A Randomized, Open-Label, International, Multi-Center, Phase 3 Clinical Study of PD-1 Antibody SHR-1210 Plus Apatinib (Rivoceranib) Mesylate Versus Sorafenib as First-Line Therapy in Subjects with Advanced Hepatocellular Carcinoma (HCC) Who Have Not Previously Received Systemic Therapy

Protocol number:	SHR-1210-III-310
Trial phase:	Phase 3
Compound name:	Camrelizumab for Injection (SHR-1210 for Injection), Rivoceranib Mesylate
Person liable for protocol:	[redacted]
Principal investigator:	[redacted]
Version No.:	6.0
Version date:	21 Sep 2022

Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.
[redacted]

Version History / Amendment History

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1.0	10 Sep 2018	NA
2.0	12 Nov 2018	Primary Study Objective: • Updated from "To compare the overall survival (OS) of SHR-1210 combined with apatinib mesylate (experimental arm) with sorafenib (control arm) as first-line therapy for subjects with advanced HCC who have not previously received systemic therapy" to "To compare the overall survival (OS) **and progression-free survival (PFS)** of SHR-1210 combined with apatinib mesylate (experimental arm) with sorafenib (control arm) as first-line therapy for subjects with advanced HCC who have not previously received systemic therapy"; Secondary Study Objective: • Updated from "To evaluate the immunogenicity of SHR-1210 and analyze it in combination with the concentration of SHR-1210" to "To evaluate **pharmacokinetics (PK) of SHR-1210 and apatinib** and immunogenicity of SHR-1210, and to analyze the immunogenicity of SHR-1210 in combination with the concentration of SHR-1210"; Exploratory Study Objectives: • Added the following 2 exploratory study objectives: To compare the efficacy of SHR-1210 combined with apatinib mesylate (experimental arm) versus sorafenib (control arm) as first-line therapy in subjects with advanced HCC through evaluations of PFS, TTP, ORR, DCR and DoR based on immune-modified Response Evaluation Criteria in Solid Tumors (imRECIST); To explore the correlation between biomarkers and the efficacy of combined therapeutic regimen; Primary Study Endpoints: • Updated from "overall survival (OS)" to "OS **and PFS evaluated by the blinded independent review committee (BIRC) based on Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)**" as the co-primary study endpoints; Secondary Study Endpoints: • Secondary efficacy endpoint evaluated by BIRC updated from based on "imRECIST" to base on "RECIST v1.1 and mRECIST"; secondary efficacy endpoints evaluated by

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		investigator updated from based on "RECIST v1.1 and imRECIST" to base on "RECIST v1.1"; • Added PK endpoint "serum concentration of SHR-1210 and plasma concentration of apatinib"; <u>Exploratory Study Endpoints:</u> • Added exploratory study endpoint "PFS, TTP, ORR, DCR and DoR evaluated by investigator based on imRECIST"; • Added exploratory study endpoint "The expression level of PD-L1, proportion of strong expression of PD-L1 in tumor tissue and tumor mutation burden (TMB) as well as their correlation with the efficacy of SHR-1210 combined with apatinib mesylate (including but not limited to ORR, OS)"; <u>Other Changes:</u> • The statistical hypothesis determined sample size and statistical analysis method were updated along with the change of primary study endpoints; • "Etiology (hepatitis B vs. hepatitis C vs. other)" was removed from the stratification factors; • Inclusion criteria: Child-Pugh hepatic function score was updated from "≤7" to "Grade A"; • The administration method of sorafenib is unified in accordance with the package insert approved by the FDA. Dose adjustment of sorafenib is supplemented in accordance with the package insert approved by the FDA; • Drugs used cautiously for subjects given sorafenib were supplemented; • Section of collection of tumor tissue sample and biomarker test added (exploratory study objective, study endpoint, inclusion criteria, study flow chart, evaluation and analysis of exploratory tumor markers); • Criteria on tumor evaluation updated to RECIST v1.1 (investigator and BIRC evaluated), mRECIST (only BIRC evaluated) and imRECIST (only investigator evaluated); • The AE/SAE collection period was updated; • The safety follow-up period was updated; • The concomitant therapy collection period was updated; • "≥ grade 2 capillary endothelial proliferation with hemorrhage or ≥ grade 3 capillary endothelial proliferation" was removed from

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		the adverse events of special interest; • Day 60 and Day 90 were deleted from the time of collection of immunogenicity samples. The collection method and volume of blood for immunogenicity and PK sampling were updated; • The definition of end of study was updated from "338 OS events obtained from LSLV" to "354 OS events obtained from LSLV"; • The coordinating investigator was updated to Professor Andrew ZHU; • In Appendix 2, expanded subsection "Comparison of imRECIST with RECIST v1.1", and added subsection "Comparison of mRECIST with Conventional RECIST". Detailed changes will be provided in a separate document: Description of Amendment to SHR-1210-III-310 Study Protocol v2.0.
3.0	17 Dec 2018	• Cover page: Updated the compound name from "Camrelizumab" to "Camrelizumab **for Injection**"; • Updated wording for exploratory study objectives, i.e., "experimental arm vs control arm" was clarified as "SHR-1210 combined with rivoceranib mesylate vs sorafenib"; • Updated the "utility score for economic assessment" in an exploratory study objective to the "utility score for **health** economic assessment"; • Updated the CTCAE version from 5.0 to **4.03**; • Removed the detection of tumor mutation burden (TMB) throughout the protocol, revised its pertinent exploratory study endpoint, and reduced the number of unstained FFPE slides to 5; • Included "rivoceranib", the international nonproprietary name [INN] for apatinib; • Increased the sample size to 510 subjects, added the interim OS analysis, and updated efficacy analyses accordingly; • Modified the dose of SHR-1210 to 200 mg, added the rationale for dose selection of the combination therapy, updated the administration route of SHR-1210 from "IV" to the more specific term "intravenous infusion"; • In the inclusion criteria, the antiviral therapy guideline for subjects with positive HCV-RNA was clarified as the "local standard treatment guideline"; • Added strong inducers and strong inhibitors of CYP2C19 as prohibited medications in the exclusion criteria and in the section

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		regarding prohibited medications; • In sections regarding PK and immunogenicity sampling, added "When SHR-1210 is interrupted for longer than 30 days and finally is confirmed to be unable to resume, for this situation, the subject is required to come for a site visit and collect blood sample immediately when investigator confirms the subject is permanently terminated SHR-1210 treatment". The volume of blood to be collected was updated to "approximately 8 mL" for detection of immunogenicity and drug concentrations and to "approximately 6 mL" for detection of SHR-1210. Removed details on aliquots in blood sample handling and processing, and stated that detailed procedures are described in the laboratory manual; • Set back study milestones by 1 month; • Updated the initiation date of the screening period from Day -3 to Day -7; • Added Child-Pugh class in the schedule of activities and study procedures; • Added "physical examination of reactive capillary endothelial proliferation needs to be performed on the experimental arm"; • Added "γ-glutamyl transferase, direct bilirubin and indirect bilirubin" in blood biochemistry; • Updated known potential risks of SHR-1210 and rivoceranib based on the most recent clinical study results; • Added criteria of abnormal liver function tests for SHR-1210 dose delay; updated criteria for permanent discontinuation of SHR-1210; • Updated rules for safety management of immuno-oncology drugs; • Added liver function test abnormalities to the list of special interest AEs; • Updated the section of pregnancy; • Updated treatment procedures for common immune-related AEs in Appendix 6 based on ESMO guidelines in combination with this protocol to make these procedures more practical. Detailed changes will be provided in a separate document: Description of Amendment to SHR-1210-III-310 Study Protocol v3.0.
3.1	26 Mar 2019	<u>Administrative:</u> • Cover page: Corrected title for Andrew ZHU, MD to Co-

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		investigator Schedule of Events: • ECG and PK Timepoints • Footnotes 2, 5, and 32 PK collection and language added • Footnote 4: ECG and PK added to C1D1 • Footnote 25: ECG and PK additional verbiage added Protocol Sections: • Section 5.3.1.1: Drugs and Therapies Prohibited for all subjects during the study. • Section 6.1: PK collection added • Section 6.2.1: ECG assessment added to C1D1 study procedures • Section 6.2.1: PK language added • Sections 6.2.2; 6.2.3; 6.3; and 6.4: PK language added Appendix: • Appendix 11: Additional information regarding Concomitant use of drugs effecting CYP enzymes, acid reducing agents or QT interval
3.2	27 Mar 2019	Protocol Section: • 5.1.6.1.5: changed verbiage (language)
3.3	28 Mar 2019	Protocol Section: • 5.3.1: Concomitant Therapy • Table 12 - removed • Appendix 11 - updated
4.0	16 Apr 2019	• Subject contraception requirements revised; • Inclusion and exclusion criteria updated; • The requirements of order of administration for SHR-1210 and rivoceranib with meal; • The study design schematic diagram adjusted; • The end time of study drug treatment clarified: Study treatment will continue until the subject develops intolerable toxicity, withdrawal of informed consent, or disease progression confirmed by BIRC in accordance with RECIST v1.1 and after comprehensive assessment investigator considers the subject no longer has clinical benefit based on radiological, laboratory data, and clinical status (e.g., tumor-related symptoms worsen), or

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		other criteria for discontinuation of treatment as specified in the protocol, whichever occurs first. When the subject develops disease progression that conforms to the definition by RECIST v1.1 according to the investigator's assessment, and BIRC also confirms the disease progression (according to RECIST v1.1), if the investigator assesses that the subject still has clinical benefit and is tolerated to study treatment, subject will continue SHR-1210 alone or in combination with rivoceranib (experimental arm) or sorafenib (control arm) (see Section 6.6 of the main text for continued treatment after progression); • Specific timing of tumor assessment clarified: Tumor radiological assessment will continue until the occurrence of disease progression confirmed by BIRC according to RECIST v1.1 criteria or study treatment termination, whichever occurs later. Subjects who discontinues treatment for other reasons than BIRC-confirmed disease progression (according to RECIST v1.1) will also continue with regular follow-up by tumor radiological assessments after treatment is completed. If the subject withdraws the informed consent before BIRC confirms the disease progression according to the RECIST v1.1 criteria or the treatment is discontinued, other anti-tumor treatment has begun (except for traditional Chinese medicine), or the subject dies, there is no need to continue the radiological evaluation. If the subject does not meet the above criteria for stopping radiological assessment, the efficacy evaluation of the three efficacy evaluation criteria (RECIST v1.1, mRECIST, imRECIST) needs to continue even if disease progression under a certain efficacy evaluation criterion occurs; • Flow chart for disease progression added; • The specific procedures of immunogenicity and PK blood collection in the experimental arm were clarified; and the blood sample collection table was added; • Safety visits schedule adjusted; • The survival follow-up was defined to start from the last safety visit; • The description of the sample size calculation section clarifies that the expected mOS of the experimental arm will be14.6 months and the mPFS will be 6 months; • Updated assessment of subject self-reported outcomes: EORTC QLQ-C30 (version 3.0), EORTC QLQ-HCC18 and EQ-5D-5L questionnaire will be completed by all subjects from the first cycle, on the first day of each cycle prior to study drug administration and prior to any other study evaluation at the

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		clinical site. In addition, all subjects will be required to conduct the above questionnaire assessment at the end-of-treatment visit and during the first safety follow-up period. Before the subject leaves the site, the study staff should review all the questionnaires for completeness; • The handling method of a missed dose added; • Revision to the dose adjustment of rivoceranib; • Suggestions on management of immune related AEs in Table 10 was deleted; • Deleted the treatment recommendations for immune-related adverse reactions in Table 10; • Revised description of each efficacy endpoint; • The efficacy analysis population was updated from FAS to ITT; • Updated efficacy endpoint analysis, interim analysis, multiple comparisons/multiplicity; • Deleted the estimated time of the study progress; • Clarify the storage of trial data: The sponsor should maintain clinical trial data for at least 15 years after the study medication is approved for marketing in the last country or region or after this clinical study is early terminated; • References updated; • PFS event definition and BOR definition under the imRECIST criteria added; • The classification and management of reactive capillary proliferation updated.
5.0	1 May 2020	• Co-investigator and relevant content removed; • Abbreviation table updated; • Background updated, include the description of the most recent data from previously conducted studies and most recent newly initiated studies. • Scientific rationale for antibody affinity study data updated. • SHR-1210 clinical studies progress updated. • Clarified that “vascular invasion” was “macrovascular invasion” in the randomization stratification factors. • Inclusion/exclusion criteria modified. • Removed “subject death” from the criteria of withdrawal from

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		study. • Improved the storage conditions of rivoceranib. • Removed "subsequent dosing time is calculated based on the actual date of previous administration" from dosing regimen; added missed dose rules. • Modified the description of the management of reactive capillary endothelial proliferation in the SHR-1210 dose delay criteria. • The description which interval of test frequency cannot exceed 6 weeks for the safety visit and laboratory examination when dose delay occurs was modified to be "the required examinations during study treatment need to be performed as planned or more frequently when clinically indicated". • Modified table of dosage adjustment plan of rivoceranib. • Modified table of dosage adjustment plan of sorafenib. • The requirement for daily blood pressure in both rivoceranib and sorafenib adverse reaction management was modified to recommended daily monitoring of blood pressure. • Modified the use of systemic corticosteroids in the prohibited medication for subjects given SHR-1210 during the study. • Modified the prohibited and cautiously used medication of rivoceranib. • Modified the description of antiviral therapy during study treatment. • Added "tumor tissue collection" in the screening period. • Among tumor image evaluation, "enhanced CT of chest, abdomen, pelvic cavity and lesion site" was modified to be "enhanced CT/MRI of chest, abdomen, pelvic cavity and lesion site". • Serum biochemistry and serum HCG tests were modified to be blood biochemistry and blood HCG tests. • Added TT3 tests as the alternative test in the thyroid function examination. • Removed the "indirect bilirubin" in the blood biochemistry test. • Clarified the immunogenicity blood samples and PK blood samples collection rules. • Modified the definition of efficacy endpoints based on imRECIST.

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		• Modified the viral tests requirement (include HBV and HCV). • Modified the definition of TTD. • Modified the reporting requirement of Grade 5 SAE term caused by disease progression. • Delete duplicated descriptions regarding the use of the independent nominal alpha of 0.001% for OS at the time of the planned PFS analysis when OS events < 251 and that the study will not stop based on this result. The study will continue to the next planned OS interim analysis (70%) and could continue to final analysis after ~251 OS events and ~359 OS events are observed, respectively, according to the efficacy boundaries as described. Other minor changes such as typographical error were also made. • Improved the Data Monitoring Committee Part. • Reference updated. • Modified BCLC stage in appendix 1.
5.1	10 March 2021	• Additional information about risk of Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) management guidelines for these events has been provided. • Removed "PK collection" on C1D15 in Section 6.2.1 to consistent with SCHEDULE OF ACTIVITIES. • Revised PPI drugs in APPENDIX 11 due to typo error. • Changed the emailbox for Sponsor receiving safety report to hengrui_drug_safety@hengrui.com
6.0	21 Sep 2022	• Disease progression will only be confirmed by investigator instead of BIRC upon protocol v6.0 approval. • Definition of end of study was updated. • Added extension phase to provide study drug for subjects who still continue on treatment at the time of study closure.

Signature Page of Sponsor

I have read and confirmed this protocol (protocol number: SHR-1210-III-310; version number: 6.0; version date: 21 Sep 2022). I agree that relevant responsibilities must be fulfilled in accordance with ICH-GCP, any appropriate laws and regulations and this study protocol.

Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Signature Page of Principal Investigator (Lead Institution)

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

Study Center: [redacted]

[redacted]

Signature Page of Principal Investigator (Participating Institution)

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

Study Center: _____

Principal Investigator (Print Name)	Principal Investigator (Signature)	Signature Date (Day/Month/Year)

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SYNOPSIS OF PROTOCOL

Study Title	A Randomized, Open-Label, International, Multi-Center, Phase 3 Clinical Study of PD-1 Antibody SHR-1210 Plus Apatinib (Rivoceranib) Mesylate Versus Sorafenib as First-Line Therapy in Subjects with Advanced Hepatocellular Carcinoma (HCC) Who Have Not Previously Received Systemic Therapy
Protocol Number	SHR-1210-III-310
Version Number	6.0
Sponsor	Jiangsu Hengrui Pharmaceuticals Co., Ltd.
Principle Investigator	[redacted]
Study Centers	Approximately 140 centers globally
Study Objectives	**Primary Objective:** • To compare the overall survival (OS) and progression-free survival (PFS) of SHR-1210 combined with apatinib (hereafter referred to as "rivoceranib", its international nonproprietary name [INN]) mesylate (experimental arm) with sorafenib (control arm) as first-line therapy for subjects with advanced HCC who have not previously received systemic therapy. **Secondary Objectives:** • To compare the efficacy of SHR-1210 combined with rivoceranib versus sorafenib as first-line therapy in subjects with advanced HCC, who have not previously received systemic therapy, through evaluations of PFS, time to progression (TTP), objective response rate (ORR), disease control rate (DCR), and duration of response (DoR); • To evaluate the safety of SHR-1210 combined with rivoceranib versus sorafenib as a first-line therapy in subjects with advanced HCC; • To evaluate the pharmacokinetics (PK) of SHR-1210 and rivoceranib and the immunogenicity of SHR-1210, and to analyze the immunogenicity combined with the concentration of SHR-1210. **Exploratory Objectives:** • To evaluate the quality of life (QoL), including health related quality of life (HRQOL) / general health status (GHS), physical functioning and role functioning, of subjects with advanced HCC who receive SHR-1210 combined with rivoceranib mesylate as first-line therapy versus those who receive sorafenib as first-line therapy; • To evaluate the health status of subjects with advanced

	HCC who receive SHR-1210 combined with rivoceranib as first-line therapy versus those who receive sorafenib as a first-line therapy, so as to generate a utility score for health economic assessment; • To compare the efficacy of SHR-1210 combined with rivoceranib versus sorafenib as first-line therapy in subjects with advanced HCC through evaluations of PFS, TTP, ORR, DCR and DoR based on immune-modified Response Evaluation Criteria in Solid Tumors (imRECIST); • To explore the correlation between biomarkers and the efficacy of combined therapeutic regimen; • To evaluate the potential effect of immunogenicity of SHR-1210 on the efficacy and safety of SHR-1210 combined with rivoceranib as a first-line therapy in subjects with advanced HCC.
Study Endpoints	**Primary Endpoints:** • OS; • PFS evaluated by the blinded independent review committee (BIRC) based on Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1). **Secondary Endpoints:** Efficacy: • TTP, ORR, DCR and DoR evaluated by the BIRC based on RECIST v1.1; • PFS, TTP, ORR, DCR and DoR evaluated by investigator based on RECIST v1.1; • PFS, TTP, ORR, DCR and DoR evaluated by the BIRC based on modified RECIST (mRECIST). Safety: • Incidence and severity of adverse events (AEs) and serious adverse events (SAEs) judged in accordance with NCI-CTCAE v4.03; vital signs, ECG and abnormal laboratory examinations. PK and Immunogenicity parameters: • Serum concentration of SHR-1210 and plasma concentration of rivoceranib; proportion of anti-SHR-1210 antibody (ADA) and neutralizing antibody (Nab) formed during the study from baseline; and analysis of the immunogenicity of SHR-1210 combined with the concentration of SHR-1210. **Exploratory Endpoints:** • Time to deterioration (TTD): defined as time from randomization to first deterioration (a score decrease of

	≥10 from baseline) maintained for two consecutive time points, or one time-point followed by death (from any cause] within 4 weeks, as determined by following subscales of European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30): - HRQoL/Global health status - Physical Functioning - Role Functioning • Average score and its change in the score from baseline in all the subscales of EORTC QLQ-C30 and EORTC QLQ-HCC18 (by cycle); • Health utility index and VAS score of EQ-5D-5L questionnaire; • PFS, TTP, ORR, DCR and DoR evaluated by investigator based on imRECIST; • The correlation of the expression level of PD-L1 and proportion of strong expression of PD-L1 in tumor tissue with the efficacy of SHR-1210 combined with rivoceranib mesylate (including but not limited to ORR, OS); • Efficacy endpoints (e.g., best overall response (BOR), ORR, etc.), and safety endpoint (e.g., immune-related adverse events [irAEs], ≥ Grade 3 treatment-related adverse events, treatment-related SAEs, etc.) listed according to the ADA / Nab status of SHR-1210 in the experimental arm.
Study Subjects	Subjects with incurable, locally advanced or metastatic HCC who have not received previous systematic treatment
Study Design	This is a randomized, open-label, international, multi-center, phase 3 trial to evaluate the efficacy and safety of PD-1 antibody SHR-1210 plus rivoceranib mesylate versus sorafenib as first-line therapy in subjects with incurable advanced HCC. The study will be conducted in subjects with incurable, locally advanced or metastatic HCC who have not received previous systematic treatment. Primary efficacy endpoints include both OS and PFS evaluated by the BIRC based on RECIST v1.1, and approximately 510 subjects will be enrolled. Eligible subjects will be randomized to receive either SHR-1210 combined with rivoceranib mesylate (experimental arm) or sorafenib (control arm) in a 1:1 ratio. The stratification factors for randomization include: 1. Macrovascular invasion and/or extrahepatic metastasis (presence vs. absence) 2. Geographical region (Asia vs. countries outside of Asia) 3. Baseline AFP (AFP < 400 ng/mL vs. AFP ≥ 400 ng/mL)

	Subjects will receive study treatment after being informed of all pertinent aspects of the study, signing the informed consent form and passing the screening for eligibility. Experimental arm: SHR-1210, 200 mg, via intravenous infusion, once every two weeks (Q2W) + rivoceranib 250 mg, p.o., once per day (QD), continuously, 4 weeks (28 days) per cycle of therapy. Control arm: sorafenib, 400 mg, p.o., twice per day (BID), 4 weeks (28 days) per cycle of therapy. Study treatment will continue until the subject develops an intolerable toxicity, withdrawing informed consent, disease progression confirmed by BIRC according to RECIST v1.1 (when the subject has disease progression assessed by the investigator according to RECIST v1.1, the investigator must submit the radiological data to BIRC immediately. If BIRC evaluates it as non-disease progression according to RECIST v1.1, the subject should continue to receive the study drug treatment and continue the tumor radiological evaluation; if BIRC confirms it as disease progression based on RECIST v1.1, the investigator needs to assess whether the subject still has clinical benefit. If the subject is considered to still have clinical benefit and meets the criteria for continuing treatment beyond the disease progresses [see Section 6.6 for details], the subject may continue to receive study treatment; if the subject is no longer considered to have clinical benefit, the treatment should be discontinued) or other discontinuation criteria specified in the protocol, whichever occurs first. Upon approval of Protocol v6.0, disease progression will not be evaluated by BIRC anymore, and will only be confirmed by the investigator per RECIST v1.1. Subjects will have safety visits on D1 and D15 of each cycle of therapy within the first 3 cycles for both arms. From Cycle 4 onwards, subjects will have safety visits on D1 and D15 of each cycle in the experimental arm, and on D1 of each cycle in the control arm; refer to the SCHEDULE OF ACTIVITIES for details. Subjects will continue to have safety follow-up and survival follow-up after the study treatment discontinuation. Tumor radiological examination will be performed once every 8 weeks to evaluate efficacy for the first 48 weeks from randomization, and once every 12 weeks thereafter. During the study period, radiological examination and evaluation can be added at any time if clinically indicated. Tumor radiological assessment will continue until the occurrence of disease progression confirmed by BIRC according to RECIST v1.1 criteria or treatment discontinuation, whichever occurs later. Subjects who discontinue treatment for reasons other than BIRC-confirmed disease progression (according to RECIST v1.1) will also continue with regular follow-up by tumor radiological assessments after study treatment is discontinued.

	Before BIRC confirms the disease progression according to the RECIST v1.1 criteria or the study treatment is discontinued, if the subject withdraws the informed consent, other anti-tumor treatment has begun (except for traditional Chinese medicine), or the subject dies, there is no need to continue the radiological evaluation. If the subject does not meet the above criteria for stopping radiological assessment, the efficacy evaluation of the three efficacy evaluation criteria (RECIST v1.1, mRECIST, imRECIST) needs to continue even if the disease progression under certain efficacy evaluation criteria occurs. The study extension phase will be initiated when sufficient follow up is completed and the study is ended (at least 2 years follow up of the last subject randomized). The purpose of the extension phase is to continue to provide access to study drugs for subjects who are still on study treatment and still derive clinical benefit at the time of study closure. Upon initiation of the extension phase, the Sponsor considers the safety and efficacy profile of the experimental treatment regimen within this study to have been sufficiently established and data analysis required for regulatory purposes have been completed. The study will establish a Data Monitoring Committee (DMC) to regularly monitor safety of the subjects on a periodic basis and evaluate efficacy and safety data at the time of PFS analysis and OS interim analysis. The DMC will make recommendations for continuing, revising or terminating the study based on observed safety or efficacy data. The composition, responsibilities, operation and management of the DMC will be detailed in a separate DMC charter.
Study Drug	SHR-1210 for Injection (Generic Name: Camrelizumab for Injection) (Manufacturer: Suzhou Suncadia Biopharmaceuticals Co., Ltd.) Rivoceranib Mesylate Tablet (Manufacturer: Jiangsu Hengrui Pharmaceuticals Co., Ltd.) Sorafenib Tosylate Tablet (Manufacturer: Bayer AG)
Route of Administration	Experimental Arm: Rivoceranib 250 mg will be administered orally within 30 minutes after meals, once per day, continuously. One treatment cycle is 4 weeks (28 days). SHR-1210 200 mg will be infused intravenously. Each infusion will be administered over 30 minutes (no less than 20 minutes, no more than 60 minutes) once every two weeks. One treatment cycle is 4 weeks (28 days). Where possible, completion of the administration

should be done prior to ECG assessment.

On days of rivoceranib PK blood collection (Day 1 of Cycle 1-4: C1D1, C2D1, C3D1 and C4D1), it is necessary to administer rivoceranib first at the study center, followed by SHR-1210 administration. For specific information, refer to the SCHEDULE OF ACTIVITIES and BLOOD SAMPLE COLLECTION TABLE.

Control Arm:

Sorafenib 400 mg is administered orally under fasted state (at least 1 hour prior to meal or 2 hours after meal), twice per day, continuously.

One treatment cycle is 4 weeks (28 days).

If a subject in the experimental arm (SHR-1210 in combination with rivoceranib) develops a treatment-related AE that leads to permanent discontinuation of rivoceranib and the investigator determines that the subject can benefit from SHR-1210 as monotherapy, the subject is allowed to continue to receive SHR-1210 monotherapy until the criteria for study treatment discontinuation as specified in the protocol has been met, and vice versa. In addition, during the study treatment period, if a subject in the experimental arm develops a treatment-related AE that leads to temporary discontinuation of SHR-1210 or rivoceranib, the subject may continue to receive monotherapy. The combination therapy can be resumed only after the treatment-related toxicity resolves.

Subjects continue to receive study treatment until intolerable toxicity occurs, withdrawal of informed consent, disease progression confirmed by BIRC according to RECIST v1.1 and lack of clinical benefits as determined by investigator after comprehensive evaluation of radiological and laboratory examination data as well as the subject's clinical condition (e.g., tumor symptomatic exacerbation) or other discontinuation criteria specified in the protocol, whichever comes first. Upon approval of protocol V6.0, disease progression will only need to be confirmed by investigator per RECIST v1.1.

When a subject develops disease progression that conforms to the definition of RECIST v1.1 according to the investigator's assessment, and BIRC also confirms that disease progression (according to RECIST v1.1), subject may continue treatment with SHR-1210 monotherapy or in combination with rivoceranib (experimental arm) or sorafenib (control arm), if the subject still has clinical benefit and can tolerate study treatment as determined by investigator (see Section 6.6 for treatment criteria after disease progression).

Inclusion Criteria	Subjects can be enrolled in this study only when they meet all the inclusion criteria: 1. Provided informed consent and sign the informed consent form; 2. Male or female, ≥ 18 years old; 3. Histopathologically or cytologically confirmed HCC; 4. Subjects must be able to provide fresh or archived tumor tissue (formalin-fixed, paraffin-embedded [FFPE] tissue block or at least 5 unstained FFPE slides) as well as corresponding pathological report. If less than 5 unstained slides are available or tumor tissue is not available (e.g., used up due to previous diagnostic tests), subjects may be permitted to enroll on a case-by-case basis after discussion with the medical monitor; 5. Barcelona Clinic Liver Cancer (BCLC) stage B or C (see APPENDIX 1 for BCLC classification), and not suitable for surgical or local therapy, or has progressed following surgical and/or local therapy; 6. Local regional therapy (including but not limited to surgery, radiotherapy, hepatic artery embolization, TACE, hepatic arterial infusion, radiofrequency ablation, cryoablation or percutaneous ethanol injection) must have been completed at least 4 weeks (subjects received palliative radiotherapy at least 2 weeks) prior to baseline radiological scanning, and any toxicity (except alopecia) induced by local regional therapy must have resolved to ≤ Grade 1 in accordance with National Cancer Institute – Common Terminology Criteria for Adverse Event version 4.03 (NCI-CTCAE v4.03); 7. No previous systematic treatment for advanced HCC; 8. Have at least one measurable lesion (in accordance with RECIST v1.1, major diameter ≥ 10 mm of the measurable lesion in spiral CT scan or short diameter of swollen lymph node ≥ 15 mm; the lesion with previous local therapy can be used as target lesion after the progression is confirmed in accordance with RECIST v1.1); 9. Child-Pugh class (see APPENDIX 3 for Child-Pugh classification criteria): Grade A; 10. ECOG-PS score (See APPENDIX 4 for ECOG-PS scoring criteria): 0-1; 11. With a life expectancy of ≥ 12 weeks; 12. Have the required screening laboratory values including the following parameters (within 7 days prior to the start of study treatment):

(1) Hematology: (except for hemoglobin, no blood transfusion or use of granulocyte colony-stimulating factor [G-CSF] or use of drugs for correction within 14 days prior to screening);
- Absolute neutrophil count ≥ 1.5×10^9/L;
- Platelet count ≥ 75×10^9/L;
- Hemoglobin ≥ 90 g/L;

(2) Blood biochemistry: (no infusion of albumin within 14 days):
- Albumin ≥ 29 g/L;
- Total bilirubin ≤1.5×upper limit of normal (ULN);
- Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP)≤5×ULN;
- Creatinine (Cr) ≤1.5×ULN or Cr clearance >50 mL/min (Cockcroft-Gault formula as below)

  Male: Cr clearance =((140-age) ×weight)/ (72×blood Cr)

  Female: Cr clearance =((140-age) ×weight)/ (72×blood Cr) × 0.85

  Weight unit: kg; Blood Cr unit: mg/mL;

(3) International normalized ratio (INR) ≤2.3 or prothrombin time (PT) ≤6s beyond normal range;

(4) urine protein <2+ (subjects with urine protein ≥ 2+ may undergo 24-hour (h) urine protein quantification and those with 24-h urine protein quantity of <1.0 g can be enrolled);

13. If subjects have active hepatitis B (HBV) infection: HBV- deoxyribonucleic acid (DNA) must be < 500 IU/mL(or must be < 2500 copy/mL if copy/mL is the only unit available in the study site) and are willing to receive antiviral therapy throughout the study (treatment in accordance with local standard of care, e.g., entecavir); subjects with positive hepatitis C (HCV) ribonucleic acid (RNA) must receive antiviral therapy in accordance with the local standard treatment guideline and have ≤ CTCAE Grade 1 elevated hepatic function;
14. Women of childbearing potential(WOCBP): must agree to use a reliable and valid contraception methods (refer to Section 4.4.1) following the date of signed informed consent form until at least 120 days after the last dose of study drug. The blood human chorionic gonadotropin (HCG) test must be negative within 7

	days prior to enrollment in the study; and the subject must not be in lactating period. If a female subject has menses, has not reached postmenopausal state (absence of menses for ≥ consecutive 12 months, with no other reason found except menopause) and has not received sterilization operation (e.g., hysterectomy, bilateral tubal ligation or bilateral ovariectomy), she would be considered to have childbearing potential. 15. Male subjects, whose partner are women of childbearing potential, must agree to use reliable and valid contraception method (Section 4.4.1) following the date of signed informed consent form until at least 120 days after last dose of study drug. Male subjects must also abstain from donation of sperm in the same period. Male subjects whose partners are pregnant must use a condom but other contraceptive method is not required.
Exclusion Criteria	Subjects who meet any one of the following criteria must be excluded from the study: 1. Known hepatocholangiocarcinoma, sarcomatoid HCC, mixed cell carcinoma and lamellar cell carcinoma; other active malignant tumor except HCC within 5 years or simultaneously. Cured localized tumor, for example, basal cell carcinoma of skin, squamous cell carcinoma of skin, superficial bladder cancer, carcinoma in situ of prostate, carcinoma in situs of cervix, breast cancer in situ may be enrolled; 2. Planning to or previously received organ or allogenic bone marrow transplantation; 3. Moderate-to-severe ascites with clinical symptoms, i.e., requiring therapeutic puncture or drainage, or Child-Pugh score >2, except the subjects with small amount of ascites in radiological examination but free from clinical symptoms; uncontrolled or moderate to severe pleural effusion, pericardial effusion. 4. History of gastrointestinal bleeding within 6 months prior to the start of study treatment or clear tendency of gastrointestinal bleeding, for example, at risk of bleeding or severe esophagogastric varices , locally active peptic ulcer, persistent fecal occult blood (+) (the fecal occult blood test should be repeated if it is positive at baseline, and gastroduodenoscopy [EGD] would be needed if it is still positive in repeated test; the subject can not be enrolled if the EGD shows esophageal and fundal varices with hemorrhagic risk or other gastrointestinal disorder with risk of bleeding);

