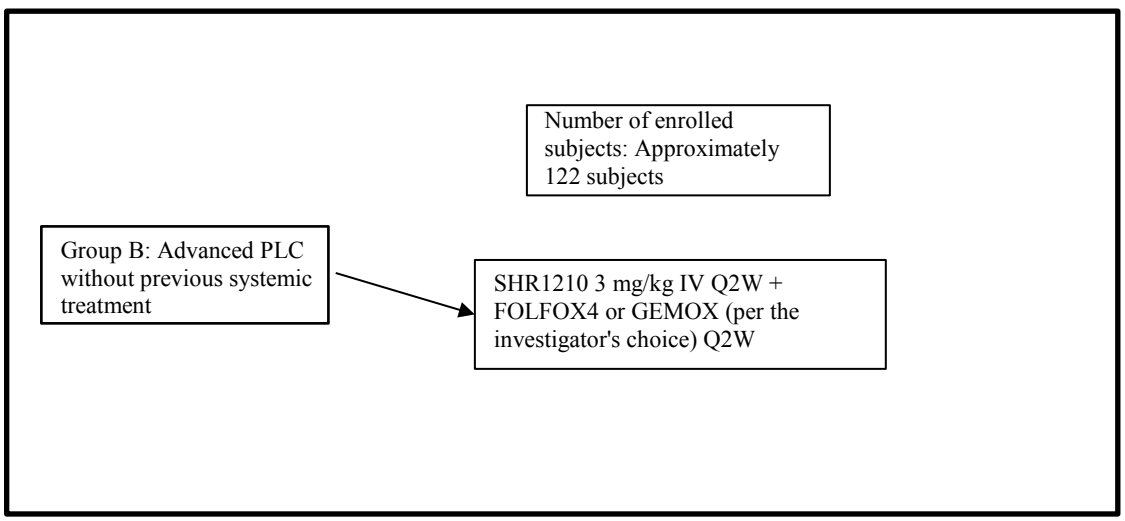
Subjects in group B will receive treatment of SHR-1210 in combination with the FOLFOX4 regimen or GEMOX regimen. The objective is to explore the safety and tolerability of the immunotherapy combined with systemic chemotherapy.

This study will consist of a screening period, a treatment period, and a follow-up period. The study treatment will continue until disease progression, intolerable toxicity, or subject withdrawal. Every 4-week is a treatment cycle.

Study Design Schematic



Dose Level	SHR-1210	Apatinib (APTN)
1	3mg/kg Q2W	125 mg QD (once a day)
2	3mg/kg Q2W	250mg QD
3	3mg/kg Q2W	375mgQD
4	3mg/kg Q2W	500mgQD



Approximately 152 subjects are intended to be enrolled in this study (group A + group B).

Subjects in group A will be given dose level 1 as the starting dose. The subjects will be enrolled in the group in sequence (see Table 10) from low dose to high dose to explore the optimal dose. The first cycle (28 days) of continuous administration is the tolerability observation period. After the tolerability observation period, if none of the 3 subjects experienced clinically significant

toxicity, the next group of dose may be explored. If 1 of the 3 subjects developed clinically significant toxicity, another 3 subjects will be enrolled. If no clinically significant toxicity was observed in the later-enrolled 3 subjects, the next group of dose may be explored. If ≥ 1 of the 3 later-enrolled subjects developed clinically significant toxicity again, the dose exploration will be terminated. The dose prior to the current one is the tolerable dose.

Also, the Bayesian logistic regression model (BLRM) was used as an auxiliary analysis to help explore the probability of clinically significant toxicity at different doses.

Finally, the optimal dose level for case extension is determined through the above-mentioned dose exploration, with 8-12 subjects enrolled, to collect sufficient safety data for the combination therapy. The dose levels for group A are detailed in Table 8 below.

Table 8. Dose levels for group A.

Dose Level	SHR-1210	Apatinib mesylate (APTN)	Number of Enrolled Subjects
1	3 mg/kg Q2W	125 mg QD (once a day)	3-6
2	3 mg/kg Q2W	250 mg QD	3-6
3	3 mg/kg Q2W	375 mg QD	3-6
4	3 mg/kg Q2W	500 mg QD	3-6

The subjects in group B will receive treatment at dose level 1 according to Table 11, with 6 subjects enrolled first. If the proportion of subjects showing clinically significant toxicity in the 6 subjects is < 0.33, some other 122 subjects will be enrolled to receive treatment at the same dose level. The dose levels for group B are detailed in Table 9 below.

Table 9. Dose levels for group B.

Dose Level	SHR-1210	FOLFOX4	Number of Enrolled Subjects
1	3 mg/kg Q2W	D1: Oxaliplatin (OXA 85 mg/m^2 (2-h infusion) + levoleucovorin (LV) 200 mg/m^2 (2-h infusion), followed by 5-Fu 400 mg/m^2 (bolus injection), and 5-Fu 600 mg/m^2 (22-h infusion) D2: Levoleucovorin (LV) 200 mg/m^2 (2-h infusion), followed by 5-Fu 400 mg/m^2 (bolus injection), and 5-Fu 600 mg/m^2 (22-h infusion) Q2W	Approximately 122 subjects
		GEMOX	
		D1: Gemcitabine 800 mg/m^2(80-min infusion) D2: OXA 85 mg/m^2 (2-h infusion) Q2W	

3.1.1 Definition of clinically significant toxicity

Any of the following toxicities that may or are definitely related to the investigational drug will be considered clinically significant toxicity:

Significant hepatotoxicity:

- ALT or AST > 10 × ULN for > 14 days;
- ALT or AST > 15 × ULN regardless of the duration;
- TBIL > 5 × ULN (> 8 × ULN for subjects with increased TBIL at baseline)

Significant hematological toxicity:

- Grade 3 treatment-related thrombocytopenia with bleeding;
- Grade 3 treatment-related neutropenia with fever;
- Grade 4 treatment-related neutropenia for > 5 days;
- Grade 4 treatment-related thrombocytopenia;

Significant non-hematological toxicity:

- Grade 2 or above treatment-related eye pain or decreased vision that are not responsive to local treatment (not resolved to grade ≤ 1 within 14 days), and requiring systemic treatment;
- Grade 3 treatment-related non-cutaneous AEs, except for the following:
  - Endocrine diseases that can be adequately controlled by replacement therapy;
  - Isolated laboratory abnormalities of no clinical significance
  - Gastrointestinal AEs persistent for < 48 h;
  - Fatigue;
  - Fever persistent for < 72 h, without neutropenia or impairment of other organ functions;
  - Hypertension that can be controlled within the normal range after medication (systolic pressure ≤ 140 mmHg, diastolic pressure ≤ 80 mmHg)
- Grade 4 treatment-related AEs, including laboratory abnormalities.

3.1.2 Definition of subjects with uncompleted tolerability evaluation

Subjects who have not completed the tolerability assessment refer to those who have not completed the tolerability observation period due to reasons other than clinically significant toxicity, and such subjects will be replaced. When a subject fails to complete the tolerability observation, the sponsor and the principal investigator of the coordinating center will jointly define the subject to be replaced.

3.1.3 Subsequent treatment for subjects with clinically significant toxicity

During the tolerability observation period, the subjects with clinically significant toxicity could receive a subsequent treatment of the investigational drug based on the investigator's judgment after they have recovered from toxicity. The dose of the investigational drug (SHR-1210 does not allow dose adjustment) can be adjusted according to the adjustment principle, or terminate the treatment. Subjects are also followed up and their data are collected according to the trial procedure.

3.2 Study Procedures

3.2.1 Screening period

The screening period is the time from the signing of the informed consent form until the start of study treatment or screen failure.

Subjects must sign the informed consent form before undergoing any screening procedures.

Unless otherwise stated, the following screening procedures should be completed within 28 days prior to the first dose:

- Signing of Informed Consent Form.
- Assigning subject number.
- Collection of demographics.
- Collection of medical history, including past treatment history, current medical history, drug allergies, and concurrent diseases.
- Collection of information on adverse events and concomitant medications.
- Tumor imaging assessment, the results of imaging assessment before the signing of informed consent form and within 28 days of the first dose are acceptable, per the RECIST 1.1 criteria.

The following information should be collected within 14 days prior to the first dose:

- Physical examination, height, weight, vital signs (including body temperature, blood pressure, heart rate, respiratory rate, to be taken after sitting for 5 minutes).
- ECOG PS.
- Routine blood test, routine urinalysis, and fecal occult blood.
- Blood biochemistry (ALT, AST, total bilirubin, ALP, LDH, albumin, urea nitrogen or serum urea, creatinine, blood sugar, amylase/lipase).
- Electrolytes (potassium, sodium, chlorine, calcium, magnesium, phosphorus).
- Coagulation function (PT-INR and/or PT).
- Child-Pugh score.
- Virologic tests (including HBV, HCV, and HIV markers).
- Test of serum AFP.
- Thyroid function (TSH, FT3, FT4).
- Echocardiography (including LVEF).

- 12-Lead ECG (the QTc interval must be indicated, which was calculated by Fridericia's formula).
- Blood or urine HCG test: For women of childbearing potential (WOCBP) only.

The following information should be collected within 72 h prior to the first dose:

- Hematology and urinalysis.
- Blood biochemistry (ALT, AST, total bilirubin, ALP, LDH, albumin, urea nitrogen or serum urea, creatinine, blood sugar, amylase/lipase).
- Electrolytes (potassium, sodium, chlorine, calcium, magnesium, phosphorus).
- Coagulation function (PT-INR and/or PT)
- 12-Lead ECG (the QTc interval must be indicated, which was calculated by Fridericia's formula).

3.2.2 Treatment period

The treatment period starts from the subject's first dose.

Each cycle during the treatment period was 28 days.

For subjects in group A, SHR-1210 at 3 mg/kg was intravenously infused within 30 min (not less than 20 min and not more than 60 min, including flushing time) on D1 and D15 of each treatment cycle; at the same time, apatinib mesylate was continuously administered (125 mg, 250 mg, 375 mg, or 500 mg, orally administered, once daily) starting from D1 of cycle 1.

For subjects in group B, SHR-1210 at 3 mg/kg was intravenously infused within 30 min (not less than 20 min and not more than 60 min, including flushing time) on D1 and D15 of each treatment cycle; at the same time, chemotherapy with FOLFOX4 was given: D1: oxaliplatin (85 mg/m^2, 2-h infusion) + levoleucovorin (200 mg/m^2, 2-h infusion), 5-Fu (400 mg/m^2, bolus injection, followed by 5-Fu at 600 mg/m^2, 22-h infusion); D2: levoleucovorin (200 mg/m^2, 2-h infusion), 5-Fu (400 mg/m^2, bolus injection, followed by 5-Fu at 600 mg/m^2, 22-h infusion)); or chemotherapy with GEMOX was given: D1: gemcitabine (800 mg/m^2, 80-min infusion), D2: oxaliplatin (85 mg/m^2, 2-h infusion); repeated once every two weeks.

During the treatment period, relevant physical examinations and laboratory tests were performed, and information on AEs and concomitant medications were collected.

The following assessments must be completed within 72 h before dosing of each visit:

For hematology, urinalysis, blood biochemistry, blood electrolytes, and 12-lead ECG, the investigator must review the laboratory results before dosing.

The following assessments must be completed before dosing on the day of each visit:

ECOG PS, physical examination, and vital signs.

The following assessments should be completed on D1 of each cycle from cycle 2:

Thyroid function, Child-Pugh score, alpha-fetoprotein, virological tests (HBV marker or HCV marker), and coagulation function.

As per RECIST v1.1, tumor assessment is supposed to be performed every 8 weeks (± 7 days), regardless of drug administration. Until disease progression or initiation of subsequent anti-tumor therapy (whichever occurs later).

Patients with progression may continue to use SHR-1210 monotherapy if they meet the criteria defined in 3.2.4.

Note: The detailed study procedures during the treatment period are shown in the schedule of study procedures.

3.2.3 Follow-up period

The follow-up period begins when the decision is made to discontinue the study treatment.

Within 90 days after the last study medication, subjects will undergo a follow-up visit every 30 days (± 7 days). The first safety follow-up (30 days after the last dose) and the third safety follow-up (90 days after the last dose) must be conducted face-to-face at the study site, and the required safety assessments (see the schedule of study procedures) must be completed; the second follow-up (60 days after the last dose) will be a telephone interview, and only survival information, concomitant medications/treatments, and adverse events are required to be collected.

The survival follow-up period starts after the end of the safety follow-up period on day 90. The investigator must conduct follow-ups every month until death, lost to follow-up, or the sponsor terminates the study. The investigator may phone the subject, his or her family, or a local physician to collect information about the subject's survival (date of death and cause of death) and any further anti-tumor treatments after the end of the study treatment. Each survival follow-up should be recorded in the original medical record.

For subjects who withdraw from the study due to toxicity or other reasons without radiographic disease progression observed, the imaging evaluation should be performed at the same frequency, until disease progression or initiation of other anti-tumor treatments. The radiographic evidence of progressive disease in these subjects must be obtained as much as possible.

3.2.4 Criteria for continuing treatment beyond progression

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

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

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

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

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

If the subject discontinues treatment due to deterioration of the general condition without objective evidence for disease progression, the progression will be reported as "general

deterioration". More objective evidences (such as imaging confirmation) of progression of these subjects should be obtained after treatment discontinuation.

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

4 RANDOMIZATION AND BLINDING

Randomization and blinding are not involved in this study.

5 SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Inclusion Criteria

1. Male and female subjects aged 18-70 years old.
2. Patients with advanced primary liver cancer or extrahepatic cholangiocarcinoma (only applicable to group B, including gallbladder cancer and common bile duct cancer) diagnosed by histopathological or cytological examinations are not suitable for surgery or local treatment and have at least one measurable lesion (RECIST 1.1 criteria).
3. Group A: Patients who have previously undergone systemic therapy for advanced primary liver cancer, molecular targeted therapy (sorafenib, etc.) and/or systemic chemotherapy (monotherapy or combination therapy) but have failed or become intolerable;

   Group B: Patients who have not previously undergone systemic treatment (molecular targeted therapy or chemotherapy) of advanced primary liver cancer or extrahepatic cholangiocarcinoma.
4. The end of the previous anti-tumor treatment must be ≥ 2 weeks from the start of medication in this study, or the drug washout period (that is, 5 times the drug half-life) is reached, and the AEs related to the previous treatment should resolve to NCI-CTCAE Grade ≤ 1.
5. Subjects with primary liver cancer or a history of liver cirrhosis should meet the Child-Pugh liver function rating: grade A and better grade B (≤ 7 points).
6. ECOG PS: 0-1.
7. Expected survival ≥ 12 weeks.

8. Subjects with chronic HBV infection must have HBV-DNA < 500 IU/mL, and patients with positive HBsAg must receive antiviral treatment in accordance with the "Guidelines for the Prevention and Control of Chronic Hepatitis B, Version 2015". Patients with positive HCV-RNA must receive antiviral treatment in accordance with the 2015 "Guidelines for the Prevention and Control of Chronic Hepatitis C" and hepatic function tests must be within the normal range.

9. Major organs must function normally, meeting the following criteria:

   (1) Hematology: (no blood transfusion or use of hematopoietic stimulating factors within 14 days before screening)

      1) HB ≥ 90 g/L;

      2) ANC ≥ 1.5×10^9/L;

      3) PLT ≥ 80×10^9/L;

   (2) Biochemistry: (no blood transfusion or use of blood products within 14 days before screening)

      1) ALB ≥ 29 g/L;

      2) ALT and AST < 2.5 × ULN;

      3) TBIL ≤ 1.5 × ULN;

      4) Creatinine ≤ 1.5 × ULN;

   (3) Prothrombin time (PT) - international normalized ratio (INR) ≤ 2.3 or prothrombin time (PT) ≤ 6 seconds from normal.

10. Female subjects of childbearing potential must have a negative serum or urine pregnancy results within 14 days prior to the start of the study treatment, and be willing to take effective contraceptive measures during the study period and within 60 days after the last dose of the investigational drug. Male subjects with partners of childbearing potential must have undergone surgical sterilization or agree to take effective contraceptive measures during the course of the study until 120 days after the last dose of the investigational drug.

11. Subject must participate voluntarily, sign the informed consent form, have good compliance, and cooperate with follow-up visits.

5.2 Exclusion Criteria

1. Known fibrolamellar cell carcinoma; having other uncured malignant tumors within the past 5 years or concurrently, except for cured localized tumors, such as skin basal cell carcinoma, cutaneous squamous cell carcinoma, superficial bladder cancer, prostate carcinoma *in situ*, cervical carcinoma *in situ*, and breast carcinoma *in situ*.
2. Current or past metastasis to the central nervous system.
3. Symptomatic ascites requiring paracentesis or drainage, or with a Child-Pugh score > 2.
4. History of gastrointestinal bleeding within the past 6 months or a high risk of bleeding such as esophageal varices with bleeding risk, active ulcers, and persistent positive fecal occult blood.
5. Known hereditary or acquired hemorrhage and thrombophilia, such as hemophilia patients.
6. Abdominal fistula, gastrointestinal perforation, or abdominal abscess within 2 months prior to the study.
7. Grade II or higher myocardial ischemia or myocardial infarction, uncontrolled arrhythmias (including QTcF interval ≥ 450 ms in males and ≥ 470 ms in females) (QTcF interval calculated using Fridericia's Formula).
8. NYHA Class III-IV cardiac insufficiency or LVEF (left ventricular ejection fraction) < 50% by echocardiography.
9. Hypertension uncontrolled by antihypertensives (systolic pressure > 140 mmHg or diastolic pressure > 90 mmHg).
10. Thromboembolism events that have occurred in the past 6 months, such as cerebrovascular events (including transient ischemia attacks) and pulmonary embolism.
11. Dysphagia, chronic diarrhea, or intestinal obstruction, which significantly affect drug intake and absorption.
12. History of hepatic encephalopathy.
13. Untreated active hepatitis (Hepatitis B: positive HBsAg with abnormal liver function and HBV DNA ≥ 500 IU/mL; Hepatitis C: positive HCV-RNA with abnormal liver function).
14. Infection with human immunodeficiency virus (HIV).

15. Subjects with active infection or unexplained fever (body temperature > 38.5 °C) during screening or prior to the first dose.
16. Received any vaccine treatment within 30 days prior to enrollment.
17. Patients planning to receive or previously received allogeneic organ or allogeneic bone marrow transplants, including liver transplant.
18. Subjects with previous or current pulmonary fibrosis, interstitial pneumonia, pneumoconiosis, radiation-induced pneumonitis, drug-induced pneumonitis, severe lung function impairment or other conditions that may interfere with the detection and management of suspected treatment-related pulmonary toxicities.
19. Urine protein ≥ 2+ and confirmed 24-h urine protein quantitation > 1.0 g.
20. Subjects with active, known, or suspected autoimmune diseases; subjects who are stable and do not require systemic immunosuppressive treatment may be enrolled.
21. Subjects requiring systemic treatment with corticosteroids (> 10 mg/day of prednisone or equivalent) or other immunosuppressive medications within 14 days prior to the administration of the investigational drug; in the absence of active autoimmune disease, inhaled or topical use of corticosteroids and an equivalent dose to > 10 mg/day of prednisone for adrenal hormone replacement are permitted.
22. Received any local treatment for liver within 4 weeks before participating in this study (including but not limited to surgery, radiation, hepatic artery embolization, TACE, hepatic arterial infusion, radiofrequency ablation, cryoablation, or percutaneous ethanol injection).
23. Palliative radiotherapy for symptomatic control of non-target lesions is permitted but must be completed at least 2 weeks prior to the start of study treatment, and no additional radiotherapy should be scheduled for the same lesion; patients with radiation-induced adverse events that have not resolved to CTCAE grade ≤ 1;
24. Subjects who have previously received other PD-1 antibody treatment or other immunotherapies targeting PD-1/PD-L1.
25. Known history of severe allergies to any monoclonal antibodies, anti-angiogenesis targeted drugs, platinums, fluorouracils, or components of the study drug.
26. Subjects requiring long-term anticoagulant therapy with warfarin or heparin; Subjects requiring long-term antiplatelet therapy (aspirin ≥ 300 mg/day or clopidogrel ≥ 75 mg/day).

27. Subjects with a known history of psychotropic substance abuse or drug abuse.
28. Pregnant or breastfeeding women.
29. Patients with any other potential factors that may result in the premature termination of the study as determined by the investigator, such as other serious illnesses or serious laboratory abnormalities or family or social factors that could affect the safety of the subject, or collection of trial data.

5.3 Concomitant Medications/Treatments

All treatments and medications used in the 28 days before the signing of the informed consent form and during the study should be documented in the eCRF in strict accordance with the GCP regulations. Subjects should be monitored closely if an adverse event occurs. Symptomatic treatment will be provided when necessary and details will be documented in the eCRF.

5.3.1 Drugs or treatments that are prohibited or used with caution during the study

5.3.1.1 Drugs and treatments that must be prohibited or used with caution for all subjects during the study

During the study period, subjects are prohibited from using NMPA-approved modern Chinese medicine preparations with indications for the treatment of liver cancer or extrahepatic cholangiocarcinoma (including but not limited to Delisheng injection, Kanglaite injection, Aidi injection, Huai'er granules, and Ganfule tablets) and immunomodulators (including but not limited to interferon, interleukin-2, and thymosin).

During the study period, subjects are not allowed to receive any local treatment for liver lesions and target lesions. Other systemic anti-tumor therapies such as chemotherapy, molecular targeted therapy, hormone therapy, immunotherapy, and Chinese medicine therapy (above) are not allowed.

During the study period, subjects are not allowed to receive immunosuppressive therapy concomitantly (except for the treatment of drug-related adverse events).

During the study period, subjects are not allowed to use other study drugs for anti-tumor therapy.

5.3.1.2 Drugs that must be used with caution for subjects in group A during the study

- Drugs that interfere with liver P450 enzymes:
  - CYP3A4 inducers: dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital, and rifapentin;

- CYP3A4 inhibitors: itraconazole, clarithromycin, voriconazole, telithromycin, and saquinavir;
- Drugs metabolized by CYP3A4: benzodiazepines, dihydropyridine, calcium ion antagonists nisodipine, and lercanidipine;
- HMG-COA reductase inhibitors: simvastatin and midazolam;
- Drugs metabolized by CYP2C9: warfarin, phenytoin, and certain sulfonylurea hypoglycemic agents such as glibenclamide;

- Drugs that prolong the QT interval: antibiotics, antiarrhythmic drugs, antipsychotics, antifungals, antimalarials, and antidepressants.

5.3.1.3 Drugs that must be used with caution or prohibited for subjects in group B during the study

- For subjects using the FOLFOX4 regimen: Antiviral drug sorivudine or drugs with similar chemical structures, such as brivudine, are not allowed. Because the clinically significant drug-drug interaction between sorivudine and 5-Fu can lead to increased toxicity of 5-Fu, which is potentially lethal. Drugs to be used with caution: phenytoin and warfarin potassium.
- For subjects using the GEMOX regimen: Gemcitabine has a radiosensitization effect, and thus should be used at least 7 days before and after radiotherapy; drugs used with caution: yellow fever vaccine and other attenuated vaccines.

In addition, for the drugs or treatments that are prohibited or used with caution for subjects in group B during the study period, the investigator may refer to the drug marketing instructions of oxaliplatin, 5-Fu, levoleucovorin calcium and gemcitabine in combination with clinical practice.

5.3.2 Drugs and treatments allowed to be used concomitantly during the study

1. Anti-viral therapy

Subjects with HBV or HCV infections are required to receive anti-viral therapy according to local standard practices. Recommendations for antiviral therapy are as follows:

Patients with HBV infection, e.g., HBsAg-positive, may continue the original antiviral therapy if they have started antiviral therapy before enrolled in the study with satisfactory virus control (HBV-DNA < 500 IU/mL). Those with unsatisfactory virus control should switch to entecavir, and be enrolled after HBV-DNA < 500 IU/mL. Patients with newly discovered HBV infection at screening should start entecavir treatment immediately, and may be enrolled after HBV-DNA < 500 IU/mL.

Patients with HCV infection, e.g., HCV-RNA-positive, must receive antiviral treatment in accordance with the "Guidelines for the Prevention and Control of Hepatitis C, Version 2015".

2. Corticosteroids

Local application of steroid hormones, such as topical, eye, nasal, intra-articular, and inhalation, is allowed; corticosteroids for adrenal replacement therapy are allowed; corticosteroids for the treatment of adverse reactions are allowed; short-term use of corticosteroids for the prevention and treatment of allergic reactions (prevention of contrast agent allergy, or treatment of other allergic reactions) is allowed.

3. Other systemic treatment

Subjects should be given optimal supportive care during the treatment. Existing hormone replacement therapies are permitted. Bisphosphonate treatment for bone metastasis is permitted.

4. Palliative local treatment

Palliative treatment is allowed for local non-target lesions that cause evident symptoms, such as bone pain lesions. Local radiotherapy or surgery may be considered, but the following conditions must be met:

1) The investigator must assess whether there was disease progression in subjects who required local treatment due to symptom exacerbations during the study;
2) Subjects with disease progression must meet the criteria for continuing treatment after progression (see 3.2.4);
3) The locally treated lesions should not be the target lesions.

A discussion with the sponsor is recommended before starting palliative local treatment. The content of palliative treatment, including the treatment date, location, treatment method and dosage and adverse drug reactions, should be documented in the eCRF and medical records in detail.

5.4 Re-screening Criteria for Subjects

In this study, re-screening is allowed, i.e., subjects who have entered the screening process but have not met the enrollment conditions and have not started treatment may be re-enrolled. When re-screening, the informed consent form must be re-signed and a new subject number will be given.

5.5 Criteria of Study Medication Discontinuation or Study Withdrawal for Subjects

The study drug must be discontinued in any of the following cases:

1. Subject withdraws informed consent and requests to withdraw from the study;
2. Imaging evaluations show disease progression, unless the subject meets the criteria for continuation of treatment beyond progression (see Section 3.2.4 for details);
3. Continuing the participation in the study is not in the best interests of the subject, due to intolerable toxicity, adverse events, laboratory abnormalities, or concurrent diseases after dose modification, as assessed by the investigator;
4. Other reasons for which the investigator considers a withdrawal necessary;
5. The subject becomes pregnant;
6. The study is terminated by the sponsor.

5.6 Subject Number

Each subject will be given a 5-digit subject number:

- First 2 digits = Study site number
- Last 3 digits = Numbers for subjects from the same study site Subjects will be numbered 001, 002, 003, and so on, according to the order in which the informed consent form is signed .

6 STUDY DRUGS

6.1 Information

Study drug: SHR-1210 for injection

Manufacturer: Shanghai Hengrui Pharmaceutical Co., Ltd.

Dosage form: lyophilized powder

Strength: 200 mg (tentative)/20 mL vial. Please refer to the drug analysis certificate for the batch number;

Route of administration: intravenous injection

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

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

Investigational drug: apatinib mesylate tablets

Manufacturer: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Dosage form: tablet

Strength: 250 mg/tablet or 375 mg/tablet

Administration: oral administration after meals (best to take at the same time on each day)

Shelf life: 2 years (tentative)

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

Study drug: Oxaliplatin for Injection

Manufacturer: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Dosage form: injection

Strength: 50 mg/vial or 100 mg/vial

Route of administration: intravenous injection

Shelf life: 2 years (tentative)

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

Study drug: Levoleucovorin calcium for injection

Manufacturer: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Dosage form: injection

Strength: 25 mg/vial

Route of administration: intravenous injection

Shelf life: 3 years (tentative)

Storage conditions: sealed, away from light, stored in a dry place.

Study drug: 5-fluorouracil (5-Fu)

Manufacturer: Tianjin KingYork Pharmaceutical Co., Ltd.

Dosage form: Small volume injection

Strength: 10 mL: 0.25 g

Route of administration: intravenous injection

Shelf life: 18 months

Storage conditions: sealed, away from light.

Study drug: Gemcitabine hydrochloride for injection

Manufacturer: Jiangsu Hansoh Pharmaceutical Group Co., Ltd.

Dosage form: lyophilized powder

Strength: 1.0 g (gemcitabine-based)

Administration: intravenous drip

Shelf life: 36 months

Storage conditions: sealed and stored in a dry place.

6.2 Packaging and Labeling of Study Drugs

See Appendix 6 for details

6.3 Drug Dispensation

The management, dispensing, and recovery of the study drugs of this study are in the charge of designated staff. The investigator must ensure that all the study drugs are only used for the subjects participating in this clinical trial. The dosage and administration should follow the trial protocol. The remaining drugs should be returned to the sponsor. The study drug should not be transferred to any non-clinical trial participant.

The drug receipt forms must be signed by two people during drug dispensing at the study site. The form is in duplicate copies, of which one is for the study site and one for the sponsor. Remaining drugs and empty boxes will be retrieved at the end of the study and a retrieval form will also be signed by both parties. The dispensing and return of every drug should be immediately documented on designated forms.

6.4 Drug Storage and Management

In accordance with the Good Clinical Practice for Drug Clinical Trials (GCP), study drugs should be stored, dispensed, and recovered by the participating study site. The study drug, SHR-1210, should be sealed, away from light, and stored at 2-8 °C in medical refrigerator, and must not be frozen.

The study drug, apatinib mesylate, should be stored in a sealed container away from light below 25 °C.

The study drugs, oxaliplatin for injection and levoleucovorin calcium for injection, in the FOLFOX4 chemotherapy regimen will be supplied by Jiangsu Hengrui Pharmaceuticals Co., Ltd.; fluorouracil injection will be purchased from Tianjin KingYork Pharmaceutical Co., Ltd.

The study drug, oxaliplatin for injection, in the GEMOX chemotherapy regimen will be supplied by Jiangsu Hengrui Pharmaceuticals Co., Ltd.; gemcitabine hydrochloride for injection will be purchased from Jiangsu Hansoh Pharmaceutical Group Co., Ltd.

The study drug, oxaliplatin for injection, should be sealed, away from the light and stored below 25 °C; the study drug, levoleucovorin calcium for injection, should be stored in a sealed container away from light in a dry environment; the study drug, fluorouracil injection, should be stored in a sealed container away from light; the study drug, gemcitabine hydrochloride for injection, should be sealed and stored in a dry place.

The study drugs are not allowed to be used except for this study.

6.5 Disposal of Remaining Drugs

The investigator should record the date and dose of administration of each subject. The total amount of study drugs is 110% of the designed dosage. The remaining study drugs should be periodically returned to the sponsor for destruction after being counted.

6.6 Method of Administration

The preparation of SHR-1210 is detailed in the pharmacy manual.

Refer to the instruction manuals for the preparation methods of the study drugs in the FOLFOX4 and GEMOX regimens.

The method of administration in this study is detailed in the following table:

Group A	SHR-1210	3 mg/kg, intravenously infused within 30 min, not less than 20 min and not more than 60 min (including flushing time), once every 2 weeks. The interval between two doses must not be less than 12 days
	Apatinib mesylate	Orally administered, once daily, with four dose groups: 125 mg, 250 mg, 375 mg, and 500 mg, for dose exploration from low dose to high dose
Group B	SHR-1210	3 mg/kg, intravenously infused within 30 min, not less than 20 min and not more than 60 min (including flushing time), once every 2 weeks. The interval between two doses must not be less than 12 days

	FOLFOX4 regimen	D1: OXA 85 mg/m^2 (2 h infusion) + levoleucovorin calcium(LV) 200 mg/m^2 (2 h infusion), followed by 5-Fu 400 mg/m^2 (bolus injection), 5-Fu 600 mg/m^2 (22 h infusion) D2: levoleucovorin calcium (LV) 200 mg/m^2 (2 h infusion), followed by 5-Fu 400 mg/m^2 (bolus injection), 5-Fu 600 mg/m^2 (22 h infusion) Once every 2 weeks
	GEMOX regimen	D1: gemcitabine (800 mg/m^2, 80 min infusion) D2: oxaliplatin (85 mg/m^2, 2 h infusion) Once every 2 weeks.