	5. Abdominal fistula, gastrointestinal perforation or intraperitoneal abscess within 6 months prior to the start of study treatment; 6. Known genetic or acquired hemorrhage (e.g., coagulation dysfunction) or thrombotic tendency, for example, subject with hemophilia; current or recent (within 10 days prior to the start of study treatment) use of full-dose of oral or intravenous anticoagulant or thrombolytic drug for the purpose of treatment (preventive use of low-dose aspirin or low molecular weight heparin is allowed); 7. Current or recent (within 10 days prior to the start of study treatment) use of aspirin (> 325 mg/day, maximum dose for antiplatelet) or dipyridamole, ticlopidine, clopidogrel and cilostazol; 8. Thrombosis or thromboembolic event within 6 months prior to the start of study treatment, for example, cerebrovascular accident (including transient ischemic attack, cerebral hemorrhage, cerebral infarction), pulmonary embolism; 9. Cardiac clinical symptom or disease that is not well controlled, for example, (1) > Grade II cardiac insufficiency in accordance with New York Heart Association (NYHA) criteria (see APPENDIX 5) or color Doppler echocardiography: LVEF (left ventricular ejection fraction) <50%; (2) unstable angina pectoris; (3) myocardial infarction within one year prior to the start of study treatment; (4) clinically significant supraventricular or ventricular arrhythmia requiring treatment or intervention; (5) QTc > 450 ms (males) or QTc > 470ms (females) (QTc interval is calculated by Fridericia formula; In case QTc value is abnormal, it can be evaluated for three times at an interval of 2 minutes and the average value will be used); 10. Hypertension that can not be well controlled through antihypertensive drugs (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg) (based on the average of BP readings acquired from ≥ 2 measurements), allowing to reach the above parameters by the use of antihypertensive therapy; previous hypertensive crisis or hypertensive encephalopathy; 11. Major vascular disease within 6 months prior to the start of study treatment (for example, aortic aneurysm requiring surgical repair or peripheral arterial thrombosis in recent days); 12. Serious, unhealed or splitting wound and active ulcer

	or untreated bone fracture; 13. Major surgical therapy within 4 weeks prior to the start of study treatment (except diagnosis), or planned major surgery during the study; 14. Inability to swallow tablets, malabsorption syndrome or any condition affecting gastrointestinal absorption; 15. Intestinal obstruction and/or clinical signs or symptoms of gastrointestinal obstruction within 6 months prior to the start of study treatment, including incomplete obstruction that is related with the original disease or needs routine parenteral hydration, parenteral nutrition or tube feeding; • If the subject has signs/symptoms of incomplete obstruction/ obstructive syndrome/intestinal obstruction at the initial diagnosis receives clear (surgical) therapy to resolve symptoms, the subject may be enrolled; 16. Evidence on intraperitoneal pneumatosis that can not be explained by puncture or recent surgery; 17. Previous or current presence of metastasis to central nervous system; 18. Metastatic disease involving main airway or blood vessels (e.g. Vena cava tumor invasion or complete occlusion of the major portal vein due to HCC, the major portal vein is defined as the part of portal vein between the union of the splenic and superior mesenteric veins and the first bifurcation into the left and right vein) or high-volume mediastinal tumor mass located in the center (distance from carina <30 mm); 19. History of hepatic encephalopathy; 20. Current interstitial pneumonia or interstitial lung disease, or history of interstitial pneumonia or interstitial lung disease which required hormonal therapy, or other pulmonary fibrosis that may interfere with the judgement and treatment of immune-related pulmonary toxicity; organizing pneumonia (e.g., obliterative bronchiolitis), pneumoconiosis, drug related pneumonitis, idiopathic pneumonia, subjects with evidence on active pneumonia or serious pulmonary function impairment on thoracic computed tomography (CT) in screening period (previous radiation pneumonitis in the radiation area will be allowed); active tuberculosis; 21. Active autoimmune disease or history of autoimmune disease and may relapse (including but not limited to autoimmune hepatitis, interstitial pneumonia, uveitis, enteritis, hypophysitis, vasculitis, nephritis,

	hyperthyroidism, hypothyroidism [with the exception that it can be controlled by hormone replacement therapy]). Subjects with skin disease that do not require systemic treatment are eligible, for example, leukoderma, psoriasis, alopecia; subjects with controlled type 1 diabetes by insulin are eligible; subjects with asthma that has been completely resolved in childhood and don't need any treatment are eligible, but subjects with asthma that require a bronchodilator as medical intervention are not eligible; 22. Use of immunosuppressive medication within 14 days prior to the start of study treatment, or systemic corticosteroid therapy to achieve the objective of immunosuppression (Prednisone at the dose of >10mg/day or equivalent); 23. Use of strong CYP3A4/CYP2C19 inducers, including rifampicin (and its analogues) and St. John's Wort, or strong CYP3A4/CYP2C19 inhibitors within 14 days prior to the start of study treatment; 24. Known history of hypersensitivity to the active substance or to any other components of each investigational medicinal product as SHR-1210, rivoceranib, sorafenib or other monoclonal antibody or targeted anti-angiogenic drug; 25. Severe infection within 4 weeks prior to the start of study treatment, including but not limited to hospitalization for infection, bacteremia or complications of severe pneumonia; oral or intravenous therapeutic antibiotics within 2 weeks prior to the start of study treatment (subjects who are treated with antibiotics for prevention, e.g., preventive urinary tract infection or exacerbation of chronic obstructive pulmonary disease are eligible for participation in the study); 26. Congenital or acquired immunodeficiency (e.g., HIV infection); 27. Hepatitis B and hepatitis C co-infection; 28. Previous treatment with other PD-1 antibody or other immunotherapy against PD-1/PD-L1, or previous use of rivoceranib or sorafenib; 29. Attenuated live vaccine therapy administered within 28 days prior to the start of study treatment, or are expected to receive such vaccines during SHR-1210 treatment or within 60 days after the last dose of SHR-1210; 30. Treatment of other investigational product(s) within 28 days or 5 half-lives (whichever is longer) prior to the

	start of study treatment; 31. Other factors that may affect the study results or lead to early study termination as judged by investigators, such as alcoholism, drug abuse, other serious diseases (including mental disorders) requiring concomitant therapy, with serious laboratory examination abnormality, with family or social factors, that may affect subject's safety.
PK And Immunogenicity Sampling	Immunogenicity and PK measurement will be assessed in the experimental arm only. Pre-dose sampling: blood samples will be collected once within 0.5 hours prior to rivoceranib administration on Day 1 from Cycle 1 to Cycle 4 (C1D1, C2D1, C3D1, C4D1); and collected once within 0.5 hours prior to rivoceranib administration on Day 1 of every 3 cycles afterwards. A blood sample will be collected 30 days (±7 days) after the last administration of SHR-1210. When SHR-1210 is interrupted for longer than 30 days and finally is confirmed to be unable to resume, subjects are required to return for a site visit as early as possible for a blood sample to be collected. If the subject has started other anti-tumor therapy, it's not necessary to collect the immunogenicity blood sample at 30 days (±7 days) after the last administration of SHR-1210. If SHR-1210 and/or rivoceranib is temporarily interrupted, pre-dose immunogenicity and PK sample will be collected on schedule. If only rivoceranib is temporarily interrupted at the sampling time above, and the blood sample should be collected within 0.5 hours before the administration of SHR-1210. The above samples will be used to measure the blood concentration and immunogenicity of SHR-1210, and the plasma concentration of rivoceranib in the C2D1-C4D1 samples. The exact time of the previous administration of rivoceranib (as provided by the subject) will be collected for C2D1, C3D1 and C4D1. ECG blood sampling: ECG examination will be performed 2.5 hours (±1 hour) after the end of the rivoceranib administration, and blood will be collected within 15 minutes after the ECG examination on the first day from C1 to C4. If rivoceranib is interrupted, blood samples within 15 minutes of ECG will not be collected. The samples above will be detected for the concentrations of rivoceranib only. The actual sampling time, the actual administration time of SHR-1210 and rivoceranib will be recorded on the day of sampling. Pre-dose sampling and ECG blood sampling will not be performed in the extension phase (refer to BLOOD SAMPLE COLLECTION TABLE).
Criteria for Study	Discontinuation from study treatment does not represent

Treatment Discontinuation	subject withdrawal from the study. Subjects who discontinue the study treatment should complete the remaining study visits as required in the protocol. Subjects should discontinue study treatment when any of the following conditions occurs: • Subject requests discontinuation of study treatment; • Efficacy evaluation meets disease progression criteria confirmed by BIRC (according to RECIST v1.1) (disease progression will be confirmed by the investigator per RECIST v1.1 upon approval of Protocol v6.0) unless investigator judges that the subject will continue to benefit from the treatment and the criteria for treatment beyond progression is met (see Section 6.6 of the protocol); • Pregnancy in female subject occurs during the study; • Unacceptable toxicity despite dose modification, or occurrence of adverse event, abnormal laboratory examination, or concomitant diseases, then it is no longer in the best interests of the subjects to continue study treatment according to the judgment of the investigator; • Overall deterioration of health status, inability to continue participation in the trial; • Significant protocol deviation or violations confirmed by sponsor, e.g., ineligibility of subjects after enrollment; • Termination of study by the sponsor; • Other reasons for inability to continue study treatment as considered by investigators.
Criteria for Withdrawal from the Study	The reasons for withdrawal from the study may include: • Withdrawal of the informed consent upon participation in the study, and refusal of further follow-up; • Other conditions that necessitate the withdrawal from the study, as considered by investigators, for example, loss of the ability to express his/her wishes freely due to imprisonment or segregation; • Lost to follow-up; • Termination of study by the sponsor.
Criteria for Study Termination	The criteria for termination of this study include but not limited to the following: • Discovery of unexpected, significant or unacceptable risk; • The efficacy data support early termination of the study; • Low compliance with study requirements.

Safety Evaluation	The severity of adverse events will be judged in accordance with CTCAE v4.03. Adverse event (AE) record forms should be filled out during the trial, including the occurrence time, severity, relationship with the study drug, duration, measures taken and outcome of the AE.
Efficacy Evaluation	To evaluate OS (co-primary efficacy endpoint), subjects after study treatment discontinued will have their survival status collected through site visits or telephone follow-up on a regular basis until death. Subject who died during the trial, their actual time of death will be recorded. PFS: defined as the time from the date of randomization to the first occurrence of radiological progression or death, whichever comes first. Evaluations of PFS (another primary efficacy endpoint) as well as TTP, ORR, DCR and DoR (secondary or exploratory efficacy endpoints) will be performed based on RECIST v1.1, mRECIST and imRECIST: From randomization to 48 weeks, the radiological evaluation will be performed once every 8 weeks; once every 12 weeks thereafter; and can be performed in a real-time manner if new lesion is suspected; the tumor response must be confirmed in 4 weeks or at next scheduled timepoint for the subjects who are initially evaluated as PR/CR. When suspected clinical progression occurs, physical examination and confirmation by radiological evaluation should be performed as soon as possible, rather than waiting until the next scheduled imaging examination. When progression of disease is confirmed by investigator according to RECIST v1.1, the investigator must submit the radiological data to BIRC immediately for evaluation of disease progression. If BIRC confirms non disease progression according to RECIST v1.1, the subject should continue with study treatment and tumor radiological evaluation; if BIRC confirms as disease progression according to RECIST V1.1, the investigator should evaluate whether the subject still has clinical benefit, if the subject is considered to have clinical benefit from study treatment and meet criteria for continuation of treatment after the disease progresses (see Section 6.6 for details), the subject may continue study treatment and efficacy assessment as originally scheduled. Tumor radiological assessment should continue until disease progression confirmed by BIRC according to RECIST v1.1 or treatment discontinuation, whichever occurs later. Subjects who discontinue study treatment for reasons other than BIRC-confirmed disease progression (according to RECIST v1.1) must continue with their regular follow-up tumor radiological assessments. Prior to BIRC confirmed disease progression according to the RECIST v1.1 or discontinuation of study treatment, if the subject has withdrawn informed consent,

	started other anti-tumor treatment (except for traditional Chinese medicine), or subject died, no further imaging assessment is required. If subject does not meet the above criteria for stopping radiological assessment, tumor efficacy evaluation of the three efficacy evaluation criteria (RECIST v1.1, mRECIST, imRECIST) needs to continue even if the disease progression under certain efficacy evaluation criteria occurs. Upon approval of Protocol v6.0, disease progression will be confirmed by the investigator per RECIST v1.1, and tumor assessments evaluated by BIRC per mRECIST will not be performed afterwards. If the investigator confirms non-disease progression, the subject should continue on study treatment and tumor radiological evaluation as required; if the investigator confirms as disease progression, the subject may continue to receive study treatment after disease progression at the investigator's discretion (see Section 6.6).
Sample Size Determination	Assuming a 1:1 randomization between sorafenib and SHR-1210+rivoceranib, and a median PFS time of 3.6 months for subjects in the sorafenib group and a median PFS of 6 months for a subject in the combination group, 332 PFS events will be sufficient to detect a hazard ratio (HR) of 0.60 with 98% power based on Log-rank test at significance level of 0.005 one-sided. Similarly, assuming a median survival time of 10.5 months for subjects in the sorafenib group and a median time of 14.6 months for subjects in combination group, 359 OS events will be sufficient to detect a hazard ratio (HR) of 0.72 with 85% power based on Log-rank test at significance level of 0.020 one-sided. Assuming an accrual period of 18 months, total duration of 36 months and 19 months for the OS and PFS, respectively, and probability of subject loss at approximately 10% per 12 months and per 6 months for the OS and PFS respectively, a sample size of 510 subjects will be enrolled for the study. Power and sample calculations were performed using EAST® 6.4.1. software package.
Data Analysis / Statistical Methods	**Efficacy Analyses** The two primary endpoints for the study are OS and PFS (assessed by BIRC based on RECIST v1.1). For the PFS, there is one planned analysis, which is expected to occur when 332 PFS events are observed at ~19 months after first subject enrolled. The OS will be evaluated in the following time points: when PFS is analyzed; when 251 OS events are observed (70% at ~ 23 months after first subject enrolled) and when 359 OS events are observed at 36 months after first subject enrolled. The hypothesis testing of OS and PFS will be evaluated by comparing SHR-1210 plus rivoceranib to sorafenib on events

	in the ITT using a stratified Log-rank test (based on randomization stratification factors). The hazard ratio (HR=SHR-1210 plus rivoceranib / sorafenib) and the corresponding 95% confidence interval (CI) will be estimated in a stratified Cox proportional hazard model with treatment group and randomization stratification factors included in the model. The survival curve for each treatment group will be estimated using the Kaplan-Meier (KM) product-limit method. A 95% CI for median survival time will be estimated by Brookmeyer-Crowley method. Objective response rate (ORR) assessed by BIRC according to RECIST v1.1 will be analyzed as a key secondary endpoint and will be analyzed when 70% OS events are observed. If both PFS and OS primary endpoints are positive, comparison between treatment groups in ORR by BIRC according to RECIST v1.1 will be performed using stratified Cochran-Mantel-Haenszel (CMH) test. Difference in proportions for ORR and its 95% CI using normal approximation will be provided. Overall response rates and their corresponding 95% exact CIs will be calculated by Clopper-Pearson method for each treatment group. The other time-to-event endpoints will be estimated using the Kaplan-Meier (KM) product-limit method, unless specified. A 95% CI for median survival time will be estimated by Brookmeyer-Crowley method, if necessary. For other binary variables, stratified CMH test will be used and two-sided 95% CI for treatment difference will be calculated using normal approximation. **Safety Analyses** Safety data including AEs and laboratory results will be summarized descriptively using summary statistics. **Other Analyses:** Exploratory endpoints including average scores and its change from baseline obtained from EORTC QLQ-C30 and EORTC QLQ-HCC18 will be summarized descriptively using summary statistics. Biomarkers (e.g. the expression level of PD-L1 and proportion of strong expression of PD-L1 in tumor tissue) will be summarized using descriptive statistics, and an *ad hoc* analysis will be performed if required. Population pharmacokinetics, drug exposure-QTc analysis and drug exposure-response relation will be analyzed and reported separately.
End of Study	For this study, end of study is defined as the date when the last subject randomized has been followed for at least 2 years. Subject who are still on treatment at the time of study closure

	will join study extension phase to continue study treatment (Section 6.7).

SCHEDULE OF ACTIVITIES

Item/evaluation time (window period)	**Screening period**			**Treatment period [4] One treatment cycle is 28 days**						**End-of-Treatment Visit [5]**	**Follow-up period**	
	Screening Period [1] (Day -28)	**Screening Period [2] (Day -14)**	**Screening Period [3] (Day -7)**	**Cycle 1**		**Cycle 2, 3**		**Cycle 4 and onwards**			**Safety follow-up [6]** Once every 30 days (±7 days)	**Survival follow-up [7]** Once every 30 days (±7 days)
				D1	**D15**	**D1**	**D15**	**D1**	**D15**			
					(±3 days)	(±3 days)	(±3 days)	(±3 days)	(±3 days)			
Baseline data												
Signature of informed consent form [8]	√											
Determination of inclusion / exclusion criteria	√	√	√									
Demographics	√											
Tumor History [9]	√											
Other past medical history [10]	√											
Laboratory examination, clinical examination/evaluation												

Item/evaluation time (window period)	**Screening period**			**Treatment period [4] One treatment cycle is 28 days**						**End-of-Treatment Visit [5]**	**Follow-up period**	
	Screening Period [1] (Day -28)	**Screening Period [2] (Day -14)**	**Screening Period [3] (Day -7)**	**Cycle 1**		**Cycle 2, 3**		**Cycle 4 and onwards**			**Safety follow-up [6]** Once every 30 days (±7 days)	**Survival follow-up [7]** Once every 30 days (±7 days)
				D1	**D15**	**D1**	**D15**	**D1**	**D15**			
					(±3 days)	(±3 days)	(±3 days)	(±3 days)	(±3 days)			
Child-Pugh class [11]			√			√		√		√	√	
ECOG-PS score [12]		√		√		√		√		√	√	
Physical examination [13]		√		√	√	√	√	√	√	√	√	
Vital signs [14]		√		√	√	√	√	√	√	√	√	
Virology [15]		√				√		√		√		
Hematology [16]			√		√	√	√	√		√	√	
Urinalysis [17]			√		√	√	√	√		√	√	
Fecal occult blood [18]		√				√		√		√		
Blood biochemistry [19]			√		√	√	√	√		√	√	
Blood electrolytes [20]			√		√	√	√	√		√	√	
Archive tumor tissue sample (or fresh biopsy sample) [21]	√											

Item/evaluation time (window period)	**Screening period**			**Treatment period [4] One treatment cycle is 28 days**						**End-of-Treatment Visit [5]**	**Follow-up period**	
	Screening Period [1] (Day -28)	**Screening Period [2] (Day -14)**	**Screening Period [3] (Day -7)**	**Cycle 1**		**Cycle 2, 3**		**Cycle 4 and onwards**			**Safety follow-up [6]** Once every 30 days (±7 days)	**Survival follow-up [7]** Once every 30 days (±7 days)
				D1	**D15**	**D1**	**D15**	**D1**	**D15**			
					(±3 days)	(±3 days)	(±3 days)	(±3 days)	(±3 days)			
Coagulation parameters [22]			√			√		√		√	√	
AFP [23]		√				√		√		√	√	
Thyroid function [24]		√				√		√		√	√	
12-lead ECG [25]		√		√	√	√		√		√	√	
Echocardiography [26]		√		If required by clinical judgement								
Blood HCG test [27]			√	If required by clinical judgement						√	√	
Concomitant medications / therapy [28]	√	√	√	√								
Collection of AE [29]	√	√	√	√								
Radiological assessment, PK and immunogenicity												
Tumor imaging evaluation [30]	√			√						√	√	√

Item/evaluation time (window period)	**Screening period**			**Treatment period [4] One treatment cycle is 28 days**						**End-of-Treatment Visit [5]**	**Follow-up period**	
	Screening Period [1] (Day -28)	**Screening Period [2] (Day -14)**	**Screening Period [3] (Day -7)**	**Cycle 1**		**Cycle 2, 3**		**Cycle 4 and onwards**			**Safety follow-up [6]** Once every 30 days (±7 days)	**Survival follow-up [7]** Once every 30 days (±7 days)
				D1	**D15**	**D1**	**D15**	**D1**	**D15**			
					(±3 days)	(±3 days)	(±3 days)	(±3 days)	(±3 days)			
Pre-dose sampling [31]				√		√		√			√	
ECG blood sampling [32]				√		√		√*				
Study treatment												
Randomization [33]				√								
Intravenous infusion of SHR-1210				√	√	√	√	√	√			
Oral administration of rivoceranib				√ continuous oral administration								
Oral administration of sorafenib				√ continuous oral administration								
Other												
Distribution, verification and return of subject's diary [34]				√	√	√	√	√	√	√		

Item/evaluation time (window period)	**Screening period**			**Treatment period [4] One treatment cycle is 28 days**						**End-of-Treatment Visit [5]**	**Follow-up period**	
	Screening Period [1] (Day -28)	**Screening Period [2] (Day -14)**	**Screening Period [3] (Day -7)**	**Cycle 1**		**Cycle 2, 3**		**Cycle 4 and onwards**			**Safety follow-up [6]** Once every 30 days (±7 days)	**Survival follow-up [7]** Once every 30 days (±7 days)
				D1	**D15**	**D1**	**D15**	**D1**	**D15**			
					(±3 days)	(±3 days)	(±3 days)	(±3 days)	(±3 days)			
Subject's self-evaluation results [35]				√		√		√		√	√	
Survival follow-up											√	√
Subsequent antitumor therapy											√	√

Note: Except the test items and time points listed in the table, the investigator may add necessary examinations at any time. The test results will be filled in the section of "Examinations at Unscheduled Visits" in the CRF.

[1] Screening period (Day -28): baseline data will be collected after signature of informed consent form and no longer than 28 days before start of study drug; if routine radiological evaluation of tumor has been performed prior to signature of the informed consent, it is unnecessary to repeat these scans during screening period in cases where these enhanced CTs or MRIs are completed within 28 days prior to the start of study drug (bone scan within 42 days prior to the start of study drug is acceptable). All baseline evaluations will be based on the results collected closest to the start of study drug.

[2] Screening period (Day -14): physical examination, vital signs, ECOG-PS score and laboratory examinations (including fecal occult blood, thyroid function, alpha- fetoprotein, and virology), 12-lead ECG and echocardiography (including LVEF) to be collected within 14 days prior to the first dose, following the signature of informed consent form. All baseline evaluations will be based on the results collected closest to the start of study drug.

[3] Screening period (Day -7): following the signature of informed consent form, data on hematology, urinalysis, blood chemistry, blood electrolytes, coagulation parameters, blood HCG (for women of childbearing potential) and Child-Pugh class must be collected within 7 days prior to the first dose. All baseline evaluations will be based on the results collected closest to the start of study drug. Subjects with screening failure can be re-screened. They must sign the informed consent form again, re-register and obtain a new subject number at the re-screening. Subjects can only be re-screened once.

[4] Treatment period: data on hematology, urinalysis, blood chemistry and blood electrolytes will be evaluated within 72h prior to administration of study drug during the scheduled visit; ECOG-PS score, physical examination and vital signs will be evaluated within 24h prior to administration of study drug during the scheduled visit (they are not needed on C1D1 in cases where they are completed within 24h prior to the first dose during the screening period). In the event of a dose delay, the required examinations at each corresponding visit during study treatment should be scheduled as planned or more frequently if clinically indicated (Immunogenicity, concentrations of SHR-1210 and rivoceranib, and patient reported outcomes should be collected at respective treatment cycles as specified in Footnotes [31] [32] [35]).

[5] End-of-treatment visit: Only after permanent discontinuation of both drugs (SHR-1210 and rivoceranib), the end-of-treatment visit shall start. End-of-treatment visit includes ECOG performance, C-P score, vital sign, physical examination, 12-lead ECG, hematology, urinalysis, blood biochemistry, blood electrolytes, coagulation, thyroid function, fecal occult blood test, virology, APF, HCG, subject's self-evaluation and tumor imaging evaluation. If tumor imaging evaluation completed within 4 weeks prior to end-of-treatment visit, or the other examinations of end-of-treatment visit completed within 7 days, then these study procedures would not be necessary to be repeated. For subjects who enter the extension phase after the end of study, all of the subject's data occurring prior to extension phase need to be captured into CRFs and EOT visit needs to be performed even the subjects continue on study treatment (detailed instruction for data entering, refer to CRF completion guideline), the EOS page in CRFs for extension subjects should be collected as well before entering the extension phase. If planned schedule visit occurred within 7 days before the time of extension phase initiation or the relevant examinations for end of treatment visit completed within 7 days, these study procedures would not be necessary to be repeated on EOT.

[6] Safety follow-up: Subject who completed end-of-treatment visit (after permanent discontinuation of both drugs) will have safety follow-up after last dose. It will end 90 days after the last dose of SHR-1210 (non-serious AE unrelated to study drug will only be collected for 30 days after the last dose) or 30 days after the last dose of rivoceranib in experimental arm (whichever comes later); and 30 days after the last dose of study drug in sorafenib (control) arm. The first safety follow-up should start 30 days (±7 days) after the last dose of study drug and must be performed at the study center, regardless of initiation of new antitumor therapy. A telephone visit will be performed 60 days (±7 days) and 90 days (±7 days) after the last dose of study drug in the experimental arm for survival status, subsequent antitumor therapy, concomitant

medications/therapy and AEs/SAEs collection (see Section 8.3 for details). When developing a safety follow-up plan, ensure that a visit is scheduled at this point in the safety follow-up period. If the date of the previously completed end-of-treatment visit has exceeded the safety follow-up period, there is no need to schedule a safety follow-up. For the subjects in experimental arm, if the date of completed end-of-treatment visit has exceeded the first safety follow-up (30 days after the last dose), but the safety follow-up period has not been reached, the subject does not need to go to the site for safety follow-up, and 1-2 telephone visits can be scheduled during the safety follow-up period. At this time, ensure that the interval between visits should not exceed 44 days, and a telephone visit should be conducted at this time point of the safety follow-up period.

[7] Survival follow-up: the subject will enter survival follow-up period after the end of safety follow-up period. the telephone follow-up will be performed 30 days (±7 days) after last safety follow-up for the first survival follow-up, after that, the frequency was once every 30 days (±7 days), collecting of data on survival and subsequent antitumor treatment.

[8] Signature of informed consent form: the informed consent on enrollment into this study needs to be completed during screening period. Prior to acquisition of the written informed consent form, no screening procedures specified in the study can be performed; there are special provisions on the baseline radiological examination of tumor, please refer to the note in radiological evaluation for tumors in this flow chart for details. Subjects with screening failure prior to treatment are allowed to have another opportunity for screening in this study and must repeat the informed consent and register again for a new subject number at re-screening.

[9] Tumor history: including previous history of HCC, history of present illness, initial diagnosis, pathological diagnosis, data on radiological examination, course of treatment (e.g., surgery, interventional therapy, local ablation, and radiotherapy).

[10] Other medical history: including history of drug allergy, history of diagnosis and treatment for other significant concomitant disease, history of tumors except hepatocellular carcinoma, and history of alcohol consumption etc.

[11] Child-Pugh class: will be performed within 7 days prior to the first dose during the screening period, on Day 1 of each cycle in Cycles ≥ 2 during the treatment period, at end-of-treatment visit and safety follow-up.

[12] ECOG-PS score: will be performed within 14 days prior to the first dose during the screening period, prior to administration on Day 1 of the subsequent cycles of therapy, at end-of-treatment visit and safety follow-up.

[13] Physical examination: including height (only for initial examination), body weight, head and face, skin system, lymph nodes, eyes (sclera, pupil), otolaryngology, mouth, respiratory system, cardiovascular system, abdomen, genitourinary system, musculoskeletal system, neurological and mental status. A full physical examination will be performed in the screening period, and only body weight and important sites (including skin, respiratory system, cardiovascular system, abdomen and mental state) will be examined during the study. Physical examination will be performed within 14 days prior to first dose during the treatment period (experimental arm: prior to administration on Day 1 and 15 of each cycle of therapy; control arm: prior to administration on Day 1 and 15 of each cycle in Cycle 1-3, prior to administration only on Day 1 from Cycle 4), at end-of-treatment visit and safety follow-up. Note: except for the physical examination during the screening period and end-of-treatment visit, it is not necessary to record complete results of physical examination in the eCRF during the trial, and only weight and abnormal results need to be recorded. In addition, physical examination of reactive capillary endothelial proliferation needs to be performed in the experimental arm, occurrence sites, such as the skin, oral mucosa, nasal mucosa, etc., should be recorded in the eCRF in detail. Reactive capillary endothelial proliferation will be followed up until it is resolved, other reasonable time points (e.g., loss of follow-up, death), or reached to a stable state without any expectation of recovery.

[14] Vital signs (5 minutes after resting state/sitting still): including temperature (whenever possible, the same method of measurement should be used throughout), blood pressure (which needs to be measured and recorded at least twice to get the mean value as the blood pressure value), pulse rate and respiratory frequency. Vital signs will be performed within 14 days prior to first dose, during the treatment period (experimental arm: prior to administration on Day 1 and 15 of each cycle of therapy; control arm: prior to administration on Day 1 and 15 of each cycle in Cycle 1-3, prior to administration only on Day 1 from Cycle 4), at end-of-treatment visit and safety follow-up.

[15] Virology: HIV-Ab (screening period only), HBV and HCV test should be included. Screening period: all subjects will be required for HBV serology test by five hepatitis B markers (HBsAg, HBsAb, HBcAb, HBeAg, HBeAb), HBV-DNA will be quantified if the HBsAg or HBcAb test is positive. All subjects will be required for HCV-Ab test, and HCV-RNA will be quantified if the HCV-Ab test is positive. Treatment period and end-of-treatment visit: Five hepatitis B markers (HBsAg, HBsAb, HBcAb, HBeAg, HBeAb) and HBV-DNA needs to be detected every two cycles of therapy (starting C3D1, C5D1, C7D1, etc.) for subjects with positive HBsAg or HBcAb at screening; HCV-RNA needs to be detected every two cycles of therapy (starting C3D1, C5D1, C7D1, etc.) for subjects with positive HCV-Ab at screening .

[16] Hematology: including complete blood count and category (white blood cell, red blood cell, lymphocyte, monocyte, neutrophil, basophil, eosinophil), hemoglobin, platelet count. CBC will be performed within 7 days prior to first dose, during the treatment period (prior to study drug administration on Day 1 of each cycle in Cycles 2-3 and on Day 15 of each cycle in Cycles 1-3, prior to administration only on Day 1 of each cycle in Cycles ≥ 4), at end-of-treatment visit and safety follow-up.

[17] Urinalysis: white blood cell, red blood cell, urine protein should be included. If urine protein level ≥ 2＋ is detected, 24h urine protein quantification must be added. Urinalysis will be performed within 7 days prior to first dose, during the treatment period (prior to study drug administration on Day 1 of each cycle in Cycles 2-3 and on Day 15 of each cycle in Cycles 1-3, prior to administration only on Day 1 of each cycle in Cycles ≥ 4), at end-of-treatment visit and safety follow-up.

[18] Fecal occult blood: If fecal occult blood test is positive during the trial, the result must be evaluated by investigators, and gastroscopy will be performed if necessary. Fecal occult blood will be performed within 14 days prior to first dose, on Day 1 of each cycle in Cycles ≥ 2 and at the end of study.

[19] Blood biochemistry: hepatic function (ALT, AST, total bilirubin, ALP, γ-glutamyl transferase [GGT], direct bilirubin), renal function (blood urea nitrogen [BUN] or urea, creatinine), albumin, amylase (lipase must be detected additionally if amylase is abnormal and clinically significant), blood glucose, LDH should be included. Blood chemistry will be performed within 7 days prior to first dose, during the treatment period (prior to study drug administration on Day 1 of each cycle in Cycles 2-3 and on Day 15 of each cycle in Cycles 1-3, prior to administration only on Day 1 of each cycle in Cycles ≥ 4), at end-of-treatment visit and safety follow-up.

[20] Blood electrolytes: potassium, sodium, calcium, phosphorus, magnesium, chlorine should be included. Blood electrolytes will be detected within 7 days prior to first dose, during the treatment period (prior to study drug administration on Day 1 of each cycle in Cycles 2-3 and on Day 15 of each cycle in Cycles 1-3, prior to administration only on Day 1 of each cycle in Cycles ≥ 4), at end-of-treatment visit and safety follow-up.

[21] If archived tumor tissue samples were collected at different time points, the sample collected just prior to participation on this study should be provided. The specific guidance on collection and shipment of tumor tissue is provided in the Laboratory Manual.

[22] Coagulation parameters: INR and/or PT (if INR can not be collected, PT will be used as judgment basis). Coagulation parameters will be performed within 7 days prior to first dose, on Day 1 of each cycle in Cycles ≥ 2 during the treatment period, at end-of-treatment visit and safety follow-up.

[23] AFP will be evaluated within 14 days prior to the first dose, on Day 1 of each cycle in Cycles ≥ 2 during the treatment period, at end-of-treatment visit and safety follow-

up.

[24] Thyroid function: TSH, FT3 or TT3, FT4 should be included. Thyroid function will be performed within 14 days prior to the first dose, once every two cycles during the treatment period, at end-of-treatment visit and safety follow-up.

[25] 12-lead ECG (following resting state/sitting still for at least 5 minutes): heart rate and QTc interval (calculated by Fridericia formula: QTcF = QT/(RR^0.33), RR is the normalized heart rate and is calculated as 60 divided by heart rate). If QTc interval is abnormal, QTc needs to be measured for three consecutive times at an interval of approximately two minutes apart;
QTc needs to be re-tested if:
- at baseline: male > 450 ms, female > 470 ms, retest 2 times and take the mean value;
- after enrollment: same as baseline, or longer than the baseline average ≥ 30 ms.

Experimental arm: The 12-lead ECG will be performed within 14 days prior to first dose in screening period, 2.5 (±1) hours post dose at each of the following days: C1D1, C1D15, D1 of Cycles 2 and afterwards, and at end-of-treatment visit and safety follow-up. When the ECG collection day is coincident with the PK collection day, time matched ECG and PK samples (within 15 minutes apart, ECG collection first) will be collected. Control arm:14 days prior to first dose in screening period, C1D1, C1D15, D1 of Cycles 2 and afterwards, and at end-of-treatment visit and safety follow-up.

[26] Echocardiography must include LVEF and can be scheduled at the investigator's discretion during the study.

[27] Blood HCG test: only for women of childbearing potential (WOCBP, any woman who has experienced menarche, has not undergone a hysterectomy, ligation of bilateral fallopian tubes or bilateral oophorectomy, and is not post-menopausal). (See definition of menopausal in Section 4.4.1) Blood HCG will be performed within 7 days prior to the first dose, at end-of-treatment visit and safety follow-up.

[28] Collection of concomitant medication/therapy: collect concomitant medication/therapy information (drugs excluding solvents) from 28 days prior to the signing of the informed consent form to the end of safety follow-up: record drug names, drug dosage, route of administration, frequency of administration, purpose of administration, and date of start and end. After the safety follow-up period, only record medication/therapy that is used to manage the study drugs related AE/SAE. Please refer to Section 5.3 (Concomitant therapy) of the protocol for details.

[29] Collection of AE: in accordance with NCI-CTCAE v4.03, AEs are observed and recorded from the signature of informed consent form, until 90 days after the last dose of SHR-1210, or 30 days after the last dose of anti-angiogenesis targeted therapy, whichever comes later. For specific AE collection periods, please refer to Section 8.3, Table of AE/SAE Collection Period. An AE/SAE will be followed up until it is resolved, returns to the baseline level or ≤ Grade 1, or reaches a stable state, or until other reasonable time points (e.g., loss of follow-up, death). Every effort should be made to ensure that the subject achieves the final outcome and definite causality assessment is obtained.

[30] Tumor radiological evaluation: all the evaluable tumor lesions should be evaluated and recorded based on RECIST v1.1 (evaluated by investigator and BIRC), mRECIST (evaluated by BIRC only) and imRECIST (evaluated by investigator only). The baseline evaluation includes the enhanced CT/MRI scan of chest, abdomen, pelvis and sites of lesions, brain enhanced MRI or enhanced CT scan (to exclude intracranial metastasis). Thoracic plain CT scan + abdominal, pelvic and brain MRI can be performed in case of allergy to the contrast agent for enhanced CT; bone scan will be performed only when clinically indicated. Tumor radiological evaluation during treatment period will be performed once every 8 weeks (56±7 days) within the first 48 weeks from randomization and once every 12 weeks (84±7 days) thereafter and can be additionally performed when clinically indicated. When there is no clear disease progression, tumor evaluation should be continued regardless of discontinuation

of study treatment, unless death, withdrawal of informed consent, start of subsequent anticancer therapy or termination of study by the sponsor, whichever comes first; the evaluation includes the enhanced CT/MRI scan of chest, abdomen, pelvis and sites of lesions. Thoracic plain CT scan + abdominal and pelvic MRI can be performed in case of allergy to the contrast agent for enhanced CT; cranial CT/MRI and bone scan will be performed only when clinically indicated. The same radiological technique should be used in each subject throughout the study. Investigators must review the results prior to administration in the next cycle. After first documentation of response (CR or PR), confirmation of tumor response should occur at 4 weeks after the first response or at the next scheduled assessment time point. When a subject develops a disease progression as assessed by the investigator according to RECIST v1.1, the investigator is required to submit radiological data immediately to BIRC. If BIRC confirms non-disease progression according to RECIST v1.1, the subject should continue to receive study drug therapy and continue to perform tumor radiological assessment; if BIRC confirms disease progression according to RECIST v1.1, then the investigator needs to assess whether the subject still has clinical benefit, and if the subject is still considered to have clinical benefit and meets the criteria for continued treatment after progression of the disease (see Section 6.6 for details), the subject may continue to receive study medication and continue the efficacy assessment at the scheduled frequency. Tumor radiological assessment will continue until the occurrence of disease progression confirmed by BIRC according to RECIST v1.1 criteria or study treatment discontinuation, whichever occurs later. Before BIRC confirms the disease progression according to the RECIST v1.1 criteria or the treatment is discontinued, if the subject withdraws the informed consent, other anti-tumor treatment has begun (except for traditional Chinese medicine), or the subject dies, there is no need to continue the radiological evaluation. If the subject does not meet the above criteria for stop radiological assessment, the efficacy evaluation of the three efficacy evaluation criteria (RECIST v1.1, mRECIST, imRECIST) needs to continue even if the disease progression under certain efficacy evaluation criteria occurs. If there has not been any disease progression confirmed by a radiological examination when the subject is about to withdraw from the study, it is recommended that a radiological examination be performed in time before the withdrawal (if the time from the last radiological examination to the withdrawal is ≤ 4 weeks, additional radiological examination will not be required at the time of withdrawal). Detailed requirements for image collection will be described in image acquisition guideline. Disease progression will rely on the investigator's confirmation per RECIST v1.1 upon approval of protocol v6.0, and radiological data will not be submitted to BIRC anymore, tumor assessment evaluated by BIRC per mRECIST will not be performed afterwards. If the investigator confirms non-disease progression, the subject should continue on study treatment and tumor radiological evaluation as required; if the investigator confirms as disease progression, the subject may continue to receive study treatment after disease progression at the investigator's discretion (see Section 6.6).

[31] Pre-dose sampling: only the blood sample in the experimental arm will be collected (including SHR-1210 combined with rivoceranib, SHR-1210 monotherapy or rivoceranib monotherapy) on Day 1 of Cycle 1-4 (C1D1, C2D1, C3D1 and C4D1) and once on Day 1 of every three cycles thereafter (The time point for sample collection will be within 0.5 hours prior to administration of rivoceranib); on 30 days (±7 days) after the last dose of SHR-1210. When SHR-1210 is interrupted for longer than 30 days and is confirmed to be unable to resume, the subject is required to come for a site visit and collect blood sample. If the subject has started other anti-tumor therapy, it's not necessary to collect the immunogenicity blood sample at 30 days (±7 days) after the last administration of SHR-1210. If SHR-1210 and/or rivoceranib is temporarily interrupted, pre-dose immunogenicity and PK sample will be collected on schedule. If only rivoceranib is interrupted, the time of sampling is 0.5 hours prior to SHR-1210 administration. On C1D1 approximately 6 mL venous blood will be collected for detection of the serum concentration and immunogenicity of SHR1210; On C2D1, C3D1 and C4D1 approximately 8mL venous blood will be collected, 6 mL will be used for detection of the serum concentration and immunogenicity of SHR-1210, and 2 mL will be used for detection of plasma concentration of rivoceranib. The exact time of the previous administration of rivoceranib concentration will be collected (provided by the subject). Approximately 6 mL venous blood will be collected for detection of the serum concentration and immunogenicity of SHR1210 at the later time points (e.g., C7D1, C10D1 etc.). Pre-dose sampling will not be performed in the extension phase. [See BLOOD SAMPLE COLLECTION TABLE for details]

[32] ECG blood sampling: ECG examination will be performed 2.5 hours (±1 hour) after the end of the rivoceranib administration, and blood will be collected within 15 minutes after the ECG examination on the first day from Cycle 1 to Cycle 4. If the rivoceranib is temporarily interrupted, a blood sample within 15 minutes after ECG

will not be collected. 2 mL venous blood will be collected at each time point for the concentration of rivoceranib. ECG blood sampling will not be performed in the extension phase. [See BLOOD SAMPLE COLLECTION TABLE for details].

[33] Randomization: subjects will be randomized into either the experimental arm or control arm after their data are reviewed and determined to be in accordance with the inclusion/exclusion criteria, and the first dose should be given within 24 hours following randomization (on Day 1 of Cycle 1).