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

7 DOSE MODIFICATION AND SAFETY MANAGEMENT

7.1 Dose Modification

7.1.1 Criteria for SHR-1210 dose modification

Dose modification of SHR-1210 is not allowed. Only dose interruption of SHR-1210 is allowed for up to 6 weeks.

7.1.2 Criteria for SHR-1210 dose delay

SHR-1210 administration should be delayed when any of the following occurs:

- Any Grade ≥ 2 treatment-related non-cutaneous AEs, except for Grade 2 treatment-related fatigue or laboratory abnormalities;
- Any Grade 3 treatment-related cutaneous AEs;
- Any Grade 3 treatment-related laboratory abnormalities, except for Grade 3 abnormalities in amylase or lipase not related to symptoms and clinical manifestations of pancreatitis;
- The administration should be delayed when the following AST or ALT abnormalities occur:
  - If the baseline AST/ALT of a subject is within the normal range and a Grade ≥ 2 drug-related toxicity occurs, the administration should be delayed;
  - If the baseline AST/ALT of a subject is within a Grade 1 increase and a Grade ≥ 3 drug-related toxicity occurs, the administration should be delayed;
- Any AEs, laboratory abnormalities, or accompanying diseases requiring that the administration be delayed as judged by the investigator.

Subjects who need delay of administration should be re-examined and monitored weekly. Monitoring frequency should be increased when clinically indicated. It is recommended to monitor once every three days until AST/ALT starts to decrease after reaching its maximum. Administration may be resumed when criteria for resuming administration are met (see Section 7.1.3).

Tumor evaluation in all subjects will continue as required by the protocol, regardless of whether the administration is delayed.

7.1.3 Criteria for resuming SHR-1210 administration

SHR-1210 treatment may be resumed when drug-related AEs recover to Grade ≤ 1 or baseline status, except for:

- Subjects with Grade 2 fatigue that is not recovered may resume treatment;
- Treatment may be resumed when cutaneous AE is still of Grade 2;
- Subjects with Grade 1 increase in AST/ALT or total bilirubin at baseline who delay administration due to causes other than treatment-related hepatic AEs may resume study treatment in the presence of Grade 2 increase in AST/ALT or total bilirubin;
- Subjects who delay administration due to treatment-related increase in AST/ALT or total bilirubin may resume study treatment when these indicators recover to baseline CTCAE levels or normal and criteria for permanent treatment discontinuation are not met (see Section 7.1.4).
- Administration may be resumed if treatment-related endocrine illnesses are fully controlled with hormone replacement at only physiological doses.

Dose delays up to 6 weeks from the previous dose are allowed. If, after a 6-week delay, the subject still does not meet criteria for resuming administration, study treatment should be discontinued permanently, except for conditions in 7.1.4. See Appendix 4 for the detailed treatment measures for adverse drug reactions.

7.1.4 Criteria for SHR-1210 permanent discontinuation

SHR-1210 must be permanently discontinued under the conditions below:

- Any Grade 2 treatment-related uveitis, eye pain, and blurred vision that are not responsive to local treatment and have not recovered to Grade ≤ 1 after dose delay; or the aforementioned AEs that require systemic treatment.
- Any Grade 3 treatment-related non-cutaneous AEs persisting > 7 days, except for:
  - Study treatment must be discontinued if any Grade 3 treatment-related uveitis, pneumonia, bronchospasm, hypersensitivity, or infusion reaction occur;
  - Study treatment may not be discontinued if Grade 3 treatment-related endocrine illnesses are and the fully controlled with hormone replacement therapy at only physiological doses;
  - Study treatment may not be discontinued if Grade 3 treatment-related laboratory abnormalities occur, but must be discontinued if Grade 3 thrombocytopenia persists > 7 days or is related to bleeding.
- Hepatotoxicity that meets the criteria below:
  - AST/ALT > 10 × ULN for > 2 weeks;
  - AST/ALT > 15 × ULN;
  - TBIL > 8 × ULN for subjects with increased TBIL at baseline, and TBIL > 5 × ULN for subjects with normal TBIL at baseline;
  - AST/ALT > 3 × ULN and TBIL > 5 × ULN for subjects with normal TBIL at baseline, and AST/ALT > 3 × ULN and TBIL > 8 × ULN for subjects with increased TBIL at baseline;
- Any Grade 4 treatment-related AEs or laboratory abnormalities, except for:
  - Grade 4 neutropenia for < 7 days;
  - Grade 4 lymphopenia or leukopenia;
  - Solitary Grade 4 pancreatic enzymes or lipases elevated without pancreatitis symptoms or clinical manifestations. The sponsor should be notified when Grade 4 amylase or lipase elevation occurs;

- Isolated Grade 4 electrolyte imbalances/abnormalities that are not accompanied by clinical sequelae and can be corrected with supplements/appropriate treatment within 72 hours of their occurrence;
- Study treatment may not be discontinued if Grade 4 treatment-related endocrine illnesses are fully controlled with hormone replacement therapy at only physiological doses.

- SHR-1210 treatment must be discontinued if dose delay of > 6 weeks is needed, except for:
  - Dose delays of > 6 weeks due to dose tapering of corticosteroids that are used for treatment-related AEs are permitted. Must discuss with the sponsor before resuming administration. Tumor evaluations should be continued as required by the protocol during dose delay. Safety follow-ups and laboratory tests should also be performed at the original frequency or more frequently when clinically indicated;
  - Must discuss with the sponsor before resuming administration for dose delays of > 6 weeks due to reasons unrelated to study drugs. Tumor evaluations should be continued as required by the protocol during dose delay. Safety follow-ups and laboratory tests should also be performed at the original frequency or more frequently when clinically indicated.
- Any AEs, laboratory abnormalities, or accompanying diseases that render the subject significant risks from continued treatment as judged by the investigator;
- Disease progression assessed by the investigator as per RECIST 1.1 criteria (unless the subject meets the criteria in Section 3.2.4).

Tumor evaluations should be conducted for subjects who have discontinued SHR-1210 treatment as required by the protocol.

7.1.5 Standards for dose modification of apatinib mesylate

For the subjects in group A, dose modifications caused by apatinib mesylate-related toxicity include: dose interruption (not more than 28 days), dose reduction (except for the 125 mg dose group), and dose discontinuation (see Table 12 and Table 13).

The dose should be interrupted and reduced in the case of Grade ≥ 3 hematological toxicity or Grade ≥ 2 non-hematological toxicity. Among the events of non-hematological toxicity, controllable nausea and vomiting as well as fever (under 38 °C) with a clear cause may be handled with active symptomatic treatments without the need for dose interruption and dose reduction.

During the medication period, changes in blood pressure should be routinely monitored. When a grade 3 increase in blood pressure occurs (systolic pressure ≥ 160 mmHg or diastolic pressure ≥ 100 mmHg, or more than one antihypertensive medication required), it is recommended that the use of apatinib mesylate be interrupted and the patient be treated with antihypertensive treatment under the guidance of a specialist. When the blood pressure decreases to the normal range (systolic pressure ≤ 140 mmHg and diastolic pressure ≤ 90 mmHg), the medication of apatinib mesylate may be resumed. If hypertension persists, apatinib mesylate must be reduced by one dose level. For patients with hypertensive crisis (systolic pressure ≥ 180 mmHg or diastolic pressure ≥ 120 mmHg, and/or accompanied by manifestations of progressive target organ dysfunction), treatment should be interrupted immediately and active symptomatic treatment should be administered (hypertension, dehydration, and convulsion control).

When apatinib mesylate-related toxic reactions occur, the dose should be interrupted first. Medication may be resumed after the toxicity recovers at the original dose or a dose level lower. The dose level may be lowered to 125 mg/d at minimum. If the toxic reaction still cannot be tolerated after lowering the dose to 125 mg/d, apatinib mesylate should be permanently discontinued (see Table 10). Dose increase for apatinib mesylate is not allowed during the study period.

Table 10. Rules for dose modification of apatinib mesylate (applicable to group A).

Apatinib Mesylate-Related Toxicities	Grade	Whether to Suspend	Criteria for Dose Resumption	Dose Modification	Criteria for Dose Discontinuation
Hematological Toxicity	Grade 1 to 2	No	—	—	—
	Grade 3	Yes	Toxicity returns to Grade ≤ 2	Resume at original dose	Interruption of apatinib mesylate for more than 28 days;
	Grade 4	Yes	Toxicity returns to Grade ≤ 2	Reduce apatinib mesylate by a dose level (dose discontinuation for the 125 mg/d dose group)	
Non-Hematological Toxicity	Grade 1	No	—	—	—
	Grade 2 (lasts for ≥ 7 d)	Yes	Toxicity returns to Grade ≤ 1	Resume at original dose	Interruption of apatinib mesylate for more than 28 days;
	Grade 3	Yes	Toxicity returns to Grade ≤ 1	Apatinib mesylate was reduced by one dose level (dose discontinuation for the 125 mg/d dose group)	

Apatinib Mesylate-Related Toxicities	Grade	Whether to Suspend	Criteria for Dose Resumption	Dose Modification	Criteria for Dose Discontinuation
Hypertension	Grade 3 (after corrective treatment)	Yes	Toxicity returns to Grade ≤ 1	Consider resuming medication at the original dose; reduce apatinib mesylate by a dose level if grade 3 hypertension occurs again (dose discontinuation for the 125 mg/d dose group)	Interruption of apatinib mesylate for more than 28 days
Proteinuria (without significant increase in blood creatinine)	Grade 3 (24 h protein urine quantification)	Yes	Toxicity returns to Grade ≤ 2	Apatinib mesylate was reduced by one dose level (dose discontinuation for the 125 mg/d dose group)	Interruption of apatinib mesylate for more than 28 days
Hand-and-Foot syndrome	Grade 3	Yes	Toxicity returns to Grade ≤ 1	Apatinib mesylate was reduced by one dose level (dose discontinuation for the 125 mg/d dose group)	Interruption of apatinib mesylate for more than 28 days
Headache	Grade 2 (last for ≥7 d) or Grade 3	Yes	Toxicity returns to Grade ≤ 1	Apatinib mesylate was reduced by one dose level (dose discontinuation for the 125 mg/d dose group)	Interruption of apatinib mesylate for more than 28 days

7.1.6 Standards for dose modification of chemotherapy regimen in group B

For the subjects in group B, dose modifications caused by the toxicity of chemotherapy drugs are shown in Table 11 and Table 12. If Grade ≥ 3 toxicity occurs repeatedly even the dose is reduced, chemotherapy must be interrupted.

During the course of treatment, if the dose of the chemotherapy study drug is reduced due to toxicity, the dose will not be allowed to be increased during subsequent treatment.

Table 11. Rules for dose modification of chemotherapy (applicable to group B).

Toxicity Type NCI-CTC 4.03 Grade (Except for sensory neurotoxicity)	**FOLFOX4 Initial Dose (mg/m^2)**		
	5-Fu bolus injection	**5-Fu continuous intravenous drip**	**Oxaliplatin**
	400 ×2	**600 ×2**	**85**
	Dose modification of investigational drug (mg/m^2)		
Hematological toxicity ≥ Grade 3-4	Suspend the FOLFOX4 treatment until the toxicity returns to Grade ≤ 1, the dose may be modified as follows		
	300 × 2	500 × 2	65
Grade 3 nausea and/or vomiting (when antiemetics were administered)	Repeat antiemetic treatment If still intolerable, discontinue FOLFOX4 treatment for the patient		
Grade 3 diarrhea	Suspend the FOLFOX4 treatment until the toxicity returns to Grade ≤ 1, the dose may be modified as follows		
	300 × 2	500 × 2	Not adjusted
Grade 4 diarrhea*	Suspend the FOLFOX4 treatment until the toxicity returns to Grade ≤ 1, the dose may be modified as follows		
	300 × 2	500 × 2	65
Grade 3 stomatitis	300 × 2	500 × 2	Not adjusted
Grade 4 stomatitis*	300 × 2	500 × 2	65
Grade ≥ 2 cardiotoxicity	Discontinue the FOLFOX4 treatment Until toxicity returns to Grade ≤ 1, adjust the dose as follows		
	Discontinue	Discontinue	65
Grade 3 or 4 skin toxicity	300 × 2	500 × 2	Not adjusted
Grade ≥ 3 allergy	Discontinue the FOLFOX4 treatment		
Cranial nerve	Discontinue the FOLFOX4 treatment		
Sensory nerve: adjust according to symptoms	Not adjusted	Not adjusted	As shown in Table 14
Alopecia (any grade)	Not adjusted	Not adjusted	Not adjusted
Local symptoms (any grade)	Not adjusted	Not adjusted	Not adjusted
Other unequivocal treatment-related toxicities: - Grade 1 and 2 - Grade 3 - Grade 4	Not adjusted 300 × 2 Discontinue	Not adjusted 500 × 2 Discontinue	Not adjusted 65 Discontinue
*Or Grade 3 recurs after 5-FU dose modification.			

Toxicity Type NCI-CTC 4.03 Grade (Except for sensory neurotoxicity)	**GEMOX Initial Dose (mg/m²)**	
	Gemcitabine	**Oxaliplatin**
	800	**85**
	Dose modification of investigational drug (mg/m²)	
Hematological toxicity ≥ Grade 3-4	Interrupt GEMOX treatment, until toxicity returns to Grade ≤ 1, adjust the dose as follows	
	600	65
Grade 3 nausea and/or vomiting (when antiemetics were administered)	Repeat antiemetic treatment If still intolerable, discontinue chemotherapy for the patient	
Other unequivocal treatment-related toxicities: - Grade 1 and 2 - Grade 3 - Grade 4	 Not adjusted 600 Discontinue	 Not adjusted 65 Discontinue

Table 12. Rules for dose modification of oxaliplatin in the chemotherapy regimen when sensory neuropathy occurs (applicable to group B).

Duration Toxicity Type	**Dose Modification of Oxaliplatin (mg/m²/course)**		
	≤ 7 days	**Does not last > 7 and < 14 days**	**Course of treatment lasts ≥ 14 days**
Cold-related Dullness	Not adjusted	Not adjusted	Not adjusted
Mild Paresthesia	Not adjusted	Not adjusted	Not adjusted
Paresthesia with Pain or Complaints	Not adjusted	• Normal physical examination Decrease: 65 mg/m² • Abnormal physical examination* Oxaliplatin was discontinued for one cycle, and then reduce to 65 mg/m²	until the symptoms was improved; if the symptom improves, restart the dose at 65 mg/m²
Paresthesia with Functional Impairment	Not adjusted	• Normal physical examination without daily activities affected Decrease: 65 mg/m² • Abnormal physical examination* or with daily activities affected Oxaliplatin was discontinued for one cycle, and then reduced to 65 mg/m²	until the symptoms was improved; if the symptom improves, restart the dose at 65 mg/m²

*Examination indicates neurological examination. If objective conditions are found, such as weakened tendon reflexes, it is considered abnormal.

7.2 Common Recommendations on Safety Management

7.2.1 Safety management procedures for immuno-oncological medications

Adverse events caused by immuno-oncology (I-O) drugs are different from those of other anti-cancer drugs, especially in terms of severity and duration. SHR-1210 is one such drug, and therefore, early identification and management of adverse events is required to reduce the incidence of severe toxicities. The safety handling rules of similar approved drugs provide references to assist the investigator in assessing and dealing with adverse events involving the following systems:

- GI tract
- Lung
- Liver
- Endocrine
- Skin

Refer to Appendix 4 for safety handling rules.

7.2.2 Management procedures for hepatic adverse events of SHR-1210

In this study, hepatic AEs of SHR-1210 are treated with the procedures below:

- Criteria for dose delays due to hepatic AEs are shown in section 7.1.2. Corticosteroids, methylprednisolone 0.5-2 mg/kg/day, or equivalent should be given if the AST/ALT level does not improve or even aggravates following a dose delay of 3-5 days.
- Corticosteroids, methylprednisolone 0.5-2 mg/kg/day or equivalent should be given immediately if AST/ALT > 8 × ULN.
- The sponsor shall be informed of the use of corticosteroids within 24 hours of its start. Consultation with the gastroenterology department is also recommended.
- The sponsor should be consulted for the use of other immunosuppressants such as mycophenolate 1 g BID if the AST/ALT level does not improve or even exacerbates following treatment with corticosteroids of 3-5 days.
- Dose tapering may start once AST/ALT decreases by 1 grade per CTCAE, with the dose reduction persisting no less than 1 month.