[34] Distribution, verification and return of subject's medication diary: in the experimental arm at D1 and D15 of each cycle, in the control arm, at D1 and D15 of Cycles 1-3, and D1 for every cycle thereafter. On C1D1, only distribution is needed. At the end-of-treatment visit, distribution of diary is not needed but verification and return are required.

[35] Subject's self-evaluation results: all subjects will complete EORTC QLQ-C30 (version 3.0), EORTC QLQ-HCC18 and EQ-5D-5L questionnaires prior to administration of study drug and any study procedure at the clinical center, starting from C1D1 and on D1 of each cycle onward. In addition, all subjects are required to complete the questionnaires at the end-of-treatment visit and during the first safety follow-up visit. Before the subject leaves the site, the study staff should review all the questionnaires for completeness.

BLOOD SAMPLE COLLECTION TABLE

	Visit period	Day	Pre-dose sampling		ECG blood sampling
			Blood sample for detection of immunogenicity and serum concentration of SHR-1210（6 mL）[6]	Blood sample for detection of concentration of rivoceranib (2 mL) [1]	Blood sample for detection of concentration of rivoceranib （2 mL）
			Before rivoceranib administration [2]		Within 15 minutes after ECG and 2.5 hours (±1 hour) after rivoceranib administration [3]
Treatment period （28 days for 1 cycle）	Cycle 1	C1D1	√		√
	Cycle 2-4	D1（±3 days）	√	√	√
	Every 3 cycles after Cycle 4 （e.g. Cycle7, Cycle 10 etc.）[4]	D1（±3 days）	√		

30 days after last dose of SHR-1210 （±7 days） [5]			√		

[1] To collect the dose time and sampling time of rivoceranib on the sampling day. It is necessary to collect the exact time of previous administration of rivoceranib, i.e. the day before the blood collection (the subject is required to provide it). If rivoceranib is temporarily interrupted on the day before the blood collection, it is necessary to collect the exact time of the dose of rivoceranib closest from this blood collection (the subject is required to provide it).

[2] If SHR-1210 and/or rivoceranib is temporarily interrupted, pre-dose immunogenicity and PK sample will be collected on schedule. If only rivoceranib is temporarily interrupted, the time point for collection is within 0.5 hours before the administration of SHR-1210.

[3] If rivoceranib is temporarily interrupted, blood samples within 15 minutes of ECG will not be collected. To collect the dose time and sampling time of rivoceranib on the sampling day.

[4] Collection on Day 1 of every 3 cycles (within 0.5 hours before the administration of rivoceranib). If rivoceranib is temporarily interrupted, the time point for collection is within 0.5 hours before the administration of SHR-1210. Blood sampling will not be performed in the extension phase.

[5] Collected once 30 days (±7 days) after the last SHR-1210 administration; If SHR-1210 is temporarily interrupted, and it is subsequently confirmed that the subject is unable to continue treatment, and it is more than 30 days since the last dose, the subject is required to return for site visit as soon as possible and collect blood samples at the same time. If the subject has started other anti-tumor therapy, it’s not necessary to collect the immunogenicity blood sample at 30 days (±7 days) after the last administration of SHR-1210. Blood sampling will not be performed in the extension phase.

[6] To collect the dose time and sampling time of SHR-1210 on the sampling day.

ABBREVIATIONS

Abbreviations	Definition
5 on 2 off	5 days on 2 days off
AASLD	American Association for the Study of Liver Diseases
AE	adverse event
ADA	antidrug antibody
AFP	alpha-fetoprotein
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARB	Angiotensin II receptor blocker
AST	aspartate aminotransferase
AUC	area under the concentration time curve
BCLC	Barcelona Clinic Liver Cancer
BCRP	breast cancer resistance protein
BID	twice daily
BIRC	Blinded Independent Review Committee
BOR	best overall response
BUN	blood urea nitrogen
CCR	Clinical Cancer Research
CI	Confidence interval
CK	creatine kinase
CMH	Cochran-Mantel-Haenszel
C_{max}	maximum concentration
Cr	creatinine
CT	computed tomography
CTLA4	cytotoxic T lymphocyte antigen 4
CYP	Cytochrome P450
D	Day
DCR	disease control rate
DMC	Data monitoring committee
DNA	deoxyribonucleic acid
DoR	duration of response
eCRF	electronic case report form
ECG	Electrocardiogram
ECOG-PS	Eastern Cooperative Oncology Group- Performance Status
EDC	electronic data capture
EORTC	European Organization for the Research and Treatment of Cancer
EQ-5D-5L	five-level of EuroQol-5D version
ESMO	European Society for Medical Oncology
FAS	Full analysis set
FSH	Follicle-stimulating hormone
G-CSF	granulocyte colony-stimulating factor
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
GHS	general health status

Abbreviations	Definition
h	hour
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	hepatocellular carcinoma
HCG	human chorionic gonadotropin
HCV	Hepatitis C virus
HDL-C	high-density lipoproteincholesterol
HIV	human immunodeficiency virus
HR	Hazard ratio
ICC	intrahepatic cholangiocarcinoma
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
imRECIST	immune-modified RECIST
INN	international nonproprietary name (for pharmaceutical substances)
INR	international normalized ratio
ITT	Intent-to-treat
IRB	Institutional Review Board
ITT	Intent-to-treat
LEU	leukocytes in urine
LVEF	left ventricular ejection fraction
IU	international unit
LDH	lactate dehydrogenase
LSLV	last subject last visit
LYMPH	lymphocyte
MATE	multidrug and toxin extrusion protein
MFD	maximum feasible dose
mRECIST	modified RECIST
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI-CTCAE v4.03	National Cancer Institute - Common Terminology Criteria for Adverse Events Version 4.03
NMPA	National Medical Products Administration
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed death-l
PFS	progression-free survival
P-gp	P-glycoprotein
PPI	proton pump inhibitor
PT	prothrombin time
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-HCC	Quality of Life Questionnaire-Supplement Module for HCC

Abbreviations	Definition
RCEP	Reactive Capillary Endothelial Proliferation
RCCEP	Reactive Cutaneous Capillary Endothelial Proliferation
RECIST v1.1	Response Evaluation Criteria in Solid Tumors
RO	receptor occupancy
SAE	serious adverse event
SIE	AE of special interest
SRO	subject reported outcome
SS	safety set
TBIL	total bilirubin
TEAE	Treatment Emergent Adverse Events
TTD	time to deterioration
TTP	time to progression
ULN	Upper limit of normal
VAS	visual analogue scale
WOCBP	women of childbearing potential

1. INTRODUCTION: BACKGROUND AND SCIENTIFIC RATIONALE

1.1. Study Background

1.1.1. Epidemiology and Current Treatment Status of Hepatocellular Carcinoma

Primary Carcinoma of the Liver is referred to as liver carcinoma. Primary Carcinomas of the Liver mainly include three different pathological types of Hepatocellular Carcinoma (HCC), Intrahepatic Cholangiocarcinoma (ICC), and the mixed HCC-ICC, in which HCC accounts for 90% [1]. According to data from GLOBOCAN 2012, liver carcinoma is the sixth most common cancer, with about 782,500 new cases of liver carcinoma and 745,500 deaths worldwide annually, ranking it second in the cause of death amongst male tumors worldwide [2].

The majority of HCC cases (> 80%) occur in Eastern Asia and sub-Saharan Africa, with incidence rates of > 20 per 100,000 individuals, followed by Southern European countries, such as Spain, Italy and Greece, with an incidence of 10 to 20 cases per 100,000 populations. HCC incidence is relatively lower in North America, South America, Northern Europe and Oceania (< 5 / 100,000) [3].

China is a high-risk area for liver carcinoma, with morbidity and death accounting for about 50% of the world [2]. In 2015, there were 466,100 new subjects with liver carcinoma, the fourth most common tumor, and 422,100 deaths in China. Liver carcinoma ranks the third as cause of death in China, and it ranks third in males (12.72%) and seventh in females (5.68%) [4].

The main risk factors for HCC are infection with HBV and hepatitis C virus (HCV), vinyl chloride, alcohol abuse, and nonalcoholic fatty liver; in addition, the rare causes include hereditary hemochromatosis, α-antitrypsin deficiency and autoimmune hepatitis [5]. HBV and HCV infection account for 80%~90% of total HCC cases worldwide. Chronic HBV infection is a major risk factor for HCC in most Asian regions except Japan[3],while chronic HCV infection is a major risk factor for HCC in Japan[6]. In China, up to 80% of HCC is hepatitis B virus (HBV)-related HCC [7]. A considerable proportion of subjects are already in advanced stage at diagnosis or cannot undergo surgery or local treatment due to underlying liver diseases such as combined cirrhosis.

The different treatments of HCC are selected according to disease staging, which is mainly based on BCLC staging system, Child-Pugh liver function classification system and disease degree. About 30% of HCC cases are diagnosed at an early stage (that is, BCLC stage 0 or A), and the main treatments include surgical resection, ablation technique and liver transplantation. But the 5-year recurrence rate is still as high as 70% [8].

The recommended treatment for mid-stage HCC (BCLC stage B) is hepatic artery interventional therapy, that is, transcatheter arterial chemoembolization (TACE), but the application scope is limited due to concomitant disease and liver function damage, and the subject will eventually experience progression after treatment and is no longer suitable for further TACE treatment.

The treatment options available for advanced HCC (also known as BCLC stage C) are very limited, and sorafenib, an oral multi-target inhibitor, is the first targeted drug approved globally for HCC first-line systemic treatment. Recently, the FDA approved the second oral multi-kinase inhibitor lenvatinib for the first-line treatment of advanced HCC, which has not been widely used. In addition to the above two types of targeted therapy, the first-line standard of care of HCC also includes oxaliplatin-based chemotherapy, which is also used as the first-line treatment in some regions.

1.1.2. Advances in the Treatment of Advanced Hepatocellular Carcinoma

For advanced hepatocellular carcinoma, the available treatment options are very limited. Sorafenib is an oral multi-target inhibitor (VEGFR-1, -2, -3, PDGFR, c-KIT, etc.) that directly blocks the formation of neovascularization and inhibits tumor growth. It is the first FDA-approved targeted drug for HCC first-line systemic treatment. This approval was based on the positive results from the SHARP and ORIENTAL trials. The efficacy and safety of sorafenib and placebo were compared in the treatment of advanced HCC. The results showed that the survival and safety of subjects in the sorafenib group were significantly improved compared with those in the placebo group.

The SHARP study was a randomized, phase 3 study in western populations, in which sorafenib increased progression free survival (PFS) (median: 5.5 months and 2.8 months, respectively) by 73% and overall survival (OS) (median: 10.7 months and 7.9 months, respectively) by 44% compared with placebo. ORIENTAL, another randomized phase 3 study conducted in Asian populations similar to the SHARP study in design, had the same results, increasing overall survival (OS) by 2.3 months (median OS: 6.5 months and 4.2 months, respectively)[9, 10].

In addition, the results of the phase 3 non-inferiority study on the efficacy and safety of lenvatinib (developed by Eisai) versus sorafenib in the first-line treatment of subjects with unresectable HCC (REFLECT trial [11]) showed, lenvatinib achieved the primary endpoint, demonstrating that the median OS with lenvatinib was non-inferior to that with sorafenib. Subjects treated with lenvatinib experienced a median OS of 13.6 months compared to 12.3 months with sorafenib (Hazard Ratio [HR]: 0.92); In terms of secondary endpoints, lenvatinib seemed significantly superior to sorafenib in median PFS (7.4 months vs 3.7 months), median TTP (8.9 months vs 3.7 months) and ORR (24% vs 9%). In terms of safety, the incidence of adverse events (AE) was similar in the two groups. At the 2017 CSCO Annual Meeting, Professor Qin Shukui published the data analysis results of the Asian subgroup of the trial. A total of 288 subjects were enrolled. The lenvatinib and the sorafenib groups were compared in the median PFS (9.2 months vs 3.6 months), median TTP (11 months vs 3.7 months), and ORR (21.5% vs 8.3%), showing that lenvatinib was more effective for subgroups of subjects in China's mainland, Taiwan and Hong Kong and will become a new treatment option for subjects with unresectable advanced HCC worldwide. Based on REFLECT study, lenvatinib was approved by FDA as the second first-line treatment for advanced HCC following sorafenib.

In addition to the two approved targeted therapies, Oxaliplatin-based chemotherapy is also the standard first-line treatment in some areas. The EACH study was a prospective, randomized, controlled phase 3 international clinical study of Oxaliplatin-containing FOLFOX4 chemotherapy and Doxorubicin for palliative chemotherapy in Asian

subjects with advanced hepatocellular carcinoma who are not suitable for surgery or local treatment. The study had the largest number of enrolled subjects (371 cases) in the field of systemic chemotherapy for liver carcinoma, with Chinese subjects accounting for 75%. The study confirmed for the first time that compared with doxorubicin, the regimen with Oxaliplatin-containing FOLFOX4 prolonged the median OS of subjects with advanced liver cancer from 4.97 months to 6.40 months, reduced the risk of death by 20%, improved the median PFS (2.93 months vs. 1.77 months), reduced the risk of recurrence and metastasis, and significantly increased the ORR to 8.2%, meanwhile the adverse reactions could be tolerated [12].

Regorafenib, another oral multi-kinase inhibitor, was approved by the FDA in 2017 for the second-line treatment of subjects with HCC who received previous treatment with sorafenib, based on an international multicenter, placebo-controlled phase 3 clinical study (RESORCE study [13]). The data showed a significant improvement in OS in the Regorafenib group compared with placebo (median: 10.6 months vs. 7.8 months, HR=0.62, 95% CI 0.50-0.79, P<0.001), and the risk of death was reduced by 37%. The most common adverse reactions in the Regorafenib and placebo groups were pain (55% vs. 44%), hand-foot skin reaction/palmar-plantar erythrodysesthesia (51% vs. 7%), and weakness/fatigue (42% vs. 33%), diarrhea (41% vs. 15%), hypertension (31% vs. 6%), infection (31% vs. 18%), anorexia (31% vs. 15%). It is currently approved only for second-line treatment after the progression with sorafenib treatment; the registered clinical trials do not include subjects with post-chemotherapy progression/sorafenib intolerance, and there is no data on the efficacy of second-line and later-line therapies. At the same time, the incidence of treatment-related adverse events for Regorafenib is relatively high, limiting its clinical use.

1.1.3. Development of PD-1/PD-L1 Monoclonal Antibody in Advanced Tumors

Programmed cell death protein 1 (PD-1) is the first immune checkpoint molecule to be discovered, expressed in stimulated B cells, T cells, and myeloid cells. It is initially described as "a brake on the immune response" for its role in inhibiting the immune response by binding to the ligand PD-L1. PD-1/PD-L1 immunological checkpoint inhibitor is currently the most attractive tumor immunotherapy drug, which can regulate the anti-tumor activity of T lymphocytes by blocking PD-1/PD-L1 signaling pathway, and improve the subject's own immune response to tumor, thus achieving the purpose of killing tumor cells.

Since 2014, the U.S. FDA has approved anti-PD-1 monoclonal antibodies, Bristol-Myers Squibb's nivolumab and Merck's pembrolizumab, based on outstanding efficacy, for the treatment of subjects with advanced melanoma, non-small cell lung cancer, renal cell carcinoma, head and neck cancer, Hodgkin's lymphoma, urothelial carcinoma, MSI-H or dMMR malignant tumor, gastric cancer and gastroesophageal junction adenocarcinoma, and cervical cancer as well as subjects with hepatocellular carcinoma (HCC) who have received sorafenib, including advanced subjects who have failed standard treatment without effective treatment and are advanced to first- and second-line treatments. In addition, due to the long-lasting efficacy and mild adverse reactions, hundreds of clinical trials on anti-PD-1 monoclonal antibodies (including monotherapy and combined therapy) have been conducted internationally for advanced solid tumor and haematological malignancy. The preliminary results of trials have shown greater efficacy and long-term survival compared with existing therapies. At the same time, in

terms of safety, drug-related toxicity was controllable, and the toxicity of Grade 3 and above was lower than that of traditional chemotherapy drugs [14].

1.1.3.1. PD-1/PD-L1 Monotherapy and Hepatocellular Carcinoma

In advanced HCC, PD-1/PD-L1 antibody also showed significant initial efficacy: the Checkmate-040 study was a single-arm, open-label, dose escalation and expansion, phase I/II clinical study evaluating nivolumab monotherapy for advanced hepatocellular carcinoma: a total of 262 subjects (48 for dose escalation and 214 for expansion) were enrolled to evaluate the efficacy and safety of nivolumab. The results of this study indicate that the initial efficacy of nivolumab monotherapy for advanced hepatocellular carcinoma was significant. For the subjects with advanced HCC (N=154) who have been treated with sorafenib, the objective response rate (ORR) of nivolumab was 14.3%, and 91% of subjects had a duration of response (DoR) of 6 months or more. 55% of subjects had a DoR of 12 months or more [15]. Based on this study, in September 2017, the FDA approved nivolumab for subjects with advanced hepatocellular carcinoma (HCC) who had previously received sorafenib, marking the official entry into the era of immunotherapy for HCC.

In addition, the KEYNOTE 224 study also confirmed the significant efficacy of PD-1 monoclonal antibody in HCC. This study was a one-arm, open-label, phase II clinical trial of pembrolizumab monotherapy for subjects with advanced HCC who had failed or were intolerant to sorafenib alone. A total of 104 subjects with advanced HCC were enrolled in the study. The results showed that the ORR of pembrolizumab was 17%, the DCR was 62%, the median PFS was 4.9 months, and the median OS was 12.9 months [16]. Based on this study, in November 2018, the FDA approved pembrolizumab indicated for the treatment of subjects with advanced HCC who have previously failed sorafenib treatment. Because of the prominent efficacy of PD - 1 antibodies in liver carcinoma, the domestic and foreign companies have carried out a number of randomized, controlled phase 3 studies of PD-1 antibody monotherapy for advanced hepatocellular carcinoma.

Despite the unprecedented success of PD-1/PD-L1 antibodies, it should not be overlooked that nearly 50% of solid tumor subjects do not benefit from this therapy. Taking advanced hepatocellular carcinoma accompanied with HBV infection as an example (about 90% of subjects with hepatocellular carcinoma in China are accompanied by HBV infection), the ORR of nivolumab was only 14%, and the DCR was only 55%. Nearly half of the subjects developed disease progression after 8 weeks of treatment. How to optimize the efficacy of anti-PD-1 antibody in advanced HCC on the basis of monotherapy effectiveness has become an urgent problem to be solved.

1.1.3.2. PD-1/PD-L1 Combined with Anti-angiogenic Targeted Drugs

At present, there are two methods for improving the efficacy of PD-1/PD-L1 immunotherapy. Firstly, molecular markers that predict efficacy have been explored. In this direction, the therapeutic effect of PD-1/PD-L1 is improved by detecting and enriching subjects with molecular markers such as the expression level of PD-L1 in tumor tissue, the level of tumor mutational burden (TMB), high microsatellite instability (MSI-H) and dMMR. Secondly, a suitable combination regimen for immunological combination therapy are being sought. At present, a large number of

clinical studies have been carried out on the combination of PD-1/PD-L1 inhibitors with other immunological checkpoint inhibitors, traditional chemotherapeutic drugs or targeted anti-tumor drugs.

Among them, PD-1/PD-L1 inhibitors combined with anti-angiogenic targeted drugs have a significant synergistic effect on efficacy. Currently, the FDA has granted breakthrough therapy designation for the multiple PD-1/PD-L1 inhibitors combined with anti-angiogenic targeted drugs. In a phase Ib clinical study of pembrolizumab combined with Axitinib for the treatment of advanced renal cell carcinoma, a total of 52 subjects with advanced renal cell carcinoma who had not received systemic treatment were recruited in the study. The optimal dose of the combination was taken as the primary endpoint, and the efficacy endpoints such as ORR, DoR, and PFS were also assessed. The observation results of tolerance showed that the combination of Axitinib standard dose (5 mg, BID) and pembrolizumab, 2 mg/kg Q3W was well tolerated. The efficacy results showed that the anti-tumor effect of combined therapy was far superior to that of Axitinib or anti-PD-1 monotherapy, and ORR reached 73%, among which 8% achieved complete response. More than 90% of subjects showed tumor shrinkage and mPFS was over 20 months, far exceeding Axitinib monotherapy for control of disease progression (mPFS = 10-15 months). While there are still no data on pembrolizumab monotherapy for renal cell carcinoma, the synergistic effect of Axitinib and pembrolizumab in the treatment of renal cell carcinoma is superior to that of nivolumab (ORR = 13%) and atezolizumab (untreated: ORR = 25%, mPFS = 6 months; treated: ORR = 15%, mPFS = 6 months) monotherapy[17]. In addition, based on excellent efficacy data, pembrolizumab combined with lenvatinib in the treatment of advanced renal cell carcinoma and advanced endometrial cancer, as well as PD-L1 monoclonal antibody Avelumab combined with Axitinib in the treatment of advanced renal cell carcinoma has been granted breakthrough therapy designation by the FDA.

In addition to renal cell carcinoma, combinations of anti-PD-1/PD-L1 inhibitors and VEGFR inhibitors have shown good efficacy in many solid tumors such as non-small cell lung cancer, hepatocellular carcinoma, and endometrioid carcinoma. A number of phase 3 studies are ongoing.

In the combination therapy of advanced hepatocellular carcinoma, anti-angiogenic targeted drugs have also achieved breakthroughs in combination with PD-1/PD-L1 antibodies. Several studies have confirmed that PD-1/PD-L1 antibodies and anti-angiogenic targeted drugs, including small molecule VEGFR inhibitors and VEGF/VEGFR antibodies, are safe and well tolerated, and can achieve synergistic effects.

In 2019, the updated efficacy of atezolizumab in combination with bevacizumab in the treatment of advanced hepatocellular carcinoma was reported in ESMO. This study was performed with atezolizumab in combination with bevacizumab in subjects with advanced hepatocellular carcinoma who had not received systemic therapy. Of the 104 evaluable cases, a total of 37 cases of response were observed, with an confirmed ORR of 36%, DCR was 71%, mPFS was 7.3 months (95%CI: 5.4, 9.9), mOS was 17.1months (95%CI:13.8, NE) [18]. A randomized, controlled phase 3 clinical study of atezolizumab in combination with bevacizumab versus sorafenib in the treatment of unresectable locally advanced or metastatic hepatocellular carcinoma had been initiated since 2018 (IMbrave150, NCT03434379), of which primary endpoints were OS and BIRC

evaluated PFS per RECIST v1.1, and the positive result was reported during the ESMO-Asia 2019. A total of 501 advanced HCC subjects were randomized at 2:1 to receive atezolizumab combined with bevacizumab (336 subjects) or sorafenib (165 subjects). The mOS in the experimental arm has not reached, the mOS in the control arm was 13.2 months, HR=0.58. The mPFS was 6.8 months (95%CI: 5.7, 8.3) and 4.3 months (95%CI: 4.0, 5.6) in experimental arm and control arm respectively [19]. The Chinese subgroup data was released in the following EASL 2020, a total of 194 Chinese subjects (137 of them were from the study of IMbrave 150, and 57 of them were from the extended enrollment in China； experimental arm 133 subjects, control arm 61 subjects) were enrolled in this study. The mOS in the experimental arm has not reached, the control arm mOS was 11.4 months, HR=0.44. The mPFS was 5.7 months (95%CI: 4.2, 8.3) and 3.2 months (95%CI: 2.6, 4.8) in experimental arm and control arm respectively, HR=0.60 [20].

In another phase Ib study of pembrolizumab combined with lenvatinib for unresectable hepatocellular carcinoma which was reported during ESMO 2019, all 67 subjects with hepatocellular carcinoma who were enrolled in efficacy expansion stage of the study had never received sorafenib treatment. Based on IRC assessment according to RECIST v1.1, the ORR and DCR was 32.8% (95% CI: 21.8, 45.4) and 85.1% (95% CI: 74.3, 92.6), mPFS was 9.5 months (95%CI: 5.6, 11.8) and mOS was 20.4 months (95%CI: 11.0, NE) [21]. Based on above phase Ib data, a phase III, randomized, double-blind study of pembrolizumab combined with lenvatinib versus lenvatinib as the first-line treatment for advanced HCC is ongoing.

The preliminary results of an exploratory clinical study of SHR-1210 combined with the VEGFR inhibitor rivoceranib in hepatocellular carcinoma and gastric cancer were also published in 2018. For the dose group of SHR-1210 200 mg, Q2W combined with rivoceranib 125 mg, 250 mg or 500 mg, QD. Total 18 subjects with HCC enrolled, 16 were evaluable (all HBV-positive, 15 of which failed after sorafenib), 8 of which were evaluated as disease remission, the objective response rate (ORR) was 50% (95%CI: 24.7, 75.4), DCR was 93.8% (95% CI: 69.8, 99.8), median time to response was 3.4 months (range, 1.4, 9.7), mPFS was 5.8 months (95% CI: 2.6, NR), and the initial effect was significant[22].

It can be seen that sorafenib is still a widely recognized first-line treatment for advanced hepatocellular carcinoma after 10 years on the market. However, the overall efficacy of sorafenib for hepatocellular carcinoma is relatively poor. A number of studies have confirmed that the ORR of sorafenib in the treatment of advanced liver carcinoma is <10%, with mOS <10 months [9, 10, 11]. At present, the first-line systemic treatment of Chinese subjects with advanced HCC is mainly based on sorafenib and Oxaliplatin-containing systemic chemotherapy, but the ORR is low and the survival benefit is limited [10, 12]. Another first-line treatment of lenvatinib has not been widely used yet. Therefore, there is an urgent need to develop a new and effective treatment regimen for advanced HCC.

Multiple studies of immunological checkpoint inhibitors, such as PD-1/PD-L1 monoclonal antibody, have shown good efficacy in the treatment of HCC. Compared with other systemic therapies, they have the features of high ORR, long response time and prolonged survival [15-16].

Therefore, this study is a registration study of PD-1 monoclonal antibody SHR-1210 combined with rivoceranib in the treatment of advanced primary hepatocellular carcinoma and hopes to provide guidance and experience for the new combination therapy of immunotherapy combined with targeted therapy in the future, so as to improve the anti-tumor effect of monotherapy, minimize toxic side effects, and ultimately bring better survival benefits to the majority of subjects.

1.2. Scientific Rationale

1.2.1. Preclinical Studies with SHR-1210

1.2.1.1. Drug Name and Physicochemical Properties

[Generic name]: Camrelizumab for Injection

[English name]: Camrelizumab

[Drug number]: SHR-1210

[Molecular weight]: about 146.3 kDa

1.2.1.2. Pharmacological Class and Mechanism of Action

Programmed death-1 (PD-1) is a protein receptor expressed on the T cell surface that was discovered in 1992 [23] and involved in the process of apoptosis. PD-1 belongs to the CD28 family, possessing 23% amino acid homology with cytotoxic T lymphocyte antigen 4 (CTLA-4), but its expression is mainly on activated T cells, B cells and myeloid cells, which is different from that of CTLA-4. PD-1 has two ligands, PD-L1 and PD-L2, respectively. PD-L1 is mainly expressed on T cells, B cells, macrophages and dendritic cells, and can be up-regulated on activated cells [24]. The expression of PD-L2 is relatively limited, mainly on antigen-presenting cells, such as activated macrophages and dendritic cells. The humanized anti-PD-1 monoclonal antibody specifically binds to PD-1 and blocks the interaction of PD-1 with its ligand, allowing T cells to recover immune response against the tumor cells.

1.2.1.3. Pharmacodynamic Studies

1) Affinity of antibody

The affinity of SHR-1210 for human, mouse, and cynomolgus and rhesus monkey PD-1 was determined using Surface Plasmon Resonance (SPR) technology. The K_d values for human and cynomolgus and rhesus monkey PD-1 are shown in Table 1. The binding affinity of SHR-1210 to mouse PD-1 was also measured; however, no binding was detected at the highest concentration tested (400 nM).

Table 1 Binding Affinity of Antibody SHR-1210 to Human and Cynomolgus and Rhesus Monkey PD-1

	Human K_d (nM)	Cynomolgus K_d (nM)	Rhesus K_d (nM)
SHR-1210	2	8	4

Binding of SHR-1210 to human and cynomolgus monkey neonatal Fc receptor (FcRn) was investigated. SHR-1210 binds to human and cynomolgus monkey FcRns with similar K_d values.

The binding of SHR-1210 to different FcγR proteins was also evaluated using SPR technology. The data indicate that the binding of SHR-1210 to different FcγR proteins is consistent with an IgG4 antibody isotype.

From the detection of the binding affinity, the affinity of SHR-1210 to antigen (human PD-1) was 3.0 nM, which was comparable to that of control antibodies nivolumab and MK3475 (pembrolizumab). The results are shown in Table 2.

Table 2 Binding Affinity of Antibody SHR-1210, Nivolumab and MK3475 to Human PD-1 Antigen

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

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

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

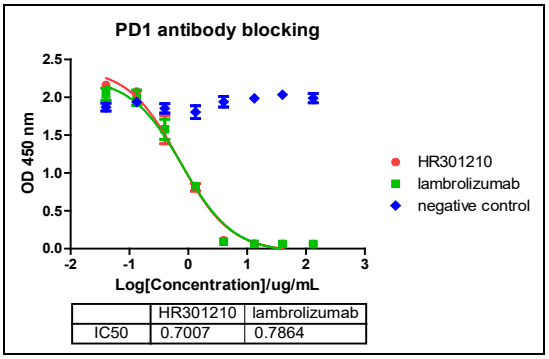


Figure 1. SHR-1210 and Pembrolizumab Blocking the Binding of PD-1/PD-L1

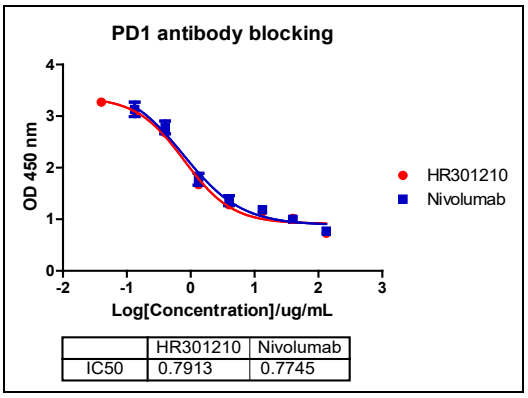


Figure 2. SHR-1210 and Nivolumab Blocking the Binding of PD-1 / PD-L1

1.2.1.4. Toxicology Studies

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

In the completed pre-clinical study of chronic toxicity in cynomolgus monkeys, male and female cynomolgus monkeys SHR-1210 was well tolerated when intravenously injected at 20, 50 and 100 mg / kg once weekly for 4 weeks (5 times in total) or 26 weeks (26 times in total). No changes in clinical signs associated with SHR-1210 were observed, including injection site irritation, body weight, food consumption, body temperature, 12-lead ECG, blood pressure, heart rate and respiratory parameters; No changes in B and T lymphocyte typing, cytokine, immunoglobulin and complement parameters were observed; No changes in organ weights, gross lesions and histopathological changes associated with SHR-1210 were observed.

1.2.1.5. Pharmacokinetic Studies

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

Table 3 Pharmacokinetic Parameters of Cynomolgus Monkeys After Single Intravenous Infusion of SHR-1210 at Different Doses

Dose (mg/kg)	Gender	$T_{1/2}$ (h)	T_{max} (h)	C_{max} (μg/mL)	AUC_{last} (h*μg/mL)	Vz (mL/kg)	Cl (mL/h/kg)	MRT_{last} (h)
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

Dose (mg/kg)	Gender	$T_{1/2}$ (h)	T_{max} (h)	C_{max} (μg/mL)	AUC_{last} (h*μg/mL)	Vz (mL/kg)	Cl (mL/h/kg)	MRT_{last} (h)
	Total	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
	Total	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
	Total	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

1.2.2. Clinical Studies with SHR-1210

1.2.2.1. Safety Summary of SHR-1210 in the Treatment of Advanced Solid Tumors

After obtaining clinical trial approval in 2016, three phase I clinical studies have been carried out in China for SHR-1210. They are all safety and tolerability studies in subjects with advanced solid tumors. As of February 28, 2018, three phase I studies included 258 subjects with advanced solid tumors who have failed standard treatment. The safety summary analysis is as follows:

At least one AE occurred in 258 subjects (100.0%). AEs with an incidence of ≥ 10% mainly included: skin and subcutaneous tissue disorders: reactive cutaneous capillary endothelial proliferation (81.8%), pruritus (22.5%), rash (16.3%); abnormal liver function: elevated asparagine transaminase (22.1%), elevated alanine aminotransferase (19.0%), elevated conjugated bilirubin (17.8%), elevated blood bilirubin (13.2%); hematologic toxicity: anemia (29.5%), decreased white blood cell count (17.1%), decreased neutrophil count (10.5%); general disorders: fatigue (38.4%), fever (22.1%); gastrointestinal AE: 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%), decreased serum sodium concentration (18.2%), anorexia (12.0%); renal and urinary disorders: proteinuria (22.5%); endocrine disorders: hypothyroidism (20.9%). A total of 98 (38.0%) subjects experienced at least one AE of Grade 3 or above, and AEs of Grade 3 or above with an incidence of ≥ 2% mainly included anemia (7.0%), pulmonary infection (6.6%), decreased serum sodium concentration (4.3%), elevated conjugated bilirubin (3.9%), progressive tumors (3.5%), death (3.1%), elevated asparagine transaminase (2.7%), elevated alanine aminotransferase (2.3%), and elevated blood bilirubin (2.3%).

In 258 subjects, 256 subjects (99.2%) experienced at least one drug-related AE. Drug-related AEs with an incidence of ≥ 10% included: skin and subcutaneous tissue disorders: reactive cutaneous capillary endothelial proliferation (81.8%), pruritus

(22.1%), rash (16.3%); general disorders: fatigue (37.6%) , fever (20.9%); abnormal liver function: elevated asparagine transaminase (21.7%), elevated alanine aminotransferase (18.6%), elevated conjugated bilirubin (16.7%), elevated blood bilirubin (12.0%); hematologic toxicity: anemia (27.5%), decreased white blood cell count (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: hypoproteinemia (19.4%), decreased serum sodium concentration (14.3%); renal and urinary disorders: proteinuria (22.1 %); endocrine disorders: hypothyroidism (19.8%). 82 (31.8%) subjects had at least one drug-related AE of Grade 3 or above, and the drug-related AEs of Grade 3 or above with incidence of ≥ 2% mainly included anemia (6.2%), pulmonary infection (5.8%), elevated conjugated bilirubin (3.9%), decreased serum sodium concentration (3.5%), death (3.1%), elevated asparagine transaminase (2.7%), elevated alanine aminotransferase (2.3%), and elevated blood bilirubin (2.3%).

Among 258 subjects, AEs of Grade 3 or above with an incidence of ≥ 2% mainly included anemia (7.0%), pulmonary infection (6.6%), decreased serum sodium concentration (4.3%), and elevated conjugated bilirubin (3.9%), progressive tumor (3.5%), death (3.1%), elevated asparagine transaminase (2.7%), elevated alanine aminotransferase (2.3%), elevated blood bilirubin (2.3%).

Overall, the AEs of SHR-1210 were similar to those of the already marketed same kind of drugs in subjects with advanced solid tumors except for reactive cutaneous capillary endothelial proliferation (RCCEP). Most of the RCCEP occurred within 1-2 months after the start of the study drug. The early ones could appear several days after the administration, and the late ones could appear about 5 months after the administration, mainly in the trunk or limbs. The vast majority (99.5%) were CTCAE 1-2, and only one subject reported Grade 3. The subject was rated as Grade 3 AE due to hospitalization from surgical resection, and no subjects discontinued medication due to this AE. A small number of subjects with bleeding symptoms received local symptomatic treatment. The symptoms usually resolved after stopping SHR-1210 treatment. Overall, SHR-1210 has good safety and tolerability.

1.2.2.2. Preliminary Results of SHR-1210 Monotherapy for HCC Study

The study was a single-arm study of SHR-1210 in subjects with advanced HCC who had undergone systemic therapy (NCT02989922). SHR-1210 was administered at a dose of 3 mg/kg once every 2 weeks or every 3 weeks. The enrollment of this study has been completed, the data was published in Lancet Oncology [25]. As of November16, 2018 (data cut-off date), 12 months after last subject received first dose, 217 subjects received at least one dose of SHR-1210.

Of 217 subjects treated, 206 (94.9%) were BCLC stage C subjects; all subjects received at least ≥ 1 line systemic therapies, 49 (23%) subjects underwent at least ≥ 2 line systemic therapies before enrollment; 177 (82%) subjects had extrahepatic metastasis at baseline; 171 (79%) subjects had a baseline ECOG-PS score of 1; 111(51%) subjects had baseline AFP ≥ 400 ng/mL, 181 (83%) subjects had HBV infection. 217 subjects met the definition of the full analysis set and were included in the full analysis set.

Efficacy results: based on the judgment of the Independent Imaging Center (IRC) tumor

assessment data (as of November 16, 2018, RECIST Version 1.1), overall ORR was 14.7% (95% CI: 10.3, 20.2). The ORR of the Q2W group was 11.9% (95% CI: 6.5, 19.5), and the ORR of the Q3W group was 17.6% (95% CI: 10.9, 26.1).

The 6-month OS rate was 74.7% (95% CI: 68.3, 79.9). The Q2W group was 75.9% (95% CI: 66.6, 82.9), and the Q3W group was 73.0% (95% CI: 63.6, 80.4).

As of data cut-off of November16, 2018, the median follow-up was 12.5 months and the observed median OS was 13.8 months (95% CI: 11.5, 16.6).