Study treatment may be resumed when AST/ALT recovers to baseline level, unless the criteria for permanent discontinuation are met.

7.2.3 Recommendations on treatment for SHR-1210 infusion reactions

SHR-1210 is a fully humanized monoclonal antibody, and thus the possibility of infusion or allergic reactions is small and there is no need for preventive medication before infusion. An allergic reaction is most likely to occur within 24 h after infusion. Once occurs, the infusion should be slowed or interrupted accordingly, and a supportive treatment should be given. Also, premedications should be given before further administrations. Possible allergic reactions include fever, chills, shiver, headache, rash, pruritus, joint pain, hypotension/hypertension, or bronchospasm. The sponsor should be notified of any Grade ≥ 3 infusion reaction within 24 h. The Hengrui Clinical Trial AE of Special Interest Report should be filled out and the CFDA SAE Report be filled out, and if the event meets the criteria for SAEs, an SAE report should also be filled. See section 8.2.6 for reporting methods in detail.

Management of allergic reactions should be based on the medical practice and guidelines of the trial site. The treatment recommendations for infusion reactions are shown below for reference.

CTCAE Grade	Clinical Symptoms	Clinical Management	SHR-1210 Treatment
Grade 1	Mild and transient reactions	Bedside observation and close monitoring until recovery. Pre-dose prophylactics are recommended for subsequent administrations: 50 mg of diphenhydramine or equivalent, and/or 325-1000 mg of acetaminophen, at least 30 minutes before the administration of SHR-1210.	Continuation.
Grade 2	Moderate reactions requiring treatment or interruption; rapidly resolve after symptomatic treatment (such as antihistamines, non-steroidal antiphlogistics, anesthetics, bronchodilators, intravenous fluids, etc.)	Intravenous administration of normal saline: 50 mg of diphenhydramine IV or equivalent and/or 325-1000 mg of acetaminophen; Bedside observation and close monitoring until recovery. Corticosteroids or bronchodilators can be considered based on clinical needs; The amount of study drug infused should be recorded in the original medical record; Pre-dose prophylactics are recommended for subsequent administrations: 50 mg of diphenhydramine or equivalent, and/or 325-1000 mg of acetaminophen can be given at least 30 minutes before the administration of SHR-1210. Use corticosteroids (equivalent to 25 mg of hydrocortisone) when necessary.	Interruption. Re-administer at 50% of the initial rate after symptoms resolve. Restore the original infusion rate (100%) if no complications occur within 30 minutes. Closely monitor. If symptoms return, the administration of the current SHR-1210 dose will be terminated.

CTCAE Grade	Clinical Symptoms	Clinical Management	SHR-1210 Treatment
Grade ≥ 3	Grade 3: Severe reaction without rapid recovery with treatment and/or interruption; or symptoms recur after alleviation; or the subject develops sequelae that requires hospitalization. Grade 4: Life-threatening	Immediately discontinue SHR-1210; Intravenous administer normal saline. •Bronchodilators are recommended. Subcutaneous injection of 0.2-1 mg of 1:1000 adrenaline solution or slow intravenous infusion of 0.1-0.25 mg of 1:10000 adrenaline solution, and/or 50 mg of diphenhydramine plus 100 mg methylprednisolone or equivalent by intravenous injection if necessary; •Based on the guidelines for anaphylaxis of the study site; Bedside observation and close monitoring until recovery.	Discontinuation

7.2.4 Principles for handling immune-related adverse events

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

The treatment of immune-related adverse drug reactions should be based on the medical practice and guidelines of the study site. The treatment recommendations for immune-related adverse drug reactions are as follows (see Table 13) for reference. See Appendix 4 for the management procedures for immune-related adverse drug reactions of common organ systems.

Table 13. Treatment recommendations for immune-related adverse drug reactions.

CTCAE Grade	Clinical Management*	SHR-1210 Treatment
Grade 1 (mild)	Close observation; symptomatic and supportive treatment	Continuation
Grade 2 (moderate)	Closely monitoring; Symptomatic and supportive treatment Topical or systemic use of steroids at 0.5-1 mg/kg/day, equivalent prednisone	Interrupt medication; resume when recovering to Grade ≤ 1; Medication may be continued for skin and endocrine disorders
Grade 3 (severe)	Hospitalization recommended; Intravenous or oral use at 1-2 mg/kg/day, equivalent prednisone Consider adding other immunosuppressants if steroid treatments were not responsive after 3-5 days Consultation with specialists recommended	Interrupt medication; whether to resume medication should be determined after comprehensive consideration of the risk/benefit ratio and discussion

Grade 4 (life-threatening)	Intravenous injection of methylprednisolone at 1-2 mg/kg/day Consider adding other immunosuppressants if steroid treatments were not responsive after 3-5 days Consultation with specialists recommended	Permanent discontinuation

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

7.2.5 Principles for handling apatinib mesylate-related adverse drug reactions

(1) Hand-and-foot syndrome

Hand-and-foot syndrome is skin toxicity with palmar-plantar dysesthesia 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. Hand-and-foot syndrome is characterized by numbness, dysesthesia, paraesthesia, tingling, no pain or pain, skin swelling, or erythema, desquamation, chapping, scleroma-like blisters, and severe pain.

Symptomatic treatment and management of hand-and-foot syndrome:

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 hand-and-foot syndrome of Grade 3 or higher occurs for 3 consecutive times with an aggravating trend, the treatment with apatinib mesylate should be discontinued.

(2) Hypertension

Subjects should be strictly screened according to blood pressure requirements in the inclusion and exclusion criteria prior to enrollment. Subjects 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).

Monitoring and handling of hypertension:

During the first 2 cycles of apatinib mesylate medication, blood pressure should be monitored at least 3 times per week.

Once hypertension occurs, the following standard treatments can be given: Angiotensin II receptor blocker (ARB), angiotensin converting enzyme inhibitor (ACEI), beta blocker, etc., or the combined application of above drugs.

If hypertension occurs or aggravates during the administration:

1) Adjust the study drug per the protocol (see 7.1.5);

2) Start administering antihypertensive or adjust the dosage of medication.

Subjects should record the daily blood pressure values in the subject diary card. If taking hypertensive drugs at the same time, the drug name, dose, method and frequency of administration, as well as relevant complaints or symptoms should be recorded.

During the trial, the following antihypertensive drugs are recommended:

1) Angiotensin converting enzyme inhibitors (ACEIs);

2) Angiotensin II receptor antagonists (ARBs);

3) Dihydropyridine calcium channel antagonists;

4) Beta blockers.

Diuretic antihypertensive drugs are not recommended. Antihypertensive drugs with inhibitory effects on CYP3A4, such as nicardipine, diltiazem and verapamil, are prohibited. For those with hypertensive crisis, the application of apatinib mesylate should be terminated.

(3) 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 ≥ 2+ in 2 consecutive tests, a 24-h urine protein assay is required.

Note: In case of nephrotic syndrome, apatinib mesylate should be discontinued.

(4) Gastrointestinal bleeding

Symptomatic treatment should be actively given for gastrointestinal hemorrhage, including persistently positive fecal occult blood, 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. And adjust the dose following Section 7.1.5 of the protocol.

(5) Thrombosis

If any arterial thrombosis (such as cerebral ischemia, stroke, angina pectoris, myocardial infarction, etc.) occurs, apatinib mesylate should be discontinued. In case of any symptomatic venous thrombosis, apatinib mesylate should be discontinued.

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

7.2.6 Rules for handling adverse drug reactions of FOLFOX4 chemotherapy

Since the FOLFOX4 chemotherapy regimen has been approved by the CFDA (now NMPA) and the Ministry of Health (now National Health Commission) for the treatment of patients with advanced hepatocellular carcinoma and has accumulated much experience in the clinical application, the treatment of FOLFOX4 chemotherapy-related adverse drug reactions in this study protocol may be carried out based on clinical practice. The following suggestions are for reference.

(1) Peripheral neuropathy

Peripheral neuropathies of oxaliplatin include two types, symptoms of which include hand, foot, and perioral paresthesias and hypoesthesia. It is recommended that patients treated with oxaliplatin in the study keep warm, especially during the 3-5 days after the oxaliplatin medication, avoid cold drinks and exposure to cold water or cold air. For peripheral neuropathy, the dose of oxaliplatin may be modified following the methods in Table 12.

(2) Throat paresthesia

Occasionally, an acute paraesthetic reaction of the throat may be observed when using oxaliplatin. Patients may experience loss of respiratory sensation (acute respiratory depression) without objective signs of respiratory depression (such as hypoxia, laryngospasm, or bronchospasm). This reaction may be induced or exacerbated by cold stimulation. Therefore, patients who use oxaliplatin should avoid cold stimulation on the first day of each cycle, and must not drink cold drinks or eat cold food.

If the patient develops acute throat paresthesia, the patient's blood oxygen saturation should be evaluated. If it is normal, the patient may be given comprehensive explanation and psychological support, and benzodiazepines or other anti-anxiety drugs may be considered. Whenever necessary, the infusion rate of oxaliplatin should be reduced, and the patient should be closely observed until the symptoms are completely relieved.

(3) Allergic reaction

If Grade 1 or 2 allergic reactions occur, dexamethasone (20 mg intravenously), diphenhydramine (50 mg intravenously), or other drugs should be given prophylactically 30 min before the FOLFOX4 chemotherapy.

For grade ≥ 3 allergic reactions, the FOLFOX4 treatment should be discontinued immediately.

(4) Pulmonary fibrosis

If respiratory symptoms, such as non-spontaneous coughing, dyspnea, crackles, rales, blisters, hypoxia, shortness of breath, or radiographic images showing lung exudate, suggest pulmonary fibrosis, the oxaliplatin medication should be interrupted for further investigation. If interstitial pulmonary fibrosis is diagnosed, the FOLFOX4 treatment should be permanently discontinued.

(5) Nausea/vomiting

It is recommended to use 5-HT3 antagonists (granisetron, ondansetron or isomers) and corticosteroids (such as dexamethasone) to prevent and treat oxaliplatin-induced vomiting. Oral administration of metoclopramide is recommended for nausea/vomiting caused by 5-Fu. If Grade ≥3 nausea and/or vomiting occur, chemotherapy should be discontinued immediately until these symptoms are relieved or recovered to Grade ≤ 1.

(6) Diarrhea

Patients with severe diarrhea should be closely observed. If dehydration occurs, supportive treatment for rehydration should be given to supplement water and electrolytes. Follow Table 13 for the dose modification of FOLFOX4 chemotherapy.

(7) Hand-foot syndrome

Necessary symptomatic and supportive treatments may 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. And adjust the dose of FOLFOX4 following Table 13.

(8) Cardiotoxicity

For patients with Grade ≥ 2 cardiotoxicity caused by 5-Fu, the FOLFOX4 treatment should be interrupted. The oxaliplatin treatment may be resumed when the toxicity returns to Grade ≤ 1.

7.2.7 Rules for handling adverse drug reactions of GEMOX chemotherapy

The GEMOX chemotherapy regimen is a systemic treatment regimen recommended in the NCCN guidelines for advanced cholangiocarcinoma. The regimen has mature applications in non-small cell lung cancer and advanced metastatic breast cancer. In this study, the treatments of adverse drug reactions are as follows:

(1) Oxaliplatin-related toxic and adverse effects are the same as those described in Section 7.2.6.

(2) Bone marrow suppression: Gemcitabine has a bone marrow suppression effect. Symptoms such as anemia, leukopenia, and thrombocytopenia may appear after medication. Febrile neutropenia has also been reported. If Grade 3 or higher hematological toxicity occurs, the treatment of GEMOX chemotherapy regimen should be suspended and symptomatic supportive treatment should be given. The medication should be discontinued for recurrent Grade 3-4 hematological toxicities that are not controllable.

(3) Gastrointestinal reactions: Gastrointestinal reactions such as nausea, vomiting, and diarrhea may appear in approximately 1/3 of subjects but are generally of Grade 1-2 and easy to control with symptomatic medication. For gastrointestinal reactions uncontrollable with drugs, the dose should be reduced or discontinued.

(4) Abnormal liver function: More than half of the subjects may experience transient liver enzyme elevations, which are generally mild and do not require dose discontinuation. However, liver function should still be routinely monitored during medication, and if necessary, symptomatic liver protection treatment should be given.

(5) Renal toxicity: Approximately half of the subjects may experience mild proteinuria and hematuria; if accompanied by abnormalities of creatinine and urea nitrogen, renal impairment should be alerted. The medication should be suspended immediately and symptomatic treatment should be given; more attention should be paid to changes in renal function for subjects with underlying renal insufficiency.

(6) Allergic reactions: They are generally mild skin reactions such as rash and pruritus, but large-area rash, peeling, ulcers, and other rare severe skin reactions have also been reported. During and within a few hours after the use of gemcitabine, the subjects may experience bronchial spasm, manifested as mild, short-term and continuous dyspnea, most of which can stop without special treatment. Once severe and persistent dyspnea occurs, the following treatments are required: 1. Stop the chemotherapy;
2. Intravenously administer anti-allergic drugs such as epinephrine or diphenhydramine; and 3. Administer oxygen inhalation and other emergency treatment in time.

(7) Edema: Mild to moderate local edema may occur in 30% of subjects, some of whom may experience local pain. A very small number of subjects may experience pulmonary edema. Severe edema generally recovers after dose interruption.

(8) Oral mucositis: Attention should be paid whether the subjects experience symptoms of oral bleeding, erythema, and ulceration. The subjects should be educated to keep their oral cavity clean, adjust their diet reasonably, enhance supportive treatment, and, when necessary, symptomatic treatment should be given: If symptoms of fungal infection occur, antifungal drugs should be applied by mouthwash or oral administration, and appropriate local treatment of oral ulcers should be taken;

(9) Other adverse drug reactions: Such as flu-like manifestations, alopecia, and drowsiness, which are generally mild, and will be relieved after the treatment.

Refer to the drug instruction details.

8 SAFETY EVALUATION

8.1 Adverse Event (AE)

8.1.1 Definition of AE

AE refers to any untoward medical occurrence in a study subject administered a medicinal product, and which does not necessarily have a causality with this treatment. In this study, AEs should be documented from the signing of the informed consent form until 90 days after the last study dose or the start of new anti-tumor treatment (whichever comes first). AEs can include any unfavorable and unintended symptoms, signs, abnormal laboratory finding, or diseases, including the follows:

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

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

3) Clinically significant abnormal laboratory findings.

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

8.1.2 AE severity grading criteria

The severity of AE is determined using NCI-CTCAE 4.03. Refer to the following criteria for AEs not listed in NCI-CTCAE 4.03:

Grade	Clinical Description of Severity
1	Mild; asymptomatic or mild clinical symptoms; clinical or laboratory test abnormality only; medical intervention not indicated.
2	Moderate; minimal, local, or non-invasive interventions required; limited age-appropriate instrumental activities of daily living (ADL), e.g., cooking, shopping, using the telephone, counting money, etc.
3	Severe or medically significant symptoms but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. Self-care ADL: refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden
4	Life-threatening consequences; urgent intervention indicated
5	Death due to AEs

8.1.3 Causality assessment

All discomforts complained by the subject and abnormal changes in laboratory tests during the treatment period should be documented truthfully. The severity, duration, measures taken, and outcome of the AE shall be noted. The research physician should assess the relationship between the AE and the investigational drugs, such as whether there is a plausible temporal relationship with the investigational drug, the characteristics of the investigational drug, the toxicological and pharmacological effects of the investigational drug, whether there are concomitant medications, the subject's underlying diseases, medical history, family history, as well as stimulation and re-stimulation reactions, etc. The potential relationship between the AE and the investigational drug should be assessed with 5 grades of causality: definitely related, possibly related, unlikely related, not related, and indeterminable. All "definitely related", "possibly related", and "indeterminable" events were listed as adverse drug reactions.