Safety results: the category and frequency of common AE were similar to those in phase I clinical studies of this study drug. The most common drug-related AEs (incidence of any group ≥ 10%) were reactive cutaneous capillary endothelial proliferation, elevated transaminases, proteinuria, hyperbilirubinemia, hypothyroidism, thrombocytopenia, leukopenia and fatigue. 22% of subjects had at least one drug-related AE of Grade 3 or Grade 4. 4% of subjects discontinued experimental drugs due to drug-related AE. At least one drug-related SAE occurred in 11% of subjects.

In this study, 145 (67%) subjects developed reactive capillary endothelial proliferation (all in skin, of which three were accompanied in oral mucosa, two cases nasal mucosa, two cases palpebral conjunctiva). Except one case was grade 3, others reactive capillary endothelial proliferation cases were grade 1-2, mild, self-limiting and clinically manageable.

Clinically significant results in laboratory tests were reported as AE, with no other indicators of special attention. Vital signs were stable and there were no extreme values.

Detailed progress of research on SHR-1210 can be referred to in its investigator's brochure.

1.2.3. Progress in Clinical Research of Rivoceranib Monotherapy for Advanced HCC

This clinical study also involved rivoceranib mesylate tablets (trade name: Aitan), which was launched in 2014 by Jiangsu Hengrui Pharmaceuticals Co., Ltd. Rivoceranib is a small molecule targeted drug, a vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor, which exerts anti-angiogenic effects on malignant tumors mainly through inhibiting VEGFR. Preclinical studies show that its anti-tumor effect is superior to similar drugs. In 2014, rivoceranib was approved in China for treatment of progression or recurrence of advanced gastric adenocarcinoma or adenocarcinoma of gastroesophageal junction after previous use of at least two systemic chemotherapies.

HCC is also a typical tumor with an abundant blood supply, and its occurrence, development, metastasis and invasion are closely related to angiogenesis. In 2010-2013, the 81st hospital of the Chinese People's Liberation Army led a randomized, open-label, multicenter phase II clinical trial of rivoceranib mesylate tablets in the treatment of advanced hepatocellular carcinoma (NCT01192971) [26], and a total of 121 subjects received the medication. In the full analysis set, the median time to progression (mTTP) and median overall survival (mOS) were 4.21 months and 9.71 months in the 850 mg group, and the mTTP and mOS in the 750 mg group were 3.32 months and 9.82 months.

There were no statistically significant differences in mTTP and mOS between the 850 mg and 750 mg groups. The incidence of adverse reactions was 95.71% and 90.20% in 850 mg and 750 mg groups, respectively; the incidence of severe adverse reactions was 58.57% and 58.82%, respectively, the difference was not statistically significant. Therefore, a well-tolerated 750 mg is recommended as the dose for the phase 3 clinical study. The recommended dosing regimen is 750 mg, PO, QD; 28 days is a cycle (excluding the time for discontinuance), and continuous administration until the disease progression or an intolerable adverse reaction. If a Grade 3/4 hematologic or non-hematologic adverse reaction occurs, it is recommended to suspend the medication (not more than 2 weeks) or to reduce the dose to 500 mg or 250 mg.

A randomized (2:1), open-label, placebo-controlled, multicenter, phase 3 clinical trial of rivoceranib (NCT02329860) is currently ongoing to investigate the efficacy and safety of rivoceranib in the second-line treatment of advanced HCC. The trial recruited subjects with advanced HCC who have failed, relapsed or are intolerant to side effects with sorafenib or systemic chemotherapy. As of December 2017, 400 subjects have been enrolled. Adverse events that have been observed include proteinuria, elevated blood pressure, thrombocytopenia, hand-foot syndrome, and elevated total bilirubin. For more information on the rivoceranib mesylate tablets, please refer to the package insert of the rivoceranib mesylate tablets and the investigator's brochure provided by the sponsor.

Based on the above-mentioned large-scale data from these randomized controlled clinical studies, the main adverse reactions are hand and foot skin reactions, hypertension, elevated transaminases, elevated bilirubin, leukopenia, thrombocytopenia, diarrhea, esophagitis, nausea, and fatigue, most of which are mild to moderate reactions.

Detailed progress of research on rivoceranib can be referred to in its investigator’s brochure.

1.2.4. Preliminary Data of SHR-1210 Combined with Rivoceranib

1.2.4.1. Potential Mechanisms of Combination Administration and Preclinical Studies

The VEGFR signaling pathway plays an important role in mediating tumor immune escape, and inhibition of this pathway may enhance the activation of tumor immunity by PD-1 antibodies.

Preclinical data from Jiangsu Hengrui Pharmaceuticals Co., Ltd. suggested that SHR-1210 combined with rivoceranib could significantly reduce the regulatory T cell (T_{reg}) levels in peripheral blood and increase the ratio of effector T cell (T_{eff}) to T_{reg}.

The results of animal studies showed that SHR-1210 combined with rivoceranib significantly enhanced the tumor growth inhibition of SHR-1210 without increasing significant toxicity (no significant change in animal body weight):

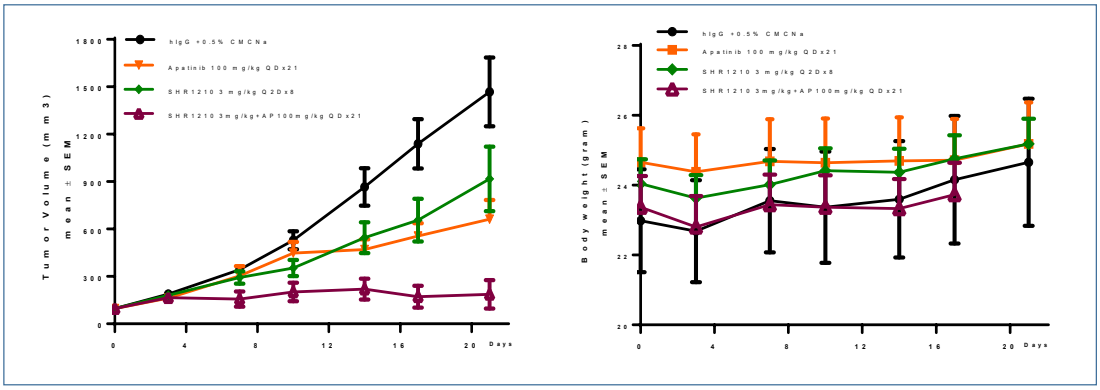


Figure 3. Evaluation of the Effect of SHR-1210 Combined with Rivoceranib on MC38 Colorectal Cancer in Tg Mice Expressing Human PD-1

Preclinical findings suggest that the use of SHR-1210 in combination with rivoceranib may increase the ORR of the tumor while preserving the efficacy and persistence of immunotherapy.

1.2.4.2. Exploration of Combination Administration in Preliminary Clinical Studies

Since October 2016, Jiangsu Hengrui Pharmaceuticals Co., Ltd. has served as a funder or sponsor to conduct a number of clinical trials of SHR-1210 combined with rivoceranib mesylate, involving a variety of solid tumors such as advanced hepatocellular carcinoma, advanced lung cancer, advanced intrahepatic cholangiocarcinoma, advanced gastric adenocarcinoma and advanced triple-negative breast cancer. These studies explored the safety and tolerance of SHR-1210 combined with rivoceranib mesylate and the initial efficacy against a variety of tumors.

Preliminary results confirm: for SHR-1210 200 mg fixed dose, once every two weeks (Q2W) combined with rivoceranib mesylate 250 mg/d, continuous oral dose level is tolerable, while the combination regimen for a variety of tumors have shown a significant efficacy, significantly increasing the proportion of subjects benefiting from treatment.

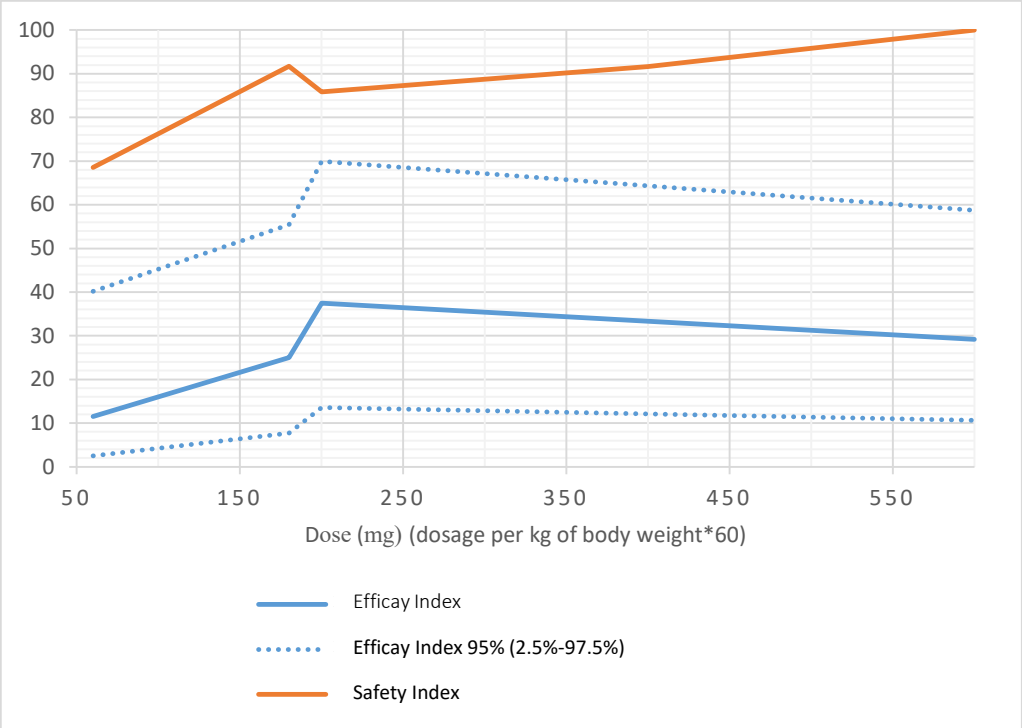
Study Title	Study Design	First Subject Enrolled/Subject Number Enrolled	Registration Number of Clinical Trial
Exploratory clinical study of PD-1 antibody SHR-1210 combined with rivoceranib mesylate in the treatment of advanced gastric cancer and hepatocellular carcinoma	Dose-finding, dose expansion, phase Ib study	2016-10/48	NCT02942329
Phase II clinical study of PD-1 antibody SHR-1210 combined with rivoceranib mesylate in the treatment of advanced non-small cell lung cancer	Dose-finding, dose expansion, phase II study	2017-3/201	NCT03083041
Phase II clinical study of PD-1 antibody SHR-1210 combined with rivoceranib mesylate or	Dose-finding, dose expansion, phase II study	2017-4/154	NCT03092895

Study Title	Study Design	First Subject Enrolled/Subject Number Enrolled	Registration Number of Clinical Trial
chemotherapy in advanced primary liver cancer or extrahepatic cholangiocarcinoma			
One-arm, open-label, prospective, multicenter clinical study of the efficacy and safety of rivoceranib mesylate in combination with PD-1 antibody (SHR-1210) in the treatment of progressive osteosarcoma with chemotherapy failure	One-arm, open-label, phase II study	2017-12/43	NCT03359018
Two-arm, open-label, investigator-initiated phase II clinical trial of anti-PD-1 antibody SHR-1210 in combination with rivoceranib mesylate in the treatment of recurrent metastatic triple-negative breast cancer	Two-arm, open-label, phase II study	2017-12/40	NCT03394287
One-arm, open-label, phase II clinical trial of anti-PD-1 antibody SHR-1210 combined with rivoceranib mesylate in the treatment of advanced hepatocellular carcinoma	One-arm, open, phase II study	2018-3/190	NCT03463876
Phase II clinical study of SHR-1210 combined with rivoceranib mesylate in the treatment of extensive-stage small cell lung cancer with first-line standard of care failure	Dose-finding, dose expansion, phase II study	2018-4/59	NCT03417895

Cut-off date: 24 Aug. 2019

1.2.4.3. Selection of Doses for Combined Therapy

The dose-response relationship analysis was performed on the safety and efficacy data of three phase I studies of SHR-1210-101, SHR-1210-102 and SHR-1210-103. This analysis defines SHR-1210 (ORR+DCR)/2 as the efficacy index and (number of subjects with at least one drug-related AE + skin and subcutaneous tissue disease)/2 as the safety index. Figure 4 shows that the efficacy index reaches a steady state at a dose of 200 mg Q2W; the safety index increases with the dose. The optimal benefit dose for subjects can be defined as the dose with the least severe side effects in the case of maximum efficacy. The efficacy index and safety index show that 200 mg Q2W is the best benefit dose for subjects.



*Efficacy Index = (ORR+DCR)/2; Safety Index = (number of subjects with at least one drug-related AE + skin and subcutaneous tissue disease)/2

Figure 4. Relationship of Efficacy and Safety Indexes with Doses

In one exploratory clinical study on SHR-1210 combined with rivoceranib mesylate in treatment of advanced hepatocellular carcinoma and gastric cancer [20.] (NCT02942329), the tolerability of SHR-1210 200 mg at the fixed dose of once every two weeks (Q2W) combined with rivoceranib mesylate 125 mg/d, 250 mg/d or 500 mg/d for continuous administration was observed, and the results showed that rivoceranib 125 mg QD po combined with SHR-1210 200 mg Q2W was well tolerated without dose-limiting toxicity (DLT); 3/5 subjects given rivoceranib 500 mg QD po combined with SHR-1210 200 mg Q2W had Grade 3 immune-related pneumonia that could not be tolerated during observation of tolerability; 1/5 subject given rivoceranib 250 mg QD po combined with SHR-1210 200 mg Q2W had Grade 3 elevated lipase with no clinical symptoms during observation of tolerability, the symptoms disappeared after symptomatic treatment, see Table 4 for the detail.

The observation of tolerability showed that rivoceranib 250mg/d po continuously combined with SHR-1210 200 mg, Q2W was tolerable in treatment of advanced hepatocellular carcinoma, gastric cancer and gastroesophageal junction carcinoma. This dose level was selected for efficacy extension in the study subsequently.

Table 4 Occurrence of DLT in Each Dose Group in the Studies on SHR-1210 Combined with Rivoceranib in Treatment of Advanced Hepatocellular Carcinoma and Gastric Cancer

Dose Level of Rivoceranib	Number of Subjects/ Number of Subjects with Evaluable DLT	Number / Proportion of Subjects with DLT	DLT Details

125mg/d	5/5	0/0	Not Detected
250mg/d	5/5	1/20.0%	Grade 3 elevated lipase with no clinical symptoms
500mg/d	5/5	3/60.0%	Grade 3 immune-related pneumonia

In one phase II study on SHR-1210 combined with rivoceranib mesylate for treatment of advanced non-squamous cell, non-small cell lung cancer (NCT03083041), the tolerability of SHR-1210 200 mg fixed dose once every two weeks (Q2W) combined with rivoceranib mesylate 250 mg/d, 375mg/d or 500mg/d for continuous administration was observed. The preliminary study results during observation of tolerability showed that, in the 12 subjects participating in the tolerability observation of SHR-1210 200 mg fixed dose once every two weeks (Q2W) combined with rivoceranib mesylate 250 mg qd, the clinically significant toxicity was observed in only 2 subjects during observation of tolerability, which was 1 case of dose interruption of rivoceranib for > 7 days caused by increased hydrothorax (suspected pleural fistula) and 1 case of dose interruption of rivoceranib for > 7 days caused by anorexia with weakness. The incidence of clinically significant toxicity was 16.7% (2/12), the dose level was tolerable; in the subsequent observation of the tolerability of SHR-1210 200 mg fixed dose once every two weeks (Q2W) combined with rivoceranib mesylate 375 mg QD, a total of 4/12 evaluable subjects had Grade 3 rash during observation of tolerability, the incidence of clinically significant toxicity was 33.3%(4/12), the proportion of subjects with significant toxicity reached 1/3, and the dose level was intolerable.

Table 5 Occurrence of Clinically Significant Toxicity in Each Dose Group in the Study on SHR-1210 Combined with Rivoceranib in Treatment of Advanced Non-Small Cell Lung Cancer

Dose Level of Rivoceranib	Number of Subjects/ Number of Subjects with Evaluable DLT	Number/ Proportion of Subjects with Clinically Significant Toxicity	Details
250mg/d	12/12	2/16.7%	1 case of suspected bronchopleural fistula (increased hydrothorax), leading to dose interruption of rivoceranib for >7d 1 case of fatigue with anorexia, leading to dose interruption of rivoceranib for >7d
375mg/d	12/12	4/33.3%	4 cases of Grade 3 rash that could be relieved after symptomatic treatment; Dose adjustment in 5 subjects in the first two cycles, including down-titration of rivoceranib to 250mg/d in 3 subjects

The observation of tolerability showed that rivoceranib 250 mg/d po continuously combined with SHR-1210 200 mg, Q2W was tolerable in treatment of advanced non-squamous cell, non-small cell lung cancer. This dose level was selected for efficacy extension in the study subsequently.

Combined with the analysis results of the pharmacokinetics, efficacy and safety in the

above studies, it has been decided that the clinically observed tolerable dose will be selected in the upcoming phase 3 studies on SHR-1210 combined with rivoceranib mesylate as the first-line therapy for advanced hepatocellular carcinoma: SHR-1210 200 mg, Q2W combined with rivoceranib 250 mg QD po continuously as combined therapy dose.

1.2.4.4. Preliminary Efficacy of Combined Therapy

In the exploratory clinical study on SHR-1210 combined with rivoceranib mesylate for treatment of advanced hepatocellular carcinoma and gastric cancer, it was found through the efficacy extension in SHR-1210 200 mg, Q2W combined with rivoceranib 250 mg QD continuously that this combined regimen had significant efficacy in advanced hepatocellular carcinoma: in the 14 subjects with liver cancer enrolled at this dose level, there were 13 evaluable subjects (all positive HBV, including 12 subjects with failure of sorafenib), 7 subjects were evaluated as disease remission, the objective response rate (ORR) reached 53.8% and the remission was durable, no progression of disease was seen in 6 subjects with disease remission after treatment for 18-72 weeks; PFS rates of 6-month and 9-month were 51.3% (95% CI: 21.4, 74.9) and 41.0% (95% CI:13.8, 66.9) respectively, and the median PFS was 7.2 months (95% CI: 4.1,NR), the preliminary efficacy was significant[22].

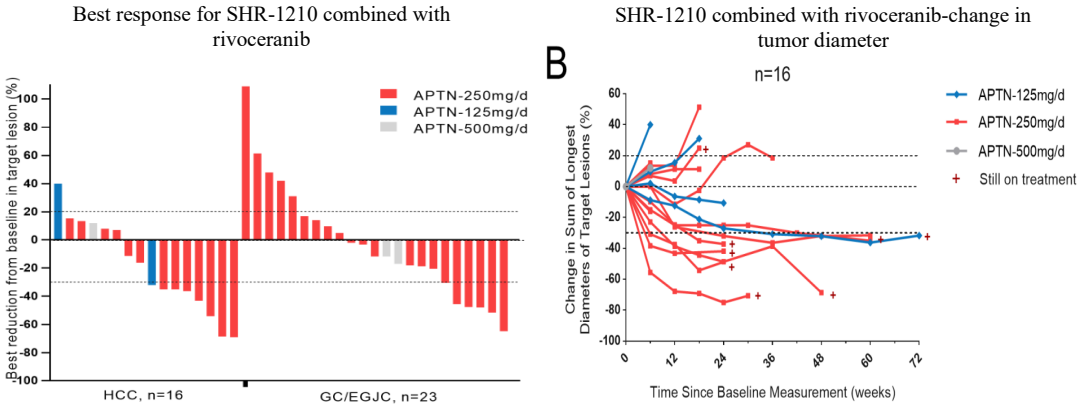


Figure 5. The Best Response of SHR-1210 Combined with Rivoceranib in Advanced Hepatocellular Carcinoma and Change in the Diameter of Target Lesions After Administration

Above preliminary data demonstrated that compared with current therapeutic regimen, such as sorafenib, the ORR was <10%; while the ORR of Nivolumab treatment for advanced HCC after sorafenib exposure was 14.3%, DCR was 55%. Per above preliminary results, SHR-1210 combined with rivoceranib mesylate looks having an obvious advantage in treatment of advanced HCC.

In summary, under the selected dose, SHR-1210 combined with rivoceranib had a good tolerability and significant preliminary efficacy observed in advanced hepatocellular carcinoma. The randomized, controlled study of SHR-1210 combined with rivoceranib versus sorafenib in uncurable HCC is expected to achieve positive outcome and provide a more effective therapeutic option for vast subjects with HCC.

1.2.5. Selection Rationale of Control Arm

Sorafenib was approved by the FDA as a targeted therapy for HCC in 2007. Sorafenib is an oral multitarget inhibitor (VEGFR-1, -2, -3, PDGFR and c-KIT) that blocks tumor neovascularization and inhibits tumor growth directly. The approval of sorafenib is based on the active results from SHARP and ORIENTAL trials. SHARP trial is a phase 3 trial conducted mainly in European and American subjects to compare the efficacy and safety of sorafenib versus placebo in treatment of advanced HCC. The results showed a significantly improved survival in sorafenib group compared with placebo group. The ORIENTAL trial in parallel to SHARP trial enrolled subjects with advanced HCC in Asian-Pacific region using the same design. The results showed a similar significant improvement in survival with sorafenib in Asian subjects. A total of 3,371 subjects with unresectable advanced HCC were enrolled in GIDEON study intended to acquire the clinical safety data of sorafenib. The results showed an OS of 13.6, 5.2 and 2.6 months, and median TTP of 4.7, 4.4 and 3.6 months in subjects with CHILD Grade A, B and C, indicating better benefit for earlier treatment with sorafenib.

Table 6 Phase 3 Clinical Trial on Sorafenib in Advanced Hepatocellular Carcinoma

Study Endpoints	SHARP (North America and Europe)	ORIENTAL (Asia-Pacific region)
	Sorafenib vs Placebo	Sorafenib vs Placebo
Median TTP (months)	5.5 vs 2.8	2.8 vs 1.4
Median OS (months)	10.7 vs 7.9	6.5 vs 4.2
DCR (%)	74.3 vs 67.7	35.3 vs 15.8
ORR (%)	2.3 vs 0.7	4.3 vs 1.3

To summary, sorafenib is recognized throughout the world as a first-line standard of care therapy for advanced HCC and thus has been selected for comparison of first-line treatment of participants assigned to the control arm.

1.3. Potential Risks and Benefits

As described above, current therapies have limited efficacy in advanced hepatocellular carcinoma, only less than 10% of subjects can achieve response from the 1st-line therapy with sorafenib. Lenvatinib was approved by the FDA in August 2018 as the first-line therapy for subjects with unresectable hepatocellular carcinoma and has not been widely used yet. The PD-1 antibodies nivolumab and pembrolizumab that were approved in recent years have achieved significant response in the exploratory application in HCC. For example, for subjects with advanced hepatocellular carcinoma who have received sorafenib for treatment, the ORR is 14.3% in those who have received PD-1 antibody (nivolumab) and is superior to current therapeutic approaches. In particular, when PD-1/PD-L1 antibody is combined with anti-angiogenesis targeted drug, efficacy is enhanced; moreover, the combined therapy is safe, well tolerated and can achieve a synergistic effect. SHR-1210 is one humanized PD-1 antibody that is independently researched and developed by Jiangsu Hengrui Pharmaceuticals Co., Ltd. The preclinical data in animal experiments showed a similar affinity and antitumor effect with nivolumab and pembrolizumab. At the same time, SHR-1210 combined with rivoceranib has achieved an encouraging preliminary result in treatment of advanced

hepatocellular carcinoma. Participation in the phase 3 study to receive the study drug may provide clinical benefit to subjects with advanced HCC and offer a useful therapeutic option for them.

1.3.1. Known Potential Risks

In the previous clinical studies for multiple solid tumors (including HCC) and hematological tumors, the most common (≥ 10%) adverse reactions induced by SHR-1210 included: reactive capillary endothelial proliferation (RCEP), various rashes, immune endocrine dysfunction such as hyperthyroidism/hypothyroidism, fatigue, elevated transaminase, most of which were Grade 1-2 and could be recovered after symptomatic treatment or dose interruption, had relatively small effect on subject's physiological function and quality of life, and did not hinder continuation of the study treatment. RCCEP is a unique skin reaction of SHR-1210. Although with a relatively high incidence in the SHR-1210 monotherapy, RCEP was relatively mild in severity and clinically tolerable, and could be recovered after discontinuation of the drug. Moreover, in the treatment of SHR-1210 combined with rivoceranib, the incidence of RCEP was significantly reduced, which may be related to the anti-angiogenic effect of rivoceranib. The most common serious adverse reactions of SHR-1210 include pneumonitis, abnormal liver function, lung infection and thrombocytopenia. Various immune-related adverse reactions are potential risks of SHR-1210, which are class effects of PD-1 antibody preparations and include pneumonitis, hepatitis, thyroiditis, myocarditis, enteritis, severe cutaneous adverse reactions (including Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)) etc. Symptomatic treatment will be given in accordance with EMSO/NCCN guideline on management of immunotoxicity and can ensure the safety of subjects during the trial. Please refer to the investigator's brochure for more details on adverse drug reactions associated with SHR-1210.

Rivoceranib mesylate tablets were approved by the Chinese drug regulatory authorities for the treatment of advanced gastric cancer in October 2014. The recommended initial dose is 850 mg, orally, once daily. The most common (≥ 10%) adverse reactions of rivoceranib (850 mg QD) are hand and foot skin reactions, hypertension, elevated transaminases, elevated bilirubin, elevated alkaline phosphatase, elevated γ-glutamyl transferase, proteinuria, diarrhea, leukopenia, thrombocytopenia, anemia, fatigue, etc., most of which are mild to moderate reactions and can be recovered or improved after the drug is temporarily discontinued and treatment is given. In addition, the use of rivoceranib requires special attention to events that have a low incidence but may cause serious consequences or even deaths, including various types of bleeding and thrombotic events, cardiotoxicity (QT interval prolongation, arrhythmia) and liver toxicity. Please refer to the investigator's brochure for more details on adverse drug reactions associated with rivoceranib mesylate. Currently, the known safety information on rivoceranib mesylate mainly comes from the experience of dose regimen of 850 mg QD, and the experience of 250 mg QD is relatively limited.

Although the mechanism of action for SHR-1210 and rivoceranib is completely different, their pharmacological effects may extensively affect multiple organ systems of the body. Based on the preliminary safety data, and given that there could be overlapped adverse reactions associated with both drugs during the treatment of SHR-1210 in combination with rivoceranib 250 mg QD, overlapped adverse reactions that require the investigator's special attention include but not limited to: severe cutaneous

adverse reaction, hematological toxicity, abnormal liver function, diarrhea, anorexia, proteinuria and fatigue.

1.3.2. Known Possible Benefits

In the two currently ongoing phase II clinical studies in subjects with advanced HCC, the efficacy has been preliminarily shown for SHR-1210 alone or SHR-1210 in combination with rivoceranib. So the HCC subjects enrolled in this study may achieve partial or even complete response, and some subjects may obtain sustained stable disease. The above trial data will provide a strong guidance for the clinical practice for HCC treatment and allow more subjects to access and benefit from new therapeutic methods.

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective	**Primary Endpoints**
• To compare the overall survival (OS) and progression-free survival (PFS) of SHR-1210 combined with rivoceranib mesylate (experimental arm) with sorafenib (control arm) as first-line therapy for subjects with advanced HCC who have not previously received systemic therapy.	• Overall survival (OS); • PFS evaluated by the blinded independent review committee (BIRC) based on RECIST v1.1.
Secondary Objectives	**Secondary Endpoints**
• To compare the efficacy of SHR-1210 combined with rivoceranib mesylate versus sorafenib as first-line therapy in subjects with advanced HCC, who have not previously received systemic therapy, through evaluations of PFS, time to progression (TTP), objective response rate (ORR), disease control rate (DCR), and duration of response (DoR);	• Time to progression (TTP), objective response rate (ORR), disease control rate (DCR), and duration of response (DoR) evaluated by BIRC based on RECIST v1.1; • PFS, TTP, ORR, DCR and DoR evaluated by investigator based on RECIST v1.1; • PFS, TTP, ORR, DCR and DoR evaluated by BIRC based on modified RECIST (mRECIST).
• To evaluate the safety of SHR-1210 combined with rivoceranib mesylate versus sorafenib as a first-line therapy for advanced HCC;	• Incidence and severity of adverse event (AE) and serious adverse event (SAE) judged in accordance with NCI-CTCAE v4.03; vital signs, ECG, and abnormal laboratory examinations;
• To evaluate the PK of SHR-1210 and rivoceranib and the immunogenicity of SHR-1210, and to analyze the immunogenicity combined with the concentration of SHR-1210.	• Serum concentration of SHR-1210 and plasma concentration of rivoceranib; proportion of anti-SHR-1210 antibody (ADA) and neutralizing antibody (Nab) formed during the study from baseline; analysis of the immunogenicity of SHR-1210 combined with the concentration of SHR-1210.
Exploratory Objectives	**Exploratory Endpoints:**
• To evaluate the quality of life (QoL), including health related quality of life (HRQOL) / general health status (GHS), physical functioning and role	• Time to deterioration (TTD): defined as time from randomization to first deterioration (a score decrease by ≥ 10 from baseline) maintained for two consecutive time points, or one time-

functioning, of subjects with advanced HCC who receive SHR-1210 combined with rivoceranib mesylate as a first-line therapy versus those who receive sorafenib as a first-line therapy;	point followed by death (from any cause) within 4 weeks, as determined by following subscales of European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30): - HRQoL/Global health status - Physical Functioning - Role Functioning
	• Average score and its change in the score from baseline in all the subscales of EORTC QLQ-C30 and EORTC QLQ-HCC18 (by cycle);
• To evaluate the health status of subjects with advanced HCC who receive SHR-1210 combined with rivoceranib mesylate as a first-line therapy versus those who receive sorafenib as a first-line therapy, so as to generate the utility score for health economic assessment;	• Health utility index and VAS score in EQ-5D-5L questionnaire;
• To compare the efficacy of SHR-1210 combined with rivoceranib mesylate versus sorafenib as first-line therapy in subjects with advanced HCC through evaluations of PFS, TTP, ORR, DCR and DoR based on immune-modified Response Evaluation Criteria in Solid Tumors (imRECIST);	• PFS, TTP, ORR, DCR and DoR evaluated by investigator based on imRECIST;
• To explore the correlation between biomarkers and the efficacy of combined therapeutic regimen;	• The correlation of the expression level of PD-L1 and proportion of strong expression of PD-L1 in tumor tissue with the efficacy of SHR-1210 combined with rivoceranib mesylate (including but not limited to ORR, OS);
• To evaluate the possible effect of immunogenicity of SHR-1210 on the efficacy and safety of SHR-1210 combined with rivoceranib mesylate as a first-	• Efficacy (e.g., best overall response (BOR), ORR, etc.), and safety endpoint (eg, immune-related adverse events [irAEs], ≥ Grade 3 treatment-related adverse events, treatment-related SAEs,

line therapy for advanced HCC.	etc.) listed according to the ADA / Nab status of SHR-1210 in the experimental arm.

3. STUDY DESIGN

3.1. Overall Design

This is a randomized, open-label, international, multi-center, phase 3 trial to evaluate the efficacy and safety of PD-1 antibody SHR-1210 plus rivoceranib mesylate versus sorafenib as first-line therapy in subjects with incurable advanced HCC.

The study will be conducted in subjects with incurable, locally advanced or metastatic HCC who did not receive systematic treatment previously. Primary efficacy endpoints include both OS and PFS evaluated by the BIRC based on RECIST v1.1, and approximately 510 subjects will be enrolled. Eligible subjects will be randomized to receive either SHR-1210 combined with rivoceranib mesylate (experimental arm) or sorafenib (control arm) in a 1:1 ratio.

The stratification factors for randomization include:

1. Macrovascular invasion and/or extrahepatic metastasis (presence vs. absence)

2. Geographical region (Asia vs. countries outside of Asia)

3. Baseline AFP (AFP < 400 ng/mL vs. AFP ≥ 400 ng/mL)

Subjects will receive study treatment after being informed of all pertinent aspects of the study, signing the informed consent form and passing the screening for eligibility. Experimental arm: SHR-1210, 200 mg, via intravenous infusion, once every two weeks (Q2W) + rivoceranib 250 mg, p.o., once per day (QD), continuously, 4 weeks (28 days) per cycle of therapy. Control arm: sorafenib, 400 mg, p.o., twice per day (BID), continuously, 28 days per cycle of therapy. Study treatment will continue until the subject develops an intolerable toxicity, withdrawing informed consent, and disease progression confirmed by BIRC according to RECIST v1.1 (when the subject has disease progression assessed by the investigator according to RECIST v1.1, the investigator must submit the radiological data to BIRC immediately. If BIRC evaluates it as non-disease progression according to RECIST v1.1, the subject should continue to receive the study drug treatment and continue the tumor radiological evaluation; if BIRC confirms it as disease progression based on RECIST V1.1, at this time, the investigator needs to assess whether the subject still has clinical benefit. If the subject is considered to still have clinical benefit and meet the criteria for treatment beyond disease progresses (see Section 6.6 for details), the subject may continue to receive study medication; if the subject is no longer considered to have clinical benefit, the treatment may be discontinued), or other termination criteria specified by the protocol, whichever occurs first.

Subjects will have safety visits on D1 and D15 of each cycle of therapy within the first 3 cycles for both experimental and control arms. Beginning from the cycle 4, subjects will have safety visits on D1 and D15 of each cycle in the experimental arm; subjects in the control arm will only have safety visits on D1 of each cycle; refer to the

SCHEDULE OF ACTIVITIES for details. Subjects will continue with safety visits and survival follow-up after the end- of- treatment. The study design is shown in Figure 6.

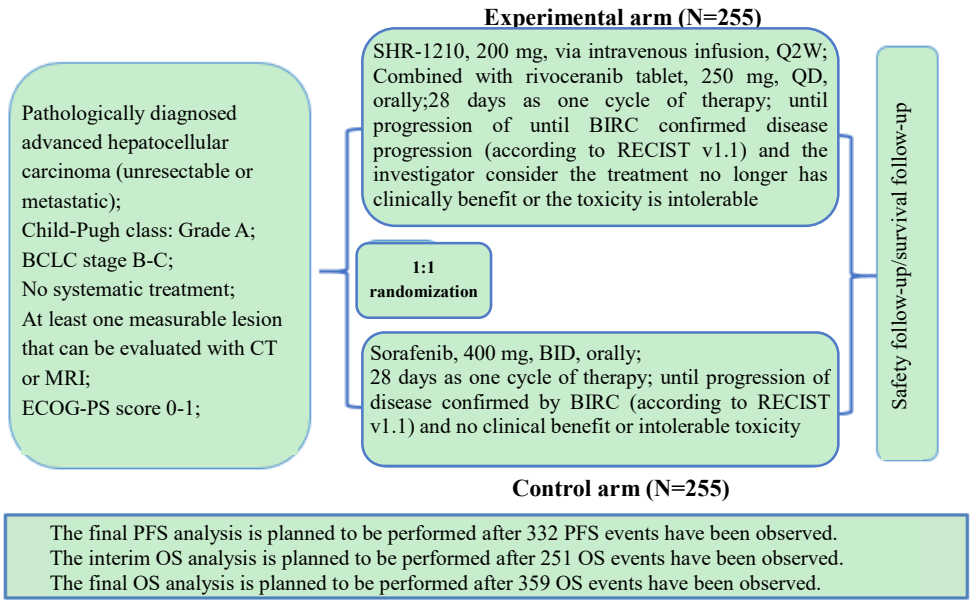


Figure 6. Study Design Chart

Tumor radiological evaluation will be performed every 8 weeks (56 days) ± 7 days from the randomization through the first 48 weeks, to assess the efficacy, and every 12 weeks (84 days) ± 7 days after 48 weeks. During the trial period, radiological examination and evaluation can be added at any time if clinically indicated. Tumor radiological assessment will continue until the occurrence of disease progression confirmed by BIRC according to RECIST v1.1 criteria or study treatment discontinuation, whichever occurs later. Subjects who discontinue treatment for reasons other than BIRC-confirmed disease progression (according to RECIST v1.1) will also continue with regular follow-up by tumor radiological assessments after study treatment is discontinued.

If the subject withdraws informed consent before BIRC confirms disease progression according to the RECIST v1.1 criteria or the study treatment is discontinued, other anti-tumor treatment has begun (except for traditional Chinese medicine), or the subject dies, there is no need to continue the radiological evaluation. If the subject does not meet the above criteria to stop radiological assessment, the efficacy evaluation of the three efficacy evaluation criteria (RECIST v1.1, mRECIST, imRECIST) needs to continue even if the disease progression under certain efficacy evaluation criteria occurs.

Upon approval of Protocol v6.0, disease progression will be confirmed by the investigator per RECIST v1.1. If the investigator confirms non-disease progression, the subject should continue on study treatment and tumor radiological evaluation as required; if the investigator confirms as disease progression, the subject may continue to receive study treatment after disease progression at the investigator's discretion (see Section 6.6).

The study extension phase will be initiated when sufficient follow up is completed and the study is ended (at least 2 years follow up of the last subject randomized). The

purpose of the extension phase is to continue to provide access to study drugs for subjects who are still on study treatment and still derive clinical benefit at the time of end of study. Upon initiation of the extension phase, the Sponsor considers the safety and efficacy profile of the experimental treatment regimen within this study to have been sufficiently established and data analysis required for regulatory purposes to have been completed. The Sponsor will notify the sites when will the study enter the extension phase.

In the extension phase, subjects randomized in the experimental arm will continue on SHR-1210 in combination with rivoceranib, and subjects randomized in the control arm may have the option to crossover to receive experimental treatment and the decision made is upon investigator's clinical judgment. Subjects who are not eligible to crossover to experimental treatment per investigator clinical judgment can continue on sorafenib treatment. Subjects will continue to receive study treatment until they are no longer benefiting from treatment as assessed by investigator's clinical judgment.

The study clinical database will be closed at the initiation of the extension phase. Important safety information collection in the extension phase will be captured in the safety database. Only data collected prior to implementation of extension phase will be summarized in the clinical study report.

3.2. Measures to Minimize Bias

3.2.1. Randomization

See Section 4.3 for randomization criteria.

3.2.2. Evaluation of Success of Blinding

Not applicable.

3.2.3. Breaking the Study Blind/Participant Code

Not applicable.

4. SELECTION AND WITHDRAWAL OF SUBJECTS

Subjects will be allowed to participate in this study only when they meet the following criteria. All the medical and non-medical conditions of each subject should be considered as to whether they meet the study criteria.

Investigators should review, confirm and record whether the subject is suitable for participation in this study prior to enrollment.

4.1. Inclusion Criteria

Subjects can be enrolled in this study only when they meet all the inclusion criteria:

1. Provided informed consent and sign the informed consent form;
2. Male or female, ≥ 18 years old;
3. Histopathologically or cytologically confirmed HCC;

4. Subjects must be able to provide fresh or archived tumor tissue (formalin-fixed, paraffin-embedded [FFPE] tissue block or at least 5 unstained FFPE slides) as well as corresponding pathological report. If less than 5 unstained slides are available or tumor tissue is not available (e.g., used up due to previous diagnostic tests), subjects may be permitted to enroll on a case-by-case basis after discussion with the medical monitor;
5. Barcelona Clinic Liver Cancer (BCLC) stage B or C (see APPENDIX 1 for BCLC classification), and not suitable for surgical or local therapy, or has progressed following surgical and/or local therapy;
6. Local regional therapy (including but not limited to surgery, radiotherapy, hepatic artery embolization, TACE, hepatic arterial infusion, radiofrequency ablation, cryoablation or percutaneous ethanol injection) must has been completed at least 4 weeks (subjects received palliative radiotherapy at least 2 weeks) prior to baseline radiological scanning, and any toxicity (except alopecia) induced by local regional therapy must have resolved to ≤ Grade 1 in accordance with National Cancer Institute – Common Terminology Criteria for Adverse Event version 4.03 (NCI-CTCAE v4.03);
7. No previous systematic treatment for advanced HCC;
8. Have at least one measurable lesion (in accordance with RECIST v1.1, major diameter ≥ 10 mm of the measurable lesion in spiral CT scan or short diameter of swollen lymph node ≥ 15 mm; the lesion with previous local therapy can be used as target lesion after the progression is confirmed in accordance with RECIST v1.1);
9. Child-Pugh class (see APPENDIX 3 for Child-Pugh classification criteria): Grade A;
10. ECOG-PS score (see APPENDIX 4 for ECOG-PS scoring criteria): 0-1;
11. With a life expectancy of ≥ 12 weeks;
12. Have the required screening laboratory values including the following parameters (within 7 days prior to the start of study treatment):
    (1) Hematology: (except for hemoglobin, no blood transfusion or use of granulocyte colony-stimulating factor [G-CSF] or use of drugs for correction within 14 days prior to screening);
        - Absolute neutrophil count ≥1.5×10^9/L;
        - Platelet count ≥ 75×10^9/L;
        - Hemoglobin ≥ 90 g/L;
    (2) Blood biochemistry: (no infusion of albumin within 14 days):
        - Albumin ≥ 29 g/L;
        - Total bilirubin ≤ 1.5×upper limit of normal (ULN);
        - Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) ≤5×ULN;
        - Creatinine (Cr) ≤ 1.5×ULN or Cr clearance >50 mL/min (Cockcroft-Gault formula as below)
        - Male: Cr clearance =((140-age) ×weight)/ (72×blood Cr)

- Female: Cr clearance =((140-age) ×weight)/ (72×blood Cr) × 0.85
- Weight unit: kg; Blood Cr unit: mg/mL;

(3) International normalized ratio (INR) ≤2.3 or prothrombin time (PT) ≤6s beyond normal range;

(4) urine protein <2+ (subjects with urine protein ≥ 2+ may undergo 24-hour (h) urine protein quantification and those with 24-h urine protein quantity of <1.0 g can be enrolled);

13. If subjects have active hepatitis B (HBV) infection: HBV- deoxyribonucleic acid (DNA) must be < 500 IU/mL (or must be < 2500 copy/mL if copy/mL is the only unit available in the study site) and are willing to receive antiviral therapy throughout the study (treatment in accordance with local standard of care, e.g., entecavir); subjects with positive hepatitis C (HCV) ribonucleic acid (RNA) must receive antiviral therapy in accordance with the local standard treatment guideline and have ≤CTCAE Grade 1 elevated hepatic function;
14. Women of childbearing potential (WOCBP): must agree to use a reliable and valid contraceptive method (refer to Section 4.4.1) following the date of signature of informed consent form until at least 120 days after the last dose of study drug. The blood HCG test must be negative within 7 days prior to enrollment in the study; and the subjects must not be in lactating period.

    If the female subject has menses, has not reached postmenopausal state (absence of menses for ≥ consecutive 12 months, with no other reason found except menopause) and has not received sterilization operation (e.g., hysterectomy, bilateral tubal ligation or bilateral ovariectomy), she would be considered to have childbearing potential.

15. Male subjects whose partner are women of childbearing potential must agree to use reliable and valid contraceptive method (Section 4.4.1) following the date of signature of informed consent form till at least 120 days after the last dose of study drug. Male subjects must also agree to abstain from donation of sperm in the same period. Male subjects whose partners are pregnant must use a condom and no other contraceptive method is not required.

4.2. Exclusion Criteria

Subjects who meet any one of the following criteria must not be enrolled in this study:

1. Known hepatocholangiocarcinoma, sarcomatoid HCC, mixed cell carcinoma and lamellar cell carcinoma; other active malignant tumor except HCC within 5 years or simultaneously. Cured localized tumor, for example, basal cell carcinoma of skin, squamous cell carcinoma of skin, superficial bladder cancer, carcinoma in situ of prostate, carcinoma in situs of cervix, breast cancer in situ may be enrolled;
2. Planning to or previously received organ or allogenic bone marrow transplantation;
3. Moderate-to-severe ascites with clinical symptoms, i.e., requiring therapeutic puncture or drainage, or Child-Pugh score >2, except the subjects with small amount of ascites in radiological examination but free from clinical symptoms;

uncontrolled or moderate to severe pleural effusion, pericardial effusion.

4. History of gastrointestinal bleeding within 6 months prior to the start of study treatment or clear tendency of gastrointestinal bleeding, for example, at risk of bleeding or severe esophagogastric varices, locally active peptic ulcer, persistent fecal occult blood (+) (the fecal occult blood test should be repeated if it is positive at baseline, and gastroduodenoscopy [EGD] would be needed if it is still positive in repeated test; the subject can not be enrolled if the EGD shows esophageal and fundal varices with hemorrhagic risk or other gastrointestinal disorder with risk of bleeding);
5. Abdominal fistula, gastrointestinal perforation or intraperitoneal abscess within 6 months prior to the start of study treatment;
6. Known genetic or acquired hemorrhage (e.g., coagulation dysfunction) or thrombotic tendency, for example, subject with hemophilia; current or recent (within 10 days prior to the start of study treatment) use of full-dose of oral or intravenous anticoagulant or thrombolytic drug for the purpose of treatment (preventive use of low-dose aspirin or low molecular weight heparin is allowed);
7. Current or recent (within 10 days prior to the start of study treatment) use of aspirin (> 325 mg/day, maximum dose for antiplatelet) or dipyridamole, ticlopidine, clopidogrel and cilostazol;
8. Thrombosis or thromboembolic event within 6 months prior to the start of study treatment, for example, cerebrovascular accident (including transient ischemic attack, cerebral hemorrhage, cerebral infarction), pulmonary embolism;
9. Cardiac clinical symptom or disease that is not well controlled, for example, (1) > Grade II cardiac insufficiency in accordance with New York Heart Association (NYHA) criteria (see APPENDIX 5) or color Doppler echocardiography: LVEF (left ventricular ejection fraction) <50%; (2) unstable angina pectoris; (3) myocardial infarction within one year prior to the start of study treatment; (4) clinically significant supraventricular or ventricular arrhythmia requiring treatment or intervention; (5) QTc > 450ms (man) or QTc > 470ms (woman) (QTc interval is calculated by Fridericia formula; In case QTc is abnormal, it can be evaluated for three times at an interval of 2 minutes and the average value will be used);
10. Hypertension that can not be well controlled through antihypertensive drugs (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg) (based on the average of BP readings acquired from ≥ 2 measurements), allowing to reach the above parameters by the use of antihypertensive therapy; previous hypertensive crisis or hypertensive encephalopathy;
11. Major vascular disease within 6 months prior to the start of study treatment (for example, aortic aneurysm requiring surgical repair or peripheral arterial thrombosis in recent days);
12. Serious, uncured or splitting wound and active ulcer or untreated bone fracture;
13. Major surgical therapy within 4 weeks prior to the start of study treatment (except diagnosis), or expected major surgery during the study;

14. Inability to swallow tablets, malabsorption syndrome or any condition affecting gastrointestinal absorption;
15. Intestinal obstruction and/or clinical signs or symptoms of gastrointestinal obstruction within 6 months prior to the start of study treatment, including incomplete obstruction that is related with the original disease or needs routine parenteral hydration, parenteral nutrition or tube feeding;
    - If the subject has signs/symptoms of incomplete obstruction/ obstructive syndrome/intestinal obstruction at the initial diagnosis receives clear (surgical) therapy to resolve symptoms, the subject may be enrolled;
16. Evidence on intraperitoneal pneumatosis that can not be explained by puncture or recent surgery;
17. Previous or current presence of metastasis to central nervous system;
18. Metastatic disease involving main airway or blood vessels (e.g. vena cava tumor invasion or complete occlusion of the major portal vein due to HCC, the major portal vein is defined as the part of portal vein between the union of the splenic and superior mesenteric veins and the first bifurcation into the left and right vein) or high-volume mediastinal tumor mass located in the center (distance from carina <30 mm);
19. History of hepatic encephalopathy;
20. Current interstitial pneumonia or interstitial lung disease, or history of interstitial pneumonia or interstitial pneumonia requiring hormonal therapy, or other pulmonary fibrosis that may interfere with the judgement and treatment of immune-related pulmonary toxicity; organizing pneumonia (e.g., obliterative bronchiolitis), pneumoconiosis, drug related pneumonitis, idiopathic pneumonia, subjects with evidence on active pneumonia or serious pulmonary function impairment on thoracic computed tomography (CT) in screening period (previous radiation pneumonitis in the radiation area will be allowed);active tuberculosis;
21. Active autoimmune disease or history of autoimmune disease and may relapse (including but not limited to autoimmune hepatitis, interstitial pneumonia, uveitis, enteritis, hypophysitis, vasculitis, nephritis, hyperthyroidism, hypothyroidism [with the exception that it can be controlled by hormone replacement therapy]). Subjects with skin diseases that do not require systemic treatment are eligible, for example, leukoderma, psoriasis, alopecia, subjects with controlled type 1 diabetes by insulin are eligible; subjects with asthma that has been completely resolved in childhood and don’t need any treatment are eligible, but subjects with asthma that require a bronchodilator as medical intervention are not eligible;
22. Use of immunosuppressive medication within 14 days prior to the start of study treatment, or systemic corticosteroid therapy to achieve the objective of immunosuppression (Prednisone at the dose of >10 mg/day or equivalent);
23. Use of strong CYP3A4/CYP2C19 inducers, including rifampicin (and its analogues) and St. John’s Wort, or strong CYP3A4/CYP2C19 inhibitors within 14 days prior to the start of study treatment;

24. Known history of hypersensitivity to the active substance or to any other components of each investigational medicinal product as SHR-1210, rivoceranib, sorafenib or other monoclonal antibody or targeted anti-angiogenic drug;
25. Severe infection within 4 weeks prior to the start of study treatment, including but not limited to hospitalization for infection, bacteremia or complications of severe pneumonia; oral or intravenous therapeutic antibiotics within 2 weeks prior to the start of study treatment (subjects who are treated with preventive antibiotics for prevention, e.g., preventive urinary tract infection or exacerbation of chronic obstructive pulmonary disease are eligible for participation in the study);
26. Congenital or acquired immunodeficiency (e.g., HIV infection);
27. Hepatitis B and hepatitis C co-infection;
28. Previous treatment with other PD-1 antibody or other immunotherapy against PD-1/PD-L1, or previous use of rivoceranib or sorafenib;
29. Attenuated live vaccine therapy administered within 28 days prior to the start of study treatment, or are expected to receive vaccines during SHR-1210 treatment or within 60 days after the last dose of SHR-1210;
30. Treatment of other investigational product(s) within 28 days or 5 half-lives (whichever is longer) prior to the start of study treatment;
31. Other factors that may affect the study results or lead to forced termination of the study early as judged by investigators, such as alcoholism, drug abuse, other serious diseases (including mental disorders) requiring concomitant therapy, with serious laboratory examination abnormality, with family or social factors, that may affect subject's safety.

4.3. Randomization Criteria

Subjects who enter screening and meet the inclusion/exclusion criteria after signing the informed consent form, will be randomized in a 1:1 ratio to SHR-1210 combined with rivoceranib mesylate group (experimental arm) or sorafenib group (control arm). Randomization stratification factors are as follows:

1. Macrovascular invasion and/or extrahepatic metastasis (presence vs. absence)
2. Geographical region (Asia vs. countries outside of Asia)
3. Baseline AFP (AFP < 400 ng/mL vs. AFP ≥ 400 ng/mL)

4.4. Lifestyle Requirements

4.4.1. Contraception

Male subjects with azoospermia (due to vasectomy or other underlying disease) and partners do not need to take contraception.

Female subjects are considered as not of childbearing potential if:

(1) Postmenopausal (defined as absence of menses for at least 12 months without other medical reasons; female subjects younger than 45 years of age without hormonal

contraception or hormone replacement therapy whose follicle-stimulating hormone (FSH) levels reached postmenopausal levels). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient;

Or

(2) having hysterectomy and/or bilateral ovariectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion surgery at least 6 weeks prior to screening;

Or

(3) the presence of congenital or acquired conditions leading to infertility.

Female subjects of childbearing potential and male subjects with partners who are women of childbearing potential are required to use to contraception and follow one of the following contraception requirements, from the time the subject signs the informed consent until at least 120 days after the last dose of study drug:

(1) Abstinence (avoid heterosexual intercourse) †.

Or

(2) use a reliable and effective method of contraception during heterosexual intercourse.

Reliable, effective methods of contraception include:

Single method of contraception (any one of the following methods):

- Intrauterine device (IUD)
- Subcutaneous implant contraception

Two methods combined contraception (two of the following methods must be used simultaneously):

- Vaginal diaphragm/spermicide (cannot be combined with cervical cap/spermicide) *
- Cervical cap/spermicide (only for women who have not given birth) *
- Contraceptive sponge (only for women who have not given birth) *
- Male condom or female condom (not used concurrently)
- Hormonal contraception: Oral contraceptives (estrogen/progesterone or progesterone), contraceptive patch, vaginal contraceptive ring, or subcutaneous injection contraceptives

† For those who choose to completely not have a sexual life, abstinence (avoiding heterosexual intercourse) can be used alone for contraception. Periodic abstinence (e.g., based on ovulation, symptomatology etc.) and external ejaculation are not reliable and effective contraception.

In addition, the subject needs to be aware that once he/she stops using the selected contraceptive method, or he/she or his/her partner is suspected or confirmed to be pregnant, the investigators need to be notified immediately.

4.5. Subjects' Withdrawal from the Study or Discontinuation of Study Treatment

4.5.1. Criteria for Discontinuation of Study Treatment

Discontinuation of study treatment do not represent withdrawal from the study. Subjects who discontinued study treatment should continue to complete the remaining study visits as required in the protocol. Subjects should discontinue study treatment when any of the following conditions occurs:

- Subject requests discontinuation of study treatment;
- Efficacy evaluation meets criteria for progression of disease confirmed by BIRC (according to RECIST v1.1), unless investigator considers the subject still has clinical benefit and meets the criteria for treatment beyond progression (Disease progression will be confirmed by the investigator per RECIST v1.1 upon approval of Protocol v6.0; other procedures and criteria remain unchanged, see Section 6.6 of the protocol);
- Pregnancy in female subject occurs during the study;
- Unacceptable toxicity despite dose modification, or occurrence of adverse event, abnormal laboratory examination, or concomitant diseases, then it is no longer in the best interests of the subjects to continue study treatment according to the judgment of the investigator;
- Overall deterioration of health status, inability to continue participation in the trial;
- Significant protocol deviation or violations confirmed by sponsor, e.g., ineligibility of subjects after enrollment;
- Termination of study by the sponsor;
- Other reasons for inability to continue study treatment, as considered by investigators.

4.5.2. Criteria for Withdrawal from the Study

Subjects can withdraw from the study voluntarily at any time, or at the request of the investigator or the sponsor for safety or behavioral reasons, or inability to comply with the visit schedule or procedure required in the protocol at his/her study site.

The reasons for withdrawal from the study may include:

- Withdrawal of the informed consent on participation in the study, and refusal of further follow-up;
- Any conditions which require subject's withdrawal, per Investigator's discretion e.g., subject's loss of the ability to express his/her wishes freely due to imprisonment or segregation;
- Lost to follow-up;
- Termination of study by the sponsor.

4.5.3. The Procedures of Withdrawal from the Study or Discontinuation of Study Treatment

Subjects should comply with the follow-up schedule specified in the protocol after discontinuation of study treatment. The efficacy and safety examination specified in the protocol at the end of treatment, and safety follow-up should be completed, and the full records of AEs and outcomes, concomitant medications/therapy should be provided. Investigators can advise or provide new or alternative therapeutic method to subjects according to their actual condition. The subjects with no progression of disease need to continue the radiological evaluation according to the scheduled frequency and time, until start of a new antitumor therapy or progression of disease. The radiological evidence on progression of disease should be obtained as much as possible for such subjects.

If subject refuses to return to the site for further visit, his/her survival status should still be followed up, unless the subject withdraws the consent on disclosure of further information or continuous contact. If the subject requests withdrawal from the study clearly, the investigator should record the extent of subject's request on withdrawal from the study procedure in a written form, i.e., only withdrawal from study treatment and/or withdrawal from post-treatment follow-up. When it is necessary to know the survival state, only the publicly available information should be used appropriately to determine whether the subject survives.

4.5.4. Lost to Follow-Up

Every possible effort must be made to know and report the subject's status, including contact with the subject. Lost to follow-up is defined as no response to at least three contacts. The contact method includes but is not limited to any of the following: telephone, fax, message, social media tools and email. All the attempts to make contact should be recorded in the medical document. If the subject is confirmed to be dead, the study center will use a permitted method to acquire the information on death and cause of death. The study center can also utilize public resources, for example, community health registry and database, to obtain the contact information. If the subject's status can still not be acquired after all the attempts have been made, investigators should report the last date when the subject is known to be survived and record it in the medical record.

4.6. Early Termination or Suspension of Study

The study can be terminated or interrupted prematurely if the reason is sufficient. This may be due to the decision of regulatory agency, IRB/EC's opinion, Data Monitoring Committee (DMC)'s opinion, or efficacy or safety issues of the investigational product, or base on the sponsor's judgment. In addition, Jiangsu Hengrui Pharmaceuticals Co., Ltd. reserves the right to stop research and development of SHR-1210 at any time. The party who makes the decision on termination/interruption of the study will send a written notice which records the reason for study termination or interruption to investigators, sponsor and regulatory authorities. Investigators should notify the ethics committee and the sponsor immediately and provide relevant reasons.

The reasons for premature termination or interruption of the study may include:

- Discovery of unexpected, significant or unacceptable risk;
- The efficacy data support early termination of the study;
- Low compliance with study requirements.

Once the aforementioned drug safety, protocol compliance and data quality issues causing study interruption are solved and after obtaining the consent of the sponsor, the ethics committee or the local regulatory authority, the study can proceed.

4.7. Definition of End of Study

Definition of end of study is as follows:

The date when the last subject randomized has been followed for at least 2 years.

5. STUDY TREATMENT

5.1. Description of the Investigational Product

5.1.1. Acquisition and Accountability

Management, dispensing and recovery of the investigational product for this clinical study will be performed by designated person. Investigators must make sure all the investigational products are only used for the subjects who participate in this clinical trial, the dosage and administration method should be in accordance with the protocol, the remaining drugs should be given back to the sponsor and must not be used for any treatment besides this study.

The study drug should be stored under the conditions specified in the study protocol. The drug receipt form must be signed by both parties in duplicate when the drugs are dispensed to sites, one for the clinical research center and the other for the sponsor. At the end of the study, the remaining drugs and empty boxes will be returned, and the two parties need to sign the drug return form. The dispensation and return of study drug should be recorded on a specialized form in time.

Monitors are responsible for monitoring the supply, use, storage of the investigational drug and disposing the remaining drug.

5.1.2. Formulation, Appearance, Packaging and Storage of Drug

Information on SHR-1210 for injection, rivoceranib mesylate tablets and sorafenib tosylate tablets are as below（pls. refer to the pharmacy manual in details）:

Experimental arm: SHR-1210 for Injection

Manufacturer: Suzhou Suncadia Biopharmaceuticals Co., Ltd.

Dosage form: injection (lyophilised powder)

Strength: 200 mg /vial

Package: vial

Administration: intravenous infusion

Validity: 24 months

Storage: Store in a refrigerator (2°C - 8°C). Do not freeze, protect from light

Experimental arm: rivoceranib mesylate tablets

Manufacturer: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Dosage form: film-coated tablet

Strength: 0.25 g

Package: 10 tablets/blister/box

Administration: oral

Validity: 24 months

Storage: Protected from light, stored in closed container/closure at no more than (NMT) 25ºC

For the United States of America: Store at 20ºC to 25ºC (68°F to 77°F), excursions permitted to 15ºC to 30ºC (59°F to 86°F), [see USP Controlled Room Temperature]. Keep away from light

Control arm: sorafenib tosylate tablets

Manufacturer: Bayer AG

Dosage form: film-coated tablet/tablet

Strength: 0.2 g

Package: 10 tablets/blister*8 blisters/box (mainland of China), 28 tables/blister*3 blisters/box (other countries and regions beyond mainland of China)

Administration: oral

Validity: 36 months

Storage: Do not store above 25°C

5.1.3. Storage and Stability

Investigators or their authorized representatives (e.g., pharmacist) will ensure all the investigational products are stored in a controlled secure area that meets the storage conditions (see storage conditions in Section 5.1.2), and the storage is in accordance with the requirements of applicable laws.

The study center must be able to record the highest and lowest temperatures per working day for all study drugs storage locations (e.g., freezing, cold storage or room temperature). The cycle of recording should start with receiving drugs until all the remaining study drugs are recovered. Even though there is a continuous monitoring system, the study center should also keep record logs to ensure the correct storage temperature. The temperature monitoring devices and storage devices (e.g., freezer) should be checked on a regular basis, as to ensure it functions normally.

Any deviations from the recommended storage conditions on the product label should be reported promptly to the sponsor. The study center should take active measures as

early as possible to place the product under the storage conditions described on the label, meanwhile, the temperature deviation and measures taken will be reported to the sponsor.

The study drug affected by the temperature deviation should be isolated temporarily in the environment meeting the storage conditions, only can be used until receiving the permission by the sponsor. The sponsor will provide the study center with detailed steps to report the temperature deviation.

5.1.4. Preparation

Preparation of SHR-1210 is provided in the investigational product manual in detail.

5.1.5. Dose Regimen

Each treatment cycle is defined as 4 weeks (28 days). Dose regimens during treatment period are shown in Table 7.

Table 7 Dosing Regimens for Each Treatment Cycle

Experimental arm: SHR-1210 combined with rivoceranib	Rivoceranib	250 mg, once per day (QD) orally, after meals within 30 minutes, for administration, one treatment cycle is 4 weeks (28 days).
	SHR-1210	SHR-1210 intravenous infusion at a dose of 200 mg over 30 minutes (no less than 20 minutes and no more than 60 minutes, including a wash-out period), once every two weeks (Q2W), one treatment cycle is 4 weeks (28 days). Complete administration before ECG if possible. The interval between two doses should not be less than 12 days. **On the day of rivoceranib PK blood sampling, rivoceranib should be administrated at the study center before SHR-1210, see SCHEDULE OF ACTIVITIES and BLOOD SAMPLE COLLECTION TABLE for details.**
Control arm: Sorafenib	Sorafenib	400 mg, twice per day (BID), orally under fasted state (at least 1 hour prior to a meal or 2 hours after a meal), for continuous administration, one treatment cycle is 4 weeks (or 28 days).

If a subject in the experimental arm (SHR-1210 in combination with rivoceranib) develops a treatment-related AE that leads to permanent discontinuation of rivoceranib and the investigator determines that the subject can benefit from SHR-1210 monotherapy, the subjects may continue to receive SHR-1210 monotherapy until meeting the criteria for study treatment discontinuation as specified in this protocol, and vice versa. In addition, during the study treatment period, if a subject in the experimental arm develops a treatment-related AE that leads to temporary discontinuation of SHR-1210 or rivoceranib, the subject may continue to receive monotherapy, and the combination therapy can be resumed only after the toxicity resolves.

Study treatment will continue until the subject develops an intolerable toxicity, withdrawal of informed consent, and disease progression confirmed by BIRC according to RECIST v1.1 (when the subject appears to have met the criteria for disease

progression assessed by the investigator according to RECIST v1.1, the investigator must submit the radiological data to BIRC immediately. If BIRC evaluates it as non-disease progression according to RECIST v1.1, the subject should continue to receive the study drug treatment and continue the tumor radiological evaluation; if BIRC confirms it as disease progression based on RECIST V1.1, at this time, the investigator needs to assess whether the subject still has clinical benefit. If the subject is considered to still have clinical benefit and meets the criteria for continuing treatment after the disease progresses [see Section 6.6 for details] the subject may continue to receive study treatment; if the subject is no longer considered to have clinical benefit , the treatment may be discontinued),or other discontinuation criteria specified in the protocol, whichever occurs first. Administration 3 days after the date of intended SHR-1210 administration will be considered as delayed administration. Upon the approval of protocol v6.0, disease progression will be only judged by investigator per RECIST v1.1.

If a subject missed a dose of rivoceranib and it was ≥12 hours away from next planned dose, the rivoceranib dose should be made up on current day, if < 12 hours away from next planned dose, that dose should be skipped and dosing resumed at subsequent dose as planned, without doubling the dose of the next day. If a subject receives an overdose of rivoceranib, contact the investigator immediately.

If a subject missed a dose of sorafenib at a scheduled timepoint, the missed dose will not be made up and the next dose should be taken as planned. If the subject has an overdose of sorafenib, contact the investigator immediately.

Any vomiting after administration with sorafenib or rivoceranib should not be made up.

5.1.6. Dose Adjustment and Safety Management

5.1.6.1. Dose Adjustment

5.1.6.1.1. Criteria for Dose Adjustment of SHR-1210

Dose adjustment is not allowed for SHR-1210, only dose interruption is allowed.

5.1.6.1.2. Criteria for SHR-1210 Dose Delay

The dose of SHR-1210 should be delayed if the following conditions occur:

- Any ≥ Grade 2 drug-related non-cutaneous AE, except Grade 2 drug-related fatigue or laboratory abnormalities (unless otherwise specified);
- Any Grade 3 drug-related cutaneous AE;
- Any Grade 3 drug-related laboratory abnormalities, except Grade 3 abnormal amylase or lipase unrelated with the symptoms and clinical manifestations of pancreatitis;
- The administration will be delayed if the following AST, ALT or total bilirubin abnormalities occur:
  - AST and ALT at baseline are within the normal range, and drug-related elevated AST or ALT reaches >3×ULN;
  - AST or ALT at baseline elevates no greater than Grade 1, and drug-related

elevated AST or ALT reaches >5×ULN;

- AST or ALT at baseline elevates no greater than Grade 2, and drug-related elevated AST or ALT reaches >2 times the baseline or either AST or ALT reaches >8×ULN (whichever is lower);
- Total bilirubin at baseline is within the normal range, and drug-related elevated total bilirubin reaches >2×ULN;
- Total bilirubin at baseline elevates no greater than Grade 1, and drug-related elevated total bilirubin reaches >2 times the baseline.

- The administration needs to be delayed for any AE, laboratory abnormalities or complications, as judged by investigators;
- If RCEP occurs during the trial, refer to APPENDIX 7 for detailed suggestions on grade and management of RCEP.
- If subjects have fever (>38°C) and need medication, or obvious symptoms of asthma, shortness of breath, and asphyxia during the trial, SHR-1210 will not be given any more at this or next scheduled time point before the symptom is recovered. SHR-1210 will be resumed after the symptom is relieved and stabilized for more than 7 days, and pneumonia will be excluded through radiological examination prior to administration if necessary.

Subjects who need delayed dose should be monitored every week, and the frequency of monitoring can be increased if clinically indicated. It is recommended to monitor liver function every three days, until the highest value of AST or ALT starts to decrease. When meeting the criteria for resumption of medication (see Section 5.1.6.1.3), the study drug can be resumed.

Tumor evaluation still needs to proceed for all subjects, as required in the protocol, regardless of dose delay. During the period of dose delay, safety visits and laboratory examinations should also be performed as planned in the protocol, or more frequently when clinically indicated (see SCHEDULE OF ACTIVITIES Footnote [4]).

5.1.6.1.3. Criteria for Resumption of SHR-1210

When drug-related AE recover to Grade 1 (or lower grade) or baseline level, SHR-1210 study treatment can be resumed, except the following:

- The therapy can be resumed for the subjects with Grade 2 fatigue that has not been recovered;
- The therapy can be resumed for Grade 2 cutaneous AE;
- Subjects with AST, ALT or TBIL grade 1 elevation at baseline, and delayed SHR-1210 for reasons other than drug-related hepatic AE, the therapy can be resumed in the presence of AST, ALT or TBIL Grade 2 elevations;
- As the subjects who delay the dose for drug related elevated AST, ALT or TBIL, when these parameters are recovered to baseline CTCAE grade or normal (see Section 5.1.6.1.4) but who have not reached the criteria for permanent discontinuation of the treatment, the study drugs can be resumed;

- The therapy can be resumed for drug related grade 2 laboratory abnormalities in GGT and/or ALP increase;
- In case the drug related endocrine disorder can be sufficiently controlled only with hormone replacement at physiological dose, the treatment can be resumed.

The dose of SHR-1210 is allowed to be delayed for up to 12 weeks, as calculated from the last dose. In case the subject still does not reach the criteria for dose resumption after delay for 12 weeks, the study drug needs to be discontinued permanently, except the exception mentioned in the Section 5.1.6.1.4. The guideline on management of adverse reactions is seen in APPENDIX 6 in detail. Rules for hepatic AEs management can be referred to in Section 5.1.6.2.2.

5.1.6.1.4. Criteria for Permanent Discontinuation of SHR-1210

The study drug SHR-1210 must be discontinued permanently when the following conditions occur:

- Any Grade Stevens-Johnson syndrome and toxic epidermal necrolysis;
- Any Grade 2 drug-related uveitis, ophthalmodynia and blurred vision that has no response to local therapy and is not recovered to Grade 1 after delayed dose; or the above AE requiring systemic therapy;
- Any Grade 3 drug-related non-cutaneous AE lasting for >7 days, except the following:
  - When any Grade 3 drug-related uveitis, myocarditis, encephalitis, pneumonia, bronchospasm, hypersensitivity or infusion reaction occurs, the study treatment must be terminated;
  - In case the drug-related endocrine disorders can be sufficiently controlled only with hormone replacement therapy at physiological doses, the treatment does not need to be terminated;
  - The treatment does not need to be terminated for Grade 3 drug-related abnormal laboratory examination, however, the study drug must be terminated for Grade 3 thrombocytopenia >7 days or related with bleeding.
- Hepatotoxicity meeting the following:
  - AST or ALT >10 times of ULN for over two weeks;
  - ALT or AST >15 × ULN;
  - TBIL >8 times of ULN for subjects with elevated TBIL at baseline, >5 times of ULN for subjects with normal TBIL at baseline.
- Any Grade 4 drug-related AE or abnormal laboratory examination, except the following:
  - Grade 4 granulocytopenia is less than7 days;
  - Grade 4 lymphopenia or leukopenia;
  - Isolated Grade 4 elevated amylase or lipase, without symptoms or clinical manifestations of pancreatitis;

  - Isolated Grade 4 electrolyte imbalance/abnormality without clinical sequela that could be corrected through supplements/appropriate management within 72h after occurrence;
  - If Grade 4 drug-related endocrine disorders that can be sufficiently controlled only with hormone replacement therapy at physiological doses, the treatment does not need to be discontinued.

- The study treatment must be discontinued if SHR-1210 needs to be delayed for >12 weeks, except the following:
  - After the use of cortisol for treatment of drug-related AEs, the dose of SHR-1210 is allowed to be delayed for >12 weeks due to the need for dose tapering. Discussion with the sponsor must be made before resuming the dose. During the dose delay, tumor assessment should continue as required by the protocol. Safety visits and laboratory tests should also be performed at the original frequency or more frequently if clinically indicated (see SCHEDULE OF ACTIVITIES Footnote [4]);
  - SHR-1210 delay for >12 weeks due to non-drug related reasons must be discussed with the sponsor prior to resuming treatment. During the dose delay, the tumor evaluation should still proceed as required in the protocol. Safety visits and laboratory examinations should also be performed as planned in the protocol or more frequently when clinically indicated (see SCHEDULE OF ACTIVITIES Footnote [4]);
- For intolerable or persistent Grade 2 drug-related AE, the dose of SHR-1210 can be interrupted as appropriate, if the treatment-related toxicity can not be recovered to Grade 0-1 12 weeks after the last dose of SHR-1210, the drug should be discontinued permanently.
- If any drug-related AE (except endocrine lesions) of ≥ Grade 3 (≥ Grade 2 for pneumonia) reoccurs, discontinuation of the study treatment can be considered, which may be judged by the investigator according to the condition of each subject;
- Judged by investigators, clinical AE, laboratory abnormalities or complications may bring major risk to subjects who continue taking the study drug;
- Progression of disease confirmed by BIRC in accordance with RECIST v1.1 (see APPENDIX 2 for details) (unless the subject meets the criteria for treatment beyond progression in Section 6.6).

Even though SHR-1210 is discontinued, subjects must continue to perform tumor evaluation as required in the protocol.

After SHR-1210 is discontinued, subjects are allowed to continue rivoceranib monotherapy if they are judged by investigators to be able to benefit from rivoceranib monotherapy, until occurrence of the events which meet the criteria for discontinuation of treatment specified in the protocol.

5.1.6.1.5. Criteria for Dose Modification of Rivoceranib

Dose modification methods resulted from rivoceranib-related toxicities include dose interruption, adjustment of administration schedule (first adjustment: take 5 days

followed by interruption of the drug for 2 days (5 days on 2 days off [5 on 2 off]); re-adjustment: once every other day [QOD]) and termination of rivoceranib. After the administration schedule of rivoceranib is adjusted during the study, will not allow going back to initial administration schedule.

If rivoceranib-related AEs definitely occur during the trial, for example, hypertension, proteinuria, hand-foot syndrome, rivoceranib can be interrupted; when the toxicity is recovered, maintenance of dose at the current dose level, adjustment of administration schedule or discontinuation of dose can be given as appropriate. The subject can continue to receive SHR-1210 monotherapy after rivoceranib is discontinued.

Referring to the experience in phase II clinical studies, the investigator must interrupt the dose of SHR-1210 and rivoceranib at the same time (See Section 5.1.6.1.2 criteria for SHR-1210 dose delay reference), for the confirmed immune-related toxicities during the trial, in particular immune pneumonia/pneumonitis, hepatitis, increased AST, ALT, bilirubin, diarrhea or colitis, increased creatinine. The dose can be resumed when the toxicity is recovered to ≤Grade 1 or baseline level (for subjects with abnormal ALT, AST and TBIL during baseline). It is recommended to resume SHR-1210 first, and then administer rivoceranib after 7-14 days of no significant abnormality observed after administration of SHR-1210. The subsequent administration schedule for rivoceranib will be adjusted (first adjustment: 5 days on 2 days off [5 on 2 off]; re-adjustment: once every other day [QOD]).

Changes in blood pressure should be monitored routinely during rivoceranib administration. It is advisable to interrupt the dose of rivoceranib firstly in case Grade 3 elevated blood pressure occurs (systolic blood pressure ≥ 160mmHg or diastolic blood pressure ≥ 100mmHg or more than one antihypertensive agent is needed) and perform antihypertensive therapy under specialist's instructions. Rivoceranib can be resumed when the blood pressure is decreased to normal range (systolic blood pressure < 140 mmHg and diastolic blood pressure < 90 mmHg). If there is still hypertension, the administration schedule of rivoceranib must be adjusted. For subjects with hypertensive crisis (systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 120mmHg, and/or with progressive insufficiency of target organs), the rivoceranib should be discontinued immediately and symptomatic treatment should be given actively (antihypertension, dehydration, anti-convulsion and so on).

Dose interruption use and adjustment of administration schedule of rivoceranib is needed for ≥ Grade 3 hematological toxicities or ≥ Grade 2 non-hematological toxicities; for the non-hematological toxicities, symptomatic treatment can be given actively for controllable nausea, vomiting and fever with determined cause (<38ºC), with no need of immediate dose interruption or adjustment of administration schedule.