8.2 Serious Adverse Event (SAE)

8.2.1 Definition of SAE

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

- Events resulting in death;

- Life-threatening events (defined as the subject being at immediate risk of death at the time of the event if not medically treated, but does not mean that it may lead to death if the adverse events worsen);
- Events resulting in hospitalization or prolonged hospitalization;
- Permanent or serious disability/incapacity/impairment of work ability;
- Congenital anomalies or birth defects;
- Other important medical events (defined as events that may jeopardize the subject or require interventions to prevent any of the above).

8.2.2 Progressive disease

Progressive disease (PD) is defined as the deterioration of the subject's conditions caused by the primary tumor targeted by the investigational drug, including radiological progressions and progressions in clinical symptoms and signs. New metastases relative to the primary tumor, or progression of the previous metastases, are all recognized as PD. Life-threatening events, hospitalization or prolonged hospitalization, permanent or serious disability/incapacity/impairment of work ability, congenital anomalies or birth defects resulting from signs and symptoms of progressive disease should not be reported as SAEs on an expedited basis. Death caused by the symptoms and signs of PD should be reported as an SAE on an expedited basis.

8.2.3 Events of hepatic enzyme abnormalities

If the levels of AST and/or ALT are abnormal and meet the laboratory test abnormalities shown in the table below, such cases of hepatic enzyme abnormalities should be reported as SAEs. The investigator is required to strengthen the follow-up of the subjects, who should be followed up until their hepatic enzyme levels recover to the normal or baseline level.

Baseline Period	Normal (AST/ALT and TBIL)		Abnormal (AST/ALT/TBIL)	
Treatment Period	ALT ≥ 3 × ULN	AST ≥ 3 × ULN	ALT ≥ 8 × ULN	AST ≥ 8 × ULN
	Meet one of the two criteria above, with TBIL ≥ 2 × ULN and ALP ≤ 2 × ULN without hemolysis		Meet one of the two criteria above, with TBIL ≥ 3× ULN or **increase** ≥ 1 × baseline value	

8.2.4 Collection of SAEs after the start of new anti-tumor treatments

SAEs are documented starting from the signing of consent form until the completion of the safety follow-up. SAEs that result in death during the safety follow-up period must be documented and followed up, regardless of whether the subject has started other anti-tumor treatments. If the subject has otherwise started other anti-tumor treatments, SAEs that do not result in death are not required to be documented and followed up. At the end of the safety follow-up period or when other anti-tumor treatments have been started, SAEs that are suspected to be study drug-related must still be reported.

8.2.5 Hospitalization

During the clinical study, adverse events resulting in hospitalization or prolonged hospitalization should be considered as SAEs, not including non-medical hospitalization. Hospitalization or prolonged hospitalization not related to the worsening of adverse events is not considered an SAE. For example:

- Hospitalization due to pre-existing disease without occurrence of new AEs or worsening of the pre-existing disease (e.g., for testing persistent laboratory abnormalities that started before the study);
- Hospitalization for management reasons (e.g., annual routine physical examination, patients having no place to stay, hospitalization due to medical insurance reimbursement);
- Hospitalization during the study as specified in the study protocol (e.g., as required by the protocol);
- Elective hospitalization unrelated to the deterioration of an AE (e.g., elective cosmetic surgery);
- Scheduled treatment or surgery that should be documented in the entire study protocol and/or in subject's individual baseline information;
- Hospitalization merely for use of blood products.

Diagnostic or therapeutic invasive (e.g., surgery) or non-invasive procedures should not be reported as adverse events. However, the disease condition leading to such procedures should be reported if it meets the definition of an AE. 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 of the AE.

8.2.6 SAE reporting system

The reporting period for SAE begins with the signing of the informed consent form until 90 calendar days (inclusive) after the last study dose. In the event of an SAE, whether in the first report or a follow-up report, the investigator must complete the "Serious Adverse Event Report Form for New Drug Clinical Trials" immediately, with a signature and date. The SAE must be reported (via email) to the relevant regulatory authorities, the sponsor, and the ethics committee within 24 hours of knowing of the event.

The email address of the sponsor for the safety information of this project:
hengrui_drug_safety@shhrp.com

SAEs that occur 90 days after the last study dose should also be reported if they are suspected to be related to the investigational drug.

The symptoms, severity, relationship with the investigational drug, time of occurrence, treatment duration, measures taken, time and method of follow-up, and outcome should be documented in details in the SAE report. If the investigator believes that an SAE is not related to the study drug but potentially related to the study conditions (such as the termination of past treatment, or comorbidities during the trial), their relationship should be explained in the description section of the SAE report form.

If the severity of an SAE or its relationship to the study drug changes, a follow-up report should be submitted immediately. If an error is found in a previously reported SAE, such SAE may be revised, revoked, or downgraded in follow-up reports and reported in accordance with the SAE reporting procedure.

8.2.7 Follow-up of adverse events

All AEs/SAEs should be followed until recovered, resolved to baseline level or Grade ≤ 1, or stabilized. If the event cannot be resolved to baseline level or stabilized, a reasonable explanation should be documented in the case report form (e.g., lost to follow-up, death).

All SAEs, whether related to the study drug or not, should be properly handled, and the outcome and date of the SAE should be documented in the subject's case report form.

The investigator should provide follow-up information in a timely manner based on the sponsor's request.

8.3 Pregnancy

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

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

The investigator should follow up the pregnancy until 1 month after delivery, and report the results 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 a subject experiences any SAE during pregnancy, then "SAE Report Form for New Drug Clinical Trials" should be filled out and reported according to SAE reporting procedure.

8.4 Adverse Events 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 events of 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 increased

8.5 Emergency Unblinding

Not applicable.

9 DATA MANAGEMENT

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

9.1. Data Collection

Data will be collected using the eCRF. Jiangsu Hengrui Pharmaceuticals Co., Ltd. will provide an electronic data capture (EDC) system. Company staff will deliver EDC system training to the designated staff of study site. Access to EDC system will only be granted to the study site staff who have completed the training. The PI or dedicated data entry person (CRC) should input data into the EDC system in accordance with the requirements of the visit procedures and the eCRF completion guide. The logic verification program in the system will verify the integrity and logic of the clinical trial data entered into the EDC system and generate an error message prompt for questionable data. The PI or CRC is permitted to modify or explain the problematic data. After the database is locked, the investigator will receive a CD-ROM or hard copy of subject data to archive at the study site.

9.2 Data Management and Quality Control

To ensure authenticity and reliability and improve the quality of the clinical data, the CRA will monitor the integrity, consistency, and accuracy of the trial data in database following the monitoring protocol, and discuss problematic data with the investigator, if necessary, supplementation or correction will be made by the investigator. The CRA or data manager will send electronic query form to the PI or CRC for problematic data. The PI or CRC must respond and provide correction or explanation of the problematic data. Multiple queries may be raised when necessary until the problem is solved. The medical director, drug safety director, and data manager will perform consistency comparison of SAEs periodically.

At the end of the study, the data manager and medical personnel will conduct a final quality control on all data in the database, summarize all protocol deviations and violations during the trial, and hold a data verification meeting. Database locking and unblinding will be carried out after the quality requirements have been met. The data manager will export the data to the statistics department for data analysis.

9.3 Data Review and Study Site Monitoring

Before the initiation of the study, a representative from Jiangsu Hengrui Pharmaceuticals Co., Ltd. will introduce the study protocol and eCRF to the investigator and staff at the initial visit to the study site or at the researcher conference. During the study, the CRA will visit the study site routinely to monitor the integrity of the subjects' records and accuracy of the eCRF, compliance

with the study protocol and GCP, and progress of the enrollment, and to ensure that the storage, dispensing, and count of the investigational drug are performed according to the requirements. During these visits, the major research personnel are required to assist the work of CRA.

The investigator must keep the source documents of each subject, including all medical records and visit records (outpatient or inpatient record), such as demographic indicators, medical information, lab results, ECGs, and result of other examinations and evaluations. All information in eCRF must come from the source document of the subject. The investigator must also keep the informed consent forms of all the subjects.

The investigator must ensure all source documents are available for monitoring to verify the consistency with the eCRF. Jiangsu Hengrui Pharmaceuticals Co., Ltd. requires complete monitoring of all original documents related to the study, including but not limited to the informed consent forms signed by the subjects, compliance with the inclusion/exclusion criteria, visit records, AE/SAE records, and all the data required for the evaluation of the primary efficacy and safety endpoints. No information referring to the subjects' identity in the source document will be disclosed.

10 DATA ANALYSIS AND STATISTICAL METHOD

Detailed summaries and methods of statistical analyses for the data collected from the study will be included in the statistical analysis plan (SAP), which will be finalized and filed by the sponsor. The SAP should be revised accordingly if there are any changes to the study protocol that may have a significant impact on the SAP, as determined by the sponsor or principal investigator.

10.1 Determination of Sample Size

10.1.1 Group A

The sample size of group A depends on the number of dose groups and the decision made by the clinical department based on some results in the trial. According to the trial data of group A, 6-12 subjects are enrolled in the tolerable dose group for the extension study. Approximately 24-36 subjects need to be enrolled.

10.1.2 Group B

The sample size of the cholangiocarcinoma population is calculated as follows:

With reference to previous study results, an unacceptable ORR of 6%, an expected ORR of 15%, a two-sided alpha of 0.05, and a power of 80% are assumed. The Simon two-stage minimax design is adopted. Fourty-five (45) subjects are enrolled in the first stage. If at least 3 subjects

show response, then proceed to the second stage. Thirty-seven (37) subjects are enrolled in the second stage. A total of 82 subjects will finally be enrolled. If 10 or more subjects show response, then proceed to the next step of the study. Considering a proportion of non-evaluable efficacy of 10%, approximately 92 subjects with cholangiocarcinoma must be enrolled and treated.

For the population with hepatocellular carcinoma, 20-30 subjects are intended to be enrolled for evaluating the safety of combination therapy and preliminarily evaluating the efficacy. Approximately 122 subjects are enrolled in group B.

10.2 Analysis Population

10.2.1 Full analysis set

Full analysis set (FAS): All enrolled subjects who have taken at least one dose of the investigational drug will be included in this analysis set.

10.2.2 Safety analysis set

Safety Set (SS): including all enrolled subjects who have received at least one study dose and have at least one post-treatment safety assessment.

10.3 Statistical Analysis

10.3.1 General analysis

Unless otherwise stated, continuous variables will be summarized by mean, standard deviation, median, maximum, and minimum; categorical variables will be summarized by frequencies and percentages; for time-event data, the median survival will be estimated using the Kaplan-Meier method. SAS 9.2 or above will be used for statistical analysis.

Unless otherwise stated, the following analysis will be applied to both group A and group B. Different populations in group B will also be analyzed.

10.3.2 Efficacy analysis

Tumor evaluations will be conducted by the investigator as per RECIST 1.1. The evaluation data will be based on the following indicators: complete response (CR), partial response (PR), stable disease (SD), disease progression (PD), and not evaluable (NE). All efficacy analyses will be conducted based on the FAS.

The median overall survival (OS), time to tumor progression (TTP), and duration of response (DOR) with their corresponding two-sided 95% confidence intervals are estimated using the Kaplan-Meier method, and the overall survival curves are plotted.

The objective response rate (ORR) and disease control rate (DCR) and their 95% CIs will be calculated using the Clopper-Pearson method.

10.3.3 Safety analysis

Safety analysis will be based on the SS.

Adverse events will be coded per MedDRA, and graded using NCI-CTCAE4.03. Given the same SOC and/or PT, multiple cases of the same events occurred in one subject will be counted only once. For the same AE reported in one subject multiple times but varying in CTCAE grade, the greatest grade episode will be enumerated.

The frequency and percentage of events will be described based on the system organ class (SOC) and/or preferred term (PT). Analysis of adverse events, serious adverse events, adverse drug reactions, severity of adverse events, and adverse events resulting in treatment discontinuation in each dose group will be analyzed.

Adverse events of special interest will be described and summarized in SAP.

The incidence and cause of death will be summarized and listed.

Clinically significant toxicities will be summarized and listed using frequency and percentage by dose group.

The deterioration (abnormalization of normalities or exacerbation of abnormalities) of laboratory parameters, electrocardiograms, physical examinations, and others from baseline will be analyzed using freqneyc and percentage, and listed.

10.4 Bayesian Logistic Regression Model (BLRM)

One goal of the BLRM is to make the risk of clinically significant toxicity with an incidence higher than 33% at the target dose not higher than 25% (EWOC criteria: Escalation with Overdose Control). The following is the statistical model:

$$\text{logit}(\pi_d) = \log(\alpha) + \beta \log\left(\frac{d}{d^*}\right), \text{where } \text{logit } (\pi) = \log\left(\frac{\pi}{1-\pi}\right)$$

π_d represents the probability that a clinically significant toxic event will occur at dose d during the cycle of evaluating the maximum tolerable dose. d* = 250 mg is the reference dose. α is defined as the odds of clinically significant toxic event at the reference dose of 250 mg. The parameter vector of the statistical model is θ = (log(α), log(β)), where α and β are both > 0.

The probability interval of clinically significant toxic events in patients at each dose level estimated using the statistical model is as follows:

The probability interval when the dose is insufficient is [0.00, 0.16)

The probability interval when the dose reaches the target toxicity is [0.16, 0.33)

The probability interval when the dose exceeds the target toxicity is [0.33, 1.00] (these probability intervals may be adjusted according to relevant trials when necessary).

The probability of clinically significant toxicity greater than 0.33 based on the dose recommended by the EWOC standard is small (posterior probability < 25%).

The use of Bayesian statistical methods requires defining the prior probability distribution f(θ) of the unknown parameter vector θ. See Appendix 5 for details.

11 INFORMED CONSENT AND ETHICS REGULATION

11.1 Informed Consent

The clinical investigator must fully inform the subjects that participation in the clinical trial is voluntary, and subjects have the right to withdraw from the trial at any stage without being discriminated against with their medical treatment and rights unaffected, and they can continue to receive other therapies. All subjects should be informed that the participation of the trial and their personal information will be kept confidential. The subjects should also be informed of the nature, objectives, expected potential benefits, and possible risks and inconvenience of the clinical trial, other alternative treatment options, and rights and obligations of the subjects in accordance with the "Declaration of Helsinki". Subjects are given sufficient time to consider whether to participate in the trial and sign the informed consent form.

11.2 Ethics

This study protocol must first be reviewed and approved in writing by the Ethics Committee of the Hospital before being implemented. The study protocol, protocol revisions, ICF, and other relevant documents such as recruitment advertisements should be submitted to the ethics committee. This clinical trial must be conducted in accordance with the Declaration of Helsinki, NMPA's GCP, and applicable laws and 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. Also, the deviation or change and the corresponding reason, and the recommended protocol modification should be submitted to the IRB/IEC for review and discussed with the sponsor. 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.

11.3 Regulatory Considerations

Both SHR-1210 for injection and apatinib mesylate for injection are developed and submitted by Jiangsu Hengrui Pharmaceuticals Co., Ltd., and have been approved by the CFDA (now NMPA) and obtained Class I approval for new drug clinical trial. Oxaliplatin and levoleucovorin calcium in the FOLFOX4 chemotherapy regimen are chemotherapeutic drugs produced by Jiangsu Hengrui Pharmaceuticals Co., Ltd. and are in clinical use. At present, the National Clinical Research Center in the 81st Hospital of the Chinese People's Liberation Army (Nanjing) is leading the phase II clinical trial of SHR-1210 combined with apatinib mesylate or FOLFOX4 regimen in patients with advanced primary liver cancer in accordance with the "Provisions for Drug Registration" and GCP .

11.4 Confidentiality of Subject Information

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

12 QUALITY CONTROL AND ASSURANCE

- The clinical study site must be NMPA-approved drug clinical trial institutions with clinical study conditions;
- Study staff must be personnel trained for clinical trials with corresponding qualifications, and must work under the supervision of senior professionals;
- Before the trial is started, the clinical wards must be inspected to ensure that standard requirements are met and first-aid equipment are available;

- Professional nursing staff are responsible for administering the drugs and they must be fully aware of the administration process to ensure subject compliance;
- Study sites must carry out the study in strict accordance with the protocol, and the eCRF must be completed truthfully;
- The Scientific Steering Committee must be established. The Scientific Steering Committee is responsible for providing general guidance on execution and implementation of the trial, including (but not limited to) safety and enrollment rate, as well as providing guidance on published data from perspective of science.
- The CRA should follow the standard operating procedure and monitor the clinical trial to ensure that all data are documented and reported accurately and completely, all eCRFs are entered correctly and consistent with source data, and the trial is implemented as per protocol;
- In the event of SAE, the sponsor must inform all study sites immediately, and suspend the study whenever necessary;
- Participating sites must allow audits by the sponsor and regulatory authorities. It is especially important for the investigator and study staff to provide time and convenience for monitoring and auditing.

13 PUBLICATION OF STUDY RESULTS

The study outcomes belong to Jiangsu Hengrui Pharmaceuticals Co., Ltd. Hengrui does not limit the publication of any collected or research information by investigators, regardless of whether the results are beneficial to the study drug or not. However, investigators should let the sponsor have the opportunity to review any proposed publication or other forms of publication before document submission or publication to prevent unintentional leakage of confidential information or unprotected inventions. The investigator should provide Hengrui with the manuscript, abstract, or full text of all planned publications (poster, invited lectures, or guest lectures) at least 30 days prior to submission for publication or other forms of release. To protect the intellectual property, especially before the acquisition of patent, the investigator must agree to delay the publication, and the delay period will not exceed 60 days. Before open publication, Hengrui can require investigators to remove any previously unpublished confidential information (except for study results). If this study is part of a multicenter study, the investigator must agree that the first publication is an integrated result from all study sites. However, if a manuscript of the integrated analysis is not submitted after 12 months when the study is completed or terminated in all study sites, the investigator can independently publish results based on other requirements in this section.

14 TRIAL PROGRESS

Scheduled duration: Feb. 2017 to Mar. 2019.

15 TRIAL PROTOCOL COMPLIANCE

The investigator shall try his/her best to avoid protocol violations. At any time, the investigator should not contact Jiangsu Hengrui Pharmaceuticals Co., Ltd. and ask for approval of protocol violations, because any authorized protocol violation should never be allowed. If the investigator believed that a certain protocol deviation could improve the implementation of the trial, the investigator must consider protocol revisions. However, the revised protocol can only be implemented after it is approved by Jiangsu Hengrui Pharmaceuticals Co., Ltd. and the medical ethics committee. All major protocol violations should be recorded and reported on the clinical trial report.

16 STUDY SITES AND TRIAL STAFF

16.1 Coordinating Center

Name: The 81st Hospital of the Chinese People's Liberation Army

Address: 34 Thirty-Four Biao, Yang Gong Jing, Qinhuai District, Nanjing City, Jiangsu Province, China

Director of Clinical Trial Site:

Principal Investigator: Shukui Qin, Professor

Study Staff: Chief Physician Tel.:

Associate Chief Physician Tel.:

Secretary of Clinical Trial Site: Tel.:

16.2 Sponsor

Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Medical Director of the Sponsor:

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

Tel.:

E-mail:

16.3 Other Participants

To be added

17 REFERENCES

1. Torre LA, Bray F, Siegel RL et al. Global cancer statistics, 2012. CA Cancer J Clin 2015; 65: 87-108.
2. Chen W, Zheng R, Baade PD et al. Cancer statistics in China, 2015. CA Cancer J Clin 2016; 66: 115-132.
3. El-Serag HB. Hepatocellular carcinoma. N Engl J Med 2011; 365: 1118-1127.
4. Ferlay J, Shin HR, Bray F et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010; 127: 2893-2917.
5. Makarova-Rusher OV, Medina-Echeverz J, Duffy AG, Greten TF. The yin and yang of evasion and immune activation in HCC. J Hepatol 2015; 62: 1420-1429.
6. Buonaguro L, Petrizzo A, Tagliamonte M et al. Challenges in cancer vaccine development for hepatocellular carcinoma. J Hepatol 2013; 59: 897-903.
7. Worns MA, Galle PR. HCC therapies--lessons learned. Nat Rev Gastroenterol Hepatol 2014; 11: 447-452.
8. Llovet JM, Ricci S, Mazzaferro V et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008; 359: 378-390.
9. Cheng AL, Kang YK, Chen Z et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009; 10: 25-34.
10. Cheng AL, Kang YK, Lin DY et al. Sunitinib versus sorafenib in advanced hepatocellular cancer: results of a randomized phase III trial. J Clin Oncol 2013; 31: 4067-4075.
11. Cainap C, Qin S, Huang WT et al. Linifanib versus Sorafenib in patients with advanced hepatocellular carcinoma: results of a randomized phase III trial. J Clin Oncol 2015; 33: 172-179.
12. Zhu AX, Rosmorduc O, Evans TR et al. SEARCH: a phase III, randomized, double-blind, placebo-controlled trial of sorafenib plus erlotinib in patients with advanced hepatocellular carcinoma. J Clin Oncol 2015; 33: 559-566.
13. Park JW, Finn RS, Kim JS et al. Phase II, open-label study of brivanib as first-line therapy in patients with advanced hepatocellular carcinoma. Clin Cancer Res 2011; 17: 1973-1983.

14. Johnson PJ, Qin S, Park JW et al. Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: results from the randomized phase III BRISK-FL study. J Clin Oncol 2013; 31: 3517-3524.

15. Llovet JM, Decaens T, Raoul JL et al. Brivanib in patients with advanced hepatocellular carcinoma who were intolerant to sorafenib or for whom sorafenib failed: results from the randomized phase III BRISK-PS study. J Clin Oncol 2013; 31: 3509-3516.

16. Zhu AX, Kudo M, Assenat E et al. Effect of everolimus on survival in advanced hepatocellular carcinoma after failure of sorafenib: the EVOLVE-1 randomized clinical trial. JAMA 2014; 312: 57-67.

17. El-Khoueiry AB, Melero I, Crocenzi TS, et al. Phase I/II safety and antitumor activity of nivolumab in patients with advanced hepatocellular carcinoma (HCC): CA209-040. J Clin Oncol 33, 2015 (suppl; abstr LBA101)

18. Bruno Sangro, et al. Safety and antitumor activity of nivolumab (nivo) in patients (pts) with advanced hepatocellular carcinoma (HCC): Interim analysis of dose-expansion cohorts from the phase 1/2 CheckMate-040 study. J Clin Oncol 34, 2016 (suppl; Abstract 4078).

19. Ignacio Melero et al. Safety and Preliminary Efficacy of Nivolumab in Patients With Advanced Hepatocellular Carcinoma: Interim Analysis of the Phase 1/2 CheckMate 040 Study. ESMO 2016 Congress.

20. Ignacio Melero, et al. Nivolumab dose escalation and expansion in patients with advanced hepatocellular carcinoma (HCC): The CheckMate-040 study. J Clin Oncol 35, 2017 (suppl 4S; Abstract 226).

21. CheckMate 459, ClinicalTrial.gov NCT02576509

22. Wilmott JS, Scolyer RA, Long GV, Hersey P. Combined targeted therapy and immunotherapy in the treatment of advanced melanoma. Oncoimmunology 2012; 1: 997-999.

23. Liu L, Mayes PA, Eastman S et al. The BRAF and MEK Inhibitors Dabrafenib and Trametinib: Effects on Immune Function and in Combination with Immunomodulatory Antibodies Targeting PD-1, PD-L1, and CTLA-4. Clin Cancer Res 2015; 21: 1639-1651.

24. Sharma P, Allison JP. Immune checkpoint targeting in cancer therapy: toward combination strategies with curative potential. Cell 2015; 161: 205-214.

25. Amin et al.2014, J. Clin. Oncol., abstract.

26. Hato SV, Khong A, de Vries IJ, Lesterhuis WJ. Molecular pathways: the immunogenic effects of platinum-based chemotherapeutics. Clin Cancer Res 2014; 20: 2831-2837.

27. Gatti L, Cassinelli G, Zaffaroni N et al. New mechanisms for old drugs: Insights into DNA-unrelated effects of platinum compounds and drug resistance determinants. Drug Resist Updat 2015; 20: 1-11.

28. Kepp O, Senovilla L, Vitale I et al. Consensus guidelines for the detection of immunogenic cell death. Oncoimmunology 2014; 3: e955691.

29. Apetoh L, Ghiringhelli F, Tesniere A et al. Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy. Nat Med 2007; 13: 1050-1059.

30. Ghiringhelli F, Apetoh L, Tesniere A et al. Activation of the NLRP3 inflammasome in dendritic cells induces IL-1beta-dependent adaptive immunity against tumors. Nat Med 2009; 15: 1170-1178.

31. Siew YY, Neo SY, Yew HC et al. Oxaliplatin regulates expression of stress ligands in ovarian cancer cells and modulates their susceptibility to natural killer cell-mediated cytotoxicity. Int Immunol 2015; 27: 621-632.

32. Sistigu A, Yamazaki T, Vacchelli E et al. Cancer cell-autonomous contribution of type I interferon signaling to the efficacy of chemotherapy. Nat Med 2014; 20: 1301-1309.

33. Tesniere A, Schlemmer F, Boige V et al. Immunogenic death of colon cancer cells treated with oxaliplatin. Oncogene 2010; 29: 482-491.

34. Langer CJ, Gadgeel SM, Borghaei H et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol 2016; 17: 1497-1508.

35. Rizvi NA, Hellmann MD, Brahmer JR et al. Nivolumab in Combination With Platinum-Based Doublet Chemotherapy for First-Line Treatment of Advanced Non-Small-Cell Lung Cancer. J Clin Oncol 2016; 34: 2969-2979.

36. Qin S, Bai Y, Lim HY et al. Randomized, multicenter, open-label study of oxaliplatin plus fluorouracil/leucovorin versus doxorubicin as palliative chemotherapy in patients with advanced hepatocellular carcinoma from Asia. J Clin Oncol 2013; 31: 3501-3508.

37. Qin S, Cheng Y, Liang J et al. Efficacy and safety of the FOLFOX4 regimen versus doxorubicin in Chinese patients with advanced hepatocellular carcinoma: a subgroup analysis of the EACH study. Oncologist 2014; 19: 1169-1178.

38. Gong XL, Qin SK. Progress in systemic therapy of advanced hepatocellular carcinoma. World J Gastroenterol 2016; 22: 6582-6594.

39. 中华人民共和国卫生部.原发性肝癌诊疗规范(2011 年版).临床肿瘤学杂志, 2011,16(10):929-946.

40. West J, Wood H, Logan RF, et al. Trends in the incidence of primary liver and biliary tract cancers in England and Wales 1971-2001. Br J Cancer, 2006,94(11):1751-1758.

41. Alvaro D, Crocetti E, Ferretti S et al. Descriptive epidemiology of cholangiocarcinoma in Italy. Dig Liver Dis, 2010,42(7):490-495.

42. Zhu, Hong, Hezel et al. Current Management of Gallbladder Carcinoma. The Oncologist, 2010,15:168-181.)

43. Ecekl F, Schmid RM. Chemotherapy in advanced biliary tract carcinoma: a pooled analysis of clinical trials. Br J Cancer, 2007,96:896-902.

44. Romiti A, D'Antonio C, Zullo A, et al. Chemotherapy for the biliary tract cancers: moving toward improved survival time. J Gastrointest Cancer, 2012,43(3):396-404.

45. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med, 2010,362(14):1273-1281.

46. Gruenberger B, Schueller J, Heubarandtner U, et al. Cetuximab, gemcitabine, and oxaliplatin in patients with unresectable advanced or metastatic biliary tract cancer: a phase 2 study. Lancet Oncol, 2010,11(12):1142-1148.

47. Malka D, Cervera P, Foulon S et al. Gemcitabine and oxaliplatin with or without cetuximab in advanced biliary-tract cancer (BINGO): a randomised, open-label, non-comparative phase 2 trial. Lancet Oncol, 2014; 15: 819–28.

48. J. S. Chen, C. Hsu, N. J. Chiang et al. A KRAS mutation status-stratified randomized phase II trial of gemcitabine and oxaliplatin alone or in combination with cetuximab in advanced biliary tract cancer. Annals of Oncology,2015(26): 943–949.

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

1 BACKGROUND

Omitted

2 PURPOSE

Omitted

3 MEASURABILITY OF TUMOR AT BASELINE

3.1 Definition

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

3.1.1 Measurable lesions

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

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

3.1.2 Non-measurable lesions

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph node 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 Methods 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 cutaneous lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. When lesions can be evaluated by both imaging and clinical examination, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

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

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

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

Endoscopy 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 treatment in ovarian cancer.

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

4 TUMOR RESPONSE ASSESSMENT

4.1 Assessment of Overall Tumor Load and Measurable Lesions

To assess objective response or future progression, it is necessary to estimate the overall tumor load 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 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 nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

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

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition, 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 nodes since they usually have a definable size when normal and are frequently surrounded by adipose tissues as in the retroperitoneum; however, if a lymph node 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 load has increased sufficiently to the point where treatment must be discontinued. A modest increase in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

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

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

4.3.5 New Lesions

The appearance of new malignant lesions denotes 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 the characteristics of new lesions into consideration. 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) disease.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	Non	CR
CR	Non-CR/Non-PD	Non	PR
CR	Not evaluable	Non	PR

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

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

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	Non	CR
Non-CR/Non-PD	Non	Non-CR/Non-PD[a]
Not all evaluable	Non	Not evaluable
Equivocal PD	Yes or No	PD
Any	Yes	PD

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

4.4.2 Missing assessments and unevaluable description

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

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

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

[a]: If a CR is truly met at first time point, then efficacy of any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, will still evaluated as PD at that point (since disease will reappear 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 "zero" recorded on the case report form (CRF).

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

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 deterioration. Efforts should be made to evaluate objective progression even after discontinuation of treatment. Symptomatic deterioration is not a description of an objective response: it is a reason for discontinuation of treatment. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1-3.

Conditions that are defined as early progression, early death and not evaluable are study specific and 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 to perform a biopsy before evaluating the efficacy of complete remission of local lesions. FDG-PET may be used to confirm a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

4.5 Frequency of Tumor Re-evaluation

Frequency of tumor re-evaluation during treatment should be protocol specific and consistent with the type and schedule of treatment. However, in the Phase II 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 made the response rate or the time to an event (progression/death) an endpoint. If time to an event (e.g. TTP/DFS/PFS) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease should be 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 intervals or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment.

4.6 Confirmatory Measurement/Duration of Response

4.6.1 Confirmation

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

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

4.6.2 Duration of overall response

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

4.6.3 Duration of stable disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD). The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving 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 progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment 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 in the absence of a treatment effect.

Appendix 2. Child-Pugh Score of Liver Function

Parameter	Score		
	1	2	3
Hepatic encephalopathy	None	Grade 1-2	Grade 3-4
Ascites	None	Mild	Moderate and above
Prothrombin time prolonged or INR	1-3 s < 1.7	4-6 s 1.7-2.3	> 6 s > 2.3
Total Bilirubin (μmol/L)	< 34	34-51	> 51
Serum albumin (g/L)	> 35	28-35	< 28

Note: Class A is 5-6 points; Class B is 7-9 points; Class C is 10-15 points;
Subjects with Class A or good Class B (i.e., a score of 7) can be enrolled.

Appendix 3. ECOG Performance Status Scoring Criteria

0 Fully active, able to carry on all pre-disease performance without restriction;

1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work;

2 Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours;

3 Capable of only limited selfcare, confined to bed or chair 50% or more of waking hours;

4 Completely disabled; cannot carry on any selfcare, totally confined to bed or chair;

5 Death

Appendix 4. Management Principles for Immune Related Adverse Events

1. Management Principles for Gastrointestinal Adverse Events

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.