Symptomatic treatment should be given promptly for the symptom/sign or laboratory abnormalities during the trial, and it is recommended to refer to the following table for corresponding dose modification:

Table 8 Dose Adjustment Plan of Rivoceranib

Drug-related toxicity	Grade	Dose interruption of rivoceranib (Yes or No)	Criteria on dose resumption of rivoceranib	Dosage modification method of rivoceranib	Criteria on discontinuation of rivoceranib
Hematologic toxicities	Grade 1, Grade 2	No	—	—	—
	Grade 3	Yes (except lymphocyte count decreased)	When the toxicity is recovered to ≤Grade 2	First time: at original dose Second time: 5 days on 2 days off; Third time: once every other day	If Grade 3 or above hematological toxicities recur after adjustment for twice, dose of rivoceranib must be discontinued.
	Grade 4	Yes	When the toxicity is recovered to ≤Grade 2	First time: 5 days on 2 days off; Second time: once every other day	
Other non-hematologic toxicity	Grade 1	No	—	—	—
	Grade 2 (lasted for ≥ 7d)	Yes	When the toxicity is recovered to ≤Grade 1	Original dose	—;
	Grade 3	Yes	When the toxicity is recovered to ≤Grade 1 or baseline	First time: 5 days on 2 days off; Second time: once every other day	If Grade 3 non-hematological toxicities recur after adjustment for twice, rivoceranib must be discontinued*.
	Grade 4	Yes	—	Permanently discontinue rivoceranib	Terminated administration of rivoceranib

Drug-related toxicity	Grade	Dose interruption of rivoceranib (Yes or No)	Criteria on dose resumption of rivoceranib	Dosage modification method of rivoceranib	Criteria on discontinuation of rivoceranib
Hypertension	Grade 3	Yes	When the toxicity is recovered to ≤Grade 1	First time: resume the dose at original dose level Second time: 5 days on 2 days off; Third time: once every other day	If Grade 3 hypertension recurs after adjustment for twice, rivoceranib must be discontinued.
	Hypertensive crisis	Yes	—	Permanently discontinue rivoceranib	Terminated administration of rivoceranib
Proteinuria (without significantly elevated blood creatinine)	Grade 3 (24h urine protein (quantitative))	Yes	When the toxicity is recovered to ≤Grade 2	First time: 5 days on 2 days off; Second time: once every other day	If Grade 3 proteinuria recurs after adjustment for twice, rivoceranib must be discontinued.
Hand-and-foot syndrome	Grade 3	Yes	When the toxicity is recovered to ≤Grade 1	First time: 5 days on 2 days off; Second time: once every other day	If Grade 3 hand-foot syndrome recurs after adjustment for twice, rivoceranib must be discontinued.
Headache	Grade 2 headache lasted for ≥ 7d after symptomatic treatment, or Grade 3 headache	Yes	When the toxicity is recovered to ≤Grade 1	First time: 5 days on 2 days off; Second time: once every other day	If headache recurs after adjustment for twice, rivoceranib must be discontinued.

*: If cerebral hemorrhage, ≥ Grade 2 pulmonary hemorrhage, ≥ Grade 3 other hemorrhage, arterial thrombosis, leukoencephalopathy syndrome, gastrointestinal perforation, or nephrotic syndrome occurs during the trial, rivoceranib will be permanently discontinued and symptomatic treatment will be given actively, and subsequently a decision will be made on whether SHR-1210 monotherapy should be continued based on the recovery of toxicity. If Stevens-Johnson syndrome or toxic epidermal necrolysis occurs, permanently discontinue rivoceranib and SHR-1210.

For the significant toxicity that is still ongoing after symptomatic treatment during the trial, including Grade 2 non-hematological toxicities lasting for two weeks or more (except asymptomatic Grade 2 hypertension), laboratory abnormalities (except proteinuria <2g/24h), investigators can consider dose interruption based on the subject's tolerability, and adjust the administration schedule of rivoceranib subsequently after the toxicities are recovered.

During the study, in combination with the recommendations on the dose adjustment above, investigators can give appropriate dose adjustment through comprehensive analysis of the occurrence of drug-related toxicities (e.g., multiple Grade 2 toxicities related with the study drug, poor intolerability to study drug), and can consider adjust the administration schedule of rivoceranib after dose interruption and recovery of the toxicity.

5.1.6.1.6. Criteria for Dose Modification of Sorafenib

Subjects receiving sorafenib will be given 400 mg (two tablets, 200 mg per tablet) orally, twice per day, under fasted state (at least 1 hour prior to meal or at least 2 hours after a meal) with a cup of warm drinking water.

Dose adjustment resulted from drug-related toxicities include dose interruption, dose reduction and discontinuation. When dose reduction is required during treatment, sorafenib should be reduced to 400 mg once per day, if additional dose reduction is required, could refer to the locally approved drug label or local standard of care practice/treatment guideline. It is not allowed for dose level less than 400mg every other day. The criteria for interruption or discontinuation of sorafenib can be found in the label of sorafenib tosylate tablets approved by the local health authority in detail or local standard of care practice/treatment guideline. For any dose interruption, sorafenib treatment can be interrupted for up to 30 days.

Cutaneous toxicities are the most common adverse reactions of sorafenib. Cutaneous related dose modification refer to Table 9 or based on the sorafenib label of approved by the local health authority. Other toxicities related dose modifications refer to sorafenib label approved by the local health authority.

In principle, dose escalation is not allowed; however, in accordance with the package insert of sorafenib tosylate tablet approved by the FDA, "Following improvement of Grade 2 or 3 dermatologic toxicity to Grade 0–1 after at least 28 days of treatment on a reduced dose of sorafenib, the dose of sorafenib may be increased one dose level from the reduced dose." The investigator may make the decision based on the subject's condition.

Table 9 Dose Adjustment of Sorafenib When Dermatologic Toxicities Occur

Dermatologic Toxicity Grade	Occurrence	Suggested Dose Modification
Grade 1: Numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema or discomfort of the hands or	Any occurrence	Continue treatment with sorafenib and consider topic therapy for symptomatic relief

feet which does not disrupt the subject's normal activities		
Grade 2: Painful erythema and swelling of the hands or feet and/or discomfort affecting the subject's normal activities	1st occurrence	Continue treatment with sorafenib and consider topic therapy for symptomatic relief. If no improvement within 7 days, see below
	No improvement within 7 days or 2nd or 3rd occurrence	Interrupt sorafenib treatment until toxicity resolves to Grade 0–1 When resuming treatment, decrease sorafenib dose by one dose level (400 mg daily or 400 mg every other day [a])
	4th occurrence	Discontinue the sorafenib
Grade 3: Moist desquamation, ulceration, blistering or severe pain of the hands or feet, or severe discomfort that causes the subject to be unable to work or perform activities of daily living	1st or 2nd occurrence	Interrupt sorafenib treatment until toxicity resolves to Grade 0–1 When resuming treatment, decrease sorafenib dose by one dose level (400 mg daily or 400 mg every other day [a])
	3rd occurrence	Discontinue sorafenib treatment

a. Please refer to label of sorafenib approved by the local health authority if needed.

5.1.6.2. Safety Management on the Safety of Oncology Drugs

5.1.6.2.1. Rules for Safety Management of Immuno-Oncology Drugs

The AEs induced by Immuno-Oncology (I-O) drugs vary from other types of antitumor drugs, the severity and duration are special. SHR-1210 belongs to this type of drugs, thus it is required to achieve early identification and management of the AEs induced by it, in order to reduce the incidence of serious toxicities. To identify I-O drug related AEs, the investigator may refer to the following definition and diagnosis of immune-related colitis, pneumonitis and hepatitis:

Definition of immune-related colitis: A disorder characterized by inflammation of the colon.

Diagnostic work-up of immune-related colitis suggested as follows:

1) Symptoms include diarrhea, abdominal pain, hematochezia, weight loss, fever and vomiting.
2) To rule out infection: For Grade 2 AEs, work-up of blood (complete blood cell count, comprehensive metabolic panel, thyroid-stimulating hormone, erythrocyte sedimentation rate, C-reactive protein) and stool (bacterial culture, *Clostridium difficile*, parasites, viral etiology) are recommended to be performed; radiological (e.g., CT scan of the abdomen and pelvis) as well as endoscopy and biopsy should be considered. For Grade 3-4 AEs, all the work-up listed above for Grade 2 AEs should be completed immediately.

3) Consider repeating endoscopy for subjects who do not respond to immunosuppressive agents.

Definition of immune-related pneumonitis: Focal or diffuse inflammation of the lung parenchyma (typically identified on CT radiological).

Diagnostic work-up of Immune-related pneumonitis suggested as follows:

1) Respiratory events like cough and dyspnea;
2) Thoracic CT scan;
3) Hematology: including complete blood cell count, urea nitrogen, blood electrolytes, creatinine, liver function tests, thyroid function tests, blood calcium, C-reactive protein, and erythrocyte sedimentation rate;
4) Infection should be ruled out by bronchoscopy, especially for ≥ Grade 2 AEs;
5) Consider sputum sample and screening for viral, opportunistic or specific bacterial infections depending on the clinical context.

Definition of immune-related hepatitis: A disorder characterized by a viral pathological process involving the liver parenchyma.

Diagnostic work-up of immune-related hepatitis suggested as follows:

1) Assessed for signs and symptoms of hepatitis;
2) Transaminases and bilirubin measured before every cycle of treatment;
3) If hepatitis develops, disease-related causes, concomitant drug administration (including alcohol) and infectious causes, particularly viral hepatitis, should be ruled out. Other thromboembolic and outflow obstructive etiology should also be excluded through radiological;
4) Liver biopsy may be considered in assisting in the differential diagnosis of more severe hepatic reactions.

In addition, the investigator may refer to the rules for safety management of similar products in overseas markets to facilitate evaluation and management of I-O drug related AEs occurring in the following systems:

- Gastrointestinal tract
- Kidney
- Lung
- Liver
- Endocrine
- Skin

APPENDIX 6 and APPENDIX 7 provide the recommended treatment procedures for common immune-related adverse reactions. Note that the rules for management of hepatic irAEs have been amended in this protocol (see Section 5.1.6.2.3 below).

5.1.6.2.2. Principles of Management for Immune-Related Adverse Events

In overall principle, according to the severity of adverse reaction, interruption of SHR-1210 is taken as the main measure, resumption of SHR-1210 can be considered when the severity of adverse event has recovered to Grade 1 or below, and SHR-1210 should be discontinued permanently when serious Grade 3 or life-threatening Grade 4 adverse event occurs (For details, refer to Sections 5.1.6.1.2, 5.1.6.1.3 and 5.1.6.1.4 of this protocol which state criteria for dose delay, dose resumption, and permanent discontinuation of SHR-1210).

Management of immune-related adverse events should be based on the medical practice of the research center and the guidelines. Recommended treatment procedures for common immune-related adverse events are detailed in APPENDIX 6 (Note that the rules for management of hepatic irAEs have been amended in this protocol [see Section 5.1.6.2.3 below]). The classification and management of reactive capillary endothelial proliferation (RCEP) are detailed in APPENDIX 7.

5.1.6.2.3. Rules for Management on Hepatic Adverse Events of SHR-1210

Below are suggestions on management of hepatic AEs that may occur in the experimental arm during the SHR-1210 treatment period of this study:

- If the dose is delayed for 3-5 days and AST or ALT level is not improved but even exacerbated, cortisol, i.e., methylprednisolone 0.5-2 mg/kg/day or equivalent oral drugs, will be given;
- In case of AST or ALT >8 times of ULN, cortisol, i.e., methylprednisolone 1-2 mg/kg/day or equivalent oral drugs, will be given immediately, and meanwhile, a consultation from the department of gastroenterology is advised;
- If AST or ALT level is not improved but even exacerbated 3-5 days after the start of corticosteroids treatment, other immunosuppressants may need to be added, such as mycophenolate 1g BID;
- Once AST or ALT is decreased by one CTCAE Grade, the dose can be decreased gradually in no less than one month.

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

5.1.6.2.4. Infusion Reaction of SHR-1210

As SHR-1210 is one fully humanized monoclonal antibody, the possibility of infusion or allergic reaction is low, and preventive medication is not needed prior to infusion. Allergic reaction is most likely to occur within 24h after infusion. Once the allergic reactions occur, the infusion should be slowed down or interrupted based on the condition, and clinical supportive treatment is needed. The preventive medication should be given prior to the subsequent doses. The allergic reactions are possibly characterized by fever, intolerance of cold, chills, headache, rash, pruritus, arthralgia, low or high blood pressure, or bronchospasm. All the Grade 3 or 4 infusion reactions should be reported to the sponsor within 24 hours and reported as SAE in case of meeting the criteria for SAE. See detailed reporting methods in Section 8.2.

Response to allergic reactions should be based on the medical practice and guidelines of the study site. See recommendations for the treatment of infusion reactions in Table 10.

Table 10 Recommendations for the Treatment of Infusion Reactions

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

5.1.6.2.5. Rules for Management of Adverse Events of Rivoceranib

Management of rivoceranib-related adverse events can be performed according to clinical practice in this study protocol, and the following recommendations are provided for your reference.

1. Hand-and-foot syndrome

Hand-foot syndrome (HFSR): is palmar-thenar hypoesthesia or erythema at extremities, one of the cutaneous toxicity, is more obvious at the pressed or forced area when it occurs. It may appear in tumor subjects during chemotherapies or molecular targeted therapies. HFSR is characterized by numbness, hypoesthesia, paresthesia, stabbing pain, analgesia or edema pain, cutaneous swelling or erythema, desquamation, chapping, hardened blister or serious pain, etc.

Grading:

Grade 1: numbness, dysesthesia/paresthesia of hand and/or foot, painless swelling or erythema and/or discomfort that has no effect on normal activities.

Grade 2: painful erythema and swelling of hand and/or foot and/or discomfort that affects subject's daily life.

Grade 3: moist desquamation, ulcer, blister or serious pain of hand and/or foot and/or serious discomfort that makes subject unable to work or engage in daily activities. Intense pain, loss of skin function, comparably rare.

Symptomatic treatment and measures:

Recommended some necessary supportive treatments include intensive skin care, keeping skin clean to avoid secondary infection; avoiding pressure or scratching; using moisturizing cream or lubricant, including local use of lotion or lubricant containing urea and corticosteroids; and local use of anti-fungal or antibiotic therapy when necessary.

Note: If ≥ Grade 3 hand-foot syndrome occurs for consecutive three times, with an aggravating tendency, the administration of rivoceranib should be terminated.

2. Hypertension

Subjects should be enrolled strictly in accordance with the requirement of blood pressure in the inclusion/exclusion criteria, subjects with hypertension can achieve controlled through adjustment of the dose of antihypertensive agents or adding of new antihypertensive agents prior to taking the study drugs, the blood pressure should be controlled within 140/90 mmHg.

Monitoring and management of hypertension:

Daily blood pressure monitoring (based on the average of BP readings acquired from ≥ 2 measurements) is recommended after the initiation of rivoceranib mesylate treatment.

Once hypertension occurs, the following treatment can be given: Angiotensin II receptor blockers (ARB), angiotensin-converting enzyme inhibitors (ACEI), β receptor blockers, etc. Or combined use of the aforementioned drugs.

If subjects have hypertension or exacerbation of hypertension during administration, should take following actions:

1) Adjusting the administration of study drugs as specified in the protocol (see Section 5.1.6.1.5);

2) Starting to take antihypertensive agents or adjusting the dose.

Advise subjects to record daily blood pressure measurements in a subjects' diary. If they are taking hypertension drugs at the same time, they are required to keep a detailed record of the drug name, dosage, method and frequency of use, and related complaints or symptoms of discomfort.

The hypertension treatment drugs are recommended as below:

1) Angiotensin-converting enzyme inhibitors (ACEI);
2) Angiotensin II receptor antagonists (ARB);
3) dihydropyridine calcium channel antagonists;
4) β receptor blockers.

Use of diuretics is not recommended for anti-hypertensive therapy; nicardipine, diltiazem and verapamil with CYP3A4 inhibitory effect are prohibited. Rivoceranib mesylate should be discontinued in subjects with hypertensive crisis.

3. Proteinuria

Proteinuria should be closely monitored for all the subjects throughout the treatment, and intensively monitored in subjects who have history of hypertension; the 24-hour urine protein quantification must be performed for the subjects with urine protein ≥2+.

Note: Rivoceranib mesylate shall be discontinued in case nephrotic syndrome occurs.

4. Hemorrhage of digestive tract

Active symptomatic treatment should be given when gastrointestinal hemorrhage occurs, including persistently positive result of fecal occult blood, haematemesis or bloody stool. The subjects who are judged as upper gastrointestinal hemorrhage should be fasted and given acid suppression agents, drugs for gastric mucosa protection hemostasis (Transamin, Reptilase, etc.) treatment, and octreotide can be used when necessary; hemostasis, blood transfusion and supportive treatments will be given for those with lower gastrointestinal hemorrhage; surgical assistance may be required immediately if the hemorrhage can not be controlled. Adjustment of medication in accordance with the principle in Section 5.1.6.1.5 in the protocol.

5. Thrombosis

Rivoceranib mesylate should be discontinued immediately for any arterial thrombosis (e.g., cerebral ischemia, stroke, angina pectoris, myocardial infarction, etc.). Rivoceranib mesylate should be temporarily discontinued in case symptomatic venous thrombosis occurs.

Symptomatic treatment, surgery or anticoagulants should be given immediately for thrombotic symptoms.

5.1.6.2.6. Rules for Management of Adverse Events of Sorafenib

1. Skin toxicity:

Hand-foot cutaneous reactions and rash are the most common adverse reactions of sorafenib. Usually, the rash and hand-foot skin reactions are mostly CTCAE Grade 1-2 and mostly occur within 6 weeks after the start of administration of sorafenib. Recommended necessary symptomatic and supportive treatments include intensive skin care, keeping skin clean to avoid secondary infection; avoiding pressure or scratching; using moisturizing cream or lubricant, including local use of lotion or lubricant containing urea and corticosteroids; and local use of anti-fungal or antibiotic therapy when necessary. Subjects with serious and persistent cutaneous toxicities may need to discontinue sorafenib permanently. Permanently discontinued for the serious cases.

2. Gastrointestinal side effects:

It is one of the common adverse reactions of sorafenib and mainly characterized by abdominal pain and diarrhea, which are generally mild-to-moderate and may be associated with the direct irritation of gastrointestinal mucosa of sorafenib after a long absorption in digestive tract and change of pH over time during its metabolism. Generally, the symptoms can be relieved through eating less residue, low-fiber diet, and digestible food. Subjects with serious diarrhea need to be closely observed. Infusion should be given as supportive treatment in case of dehydration, which would supply enough water and electrolytes.

3. Hypertension:

The incidence of hypertension will be increased in subjects given sorafenib. Drug-related hypertension is mostly mild-to-moderate, usually occurs in early stage after taking medicine, and can be controlled with routine antihypertensive agents. The blood pressure should be monitored routinely and controlled within 140/90 mmHg. Advise subjects to record daily blood pressure measurements in the dairy card in detail. Wherever necessary, high blood pressure will be treated in accordance with standard antihypertensive regimen, and chief complaints or symptoms as well as dosing information (e.g., drug name, dose, route of administration and frequency) will be recorded in detail. Permanent discontinuation of sorafenib needs to be considered for subjects who still have serious or persistent hypertension after use of antihypertensive agents or have hypertensive crisis.

4. Hemorrhage:

The incidence of hemorrhage may be increased after administration of sorafenib. Active symptomatic treatments should be given when gastrointestinal hemorrhage occurs, including persistently positive result of fecal occult blood, hematemesis or bloody stool. The subjects who are judged as upper gastrointestinal hemorrhage should be fasted and given acid suppression agents, drugs for gastric mucosa protection, hemostasis (Transamin, Reptilase, etc.) treatment, and octreotide can be used when necessary; hemostasis, blood transfusion and supportive treatments will be given for those with lower gastrointestinal hemorrhage; surgical assistance may be required immediately if the hemorrhage can not be controlled. Once treatment is needed, it is advisable to

consider permanent discontinuation of sorafenib. Hemorrhage or elevated INR occurs occasionally in part of subjects taking sorafenib and warfarin simultaneously. INR and PT should be detected routinely and attention should be paid to the sign of clinical hemorrhage in subjects given concomitant warfarin.

5. Myocardial ischemia and/or myocardial infarction:

Discontinuation of sorafenib should be considered for subjects with drug-related myocardial ischaemia and/or myocardial infarction.

6. Gastrointestinal perforation:

Gastrointestinal perforation is rare. The incidence of gastrointestinal perforation is less than 1% reported in subjects given sorafenib. Once it occurs, sorafenib should be discontinued.

7. Liver impairment:

Sorafenib is mainly eliminated via liver, and its exposure will be elevated in the subjects with hepatic impairment. Symptomatic and supportive treatment must be taken, the dose of sorafenib must be reduced or interrupted in case of drug related abnormal hepatic function. And discontinuation of the treatment should be considered if the symptom is serious and ≥ Grade 3 on an ongoing basis.

Refer to the label of sorafenib tosylate tablets for details.

5.2. Management, Distribution and Recovery of Drugs

5.2.1. Drug Preparation

The study drug should be prepared by qualified person in accordance with the brochure of study drug.

5.2.2. The Disposal of Remaining Drugs

Investigators or their authorized representatives should record the date and dose of the drug administered for each subject. The residual investigational products will return to the sponsor regularly for destruction after being counted. If the remaining drugs should be destroyed at study sites, investigators must ensure the destruction is in accordance with applicable environmental laws and regulations, unit policies and other applicable terms, also need to provide relevant procedures for destruction. All the destructions should be well recorded.

5.3. Concomitant Therapy

All treatments and medications (excluding solvent) used from 28 days prior to the signature of informed consent form to the end of safety follow-up should be recorded in the eCRF with raw data strictly in accordance with the GCP. If adverse events occur, the subject should be closely observed, as well as actively given symptomatic treatment if necessary, which is fully documented in medical records, and the drug and non-drug treatment used shall be recorded and specified in the eCRF. Only the concomitant

medication/therapy that is used to manage the study drugs related AE/SAE should be recorded after the above collection periods.

5.3.1. Prohibited or Cautiously Used Medications and Treatments During the Study

5.3.1.1. Drugs and Therapies Prohibited for All the Subjects During the Study

Subjects are prohibited from using modern traditional Chinese medicines that have been approved by the NMPA (or by regulatory authorities in other countries) for the indication of HCC (including but not limited to Delisheng Injection, Kanglaite Injection, Aidi Injection, Huaier Granule and Ganfule Tablets) and immune-modulators (including but not limited to interferon, interleukin-2, thymosin, etc.) during the study.

During the treatment period of this study, subjects are not allowed to receive any local therapies against liver tumor lesion and targeted lesion (except palliative local therapies described in Section 5.3.2.4), and other systemic antitumor therapies, such as chemotherapies, molecular targeted therapies, hormone therapies, immunotherapies, and so on.

Subjects are not allowed to use other investigational products for antitumor therapy during the treatment period of this study.

Section 4.2 (Exclusion Criteria) of the protocol describes other drugs prohibited in this study.

5.3.1.2. Drugs Prohibited for Subjects Given SHR-1210 During the Study

Subjects are not allowed to receive immunosuppressive therapies simultaneously during the treatment period of this study (except management on the treatment-related adverse events).

Systemic corticosteroid cannot be used at the dose of >10 mg/day (Prednisone or equivalent) during SHR-1210 treatment period, except for treatment-related AEs treatments or short-term preventive therapies. SHR-1210 will be resumed until systemic corticosteroid dose has been reduced at ≤10 mg/day (Prednisone or equivalent).

Vaccination of live vaccine are prohibited within 4 weeks prior to the first dose of study drugs until 60 days after the last dose.

5.3.1.3. Drugs Used Cautiously or Prohibited for Subjects Given Rivoceranib During the Study

There was a study conducted by Bao et al [24], in which apatinib (also known as rivoceranib) was evaluated for its in vitro inhibitory effect on the major CYP enzymes including CYP3A2/4, CYP2B1/6, CYP2C9/11, CYP2D1/6, and CYP2E1 using human and rat microsomes. The IC50 and IC50-shift results indicated that rivoceranib might not be a time-dependent inhibitor. Rivoceranib was a weak inhibitor of human CYP2E1 (IC50>10 μM) but inhibited CYP2B6/2B1 and CYP2D6/2D1 in a competitive way (Ki = 3.84/0.59 and 5.41/0.87 μM), and inhibited CYP3A4/3A2 and rat CYP2E1 in a

mixed way (Ki = 11.50/1.83 and 13.06 μM). On CYP2C9, Rivoceranib exhibited the noncompetitive inhibition (Ki = 0.71 μM) while it inhibited CYP2C11 uncompetitively (Ki = 3.30 μM). These results are consistent with the findings in the JHM and LSK IB, in which rivoceranib has the most potent inhibitory effect on CYP2C9, with lesser on CYP3A4 and CYP2C19.

- In vitro studies have shown that rivoceranib is mainly metabolized by the liver P450 enzymes CYP3A, CYP2C9, and CYP2C19, strong inhibitors and inducers of CYP3A and CYP2C19 will significantly increase or decrease clearance of rivoceranib with increased or decreased exposures of rivoceranib. Therefore, the strong inhibitors and inducers of CYP3A and CYP2C19 will be prohibited (see Appendix 11 for listings of strong inhibitors and inducers of CYP3A and 2C19, there are no strong inhibitors or inducers of CYP2C9).
- Sensitive substrates of CYP3A4 will be used with caution.
- As the potential DDI for rivoceranib as a perpetrator of CYP2C9 exists, the following instructions will be implemented until further information is available: Drugs metabolized by CYP2C9 with narrow therapeutic index: warfarin, and phenytoin, will be prohibited. Drugs that are sensitive substrate of CYP2C9, such as celecoxib will be used with caution.
- Drugs metabolized by CYP2D6 with narrow therapeutic index thioridazine, and pimozide, will be prohibited. Drugs that are sensitive substrates of CYP2D6 atomoxetine, desipramine, dextromethorphan, metoprolol, nebivolol, perphenazine, tolterodine, and venlafaxine will be used with caution.

The following transporter substrates with narrow therapeutic index are prohibited: P-gp substrates dabigatran, and digoxin, MATE1, MATE-2K, OCT2 substrate dofetilide (FDA's Web site on Drug Development and Drug Interactions can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm and drug bank for narrow therapeutic index https://www.drugbank.ca/categories/DBCAT003972. See Appendix 11)

The transporter inhibitors are reported to increase transporter substrates' AUC ≥1.5 to ≥2 fold, and thus fall into the category of moderate inhibitors. They are to be advised used with caution (FDA's Web site on Drug Development and Drug Interactions http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm. See Appendix 11 for detailed listings)

- It is necessary to avoid the concomitant use of drugs that prolong the QT interval prior to (approximately 5 half-lives of the concomitant drug) and during study enrollment. These drugs may include antibiotics, fluoroquinolones, macrolides, and anti-arrhythmics, angina relieving drugs, antipsychotic drugs, antifungal drugs, antimalarial drugs, antihistamines, gastrointestinal antiemetic and promoting drugs, and antidepressants, etc.

- Subjects should be advised to restrict use of proton pump inhibitors (PPIs). Subjects should be encouraged to avoid concomitant administration of rivoceranib with acidic modifiers or H2 blockers. If these concurrent medicines are needed, they should be taken 5 hours after the studied drug administration. For other prohibited concurrent medicines please refer to Appendix 11.

5.3.1.4. Drugs Used Cautiously for Subjects Given Sorafenib During the Study

Rifampicin, one strong CYP3A4 inducer, once per day at the dose of 600 mg in healthy volunteers, for consecutive 5 days, and single dose of oral sorafenib 400 mg, can lead to decrease of average AUC of sorafenib by 37%. Therefore, strong CYP3A4 inducers (such as dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital, rifapentine, Hypericum perforatum L [also known as St John's-wort], etc.) should be avoided as concomitant medications; they may accelerate metabolism of sorafenib and decrease the concentration of sorafenib.

The combined use of sorafenib with neomycin may lead to decreased bioavailability of sorafenib by above 50%.

In addition, investigators can refer to the label of sorafenib tosylate tablets and combine with clinical practice for more detailed descriptions of the drugs prohibited or used cautiously for such subjects during the study.

5.3.2. Permitted Concomitant Medications and Treatments During the Study

5.3.2.1. Antiviral Treatment

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

Subjects with HBV infection can continue the original antiviral therapy if HBsAg is positive and they have started antiviral therapy and achieved satisfactory control of virus (HBV-DNA <500 IU/mL) prior to inclusion in the study; subjects with suboptimal viral control are recommended to switch to other standard anti-HBV medication (e.g., Entecavir) as recommended by local guidelines, and subjects can be enrolled when HBV-DNA is <500 IU/mL; subjects with newly discovered HBV infection in screening period can start standard anti-HBV treatment as recommended by local guidelines (e.g., Entecavir) immediately and can be enrolled when HBV-DNA is <500 IU/mL.

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

5.3.2.2. Steroids

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

5.3.2.3. Other Systemic Therapies

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

5.3.2.4. Palliative Local Treatment

Palliative therapy for local non-target lesions causing obvious symptoms is allowed, for example, bone pain; local radiotherapies or surgery and management of pleural effusion and ascites can be considered, however, the following conditions must be met:

- These lesions are known to be present at enrollment;
- Progression of disease must be judged by investigators, for subjects who need local therapy due to deterioration of symptoms during the study;
- Subjects with progression of disease must meet the criteria for treatment beyond progression (see Section 6.6 for the details);
- The lesions for local therapy cannot be target lesions;
- Subjects should interrupt the dose of investigational product until the end of recovery period of palliative therapy, whilst receiving palliative local therapy.

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

5.3.3. Surgery or Palliative Radiotherapy

Any surgery or palliative radiotherapy should have theoretical basis and necessity during the study. At the interval between the treatment and use of investigational products, recovery that has no effect on the wound and search for the reason of unknown hemorrhage must be performed as much as possible. In accordance with the label of rivoceranib, it is advised to interrupt the dose of rivoceranib prior to the operation to 30 days and after the operation. It is recommended in the label of sorafenib that the time of dose interruption of sorafenib will be based on the type of operation and status of wound healing and depend on clinician's specific judgment. Besides that, it is recommended to interrupt the dose of study drugs at least 14 days prior to, during and at least 14 days after palliative radiotherapy, in this protocol, the dose resumption in the subjects receiving surgery depends on the clinical evaluation of wound healing and postoperative recovery.

6. STUDY PROCEDURES

The utmost efforts will be made to ensure all the tests and procedures required in the protocol go as planned. However, unexpected things may happen sometimes and be beyond investigator's control, making it difficult to test. In these cases, the investigator will take all steps necessary to ensure the safety and interests of the subject. When one test required in the protocol can not be performed, investigators need to record the

reason. In addition, the study team need to be informed of the accidental situation in time.

6.1. Screening Period

The screening period begins with the signing of the informed consent form and ends with the randomization or screening failure. Termination of this study after signing the informed consent form and prior to randomization will be regarded as screening failure. Subjects with screening failure can be re-screened. They must sign the informed consent form again, re-register and obtain a new subject number at the re-screening. Subjects can only be re-screened once.

Subjects must sign the informed consent form before performing any screening procedure specified in this study. In case routine radiological evaluation has been performed for tumors prior to the signing of the informed consent form, computed tomography (CT), magnetic resonance radiological (MRI) or bone scan does not need to be repeated in screening period as long as they are completed within 28 days prior to the start of study drug (42 days prior to start of study drug is acceptable for bone scan), and meet the requirement for radiological evaluation in this study.

Unless otherwise noted, collection of the following data should be completed within 28 days prior to the start of study drug:

- Obtain the informed consent form signed by the subject;
- Assign subject number (subjects will be assigned a unique number in the study: the subject number reflects the numbering of study sites and numbering of subjects within the same study site; the numbering of subjects shall be in accordance with the sequence in which the subjects sign the informed consent form, for example, 001, 002, 003, etc.);
- Collect demographic characteristics;
- Collect medical history (including history of tumor and past medical history, see the SCHEDULE OF ACTIVITIES for details);
- Tumor tissue collection (for detailed instructions regarding tumor tissue sampling, refer to the laboratory manual. If tumor sample is not accessible in special case, it can be discussed with Sponsor on a case-by-case basis);
- Collect concomitant medications/therapies;
- Collect AE;
- Tumor radiological evaluation: the radiological evaluation prior to the signing of informed consent form and within 28 days prior to the first dose is acceptable, and will be performed based on RECIST v1.1 (evaluated by investigator and BIRC), mRECIST (evaluated by BIRC only) and imRECIST (evaluated by investigator only). All the measurable and evaluable tumor lesions should be evaluated and recorded, including enhanced CT/MRI scan of thorax, abdomen, pelvis and site of lesions, brain enhanced MRI or enhanced CT scan (excluding intracranial metastasis). Thoracic plain CT scan and abdominal, pelvic and brain MRI can be

performed in case of allergy to the contrast agent for enhanced CT; bone scan can be performed only when clinically indicated;

- Check eligibility criteria.

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

- ECOG-PS score (see APPENDIX 4 for details);
- Perform a careful, comprehensive physical examination: height, weight, head and face, skin, lymph nodes, eye, ear, nose, throat, mouth, respiratory system, cardiovascular system, abdomen, genitourinary system, musculoskeletal, neurological and mental status;
- Vital signs (performed after sitting still for 5 minutes): including temperature (whenever possible, the same method of measurement should be used throughout), blood pressure, pulse rate and respiratory frequency;
- Virology (including HBV, HCV, HIV markers, see study flow chart for the specific requirement);
- Fecal occult blood test;
- 12-lead ECG (performed after sitting still for at least 5 minutes): heart rate and QTc interval (calculated using Fridericia's formula);
- Echocardiography, including LVEF;
- AFP test;
- Thyroid function (TSH, FT3 or TT3, FT4);
- Collect concomitant medications/therapy;
- Collect AE;
- Check eligibility criteria.

The following information need to be collected within 7 days prior to the first dose of study drug:

- Child-Pugh class (see APPENDIX 3 for details);
- Hematology: including complete blood count and category (white blood cell, red blood cell, lymphocyte, monocyte, neutrophil, basophil, eosinophil), hemoglobin, platelet count;
- Urinalysis: including white blood cell, red blood cell, urine protein. In case urine protein is ≥ 2＋, 24-hour urine protein quantification must be added;
- Blood biochemistry: including ALT, AST, total bilirubin, γ-glutamyl transferase (GGT), direct bilirubin, ALP, LDH, albumin, blood urea nitrogen (BUN) or urea, creatinine, blood glucose, amylase (lipase test needs to be added if amylase level is abnormal and clinically significant);

- Blood electrolytes: including potassium, sodium, chlorine, calcium, magnesium, phosphorus;
- Coagulation parameters: including INR and/or PT (if INR can not be collected, PT will be used as the basis for judgment);
- Blood human chorionic gonadotropin (HCG) test for female subjects of childbearing potential;
- Collect concomitant medications/therapy;
- Collect AE;
- Check eligibility criteria;
- Subjects can be randomized if they meet all the inclusion criteria and do not meet any of the exclusion criteria.

6.2. Treatment Period

Physical examination and laboratory examinations will be performed during treatment, AE and concomitant medications will be collected, drug dispensation, recovery and verification will be recorded, the distribution, verification and return of subject's diary will be completed.

Prior to administration of study drug at specified visits and any other study evaluation conducted at clinical centers, all the subjects need to complete EORTC QLQ-C30, QLQ-HCC18 and EQ-5D-5L questionnaires.

The following information must be collected within 72 hours prior to administration of study drug at the visits specified in each cycle of therapy:

- Hematology: including complete blood count and category (white blood cell, red blood cell, lymphocyte, monocyte, neutrophil, basophil, eosinophil), hemoglobin, platelet count;
- Urinalysis: including white blood cell, red blood cell, urine protein. In case urine protein is ≥ 2＋, 24-hour urine protein quantification must be added;
- Blood biochemistry: including ALT, AST, total bilirubin, γ-glutamyl transferase (GGT), direct bilirubin, ALP, LDH, albumin, blood urea nitrogen [BUN] or urea, creatinine, blood glucose, amylase (lipase test needs to be added if amylase is abnormal and clinically significant);
- Blood electrolytes: including potassium, sodium, chlorine, calcium, magnesium, phosphorus;

The following information must be collected within 24h prior to administration of study drug at the visits specified in each cycle of therapy:

- ECOG-PS score (see APPENDIX 4 for details);
- Weight and physical examination of important sites: cutaneous system, respiratory system, cardiovascular system, abdomen and mental state. In addition, physical

examination of reactive capillary endothelial proliferation needs to be performed on the experimental arm;

- Vital signs (performed after sitting still for 5 minutes): including temperature (whenever possible, the same method of measurement should be used throughout), blood pressure, pulse rate and respiratory frequency;

If dose delay occurs, required examination during study treatment need to be performed as planned or more frequently if clinically indicated. Echocardiography and blood HCG test can be monitored at any time, if necessary. Also, in accordance with RECIST v1.1 (investigator and BIRC evaluation), mRECIST (only for BIRC evaluation) and imRECIST (only for investigator evaluation), all evaluations during the treatment period, with randomization as baseline, will be performed once every 8 weeks (56 days) ±7 days in the first 48 weeks, once every 12 weeks (84 days) ±7 days afterwards, and additionally performed when clinically indicated. When there is no BIRC determined progression of disease (according to RECIST v1.1), tumor evaluation should be continued, regardless of discontinuation of study treatment, unless death, withdrawal of informed consent, start of subsequent antitumor therapy or termination of study by the sponsor, whichever comes first; the evaluation includes the enhanced CT/MRI scan of thorax, abdomen, pelvis and site of lesions. Thoracic plain CT scan, abdominal and pelvic MRI can be performed in case of allergy to the contrast agent for enhanced CT; cranial CT/MRI and bone scan can be performed only when clinically indicated. Throughout the study, each subject must use the same procedure for radiological examination. Investigators must review the results prior to the next cycle of therapy. The subjects who have achieved remission (complete remission or partial remission) for the first time need to be confirmed by the next scheduled evaluation or repeated evaluation ≥ 4 weeks after the first evaluation.