Diarrhea/Colitis Grade (NCI CTCAE v4)	Processing	Visit
Grade 1 Diarrhea: Increase of < 4 stools per day over baseline Colitis: No symptom	• Continue I-O treatment as per 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 3 or Grade 3/4 situations
Grade 2 Diarrhea: Increase of 4-6 stools per day over baseline; intravenous infusion of < 24 h is required; daily living is not affected Colitis: Abdominal pain; hematochezia	• Delay I-O treatment as per study protocol • Symptomatic treatment	**If it is improved to Grade 1:** • Resume I-O treatment as per study protocol If symptoms persist for > 5-7 days or recurred: • 0.5-1.0 mg/kg/day of methylprednisolone IV or equivalent PO 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 as per protocol If symptoms are aggravated or persisted after > 3-5 days of oral administration of steroids: • Provide treatment according to the method for Grade 3/4 situations
Grade 3-4 Diarrhea (Grade 3): Increase of ≥ 7 stools per day over baseline; fecal incontinence; intravenous infusion of ≥ 24 h is required; daily living is affected Colitis (Grade 3): Severe abdominal pain, indications for medical intervention, peritoneal sign Grade 4: Life threatening, perforation	• Discontinue I-O treatment as per protocol • 1.0-2.0 mg/kg/day of methylprednisolone or equivalent IV dose • 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 continuing for > 3-5 days or recurring after improvement: • Add 5 mg/kg infliximab (if there are no contraindications). Note: In the case of perforation or septicemia, infliximab cannot be used

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 Adverse Events

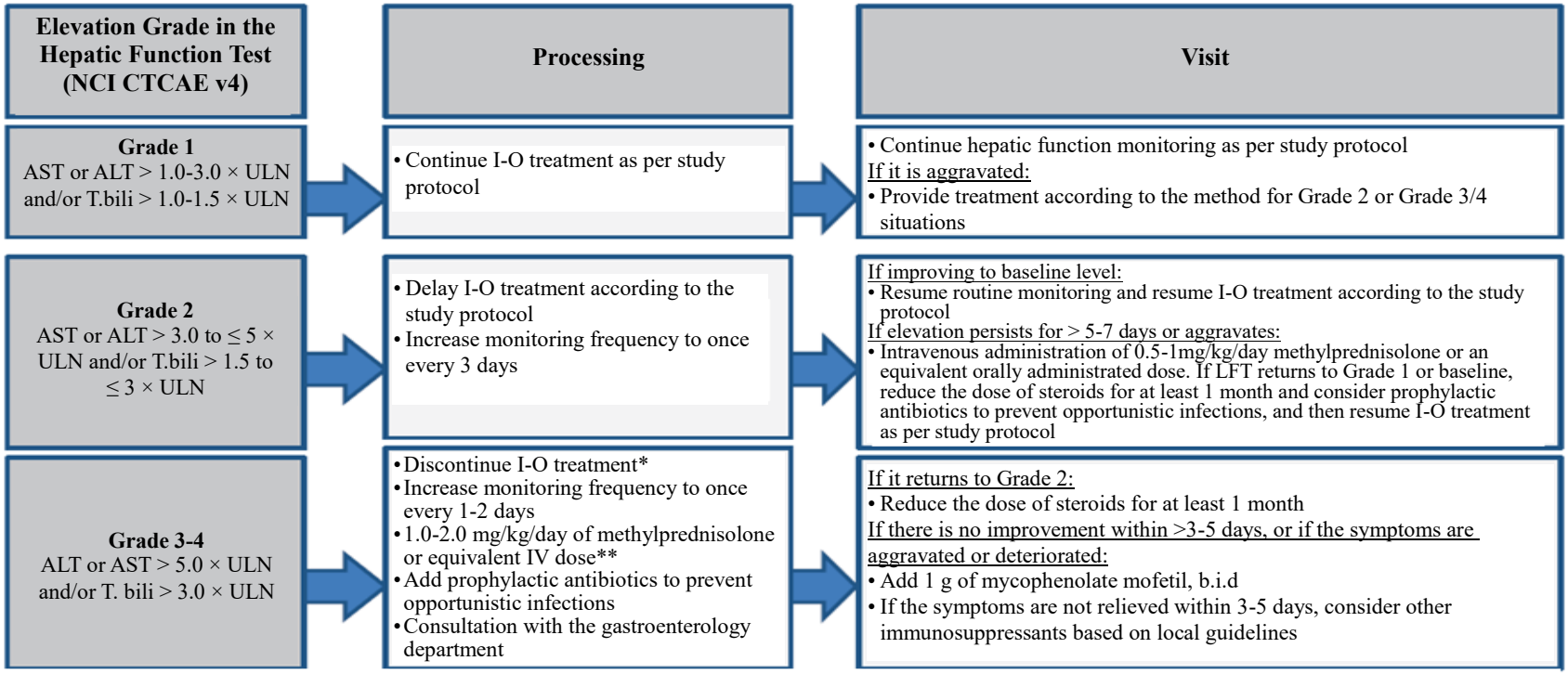
Non-inflammatory causes of disease should be excluded. If it is due to a non-inflammatory cause, a symptomatic treatment should be given while the I-O therapy should be continued. Imaging evaluation and consultations with the respiratory department should be performed.

Pneumonia Grade (NCI CTCAE v4)	Processing	Visit
Grade 1 Only radiographic changes	• Consider delaying the I-O treatment • Monitor symptoms every 2-3 days • Consider consulting with respirologist and infectious diseases specialist	• Repeat imaging examinations at least every 3 weeks If it is aggravated: • Provide treatment according to the method for Grade 2 or Grade 3-4 situations
Grade 2 Mild to moderate new symptoms	• Delay I-O treatment as per study protocol • Consulting with respirologist and infectious diseases specialist • Monitor symptoms daily and consider hospitalization • 1.0 mg/kg/day of methylprednisolone IV or equivalent PO dose • Consider bronchoscopy and lung biopsy	• Repeat imaging examinations at least every 1-3 days If symptoms improve: • When symptoms return to near baseline levels, reduce the dose of steroids for at least 1 month and then resume the I-O treatment as per study protocol while considering prophylactic antibiotics If the symptoms are not improved or aggravated after 2 weeks: • Provide treatment according to the method for Grade 3 or Grade 4 situations
Grade 3-4 Severe new symptoms; new onset/aggravation of hypoxia; life-threatening	• Discontinue I-O treatment as per study protocol • Hospitalization • Consulting with respirologist and infectious diseases specialist • 2-4 mg/kg/day of methylprednisolone or equivalent IV dose • Add prophylactic antibiotics to prevent opportunistic infections • Consider bronchoscopy and lung biopsy	If symptoms improve to the baseline level: • Gradually reduce the dose of steroids for at least 6 weeks If the symptoms are not improved or aggravated after 48 hours: • Add other immunosuppressants (e.g., infliximab, cyclophosphamide, intravenous immunoglobulin or mycophenolate mofetil)

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 Adverse Events

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



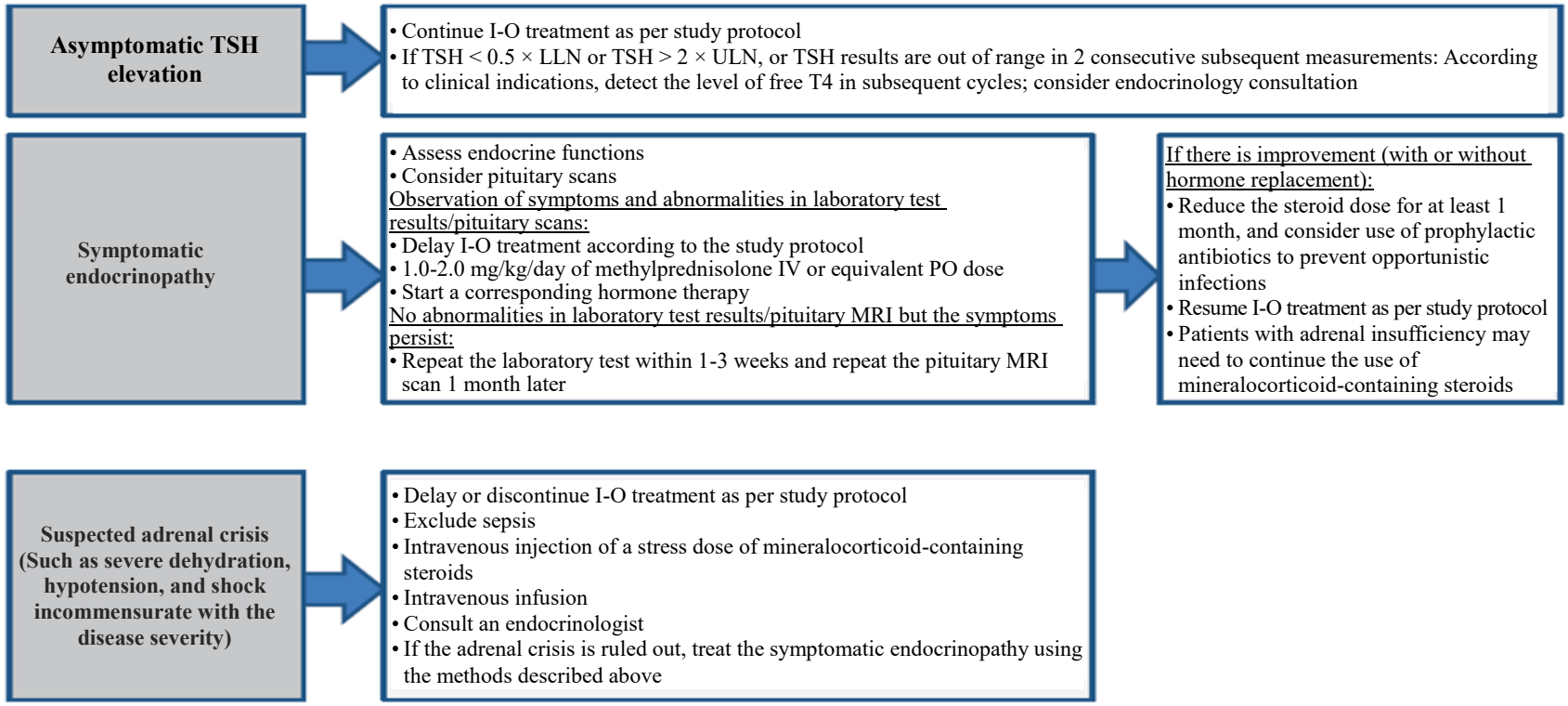
Once a patient given intravenous injections of steroids shows a sustained clinical improvement, the patient can switch to an equivalent dose of oral corticosteroids (e.g., prednisone) by the time or before the dose of steroid injections starts to be gradually reduced. When switching to oral corticosteroids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

***If AST/ALT ≤ 8×ULN and 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 2 mg/kg/day.

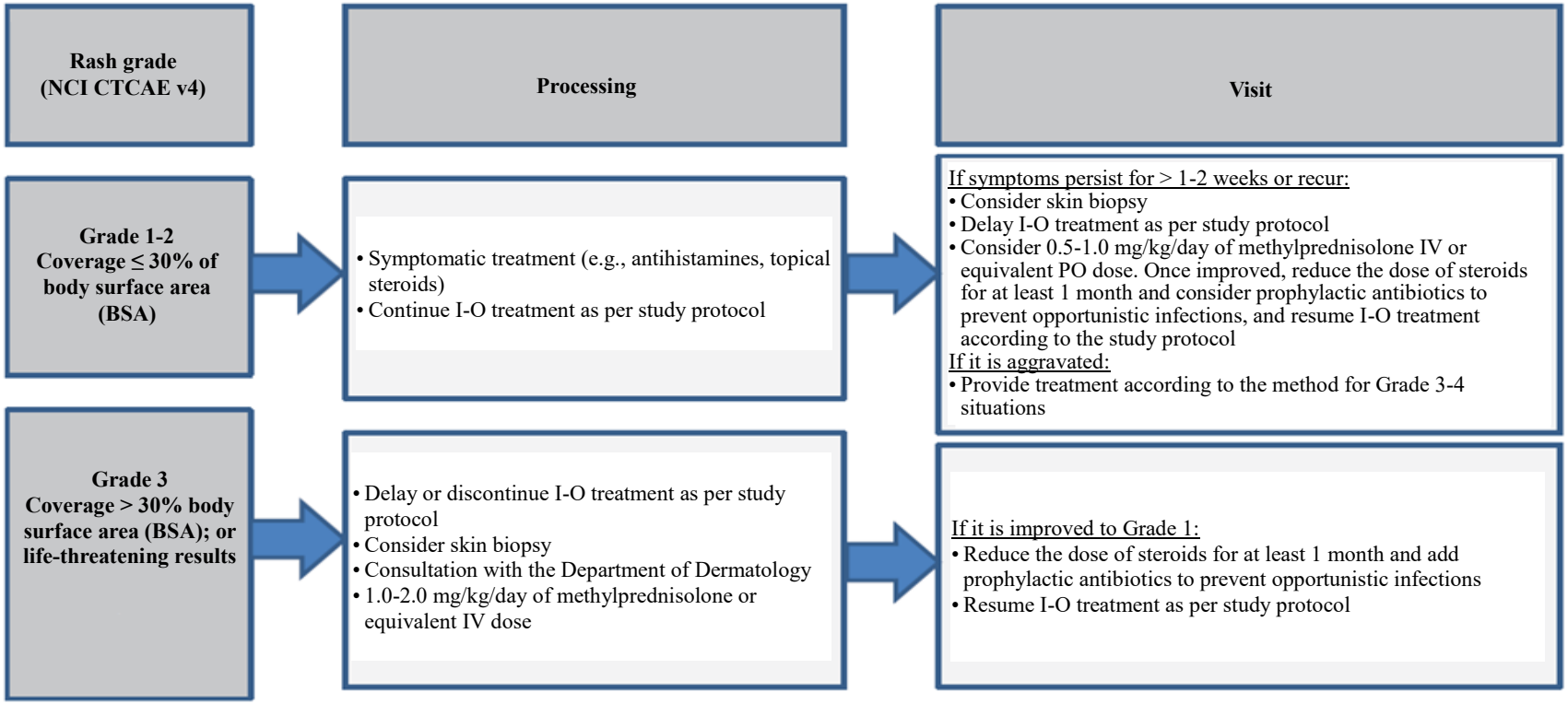
4. Management Principles for Endocrine Adverse Events

Non-inflammatory causes of disease should be excluded. If it is due to a non-inflammatory cause, a symptomatic treatment should be given while the 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 Adverse Events



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.)

Appendix 5. Definition of the prior probability distribution f(θ) of the unknown parameter vector θ in the BLRM

This trial uses a prior probability distribution with less information:

The prior distribution will be defined as a mixed-type distribution, $a(\theta) = a_1 f_1(\theta) + a_2 f_2(\theta) + a_3 f_3(\theta)$, where a_i (i = 1, 2, 3) is the corresponding weight in the mixed normal distribution ($a_1 + a_2 + a_3 = 1$) and $f_i(\theta)$ follows a multivariate normal distribution with overall parameters μ_i and Σ_i (μ_i is the mean vector of the i-th element in the mixed normal distribution, and Σ_i is the covariance matrix of the i-th element in the mixed normal distribution).

$$\Sigma_i = \begin{pmatrix} \sigma^2_{i,11} & \sigma_{i,11}\sigma_{i,22}\rho_i \\ \sigma_{i,11}\sigma_{i,22}\rho_i & \sigma^2_{i,22} \end{pmatrix}$$

The mixed-type distribution of prior probability has an advantage. They reflect different logical dose-toxic response curves, and are thus more reliable as the distribution of prior probability.