Subjects with BIRC determined progression (according to RECIST v1.1) can continue to use SHR-1210 monotherapy or combination with rivoceranib (experimental arm) or sorafenib (control arm) if investigator assess they meet the criteria defined in Section 6.6.

Upon approval of protocol V6.0, disease progression will only need to be confirmed by investigator per RECIST v1.1.

6.2.1. Cycle 1

The following examination/step or collection of the following information needs to be completed on Day 1:

- If completed within 24h prior to the first dose in screening period, no examination is needed on C1D1:
  - ECOG-PS score (see APPENDIX 4 for details);
  - Weight and physical examination of important sites: cutaneous system, respiratory system, cardiovascular system, abdomen and mental state. In addition, physical examination of reactive capillary endothelial proliferation needs to be performed on the experimental arm;

  - Vital signs (performed after sitting still for 5 minutes): including temperature (whenever possible, the same method of measurement should be used throughout.), blood pressure, pulse rate and respiratory frequency,

- 12-Lead ECG (performed after sitting still for 5 minutes): heart rate and QTc interval (the latter is calculated by Fridericia formula); for the experimental arm, the ECG should be performed 2.5 hours (±1 hour) after the administration of rivoceranib;

- Pre-dose sampling: the blood sample will be collected only from experimental arm (SHR-1210 combined with rivoceranib): 0.5 hours prior to administration of rivoceranib on Day 1 of Cycle 1 (C1D1), 6 mL venous blood will be collected for detection of the serum concentration and immunogenicity of SHR-1210;

- ECG blood sampling: Blood sample will be collected at 2.5 hours (±1 hour) after rivoceranib on Day 1 of Cycle 1 (C1D1) and ECG should be performed first; PK samples will be collected within 15 minutes after ECG. Approximately 2 mL venous blood will be collected for detection of concentration of rivoceranib;

- Randomization: subjects will be randomized into either the experimental arm or control arm after their data are reviewed and determined to be in accordance with the inclusion/exclusion criteria, and the first dose should be given within 24 hours following randomization;

- Intravenous infusion of SHR-1210 (experimental arm);

- Oral administration of rivoceranib (experimental arm) or sorafenib (control arm) (daily, continuously);

- Distribution of subject's diary;

- Subject's self-evaluation results: all the subjects will complete EORTC QLQ-C30, QLQ-HCC18 and EQ-5D-5L questionnaires prior to administration of study drug and any other study evaluation at clinical centers;

- Collect concomitant medications/therapy;

- Collect AE.

The following examinations/steps or collection of the following information needs to be completed on Day 15 (±3 days):

- Weight and physical examination of important sites: cutaneous system, respiratory system, cardiovascular system, abdomen and mental state. In addition, physical examination of reactive capillary endothelial proliferation needs to be performed on the experimental arm;

- Vital signs (measured after sitting still for 5 minutes): including temperature (whenever possible, the same method of measurement should be used throughout), blood pressure, pulse rate and respiratory frequency;

- Hematology: including complete blood count and category (white blood cell, red blood cell, lymphocyte, monocyte, neutrophil, basophil, eosinophil), hemoglobin, platelet count;

- Urinalysis: including white blood cell, red blood cell, urine protein. In case urine protein is ≥ 2＋, 24-hour urine protein quantification must be added;
- Blood biochemistry: including ALT, AST, total bilirubin, γ-glutamyl transferase (GGT), direct bilirubin, ALP, LDH, albumin, blood urea nitrogen [BUN] or urea, creatinine, blood glucose, amylase (lipase test needs to be added if amylase level is abnormal and clinically significant);
- Blood electrolytes: including potassium, sodium, chlorine, calcium, magnesium, phosphorus;
- 12-lead ECG (performed after sitting still for at least 5 minutes): heart rate and QTc interval (calculated using Fridericia's formula); it should be performed 2.5 hours (±1 hour) after rivoceranib administration in experimental arm;
- Collect concomitant medications/therapies;
- Collect AE;
- Intravenous infusion of SHR-1210 (experimental arm);
- Oral administration of rivoceranib (experimental arm) or sorafenib (control arm) (daily, continuously);
- Distribution, verification and return of subject's diary.

6.2.2. Cycles 2 and 3

The following examinations/steps or collection of the following information needs to be completed on Day 1 (±3 days):

- ECOG-PS score (see APPENDIX 4 for details);
- Child-Pugh class (see APPENDIX 3 for details);
- Weight and physical examination of important sites: cutaneous system, respiratory system, cardiovascular system, abdomen and mental state. In addition, physical examination of reactive capillary endothelial proliferation needs to be performed on the experimental arm;
- Vital signs (performed after sitting still for 5 minutes): including temperature (whenever possible, the same method of measurement should be used throughout), blood pressure, pulse rate and respiratory frequency;
- Virology (only performed on C3D1, including HBV, HCV markers, see study flow chart for specific requirement);
- Hematology: including complete blood count and category (white blood cell, red blood cell, lymphocyte, monocyte, neutrophil, basophil, eosinophil), hemoglobin, platelet count;
- Urinalysis: including white blood cell, red blood cell, urine protein. In case urine protein is ≥ 2＋, 24-hour urine protein quantification must be added;

- Blood biochemistry: including ALT, AST, total bilirubin, γ-glutamyl transferase (GGT), direct bilirubin, ALP, LDH, albumin, BUN or urea, creatinine, blood glucose, amylase (lipase test needs to be added if amylase level is abnormal and clinically significant);
- Blood electrolytes: including potassium, sodium, chlorine, calcium, magnesium, phosphorus;
- Coagulation parameters: including INR and/or PT (if INR can not be collected, PT will be used as the basis for judgment);
- Fecal occult blood test;
- AFP;
- Thyroid function (only performed on C3D1, TSH, FT3 or TT3, FT4);
- 12-lead ECG (performed after sitting still for at least 5 minutes): heart rate and QTc interval (calculated using Fridericia's formula); it should be performed 2.5 hours (±1 hour) after rivoceranib administration in experimental arm;
- Pre-dose sampling: the blood sample will be collected only from experimental arm (including SHR-1210 combined with rivoceranib, SHR-1210 monotherapy and rivoceranib monotherapy). The time point for sample collection will be with 0.5 hours prior to administration of rivoceranib on Day 1 of Cycle 2 and 3 (C2D1, C3D1). If SHR-1210 and/or rivoceranib is temporarily interrupted, pre-dose immunogenicity and PK sample will be collected on schedule. If only rivoceranib is temporarily interrupted, time point for collection is within 0.5 hours before SHR-1210 administration. Approximately 8 mL venous blood will be collected for detection of the serum concentration and immunogenicity of SHR-1210 (6 mL) and concentration of rivoceranib (2 mL); The exact time of the previous administration of rivoceranib will be collected (provided by the subject);
- ECG blood sampling: The blood samples will be collected only for the measurement of the concentrations of rivoceranib. Blood samples will be collected at 2.5 hours (±1 hour) post rivoceranib administration on Day 1 of Cycle 2 and 3 (C2D1, C3D1). ECG will be performed first followed by blood collection within 15 minutes after ECG. If rivoceranib is temporarily interrupted, the post-ECG sample will not be collected. Approximately 2 mL venous blood will be collected for determine the concentration of rivoceranib;
- Intravenous infusion of SHR-1210 (experimental arm);
- Oral administration of rivoceranib (experimental arm) or sorafenib (control arm) (daily, continuously);
- Distribution, verification and return of subject's diary;
- Subject's self-evaluation results: all the subjects will complete EORTC QLQ-C30, QLQ-HCC18 and EQ-5D-5L questionnaires prior to administration of study drug and any other study evaluation at clinical centers;
- Collect concomitant medications/therapy;

- Collect AE.

The following examinations/steps or collection of the following information needs to be completed on Day 15 (±3 days):

- Weight and physical examination of important sites: cutaneous system, respiratory system, cardiovascular system, abdomen and mental state. In addition, physical examination of reactive capillary endothelial proliferation needs to be performed on the experimental arm;
- Vital signs (measured after sitting still for 5 minutes): including temperature (whenever possible, the same method of measurement should be used throughout.), blood pressure, pulse rate and respiratory frequency;
- Hematology: including complete blood count and category (white blood cell, red blood cell, lymphocyte, monocyte, neutrophil, basophil, eosinophil), hemoglobin, platelet count;
- Urinalysis: including white blood cell, red blood cell, urine protein. In case urine protein is ≥ 2＋, 24-hour urine protein quantification must be added;
- Blood biochemistry: including ALT, AST, total bilirubin, γ-glutamyl transferase (GGT), direct bilirubin, ALP, LDH, albumin, blood BUN or urea, creatinine, blood glucose, amylase (lipase test needs to be added if amylase level is abnormal and clinically significant);
- Blood electrolytes: including potassium, sodium, chlorine, calcium, magnesium, phosphorus;
- Collect concomitant medications/therapy;
- Collect AE;
- Intravenous infusion of SHR-1210 (experimental arm);
- Oral administration of rivoceranib (experimental arm) or sorafenib (control arm) (daily, continuously);
- Distribution, verification and return of subject's diary.

6.2.3. Cycle 4 and Onwards

The following examinations/steps or collection of the following information needs to be completed on Day 1 (±3 days):

- ECOG-PS score (see APPENDIX 4 for details);
- Child-Pugh class (see APPENDIX 3 for details);
- Weight and physical examination of important sites: cutaneous system, respiratory system, cardiovascular system, abdomen and mental state. In addition, physical examination of reactive capillary endothelial proliferation needs to be performed on the experimental arm;

- Vital signs (measured after sitting still for 5 minutes): including temperature (whenever possible, the same method of measurement should be used throughout.), blood pressure, pulse rate and respiratory frequency;
- Virology (once every two cycles, for example, C5D1, C7D1), including HBV, HCV markers, see study flow chart for specific requirement);
- Hematology: including complete blood count and category (white blood cell, red blood cell, lymphocyte, monocyte, neutrophil, basophil, eosinophil), hemoglobin, platelet count;
- Urinalysis: including white blood cell, red blood cell, urine protein. In case urine protein is ≥ 2＋, 24-hour urine protein quantification must be added;
- Blood biochemistry: including ALT, AST, total bilirubin, γ-glutamyl transferase (GGT), direct bilirubin, ALP, LDH, albumin, blood urea nitrogen [BUN] or urea, creatinine, blood glucose, amylase (lipase test needs to be added if amylase level is abnormal and clinically significant);
- Blood electrolytes: including potassium, sodium, chlorine, calcium, magnesium, phosphorus;
- Coagulation parameters: including INR and/or PT (if INR cannot be collected, PT will be used as the basis for judgment);
- Fecal occult blood test;
- AFP test;
- Thyroid function (once every two cycles, for example, C5D1, C7D1), TSH, FT3 or TT3, FT4);
- 12-lead ECG (performed after sitting still for at least 5 minutes): heart rate and QTc interval (calculated using Fridericia's formula); it should be performed 2.5 hours (±1 hour) after rivoceranib administration in experimental arm;
- Pre-dose sampling: the blood sample will be collected only from experimental arm (including SHR-1210 combined with rivoceranib, SHR-1210 monotherapy and rivoceranib monotherapy). The time point for sample collection will be within 0.5 hours prior to administration of rivoceranib on Day 1 of Cycle 4 (C4D1), and on Day 1 of every three cycles afterwards (0.5 hours prior to administration of rivoceranib). If SHR-1210 and/or rivoceranib is temporarily interrupted, predose immunogenicity and PK sample will be collected on schedule. If only rivoceranib is temporarily interrupted, time point for collection will be within 0.5 hours before SHR-1210 administration. C4D1: Approximately 8 mL venous blood will be collected for detection of the serum concentration and immunogenicity of SHR-1210 (6 mL) and concentration of rivoceranib (2 mL); The exact time of the previous administration of rivoceranib will be collected (provided by the subject). For every three cycles afterwards (e.g. C7D1, C10D1 etc.), approximately 6 mL venous blood will be collected for detection of the serum concentration and immunogenicity of SHR-1210;

- ECG blood sampling: the blood samples will be collected only for the measurement of the concentrations of rivoceranib. Blood samples will be collected at 2.5 hours (±1 hour) after administration of rivoceranib on Day 1 of Cycle 4 (C4D1). ECG will be performed first followed by blood collection within 15 minutes after ECG. If rivoceranib is interrupted, the post-ECG sample will not be collected within 15 minutes after the end of ECG. Approximately 2mL venous blood will be collected for determining the concentration of rivoceranib;
- Intravenous infusion of SHR-1210 (experimental arm);
- Oral administration of rivoceranib (daily, continuously);
- Distribution, verification and return of subject's diary; experimental arm: on D1 and D15 of each cycle; control arm: only on D1 from Cycle 4;
- Subject's self-evaluation results: All the subjects will complete EORTC QLQ-C30, QLQ-HCC18 and EQ-5D-5L questionnaires prior to administration of study drug and any other study evaluation at clinical centers on the Day1 of each cycle;
- Collect concomitant medications/therapy;
- Collect AE.

The following examinations/steps or collection of the following information needs to be completed on Day 15 (±3 days) (only in experimental arm):

- Weight and physical examination of important sites: cutaneous system, respiratory system, cardiovascular system, abdomen and mental state. In addition, physical examination of reactive capillary endothelial proliferation needs to be performed on the experimental arm;
- Vital signs (measured after sitting still for 5 minutes): including temperature (whenever possible, the same method of measurement should be used throughout.), blood pressure, pulse rate and respiratory frequency;
- Collect concomitant medications/therapy;
- Collect AE;
- Intravenous infusion of SHR-1210;
- Oral administration of rivoceranib (daily, continuously);
- Distribution, verification and return of subject's diary (only in experimental arm).

6.3. End of Treatment Visit

When the subject meets any one of the reasons for end of study treatment, relevant study procedures for end-of-treatment visit need to be performed. At the end of treatment (permanent discontinuation of both of the drugs [SHR-1210 and rivoceranib] is required in experimental arm), the end-of-treatment visit will start and the following examinations/procedures need to be performed

- Subject's self-evaluation results: all the subjects will complete EORTC QLQ-C30, QLQ-HCC18 and EQ-5D-5L questionnaires prior to any other study evaluation at clinical centers;
- Hematology: including complete blood count and category (white blood cell, red blood cell, lymphocyte, monocyte, neutrophil, basophil, eosinophil), hemoglobin, platelet count;
- Urinalysis: including white blood cell, red blood cell, urine protein. In case urine protein is ≥ 2＋, 24-hour urine protein quantification must be added;
- Blood biochemistry: including ALT, AST, total bilirubin, γ-glutamyl transferase (GGT), direct bilirubin, ALP, LDH, albumin, blood urea nitrogen or urea, creatinine, blood glucose, amylase (lipase test needs to be added if amylase level is abnormal and clinically significant);
- Blood electrolytes: including potassium, sodium, chlorine, calcium, magnesium, phosphorus;
- 12-lead ECG (measured after sitting still for at least 5 minutes): heart rate and QTc interval (calculated using Fridericia's formula);
- ECOG-PS score (see APPENDIX 4 for details);
- Child-Pugh class (see APPENDIX 3 for details);
- Perform a careful, comprehensive physical examination: weight, head and face, skin, lymph nodes, eye, ear, nose, throat, mouth, respiratory system, cardiovascular system, abdomen, genitourinary system, musculoskeletal, neurological and mental status. In addition, physical examination of reactive capillary endothelial proliferation needs to be performed on the experimental arm;
- Vital signs (performed after sitting still for 5 minutes): including temperature (whenever possible, the same method of measurement should be used throughout.), blood pressure, pulse rate and respiratory frequency;
- Virology (including HBV, HCV markers, see study flow chart for specific requirement);
- Fecal occult blood test;
- AFP test;
- Thyroid function (TSH, FT3 or TT3 TF4);
- Coagulation parameters: including INR and/or PT (if INR cannot be collected, PT will be used as the basis for judgment);
- Blood human chorionic gonadotropin (HCG) test for WOCBP;
- Collect concomitant medications/therapies;
- Collect adverse events;

- Tumor radiological evaluation (If previous examination is within 4 weeks of end- of- treatment visit, there is no need to repeat these tests);
- Verification and return of subject diary.

If the ECOG performance, C-P score, vital sign, physical examination, 12-ECG, hematology, urinalysis, blood biochemistry, blood electrolyte, coagulation parameters, thyroid function, fecal occult blood, virology tests, AFP, HCG or subject's self-evaluation are completed within 7 days before withdrawal, these study procedures would not be necessary in this visit again.

6.4. Follow-up Period

Follow-up period is initiated when the end-of-treatment visit is completed. 30 days (±7 days) after the last dose of study drug, subjects must return to the study center for safety follow-up and complete the following parameters for safety evaluation, regardless of initiation of new antitumor therapy. The telephone follow-up will be performed 60 days (±7 days) and 90 days (±7 days) after the last dose of study drug, only the survival status, subsequent antitumor therapy, concomitant medication/therapy and AEs/SAEs within the timeframe specified in the protocol need to be collected. When developing a safety follow-up plan, ensure that the visit is scheduled within the safety follow-up period (for the experimental arm, 90 days after the last study dose of SHR-1210 or 30 days after the last study dose of rivoceranib (whichever is longer); for the control arm, it is after 30 days after the last study administration.) If the date of the previously completed end- of- treatment visit has exceeded the safety follow-up period, there is no need to schedule the safety follow-up visit.

For the subjects in experimental arm, if the date of completed end-of-treatment visit has exceeded the first safety follow-up (30 days after the last dose), but the safety follow-up period has not been exceeded, the subject does not need to go to the site for safety follow-up visit, and 1-2 telephone visits can be scheduled during the safety follow-up period. In this case, ensure that the interval between visits should not exceed 44 days, and a telephone visit should be conducted at the time point of the safety follow-up period.

The following will be performed at safety visit at the study center:

- Subject self-assessed outcomes: The EORTC QLQ-C30, QLQ-HCC18 and EQ-5D-5L questionnaires should be completed prior to any other clinical evaluation in the clinical center during the first safety follow-up period (30 days (±7 days) after the last study dose);
- Hematology: including complete blood count and category (white blood cell, red blood cell, lymphocyte, monocyte, neutrophil, basophil, eosinophil), hemoglobin, platelet count;
- Urinalysis: including white blood cell, red blood cell, urine protein. In case urine protein is ≥ 2＋, 24-hour urine protein quantification must be added;

- Blood biochemistry: including ALT, AST, total bilirubin, γ-glutamyl transferase (GGT), direct bilirubin, ALP, LDH, albumin, blood urea nitrogen [BUN] or urea, creatinine, blood glucose, amylase (lipase test needs to be added if amylase level is abnormal and clinically significant);
- Blood electrolytes: including potassium, sodium, chlorine, calcium, magnesium, phosphorus;
- 12-lead ECG (measured after sitting still for at least 5 minutes): heart rate and QTc interval (calculated using Fridericia's formula);
- ECOG-PS score (see APPENDIX 4 for details);
- Child-Pugh class (see APPENDIX 3 for details);
- Weight and physical examination of important sites: cutaneous system, respiratory system, cardiovascular system, abdomen and mental state. In addition, physical examination of reactive capillary endothelial proliferation needs to be performed on the experimental arm;
- Vital signs (performed after sitting still for 5 minutes): including temperature (whenever possible, the same method of measurement should be used throughout.), blood pressure, pulse rate and respiratory frequency;
- AFP test;
- Thyroid function (TSH, FT3 or TT3, FT4);
- Coagulation parameters: including INR and/or PT (if INR can not be collected, PT will be used as the basis for judgment);
- Blood human chorionic gonadotropin (HCG) test for WOCBP;
- Pre-dose sampling: the blood sample will be collected only from experimental arm (including SHR-1210 combined with rivoceranib, SHR-1210 monotherapy or rivoceranib monotherapy), 30 days (±7 days) after the last dose of SHR-1210. When SHR-1210 is interrupted for longer than 30 days and finally is confirmed to be unable to resume, for this situation, the subject is required to come for a site visit and collect blood sample immediately when investigator confirms the subject is permanently terminated SHR-1210 treatment. If the subject has started new anti-tumor therapy, it's not necessary to collect the immunogenicity blood sample at 30 days (±7 days) after the last administration of SHR-1210. Approximately 6 mL venous blood will be collected for detection of the serum concentration and immunogenicity of SHR-1210;
- Collect concomitant medications/therapies;
- Collect adverse events;
- Tumor radiological evaluation (applicable for the subjects who have not achieved radiological progression at the end of study treatment);
- Collect data on survival;
- Collect subsequent antitumor therapy.

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

Subjects who end study treatment for toxicity or other reasons with no radiological progression observed still need to receive radiological evaluation according to the original frequency, until progression of disease or start of other antitumor therapy (except for traditional Chinese medicine), the radiological evidence on PD should be obtained from such subjects as much as possible.

All the treatment-related toxicities must be followed up until they are resolved, recovered to baseline or considered as irreversible. AE should be reported and recorded according to the requirement during safety follow-up.

6.5. Unscheduled Visits

For unscheduled visits (e.g., due to AEs) that occur or are needed before the end of study, the following items should be recorded:

- Visit date;
- Reason for visit;
- Concomitant medications/therapies (within the collocation period specified in the protocol);
- AEs (within the collocation and follow-up period specified in the protocol);
- All the relevant examinations performed (including radiological examination, if any);
- Whether the subject can continue or resume study treatment, if yes, record the dose administered.

6.6. Treatment Beyond Progression

If the subject has progression confirmed by BIRC as defined per RECIST v1.1, he/she still can continue SHR-1210 alone or combined with rivoceranib (experimental arm) or sorafenib (control arm) when he/she can still clinically benefit from and tolerate study treatment, as evaluated by investigators. Upon approval of Protocol v6.0, disease progression will be confirmed by the investigator per RECIST v1.1. Subjects may continue on study treatment beyond the time of investigator-confirmed disease progression, at the discretion of the investigator if the subject is perceived to be experiencing clinical benefit.

6.6.1. Criteria on Post-Progression Continuation of SHR-1210 Alone or Combined with Rivoceranib in Subjects in Experimental Arm

A part of subjects receiving immunotherapy can still clinically benefit following radiological progression. Although the tumor is enlarged, obvious necrosis or degeneration can appear inside the tumor, decreased density inside the tumor foci can be shown on CT, it is generally considered that the subject may benefit under this circumstance. After progression of disease as defined per RECIST v1.1, and confirmed by BIRC subjects meeting all of the following criteria may continue with the study treatment until there is no longer benefit from the treatment. Subjects who continue the dose following PD will receive periodic visit and efficacy evaluation according to the visit schedule specified in the trial. Disease progression will be confirmed by the investigator per RECIST v1.1 upon approval of Protocol v6.0; other procedures and criteria remain unchanged.

- Investigators judge continuation of study treatment meets the optimal benefit for the subject, and the subject does not need to start other antitumor therapy immediately;
- The subject can tolerate study treatment;
- Stable ECOG-PS score (≤1);
- No significant clinical symptom/sign of progression of disease, including change in laboratory examination parameters;
- Non-rapid progression of disease and progression not involving major organs/sites (e.g., spinal cord compression);
- The study treatment can be continued upon the review and approval by the medical monitors from the sponsor.

6.6.2. Criteria on Post-Progression Continuation of Sorafenib Treatment in Subjects in Control Arm

The growth of HCC can be possibly inhibited with continuation of the therapy in a part of subjects receiving sorafenib after radiological progression, which makes subjects clinically benefit. Thus, the subjects meeting all of the following criteria are allowed to continue sorafenib treatment after BIRC-confirmed disease progression defined by RECIST v1.1 in this study until there is no more benefit from the treatment, disease progression will be at the investigator's confirmation per RECIST v1.1 upon approval of Protocol v6.0, other procedures and criteria remain unchanged:

- Investigators judge continuation of sorafenib treatment meets the optimal benefit for the subject, and the subject does not need to start other antitumor therapy immediately, including but not limited to the second-line Regorafenib;
- The subject can tolerate sorafenib treatment;
- Stable ECOG-PS score (≤1);
- No significant clinical symptom/sign of progression of disease, including change in laboratory examination parameters;

- Non-rapid progression of disease and progression not involving major organs/sites (e.g., spinal cord compression);
- The study treatment can be continued upon the review and approval by the medical monitors from the sponsor.

6.6.3. Other Precautions for Post-Progression Continuation of Treatment

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

If a decision is made that the subject needs to continue study treatment following progression, the subject should be treated, evaluated and followed up as required in the protocol.

The subjects who continue the treatment after PD must be sufficiently informed and sign the informed consent form for post-PD continuation of treatment: possible alternative therapies, potential risks with continuation of the treatment.

If the subject terminates the treatment for a global deterioration of health status and has no objective evidence on progression of disease, the progression will be reported as symptomatic deterioration. Every effort should be made to obtain the objective evidence on progression in these subjects after termination of the study treatment (e.g., radiological confirmation).

6.7. Study Extension Phase

The purpose of the extension phase is to continue to provide access to study drugs for subjects who are still on study treatment and still derive clinical benefit at the time of end of study. It's a post-trail treatment access phase. Upon initiation of the extension phase, the Sponsor considers the safety and efficacy profile of the experimental treatment regimen within this study to have been sufficiently established and data analysis required for regulatory purposes to have been completed. The Sponsor will notify the sites when will the study enter the extension phase.

In the extension phase, subjects randomized in the experimental arm will continue on SHR-1210 in combination with rivoceranib, and subjects randomized in the control arm may have the option to crossover to receive experimental treatment and the decision made is upon investigator's clinical judgment. Subjects who are not eligible to crossover experimental treatment per investigator clinical judgment can continue on sorafenib treatment. Sorafenib can be sourced either locally or centrally which can comply with the local regulatory and ethics requirement.

Subjects will continue to receive study treatment until they are no longer benefiting from treatment as assessed by investigator's clinical judgment. The extension phase will continue until the last subject receives the last dose of study drug (expected Jan.2025, take the actual occurrence as the standard). Subjects are to undergo periodic safety and tumor assessment. The frequency of these assessments during the extension phase are to be performed per local standard of care. The investigator should ensure site visits occur frequently enough and adequate assessments. Investigator may also refer to

the protocol to ensure the periodic visits, tumor assessment and safety management if needed.

In order to collect important safety information for subjects during the extension phase, SAEs and pregnancy will continue to be collected. See Section8.3, 8.5 and APPENDIX 12.

The study clinical database will be closed at the initiation of the extension phase. Important safety information collection in the extension phase will be captured in the safety database.

The schedule of activities for extension phase is presented in APPENDIX 12.

Subjects who continue on study treatment at the time of extension phase initiation, will undergo the end of study treatment visit and perform all the study procedures as the protocol required. Subjects who had discontinued study treatment but not yet completed the follow up visits (i.e., safety follow up) at the time of extension phase initiation (e.g., subject just completed first safety follow up), will undergo the final safety follow up visit.

The time of extension phase initiation may occur at different time points for study sites because of different processes at sites. Before extension phase, study sites need to ensure that all the data occurring prior to extension phase have been captured into CRFs, particularly for safety and survival information. In addition, for the subjects who are continuing to receive study treatment, the end of study treatment and end of study page in CRFs should be captured as well before entering into extension phase (detailed instruction for EOT and EOS page in CRFs for extension subjects. Refer to CRF completion guideline). If a scheduled visit occurred within 7 days before the time of extension phase initiation or the relevant examinations for end of treatment visit were completed within 7 days, these study procedures would not be necessary to be repeated on EOT.

Site monitoring visits will occur at a reduced frequency but must be frequent enough to ensure adherence to GCP, study drug accountability, reporting of SAEs and pregnancy.

During the extension phase, no data are to be entered into CRFs. Study central laboratory samples are not to be obtained (e.g., PK, ADA sampling), and radiographic images from the site are not to be submitted to BIRC.

7. EVALUATION

7.1. Efficacy Evaluation

The efficacy endpoints include:

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

As well as the following efficacy endpoints evaluated by the BIRC or investigator based on Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1), modified RECIST (mRECIST) and immune-modified RECIST (imRECIST):

- Progression-free survival (PFS): defined as the time from the date of randomization to the first occurrence of radiological progression by tumor image evaluation or death, whichever comes first, evaluated by the BIRC or investigator based on RECIST v1.1, mRECIST or imRECIST. (Radiological progression based on imRECIST not considered a PFS event if subsequent assessment evaluated as a response or stable after ≥ 4 weeks.)
- Time to progression (TTP): defined as the time from the date of randomization to radiological progression of disease, evaluated by the BIRC or investigator based on RECIST v1.1, mRECIST or imRECIST. (Radiological progression based on imRECIST not considered a TTP event if subsequent assessment evaluated as a response or stable after ≥ 4 weeks.)
- Objective response rate (ORR): defined as the percentage of subjects with complete response (CR) or partial response (PR) evaluated by the BIRC or investigator based on RECIST v1.1, mRECIST or imRECIST. (In respect of ORR based on imRECIST, CR and PR can occur after radiological progression).
- Disease control rate (DCR): defined as the percentage of subjects with complete response, partial response or stable disease (SD) ≥ 8 weeks evaluated by the BIRC or investigator based on RECIST v1.1, mRECIST or imRECIST. (In respect of DCR based on imRECIST, CR PR and SD can occur after radiological progression).
- Duration of response (DoR): defined as time from the date of first record of objective response (CR or PR) to the first occurrence of radiological progression or death, whichever comes first, evaluated by the BIRC or investigator based on RECIST v1.1, mRECIST or imRECIST. (Radiological progression based on imRECIST not considered a PD event of DoR if subsequent assessment evaluated as a response or stable after ≥ 4 weeks.).
- Best overall response (BOR): defined as the best response parameter between the date from randomization to objectively recorded progression or subsequent antitumor therapy, whichever comes first. For subjects with no progression or subsequent antitumor therapy documented, BOR will be determined based on all the response evaluation results. (The BOR based on imRECIST is defined as the best response between the date of randomization and the initiation of subsequent antitumor therapy or during the entire study period).

7.2. Tumor Radiological Evaluation

7.2.1. Tumor Evaluation Based on RECIST v1.1, mRECIST and imRECIST

RECIST v1.1 (investigator and BIRC evaluated), mRECIST (only BIRC evaluated) and imRECIST (only investigator evaluated) will be used for evaluation of tumor response in this study, see APPENDIX 2 for the evaluation criteria.

The tumor evaluation in screening period (at baseline) should include the enhanced CT/MRI scan of thorax, abdomen and pelvis. CT scan requires intravenous contrast agent and will scan the whole liver area, at least including 1) hepatic arterial phase and 2) portal venous phase. Enhanced MRI can be used in case of contraindications for CT contrast agent. The enhanced MRI of the whole liver should at least include 1) hepatic arterial phase and 2) portal venous phase. Cranial enhanced CT or enhanced MRI has

to be performed at baseline as well. Systemic bone scan should be performed for subjects with known bone metastasis or suspected bone metastasis (exempted in case bone scan is performed within 42 days prior to first administration), the bone lesions need to be evaluated and followed up after treatment. If clinically indicated, tumors at other sites can be evaluated.

Provision on selection of target lesions: no more than 2 target lesions in each organ, and the total number of lesions is not more than 5, more organs involved in tumors should be covered as far as possible. At baseline, the number and location of the target lesion, the major diameter of each target lesion (except lymph node) and the minor diameter of lymph node lesion, as well as the sum of diameters of all lesions should be recorded.

The baseline evaluation and post-treatment efficacy evaluation should be performed using the same method and by the same investigator as far as possible. Following randomization, the tumor evaluation will be performed once every 8 weeks (56±7 days) in the first 48 weeks, and once every 12 weeks (84±7 days) afterwards. In the absence of a BIRC determined progression of the disease (according to RECIST v1.1), tumor evaluation should be continued, regardless of whether the subject has terminated the study, until the subject dies, withdraws the informed consent, initiates subsequent anti-tumor therapy or terminated the study by sponsor, whichever comes first. Tumor evaluation during treatment includes enhanced CT/MRI scan of thorax, abdomen, pelvis and site of lesions; thoracic plain CT scan plus abdominal and pelvic enhanced MRI can be performed if the subject is allergic to the contrast agents for enhanced CT; cranial enhanced CT/MRI and bone scan can be performed only when clinically indicated. Each tumor evaluation must cover all the target lesions, and all the non-target lesions if there are no special circumstances.

Further guidance and recommendations on image acquisition are provided in the Image Acquisition Guidelines.

When clinically indicated, investigators can perform unscheduled tumor evaluation. Throughout the study, each subject must use the same procedure of radiological examination. Investigators must review the results prior to the next cycle of therapy. The subjects who have achieved response (complete response or partial response) for the first time need to be confirmed through the next scheduled evaluation or repeated evaluation ≥ 4 weeks after the first evaluation.

When the subject develops disease progression as assessed by the investigator according to RECIST v1.1, the investigator is required to submit radiological data immediately to BIRC; if BIRC assessed it as non-disease progression according to RECIST v1.1, the study drug treatment should be continued for the subject and tumor radiological evaluation should continue; if BIRC confirms disease progression according to RECIST v1.1, the investigator needs to assess whether the subject still has clinical benefit, and if the subject is still considered to have clinical benefit and meets the criteria for continued treatment after progression of the disease (see Section 6.6), the subject may continue to receive study medication and continue the efficacy assessment at the original planned frequency.

Tumor radiological assessment will continue until the occurrence of disease progression confirmed by BIRC according to RECIST v1.1 criteria or study treatment

discontinuation, whichever occurs later. Subjects who discontinue treatment for reasons other than BIRC-confirmed disease progression (according to RECIST v1.1) will also continue with regular follow-up by tumor radiological assessments after treatment is completed. Before BIRC confirms the disease progression according to the RECIST v1.1 criteria or the treatment is discontinued, if the subject withdraws the informed consent, other anti-tumor treatment has begun (except for traditional Chinese medicine), or the subject dies, there is no need to continue the radiological evaluation. If the subject does not meet the above criteria for stop radiological assessment, the efficacy evaluation of the three efficacy evaluation criteria (RECIST v1.1, mRECIST, imRECIST) needs to continue even if the disease progression under certain efficacy evaluation criteria occurs.

Once progressive disease occurs, a physical examination of the subject and radiological confirmation is required at any times, rather than waiting for the next planned radiological examination. If the unplanned radiological findings do not meet the RECIST V 1.1 criteria of progressive disease, follow-up examinations should still be performed on the original date for the next radiological examination, unless the next planned examination is less than 14 days of this one.

If there has not been any disease progression confirmed by a radiological examination when the subject is about to withdraw from the study, it is recommended that a radiological examination be performed in time before the withdrawal (if the time from the last radiological examination to the withdrawal is ≤ 4 weeks, additional radiological examination will not be required at the time of withdrawal).

Upon approval of protocol v6.0, radiographic images from the sites are not to be submitted to BIRC, therefore, disease progression confirmation by BIRC is not needed.

7.2.2. Determination Process for Disease Progression (PD)

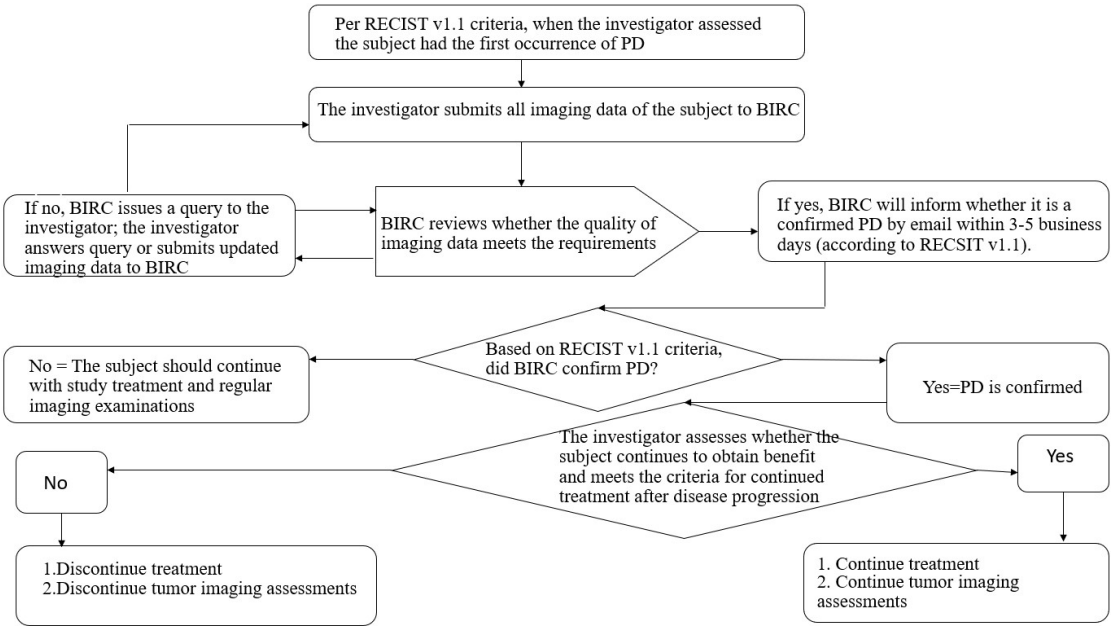


Figure 7. Disease Progression Confirmation Process

7.3. Safety Evaluation

7.3.1. Pregnancy Testing

Blood pregnancy test will be performed within 7 days prior to the start of administration, during the treatment period (if needed), end-of-treatment visit and safety follow-up for female subjects of childbearing potential. After obtaining the negative result of pregnancy test in screening period, appropriate contraceptive measures should be taken. The subject will be withdrawn from the trial if HCG test is positive and the pregnancy is confirmed by investigator.