Derivation of the prior distribution:

Due to the lack of research in similar populations, relevant human experimental data cannot be obtained in the current research field. Therefore, the three components of the mixed distribution are established according to the following principles:

1. Use a less informative prior distribution that assumes a median rate of 0.05 for clinically significant toxicities at the starting dose (125 mg), and a median rate of 0.30 for clinically significant toxicities at the expected maximum tolerable dose (500 mg). Thus obtained is the mean vector $\mu_1 = (-2.99, 0.84)$. The setting of standard deviation reflects the great uncertainty of the mean values of the parameters. With the correlation coefficient set to 0, $\sigma_{1,11} = 2$, $\sigma_{1,22} = 1$, and $\rho_1 = 0$ are obtained. The weight a_1 of $f_1(\theta)$ in the mixed prior distribution is set to 0.9.
2. Use a prior distribution assuming that the drug is more toxic but less informative to reflect that the toxicity of the compound may be higher than expected. Based on this *a priori* hypothesis, the median rate of clinically significant toxicities at the starting dose (125 mg) is 0.10, and the median rate of clinically significant toxicities at the expected maximum tolerable dose (500 mg) is 0.60. Based on the above assumptions, a $\mu_2 = (-1.09, 0.46)$ is obtained. The standard deviation and correlation coefficient are the same as the first prior distribution with less information, i.e., $\sigma_{2,11} = 2$, $\sigma_{2,22} = 1$, and $\rho_2 = 0$. The weight a_2 of the second component in the mixed prior distribution is set to 0.05.

3. Use a prior distribution assuming that the drug is less toxic but less informative to reflect that the toxicity of the compound may be lower than expected. Based on this *a priori* hypothesis, the median rate of clinically significant toxicities at the starting dose (125 mg) is 0.01, and the median rate of clinically significant toxicities at the expected maximum tolerable dose (500 mg) is 0.1. Based on the above assumptions, $\mu_3 = (-4.24, -0.69)$ is obtained, which is a flat curve. The standard deviation and correlation coefficient are set to $\sigma_{3,11} = 5$, $\sigma_{3,22} = 0.01$, and $\rho_3 = 0$. The weight a_3 of the third component in the mixed prior distribution is set to 0.05.

Table 1 summarizes the prior distribution. In addition, Table 2 shows the *a priori* probability of clinically significant toxicities at different doses and their corresponding probability of drug insufficiency, drug compliance, and drug overdose. The above table shows that the median probability of clinically significant toxicities derived from the prior probability distribution is consistent with the median prior probability derived from the prior distribution with less information. The uncertainty is high, confirming that the prior distribution can only provide limited amount of information.

Table 1. Summary of prior distribution.

Components of Prior Probability	Weight in the Mixed Distribution	Mean Vector	Standard Deviation Vector
1: Prior Probability Distribution with Less Information	0.900	-2.99 0.84	2.000, 1.000
2: Prior probability distribution assuming a strong toxicity of the drug	0.050	-1.09 0.46	2.000, 1.000
3: Prior probability distribution assuming a weak toxicity of the drug	0.050	-4.24 -0.69	5.000, 0.010

Table 2. Prior probability of clinically significant toxic events at specific doses.

Dose	Probability of Clinically Significant Toxicity Rate Falling Within the Probability Interval					Quantile		
	[0-0.16)	[0.16-0.33)	[0.33-1)	Mean	Standard deviation	2.5%	50%	97.5%
125 mg	0.894	0.054	0.052	0.061	0.143	0	0.007	0.557
250 mg	0.728	0.128	0.143	0.142	0.206	0	0.049	0.790
375 mg	0.499	0.153	0.346	0.296	0.314	0.001	0.16	0.990
500 mg	0.397	0.135	0.467	0.397	0.358	0.001	0.282	0.999

Appendix 6. Packaging and Labeling of Study Drugs.

Example of label (refer to the actual drug label)

Drug label of SHR-1210

Small box label

SHR-1210 for Injection Clinical Trial Approval No.: 2016L01455/ 2014L00877 Strength: 200 mg/vial

FOR CLINICAL STUDY USE ONLY

Study Title: A Phase II Clinical Study of PD-1 Antibody SHR-1210 Combined with Apatinib Mesylate or FOLFOX4 Regimen in the Treatment of Advanced Liver Cancer

Study No.: SHR-1210-APTN-II-203-PLC Dosage Form: Lyophilized powder,

Administration: 3 mg/kg, Q2W, intravenous drip Note: Prepare according to the pharmacy manual

Drug No._____

Quantity: 1 vial per box

Storage Method: Store at 2-8 °C away from light

Batch No.: Expiry Date: MM/DD/20YY

Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Vial Label

SHR-1210 for Injection Clinical Trial Approval No.: 2016L01455/2014L00877 Strength: 200 mg/vial

FOR CLINICAL STUDY USE ONLY

Study Title: A Phase II Clinical Study of PD-1 Antibody SHR-1210 Combined with Apatinib Mesylate or FOLFOX4 Regimen in the Treatment of Advanced Liver Cancer

Study No.: SHR-1210-APTN-II-203-PLC Dosage Form: Lyophilized powder,

Administration: 3 mg/kg, Q2W, intravenous drip Note: Prepare according to the pharmacy manual

Subject No.: _____ Drug No._____

Cycle __, Dose __

Storage Method: Store at 2-8 °C away from light

Batch No.: Expiry Date: MM/DD/20YY

Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Big Box Label

SHR-1210 for Injection Clinical Trial Approval No.: 2016L01455/2014L00877 Strength: 200 mg/vial

FOR CLINICAL STUDY USE ONLY

Study Title: A Phase II Clinical Study of PD-1 Antibody SHR-1210 in Combination with Apatinib Mesylate or FOLFOX4 Regimen in the Treatment of Advanced Liver Cancer

Study No.: SHR-1210-APTN-II-203-PLC Dosage Form: lyophilized powder, 200 mg/vial

Administration: 3 mg/kg, Q2W, intravenous drip Note: Prepare according to the pharmacy manual

Quantity: 20 vials per box (drug no. for this box of drug: xxxx-xxxx)

Storage Method: Store at 2-8 °C away from light

Batch No.: Expiry Date: MM/DD/20YY

Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Manufacturer: Shanghai Hengrui Pharmaceutical Co., Ltd.

Drug label of apatinib mesylate

Pack label for the 250 mg/tablet strength (for the use in the 125 mg dose group)

A Phase II Clinical Study of PD-1 Antibody SHR-1210 in Combination with Apatinib Mesylate or FOLFOX4 Regimen in the Treatment of Advanced Cancer

For clinical use only

Strength: 250 mg/tablet

Administration: Half a tablet per day, once a day after meals (the dosing time on each day should remain the same whenever possible)

Batch No.: ××××××

Expiry Date: 2 years, till MM/DD/20YY

Small box label for the 250 mg/tablet strength (for the use in the 125 mg dose group)

A Phase II Clinical Study of PD-1 Antibody SHR-1210 in Combination with Apatinib Mesylate or FOLFOX4 Regimen in the Treatment of Advanced Cancer

For clinical use only

Clinical Approval No.: 2016L01455/2014L00877

Drug No.:

Quantity: 10 tablets per pack, 3 packs per box

Strength: 250 mg/tablet

Method of administration: Half tablet, once a day after meals (the dosing time on each day should remain the same whenever possible)

Storage: ××××

Batch No.: ×××× Expiration Date: 2 years, till MM/DD/20YY

Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Note: Please return the remaining drugs to the pharmacist

Big box label for the 250 mg/tablet strength (for the use in the 125 mg dose group)

A Phase II Clinical Study of PD-1 Antibody SHR-1210 in Combination with Apatinib Mesylate or FOLFOX4 Regimen in the Treatment of Advanced Cancer

For clinical use only

Clinical Approval No.: 2016L01455/2014L00877

Drug No.:

Quantity: xx small boxes Strength: 250 mg/tablet

Method of administration: Half tablet, once a day after meals (the dosing time on each day should remain the same whenever possible)

Storage: ××××

Batch No.: ××××

Expiry Date: 2 years, till MM/DD/20YY

Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Note: Please return the remaining drugs to the pharmacist

250 mg/tablet, pack label (for 250 mg dose group)

A Phase II Clinical Study of PD-1 Antibody SHR-1210 in Combination with Apatinib Mesylate or FOLFOX4 Regimen in the Treatment of Advanced Cancer

For clinical use only

Strength: 250 mg/tablet

Method of Administration: 1 tablet per day, once a day after meals (the dosing time on each day should remain the same whenever possible)

Batch No.: ××××××

Expiry Date: 2 years, till MM/DD/20YY

250 mg/tablet, small box label (for 250 mg dose group)

A Phase II Clinical Study of PD-1 Antibody SHR-1210 in Combination with Apatinib Mesylate or FOLFOX4 Regimen in the Treatment of Advanced Cancer

For clinical use only

Clinical Approval No.: 2016L01455/2014L00877

Drug No.:

Quantity: 10 tablets per pack, 3 packs per box

Strength: 250 mg/tablet

Method of administration: 1 tablet, once a day after meals (the dosing time on each day should remain the same whenever possible)

Storage: ××××

Batch No.: ×××× Expiration Date: 2 years, till MM/DD/20YY

Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Note: Please return the remaining drugs to the pharmacist

Big box label for the 250 mg/tablet strength (for the use in the 250 mg dose group)

A Phase II Clinical Study of PD-1 Antibody SHR-1210 in Combination with Apatinib Mesylate or FOLFOX4 Regimen in the Treatment of Advanced Cancer

For clinical use only

Clinical Approval No.: 2016L01455/2014L00877

Drug No.:

Quantity: xx small boxes Strength: 250 mg/tablet

Method of administration: 1 tablet, once a day after meals (the dosing time on each day should remain the same whenever possible)

Storage: ××××

Batch No.: ××××

Expiry Date: 2 years, till MM/DD/20YY

Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Note: Please return the remaining drugs to the pharmacist

Pack label for the 375 mg/tablet strength

A Phase II Clinical Study of PD-1 Antibody SHR-1210 in Combination with Apatinib Mesylate or FOLFOX4 Regimen in the Treatment of Advanced Cancer

Strength: 375 mg/tablet

Method of Administration: 1 tablet per day, once a day after meals (the dosing time on each day should remain the same whenever possible)

Batch No.: ××××××

Expiry Date: 2 years, till MM/DD/20YY

Small box label for the 375 mg/tablet strength

A Phase II Clinical Study of PD-1 Antibody SHR-1210 in Combination with Apatinib Mesylate or FOLFOX4 Regimen in the Treatment of Advanced Cancer

For clinical use only

Clinical Approval No.: 2016L01455/2014L00877

Drug No.:

Medication for Cycle X

Quantity: 10 tablets per pack, 3 packs per box

Strength: 375 mg/tablet

Method of administration: 1 tablet, once a day after meals (the dosing time on each day should remain the same whenever possible)

Storage: ××××

Batch No.: ×××× Expiration Date: 2 years, till MM/DD/20YY

Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Note: Please return the remaining drugs to the pharmacist

Big box label for the 375 mg/tablet strength

A Phase II Clinical Study of PD-1 Antibody SHR-1210 in Combination with Apatinib Mesylate or FOLFOX4 Regimen in the Treatment of Advanced Cancer

For clinical use only

Clinical Approval No.: 2016L01455/2014L00877

Drug No.:

Quantity: xx small boxes Strength: 375 mg/tablet

Method of administration: 1 tablet, once a day after meals (the dosing time on each day should remain the same whenever possible)

Storage: ××××

Batch No.: ××××

Expiry Date: 2 years, till MM/DD/20YY

Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Note: Please return the remaining drugs to the pharmacist

250 mg/tablet, pack label (for 500 mg dose group)

A Phase II Clinical Study of PD-1 Antibody SHR-1210 in Combination with Apatinib Mesylate or FOLFOX4 Regimen in the Treatment of Advanced Cancer

For clinical use only

Strength: 250 mg/tablet

Method of administration: 2 tablets per day

Once a day after meals (the dosing time on each day should remain the same whenever possible)

Batch No.: ××××××

Expiry Date: 2 years, till MM/DD/20YY

250 mg/tablet, small box label (for 500 mg dose group)

A Phase II Clinical Study of PD-1 Antibody SHR-1210 in Combination with Apatinib Mesylate or FOLFOX4 Regimen in the Treatment of Advanced Cancer

For clinical use only

Clinical Approval No.: 2016L01455/2014L00877

Drug No.:

Quantity: 10 tablets per pack, 6 packs per box

Strength: 250 mg/tablet

Method of administration: 2 tablets, once a day after meals (the dosing time on each day should remain the same whenever possible)

Storage: ××××

Batch No.: ×××× Expiration Date: 2 years, till MM/DD/20YY

Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Note: Please return the remaining drugs to the pharmacist

250 mg/tablet, large box label (for 500 mg dose group)

A Phase II Clinical Study of PD-1 Antibody SHR-1210 in Combination with Apatinib Mesylate or FOLFOX4 Regimen in the Treatment of Advanced Cancer

For clinical use only

Clinical Approval No.: 2016L01455/2014L00877

Drug No.:

Quantity: XX packs per box Strength: 250 mg/tablet

Method of administration: 2 tablets, once a day after meals (the dosing time on each day should remain the same whenever possible)

Storage: ××××

Batch No.: ××××

Expiration Date: 2 years, till MM/DD/20YY

Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Note: Please return the remaining drugs to the pharmacist

Label of oxaliplatin

Box label for the 50 mg strength

A Phase II Clinical Study of PD-1 Antibody SHR-1210 in Combination with Apatinib Mesylate or FOLFOX4 Regimen in the Treatment of Advanced Cancer

For clinical use only

Clinical Approval No.: 2016L01455/2014L00877

Drug No.:

Quantity: 1 vial contained Strength: 50 mg/vial

Method of Administration: 85 mg/m^2 (intravenous infusion), repeated once every two weeks

Storage: Store in a sealed container away from light below 25 °C

Batch No.: ××××

Expiry Date: 2 years, till MM/DD/20YY

Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Note: Please return the remaining drugs to the pharmacist

100 mg box label

A Phase II Clinical Study of PD-1 Antibody SHR-1210 in Combination with Apatinib Mesylate or FOLFOX4 Regimen in the Treatment of Advanced Cancer

For clinical use only

Clinical Approval No.: 2016L01455/2014L00877

Drug No.:

Quantity: 1 vial Strength: 100 mg/vial

Method of Administration: 85 mg/m^2 (intravenous infusion), repeated once every two weeks

Storage: Store in a sealed container away from light below 25 °C

Batch No.: ××××

Expiry Date: 2 years, till MM/DD/20YY

Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Note: Please return the remaining drugs to the pharmacist

Label of levoleucovorin calcium

25 mg box label

A Phase II Clinical Study of PD-1 Antibody SHR-1210 in Combination with Apatinib Mesylate or FOLFOX4 Regimen in the Treatment of Advanced Cancer

For clinical use only

Clinical Approval No.: 2016L01455/2014L00877

Drug No.:

Quantity: 1 vial Strength: 25 mg/vial

Administration: 200 mg/m^2 (2 h intravenous infusion), on D1, D2, and repeated once every 2 weeks

Storage: Store in a sealed container away from light in a dry environment

Batch No.: ××××

Expiry Date: 3 years, till MM/DD/20YY

Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Note: Please return the remaining drugs to the pharmacist

Label of 5-fluorouracil

Box label for the 250 mg/vial, 5 vials/box strength

A Phase II Clinical Study of PD-1 Antibody SHR-1210 in Combination with Apatinib Mesylate or FOLFOX4 Regimen in the Treatment of Advanced Cancer

For clinical use only

Clinical Approval No.: 2016L01455/2014L00877

Quantity: 5 vials Strength: 250 mg/vial

Administration: 400 mg/m^2 (bolus injection), 600 mg/m^2 (22 h intravenous infusion), on D1, D2, and repeated once every 2 weeks

Storage: Sealed and kept away from light

Batch No.: ××××

Expiry: 18 months, until DD/MM/20YY

Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Note: Please return the remaining drugs to the pharmacist

Label of gemcitabine

Box label for the 1.0 g/vial, 3 vials/box strength

A Phase II Clinical Study of PD-1 Antibody SHR-1210 in Combination with Apatinib Mesylate or Chemotherapy in the Treatment of Advanced Primary Liver Cancer or Extrahepatic Cholangiocarcinoma

For clinical use only

Clinical Approval No.: 2016L01455/2014L00877/2014L00876

Quantity: 3 vials contained Strength: 1.0 g/vial

Administration: 800 mg/m^2 (intravenous drip), repeated once every 2 weeks

Storage: Store in a sealed container in a dry environment

Batch No.: ××××

Shelf life: 36 months

Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Note: Please return the remaining drugs to the pharmacist