7.3.2. Adverse Events

The evaluation of AE includes type, incidence, severity (in accordance with NCI-CTCAE v4.03), start and end time, correlation with SAE and prognosis.

7.3.3. Laboratory Safety Evaluation

Blood and urine samples will be collected in accordance with the study flow chart, analyzed and detected in local laboratory. The items of laboratory tests are shown in Table 11.

Table 11 Items of Laboratory Tests

Item	Contents
Hematology	Complete blood cell count and category (white blood cell, red blood cell, lymphocyte, monocyte, neutrophil, basophil, eosinophil), hemoglobin, platelet count.
Blood Biochemistry/ Electrolytes	Including hepatic function (ALT, AST, TBIL, ALP, GGT, direct bilirubin), renal function (BUN or urea, creatinine), albumin, amylase (lipase test must be added if Amylase level is abnormal and clinically significant), blood glucose, LDH; potassium, sodium, calcium, phosphorus, magnesium, chlorine.
Coagulation Parameters	INR and/or PT (if INR can not be collected, PT will be used as the basis for judgment)
Urinalysis	Including white blood cell, red blood cell, urine protein. It will be detected within 72 hours prior to administration at each visit. If urine protein is ≥ 2＋, 24-hour urine protein quantification must be added.
Alpha Fetoprotein Test	Alpha fetoprotein
Thyroid Function	TSH, FT3 or TT3, FT4
Virology	HIV-Ab (screening period only), HBV and HCV test should be included. Screening period: all subjects will have HBV serological test for five hepatitis B markers (HBsAg, HBsAb, HBcAb, HBeAg, HBeAb). HBV-DNA will be quantified if the HBsAg or HBcAb test is positive. All subject will have HCV-Ab test, and HCV-RNA will be quantified if the HCV-Ab test is positive. Treatment period and end-of-treatment visit: Five hepatitis B markers (HBsAg, HBsAb, HBcAb, HBeAg, HBeAb) and HBV-DNA needs to be detected every two cycles of therapy (starting C3D1, C5D1, C7D1, etc.) for subjects with positive HBsAg or HBcAb at screening; HCV-RNA needs to be detected every two cycles of therapy (starting C3D1, C5D1, C7D1, etc.) for subjects with positive HCV-Ab at screening.

7.3.4. Physical Examination and Vital Signs

Physical examination includes height (first collection only), weight, head and face, skin system, lymph nodes, eye, otolaryngology, mouth, respiratory system, cardiovascular system, abdomen, genitourinary system, musculoskeletal, neurological and mental status. The items of physical examination at different time points are provided in Section 6 in detail.

Vital signs include temperature (whenever possible, the same method of measurement should be used throughout), blood pressure (which needs to be measured and recorded at least twice to get the mean value as the blood pressure value), pulse rate and respiratory frequency (performed after sitting still for 5 minutes).

In addition, physical examination of reactive capillary endothelial proliferation needs to be performed on the experimental arm.

7.3.5. 12-lead ECG

Heart rate and QTc interval (calculated using Fridericia formula: QTcF = QT/(RR^0.33), RR is the normalized heart rate and is calculated as 60 divided by heart rate).

7.3.6. Echocardiography

Including LVEF evaluation.

7.3.7. ECOG-PS Scores

Criteria for ECOG-PS score can be found in APPENDIX 4.

7.4. Pharmacokinetics and Immunogenicity Evaluation

7.4.1. Collection Time of Blood Samples

SHR-1210 combined with rivoceranib experimental arm:

Pre-dose sampling: on Day 1 from Cycle 1 to Cycle 4 (C1D1, C2D1, C3D1, C4D1); and on Day 1 of every 3 cycles afterwards (The time point for sample collection will be within 0.5 hours prior to rivoceranib administration). Collect once at 30 days (±7 days) after the last dose of SHR-1210. When SHR-1210 is interrupted for longer than 30 days and if is confirmed to be unable to resume, the subject is required to come for a site visit and collect blood sample immediately. If the subject has started other anti-tumor therapy, it's not necessary to collect the immunogenicity blood sample at 30 days (±7 days) after the last administration of SHR-1210. If SHR-1210 and/or rivoceranib is temporarily interrupted, pre-dose immunogenicity and PK sample will be collected on schedule. If only rivoceranib is interrupted at time point mentioned above, blood sample will be collected within 0.5 hours prior to SHR-1210 administration. The above samples will be used to measure the blood concentration and immunogenicity of SHR-1210, and the plasma concentration of rivoceranib in the C2D1-C4D1 samples. The exact time of the previous administration of rivoceranib will be collected for C2D1, C3D1 and

C4D1(the subject is required to provide it).

ECG blood sampling: ECG examination is performed 2.5 hours (±1 hour) after the end of the rivoceranib administration, and blood is collected within 15 minutes after the ECG examination on the first day from Cycle 1 to Cycle 4. If rivoceranib is discontinued, blood samples within 15 minutes of ECG will not be collected. Plasma concentrations of rivoceranib will be measured in the above samples.

The actual sampling time and the time for the administration of rivoceranib and SHR-1210 will be recorded on the day of sampling. (refer to BLOOD SAMPLE COLLECTION TABLE).

7.4.2. Processing and Storing of Blood Samples

Approximately 6 mL venous blood samples for measuring the immunogenicity and concentration of SHR-1210 will be collected at each timepoint mentioned above.

2mL venous blood samples for measuring the plasma concentration of rivoceranib will be collected at each time point mentioned above.

The blood samples mentioned above will be transferred into aliquots and then be placed in a low temperature freezer until delivered to the central laboratory for detection. Detailed procedures and the shelf life are described in the Laboratory Manual.

7.4.3. Delivery of Blood Samples

The test tube samples will be delivered firstly using dry ice preservation. The back-up tube samples will be sent to the bioanalytical laboratory to confirm the receipt of the test tube samples. The frequency and information of delivery are provided in the laboratory manual in detail.

7.5. Patient Reported Outcomes (PRO)

All the subjects will complete EORTC QLQ-C30, EORTC QLQ-HCC18 and EQ-5D-5L questionnaires prior to the administration of study drug and conduction of any other study evaluation at the clinical center from Day 1 of Cycle 1, then repeat the above procedure on Day 1 of every cycle. In addition, all subjects will be assessed by above-mentioned questionnaires in the visit of end-of-treatment and first safety follow-up. Questionnaires for PRO evaluation should be validated and in subjects' local language. The questionnaires will be paper-based in this study.

Questionnaires should be completed prior to initiation of any pertinent study visit which involves other study activities (including study treatment) and contact with the investigator, to ensure that the results are not influenced by the interaction between the subject and the investigator. Provide subjects with a quiet place and advise them to complete within 30 minutes. The study site should make every effort to ensure that a complete questionnaire is obtained from each subject at each scheduled time point, so as to avoid any delay in clinical evaluations.

If there are privacy requirements for filling out questionnaires in local regulations (e.g.,

if the questionnaire is not supposed to be seen by the clinical staff), the study site should make appropriate arrangements to ensure that the requirements are met as far as possible.

7.5.1. EORTC QLQ-C30 and EORTC QLQ-HCC18

EORTC QLQ-C30 is a core scale in the quality of life measurement questionnaire system for all cancer subjects that is systematically developed by European Organization for Research and Treatment of Cancer (EORTC), and used for measurement of quality of life in all the cancer subjects (for the common part). The questionnaire is comprised of 5 functional scales (somatic, role, cognitive, emotional, social), 4 symptom scales (fatigue, pain, nausea, vomiting), one global health status scale and several separate items (including dyspnea, anorexia and insomnia). This questionnaire consists of 30 multiple-choice questions.

The specific module for different cancers is added on EORTC QLQ-C30, i.e., the specific scale for different cancers is formed, HCC module (EORTC QLQ-HCC18) is used in this study. The samples of EORTC QLQ-C30 (version 3.0)and EORTC QLQ-HCC18 scales used in this study are seen in APPENDIX 8 and APPENDIX 9.

In this study, EORTC QLQ-C30 and EORTC QLQ-HCC18 scales will be used to evaluate the quality of life (QoL), including health related quality of life (HRQOL) / general health state (GHS), physical functioning and role functioning, of subjects with advanced HCC who receive SHR-1210 combined with rivoceranib mesylate as a first-line therapy versus those who receive sorafenib as a first-line therapy. The following endpoints are included:

- TTD, defined as time from randomization to first deterioration, as determine by following subscales of EORTC QLQ-C30 (decreased by ≥ 10 points from baseline), at least maintained for two consecutive time points, or maintained for one-time point but death in the following 4 weeks (for any reason):
  - HRQOL/GHS
  - Physical functioning
  - Role functioning
- Average scores and average change from baseline in all the subscales of EORTC QLQ-C30 and EORTC QLQ-HCC18 (by cycle);

7.5.2. EQ-5D-5L

In this study, the health utility index in European five-dimensional health scale (EQ-5D-5L) and VAS score will be used to evaluate the health status of subjects with advanced HCC who receive SHR-1210 combined with rivoceranib mesylate as a first-line therapy versus those who receive sorafenib as a first-line therapy, so as to generate the utility score for health economic assessment.

EQ-5D is a validated and reliable, self-report-based measurement developed by Euro QoL Group to evaluate health- related quality of life. It is a universal scale and currently includes two versions, EQ-5D-3L and EQ-5D-5L. The EQ-5D-5L version used in this

study includes the EQ-5D-5L descriptive system and EQ visual analogue scale (EQ-VAS) (See APPENDIX 10 for a sample scale).

The EQ-5D-5L descriptive system measures subject's health state from 5 dimensions (5D): mobility, self-care ability, daily activities, pain/discomfort and anxiety/depression. Each dimension is further divided into 5 levels (5L): (1) no difficulty, (2) slight difficulty, (3) moderate difficulty, (4) serious difficulty, (5) extremely serious difficulty. Subjects will be asked to select the most appropriate level in each dimension according to their health status.

EQ-VAS is a vertical visual scale in a length of 20cm. Its top is 100 points and represents "the best health state in mind", whereas the bottom is 0 point and represents "the worst health state in mind". Subjects will be asked to mark the point that best suits to their own health state on that day on the scale, that is, to score the overall health state on that day.

EQ-5D-5L descriptive system combined with EQ-VAS can fully reflect the health state in the study population.

7.6. Evaluation of Exploratory Tumor Markers

Before enrollment, subjects must be able to provide fresh or archived tumor tissue (formalin-fixed, paraffin-embedded [FFPE] tissue block or at least 5 unstained FFPE slides) for the immunohistochemical examination of PD-L1 expression level, so as to explore the relation between biomarkers and the efficacy of combination therapy.

Biopsied specimen, such as the specimen biopsied with fine needle aspiration, cell smear from pleural effusion drainage and centrifugation or drilled biopsy are inadequate to review and evaluate biomarkers. The bone lesions without soft tissue component or decalcified tumor specimen are not acceptable. For fresh tumor biopsied specimen, the detailed description of its collection, handling, processing and shipment is provided in the Laboratory Manual.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

8.1.1. Definition

AE is defined as adverse medical events that occur after the subject who receives a drug in clinical trial, but do not necessarily have a causal relationship with the treatment. Refer to Section 8.3 for details on the AE collection period. AE can be any undesirable and unexpected symptom, sign, laboratory abnormality or disease, including at least the following conditions:

1) Aggravation of existing (prior to enrollment of clinical trial) medical conditions/disease (including exacerbation of symptoms, signs, laboratory abnormalities);
2) Any new occurrence of AE: any adverse medical conditions newly occurred (including symptoms, signs, newly diagnosed diseases);

3) Abnormal laboratory test or result of clinical significance.

The investigator should carefully record any AE occurs in the subjects, including: the description of adverse event and all relevant symptoms, time of onset, severity, the correlation-ship with investigational drugs, duration, actions taken against the study drug, final outcomes and prognosis.

The word "disease progression" should not be reported as an AE term as disease progression is an expected occurrence in the study population, except as described in 8.2.3 section. When a disease progression occurs, the occurrence that confirms disease progression should be reported as an AE. For example, if the subject has epilepsy that is determined to be related with brain metastasis, epilepsy should be recorded as the AE term, rather than "disease progression" or "brain metastasis". Progression of the disease being studied assessed by measurement of lesions on radiographs or other methods should not be reported as an AE.

8.1.2. The Judgment Standard on Severity of AE

Refer to NCI-CTC AE v4.03 grading criteria for AEs related drugs. Refer to the judgment criteria in Table 12 if any AE is unlisted in NCI-CTCAE v4.03.

Table 12 The Judgment Standard on Severity of AE

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

8.1.3. Causality Assessment

Collection of AE starts from the signing of informed consent, records are collected regardless of whether the event is related to the investigational drug, whether the subject is assigned to the experimental arm, or even whether the drug is used or not. Any discomfort or abnormal change in objective laboratory tests during the treatment should be recorded accurately. Meanwhile the severity, duration, management and outcome of the AE should be recorded. The investigator should determine the relationship between AE and study drugs, such as whether the occurrence of AE has relationship with a reasonable medication order, the properties of study drug, toxicological and pharmacological effects of study drug, subjects' use of other concomitant drugs, subjects' underlying diseases, medical history, family history and provocative and re-provocative reactions, etc. The causality relationship between AE and study drug will

be assessed to be “related” or “unrelated” which are described in the following.

Related: there is a rational relationship between AE and the study drug, the AE can be attributed to the study drug medically (pharmacologically or clinically).

Unrelated: there is lack of rational relationship between AE and the study drug, and the AE can not be attributed to the study drug medically (pharmacologically or clinically), and/or there is other rational reason to explain it, such as underlying disease, complication, and concomitant medications.

8.2. Serious Adverse Events

8.2.1. Definition of SAE

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

- Events leading to death;
- Life-threatening events (defined as the subject has is at risk of death at the time of the event);
- Events requiring hospitalization or prolonged hospitalization;
- Events that result in persistent or significant disability / incapacity / limiting working ability;
- Congenital abnormalities or birth defects;
- Other important medical events (defined as the event threatens the safety of the subject, or requires intervention measures for the prevention of any of the above outcomes).

8.2.2. Hospitalization

Adverse event which causes hospitalization (even less than 24 hours) or prolonged hospitalization should be considered as SAE.

Hospitalization does not include the following:

- Rehabilitation facilities
- Nursing homes
- Routine emergency room admissions (within 24 hours)
- Same day surgeries (as outpatient/same day/ambulatory procedures)
- Social reason (medial insurance reimbursement, etc.)

Hospitalization or prolongation of hospitalization in the absence of a deteriorating adverse events will not be considered as SAEs. For example,

- Admission for treatment of a preexisting condition without the development of new adverse events or worsening of the preexisting condition (e.g., for work-up of persistent pre-trial laboratory test abnormality);
- Administrative admission (e.g., for yearly physical exam);
- Hospitalization as per the trial protocol during the study (e.g., as required by the protocol);
- Elective admission not associated with the aggravation of adverse events (e.g., elective surgery);
- Predefined treatments or surgical procedures should be documented throughout the study program and/or in the baseline data of individual subject;
- Admission exclusively for the administration of blood products.

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

8.2.3. Disease Progression and Death

Disease progression is defined as the exacerbation of the subject caused by indications of the study drug, including radiological progression and progression of clinical symptoms and signs. New metastases relative to the primary tumor and the progression of the original metastases are both considered to be progressive disease. Events that are life-threatening, requiring initial or prolonged hospitalization due to symptoms and signs of disease progression, which can lead to persistent or significant disability / incapacity / limiting work ability are not reported as SAE. If there is any uncertainty about whether SAE is caused by the progression of disease, it should be reported as SAE.

All cases of death that occur during the study period must be reported as SAEs, whether or not the subject has received other anti-tumor therapy (see Section 8.3). The word “death” should not be reported as an AE or SAE term, but as the outcome of the event; the AE that causes or contributes to the fatal outcome should be recorded as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, the AE or SAE should be recorded as “unexplained death”, if the cause of death later becomes available, "unexplained death" should be replaced by the established cause of death

If death due to disease progression cannot be attributed by the investigator to a medical event, a Grade 5 “Tumor progression” should be recorded in the eCRF and reported as an SAE. Evidence that the death is due to disease progression (e.g., radiological changes suggesting tumor growth or progression, clinical deterioration associated with a disease process) should be provided by the investigator.

8.2.4. Reporting Procedures of SAE

In case of SAE, regardless of first report or follow-up report, the investigator must fill

in the "Clinical Trial Serious Adverse Event (SAE)/Special Interest Event (SIE) Report Form" immediately, sign and date it, report it to the sponsor within 24h after learning of it, and report it to relevant organizations in time as required by regulations.

The detailed record content of SAE should include symptoms, severity, and association with investigational drugs, time of onset, time of treatment, measures taken, follow-up time and method as well as outcome. If the investigator considers that a SAE is not related to study drug while potentially related to the study conditions (e.g., termination of the original treatment or complications during the trial), the relationship should be described in detail in the narrative section of SAE report form. If there is a change in the severity of an ongoing SAEs or its relationship with the study drug, follow-up reports should be submitted immediately. If misinformation is considered to be present in the previously reported SAE, it can be corrected, withdraw or degraded in the follow-up report, and reported in accordance with the SAE reporting procedures.

The sponsor's email to receive safety reports (SAE, SIE, pregnancy) in this study: hengrui_drug_safety@hengrui.com

8.3. Collection and Follow-Up of AE/SAE

The period for AE/SAE collection begins from the time that the subject provides informed consent, through and including 90 days after the last dose of SHR-1210 or 30 days after the last dose of targeted anti-angiogenic therapy, whichever comes later. SAEs that occur after this period, if suspected to be related to study drug, should also be collected. See Table 13 for detailed requirements. An AE/SAE will be followed up until it is resolved, returns to the baseline level or ≤ Grade 1, or reaches a stable state, or until other reasonable time points (e.g., loss of follow-up, death). Every effort should be made to ensure the final outcome and definite causality assessment is obtained.

Investigators should inquire about AE/SAE after the last visit at each visit and provide follow-up data in time according to the sponsor's queries.

For the AE/SAE that occurs after extension phase initiation, only SAE should be reported to Sponsor via email, and non-serious AE will not be collected. See Table 14 for detailed requirements. See Section 错误!未找到引用源。 for reporting requirement of pregnancy.

Table 13 AE/SAE Collection Period

Classification	Requirement for Collection/Record	
	Experimental Arm	Control Arm
AEs unrelated to study drug [a]	Collection continues until 30 days after the last dose of study drug.	Collection continues until 30 days after the last dose of study drug.
AEs related to study drug [a]	Collection continues until 90 days after the last dose of SHR-1210 or 30 days after the last dose of rivoceranib, whichever comes later.	
SAEs unrelated to study drug [b]	Fatal SAEs: Collection continues until 90 days after the last dose of SHR-1210 or 30 days after the last dose of rivoceranib, whichever comes later. Non-fatal SAEs: Collection continues until 30 days	

	after the last dose of study drug.	
SAEs related to study drug [b]	No time limit	No time limit

a. Non-serious AEs.
b. Include fatal and non-fatal SAEs.

Table 14 SAE Collection During Extension Phase

Classification	Subjects Treated with Experimental Drug(s)	Subjects Treated with Sorafenib
SAEs unrelated to study drug	Collection continues until 30 days after the last dose of study drug.	Collection continues until 30 days after the last dose of study drug.
SAEs related to study drug	No time limit.	No time limit

8.4. AEs of Special Interest

For the AE of special interest (SIE) specified in the study protocol (as below), investigators need to fill in the "Clinical Trial Serious Adverse Event (SAE)/Special Interest Event (SIE) Report Form" within 24h after the event is known, and report to the sponsor.

- ≥ Grade 3 infusion reaction
- ≥ Grade 3 immune-related AE
- AEs that meet the criteria defined in Section 8.4.1 (Liver Function Test [LFT] Abnormalities)

8.4.1. Liver Function Test (LFT) Abnormalities

Considering the specialty of abnormal liver function at baseline in HCC subjects, abnormal values in ALT and/or AST concurrent with abnormal elevations of TBIL that meet the criteria outlined below (i.e., meeting the criteria [1] and [2] for elevated ALT or AST and bilirubin as well as the criterion [3]) in the absence of other causes of LFT abnormalities should always be reported as SIEs.

1) ALT or AST ≥ 3 × ULN (normal at baseline), ALT or AST ≥ 3 × baseline value (abnormally elevated at baseline)

2) TBIL ≥ 2 × ULN (normal at baseline), TBIL ≥ 2 × baseline value (abnormally elevated at baseline)

3) Excluding other causes of LFT abnormalities (e.g., disease progression, acute viral hepatitis, cholestasis, underlying hepatic disease, and concomitant medications with hepatotoxicity).

Subjects should return to the study center as soon as possible after learning the abnormal results (preferably within 48 hours). Evaluation should include laboratory examination, detailed medical history and physical evaluation.

Besides repeated measurement of AST and ALT, the laboratory examination should also include albumin, creatine kinase, total bilirubin, direct bilirubin, γ-glutamyl transferase,

PT/ INR, and alkaline phosphatase. Collection of detailed medical history should include history of alcohol, acetaminophen, soft drugs, various supplements, family history, occupational exposure, sexual behavior history, travel history, contact history with jaundice subjects, surgery, blood transfusion, hepatopathy or allergic disease history. Further examinations also include detection of acute hepatitis A, B, C and E as well as radiological examination of liver (e.g., biliary passage).

8.5. Pregnancy

If a female subject becomes pregnant during the clinical trial, the subject must discontinue the study drug immediately; if the partner of male subject becomes pregnant during the clinical trial, the subject can continue the clinical trial.

For pregnancy of female subjects or partners of the male subjects during this study, investigators should fill in "Pregnancy Report/Follow-up Form in Hengrui Clinical Study", and report to the sponsor within 24 hours after investigator awareness, and report to the ethics committee in time.

The investigator should follow up the pregnancy outcome, until one month after delivery, and will report the outcome to Sponsor and Ethics Committee.

If the outcome of pregnancy is stillbirth, spontaneous abortion, or fetal malformations, it should be considered as an SAE and be reported to Sponsor, regardless of causality.

9. CLINICAL MONITORING

In order to make sure the subject's rights are protected, all the data should be reported accurately, completely and reliably. The trial should be conducted in accordance with currently approved protocol/revised protocol, ICH-GCP and appropriate regulations; clinical monitoring is needed for the study center.

10. STATISTICAL ANALYSIS

A statistical analysis plan (SAP) will be prepared to provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP will serve as a compliment to the protocol and where there is a discrepancy between the SAP and protocol, the SAP will supersede it. Any critical revision within the SAP of definition(s) or analysis method(s) for the primary endpoints will be included in a protocol amendment.

10.1. Sample Size Determination

Assuming a 1:1 randomization between sorafenib and SHR-1210+rivoceranib, and a median PFS time of 3.6 months for subjects in the sorafenib group and a median PFS time of 6 months for subjects in the combination group, 332 PFS events will be sufficient to detect a hazard ratio (HR) of 0.60 with 98% power based on Log-rank test at significance level of 0.005 one-sided. Similarly, assuming a median survival time of 10.5 months for subjects in the sorafenib group and a median survival of 14.6 months for subjects in the combination group, 359 OS events will be sufficient to detect a hazard ratio (HR) of 0.72 with 85% power based on Log-rank test at significance level

of 0.020 one-sided. Assuming an accrual period of 18 months, total duration of 36 months and 19 months for the OS and PFS, respectively, and probability of subject loss be approximately 10% per 12 months and per 6 months for the OS and PFS, respectively, a sample size of 510 subjects will be enrolled for the study. Power and sample calculations were performed using EAST® 6.4.1. software package.

10.2. Objectives and Statistical Hypotheses

10.2.1. Primary Objectives and Statistical Hypotheses

Objectives: To compare efficacy endpoints of OS and PFS evaluated by the BIRC based on RECIST v1.1 in 2 experimental arms (SHR-1210 in combination with rivoceranib versus sorafenib).

Hypothesis: SHR-1210 in combination with rivoceranib prolongs OS compared to sorafenib.

Hypothesis: SHR-1210 in combination with rivoceranib prolongs PFS (assessed by BIRC based on RECIST v1.1) compared to sorafenib.

10.2.2. Key Secondary Objectives and Statistical Hypotheses

Objective: To compare the ORR (assessed by BIRC according to RECIST) of SHR-1210 in combination with rivoceranib to sorafenib

Hypothesis: The ORR (assessed by BIRC according to RECIST v1.1) of SHR-1210 combined with rivoceranib is superior to sorafenib.

10.3. Analysis Populations

- Intent-to-treat (ITT): This population will include all randomized subjects. Subjects will be included in the experimental arm to which they are randomized.
- Safety Analysis Set (SS): This population will include all treated subjects who receive at least 1 dose of study treatment. For most subjects, this will be the experimental arm to which they are randomized. For subjects who take incorrect study treatment for the entire treatment period, safety data will be analyzed based on the treatment they actually receive.
- Anti-drug Antibody (ADA) Analysis Set: This population will include all subjects who receive SHR-1210 in combination with rivoceranib and had at least 1 ADA measurement.
- PK Analysis Set: This population will include all the subjects who receive PD-1 antibody SHR-1210 combined with rivoceranib and who have at least one result for drug concentration at any time during the study.

10.4. Statistical Analysis Methods

10.4.1. General Method

This is a parallel group, controlled study. All statistical tests, unless otherwise specified, will be analyzed by experimental arms and using the appropriate statistics according to

the data type. Summary statistics for continuous variables will include the mean, standard deviation, median, and range (minimum/maximum). Categorical variables will be presented as frequency counts and percentages. Time-to-event variables will be summarized by Kaplan-Meier (K–M) medians and 95% CI.

10.4.2. Subject Disposition

The number of subjects enrolled, treated, discontinued and those with major protocol deviations will be counted. The primary reason for study drug and/or study discontinuation will be summarized according to the categories in the eCRF. The end of study status (alive, dead, withdrew consent or lost to follow-up) at the data cutoff date will be summarized.

10.4.3. Demographics and Baseline Characteristics

Demographic and other baseline characteristics will be summarized using descriptive statistics. Continuous variables include age, weight, vital signs, time since initial cancer diagnosis, and time since advanced/metastatic disease diagnosis; categorical variables include, gender, ECOG-PS score, geographical region, country, race, Child-Pugh classification, hepatitis virus, BCLC staging, metastatic site, and macrovascular invasion and/or extrahepatic spread status etc.

10.4.4. Prior and Concomitant Medications

Concomitant medications will be coded using the WHO Drug Dictionary drug codes. Prior and concomitant medications will be summarized and listed by drug and drug class. Prior medications will be defined as medications taken within 28 days of the first dose of study drug that were stopped prior to study drug administration. Concomitant medications will be defined as medications that 1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or 2) started after the first dose of study drug. Prior and concomitant medications will be listed.

10.4.5. Primary Efficacy Endpoints Analyses

The two primary endpoints for the study are OS and PFS (assessed by BIRC based on RECIST v1.1). For the PFS endpoint, there is one planned analysis, which is expected to occur when ~332 PFS events are observed ~19 months after first subject enrolled. For the OS endpoint, it will be evaluated in the following time points: when PFS is analyzed (approximately 19 months after first subject enrolled); when ~251 OS events (70% at ~23 months after first subject enrolled) and when 359 OS events are observed (at ~36 months after first subject enrolled).

The hypothesis testing of OS and PFS will be evaluated by comparing SHR-1210 plus rivoceranib to sorafenib on their events in ITT using a stratified Log-rank test (based on randomization stratification factors). The hazard ratio (HR=SHR-1210 plus rivoceranib / sorafenib) and the corresponding 95% confidence interval (CI) will be estimated in a stratified Cox proportional hazard model with experimental arm and randomization stratification factors included in the model. Survival curves for each treatment group will be estimated using the Kaplan-Meier (KM) product-limit method. A 95% CI for median survival time will be estimated by Brookmeyer-Crowley method. The above analyses will be repeated without the stratification factors included in the

analysis. In case the proportional hazard is not valid, Wilcoxon test or RMST (Restricted Mean Survival Time) method may be performed for OS and PFS analysis.

Detail of multiplicity control can be found in Section 10.4.12.

Further detail, including censoring rules, will be provided in the SAP.

10.4.6. Secondary Efficacy Endpoints Analyses

Objective response rate (ORR) assessed by BIRC according to RECIST v1.1 will be analyzed as a key secondary endpoint when 70% OS events are observed. If both PFS and OS primary endpoints are positive, comparison between treatment groups in ORR by BIRC according to RECIST v1.1 will be performed using stratified Cochran-Mantel-Haenszel (CMH) test. Difference in proportions for ORR and its 95% CI using normal approximation will be provided. Overall response rates and their corresponding 95% exact CIs will be calculated by Clopper-Pearson method for each treatment group.

The other time-to-event endpoints will be estimated using the Kaplan-Meier (KM) product-limit method, unless specified. A 95% CI for median survival time will be estimated by Brookmeyer-Crowley method, if necessary.

For other binary variables, stratified CMH test will be used and two-sided 95% CI for treatment difference will be calculated using normal approximation.

Further elaborations will be provided in the SAP.

10.4.7. Pharmacokinetics and Immunogenicity

The incidence of ADA and the proportion of subjects with neutralizing active antibodies (Nab) in subjects treated with SHR-1210 in combination with rivoceranib will be summarized using descriptive statistics by experimental arm and by visit. ADA/Nab in combination with SHR-1210 concentration, safety, and efficacy will be summarized using descriptive statistics (see Section 10.4.8). Any other analysis methods will be elaborated in the corresponding analysis plan.

The population PK, exposure-QTc analysis and exposure-response analysis will be performed and reported separately.

10.4.8. Exploratory Endpoints Analyses

The time to deterioration (TTD) of EORTC QLQ-C30 endpoints will be analyzed using similar method for the primary endpoint OS (stratified Cox model and K-M curve). The scores of other scales and the average change from the baseline will be summarized using descriptive statistics by treatment cycle.

The correlation of the expression level of PD-L1 and proportion of strong expression of PD-L1 in tumor tissue with the efficacy of SHR-1210 combined with rivoceranib mesylate (including but not limited to ORR, OS) will be summarized using descriptive statistics. If necessary, an *ad hoc* analysis will be performed and results will be presented in a separate supplementary report.

Efficacy endpoints (e.g. BOR, ORR) and safety endpoints (e.g. immune-related adverse events (irAE), study drug-related AE with CTCAE grade ≥ 3, drug-related SAE) with SHR-1210 ADA/Nab status in experimental arm will be summarized using descriptive statistics. If necessary, a comparison of efficacy and safety will be performed according to the ADA status.

PFS, TTP, ORR and DoR assessed by investigator based on imRECIST will be evaluated using the same analytical methods for the secondary endpoints.

Other analytical methods for exploratory endpoints will be elaborated in the SAP.

10.4.9. Handling of Missing Data

Except for the special cases, the following rules will be applied to the missing date of the events.

If the start date of the event is all missing, it will not be imputed. If the day is missing, but the year and month are consistent with the year and month of the study drug treatment, the day of the first study drug treatment will be used. Otherwise, the first day of the month will be used. If the day of end date is missing, but the year and month are consistent with the year and month of the end of study drug treatment, the day of end - of-treatment will be used. Otherwise, the last day of the month will be used.

If the month and day of the event are missing, but the year of occurrence is consistent with the year of study drug treatment, the month and day of the first study drug treatment will be used. Otherwise, January 1 will be used.

All imputation dates should be prior to the date of withdrew consent, lost to follow-up or death.

10.4.10. Safety Analyses

10.4.10.1. Analyses of Adverse Events

Adverse events will be coded to MedDRA (v 18.1 or higher) for lower level term (LT), preferred term (PT) and primary system organ class (SOC).

A treatment-emergent adverse event (TEAE) is defined as an adverse event (AE) that had an onset date after the start of the study treatment or that worsened in severity from baseline (pretreatment).

Only those AEs that were treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and preferred term. A subject will be counted only once by the highest severity grade per NCI-CTCAE v4.03 within an SOC and preferred term, even if the subject experienced more than 1 TEAE within a specific SOC and preferred term. The number (percentage) of subjects with TEAEs will also be summarized by relationship to the study drug. Treatment-related AEs include those events considered by the investigator to be definitely, possibly related to study treatment or with missing

assessment of the causal relationship.

Subject incidence of AE, SAE, AE with CTCAE Grade ≥ 3, SAE with CTCAE Grade ≥ 3, drug related AE, drug related SAE, AE with incidence ≥ 5%, SAE with incidence ≥ 5%, AE leading to dose adjustment, AE leading to discontinued treatment etc. will be tabulated by experimental arm. Time-to-adverse events of special interest, and duration of events will be analyzed using K-M method.

10.4.10.2.Laboratory Tests Results

Clinical laboratory (e.g., hematology, blood biochemistry) values will be evaluated as appropriate. Abnormal laboratory values will be flagged and identified as those outside (above or below) the normal range. The number and percentage of subjects experiencing Clinically significant laboratory values at baseline and worst post-dosing will be summarized by shift table.

Laboratory parameters that are graded in NCI-CTCAE v4.03 will be summarized by NCI-CTCAE grade. In the summary of laboratory parameters by NCI-CTCAE grade, parameters with NCI-CTCAE grading in both high and low directions will be summarized separately.

10.4.10.3.Others

The number and percentage of findings of clinically significant abnormal for vital signs will be summarized by experimental arm. A listing will also be provided for vital signs.

The analyses of ECOG-PS will include summary statistics of baseline and highest score post baseline by experimental arm.

The analyses of ECG will include summary statistics of baseline and worst clinically abnormal grade post baseline by experimental arm.

10.4.11. Interim Analyses

In this study, there is only one planned PFS analysis, which is planned at occur when ~332 PFS events are observed (at ~19 months). OS analyses will be conducted at the following time points: at final PFS analysis, at 251 (70%) deaths if there are less than 251 deaths at the final PFS analysis, and when ~359 OS events are observed (at ~36 months.

PFS

If SHR-1210 in combination with rivoceranib arm demonstrated superiority over sorafenib (i.e., one-sided p-value < 0.005), its corresponding alpha level of 0.005 will be re-allocated to test the OS hypothesis at 0.025 one-sided with updated efficacy boundaries per Lan-DeMets O'Brien-Fleming spending function (see Table 15).

OS

A formal interim analysis (IA) for OS will be conducted after 70% (~251) of the target OS events are observed at ~23 months. The OBF was used for calculating efficacy boundaries (original 0.020/updated 0.025 alpha level). With ~251 OS events, the SHR-

1210 in combination with rivoceranib mesylate will be considered superior than the sorafenib at the interim analysis, if the one-sided p-value for OS is less than 0.005/0.007, which corresponds to an observed HR of approximately 0.725/0.735. The trial will be considered positive at the final analysis, if the one-sided p-value for OS is less than 0.018/0.023, which corresponds to an observed HR of approximately 0.802/0.810. If the null hypothesis for OS is rejected at either the interim (70%) or the final, its corresponding alpha level of 0.020 will be re-allocated to PFS so that the hypothesis for PFS maybe tested again at 0.025 one-sided. The boundary properties for the planned OS analyses based on the original and updated alpha levels can be found in Table 15 .

In an anticipation that the number of OS events is < 251 OS events at the planned PFS analysis, a nominal alpha of 0.001% will be spent at the time of the planned PFS analysis. Since the trial will not stop early if there are less than 251 deaths, the 0.001% is considered for administrative purposes to avoid trial stop early. The study will continue to the next planned OS interim analysis (70%) and could continue to final analysis after ~251 OS events and ~359 OS events are observed, respectively, according to the efficacy boundaries as described in Table 15 .

The analysis of PFS and the formal interim analysis (IA) of OS will be conducted by a Data Monitoring Committee (DMC) that recommends early discontinuation of the study for unequivocal efficacy at formal interim analysis (IA) of OS (~70% events), or continuation of the study for final analysis of OS.

10.4.12. Multiplicity

The two primary endpoints for the study are OS and PFS (assessed by BIRC based on RECIST v1.1). There is only one planned PFS analysis, which is expected to occur when approximately 332 PFS events are observed at approximately 19 months. OS analyses will be conducted at the following time points: at final PFS analysis, at 251 (70%) deaths if there are less than 251 deaths at the final PFS analysis, and when ~359 OS events are observed at ~36 months, respectively.

The Type I error of 0.025 one-side is strongly controlled using the Weighted-Holm procedure with α-reallocation approach between PFS and OS endpoints as described in Ye et al 2013 [27] and O'Brien-Fleming alpha-spending function (OBF) within OS. The allocated α between two endpoints is α_1=0.005 (one-sided) for PFS and α_2=0.020 (one-sided) for OS. If PFS endpoint is significant at α_1=0.005, its α_1 level will be re-allocated to endpoint OS so that the hypothesis for OS may be tested using its updated efficacy boundaries based on α level 0.025. Similarly, if endpoint OS is significant at α_2=0.020 according to the efficacy boundaries as determined by OBF, and PFS endpoint is not significant at α_1=0.005, its α_2 level will be re-allocated to PFS so that the hypothesis for PFS may be tested again at α level 0.025 (one-sided). The boundary properties for the planned OS analyses based on the original and updated alpha levels are summarized in Table 15 below:

Table 15 Boundary Properties for Planned Analyses of OS

Analysis	**Value**	**α=0.020**	**α=0.025**
Interim analysis：~70%	Z	-2.549	-2.440

Events：251	p (one-sided)	0.005	0.007
Months：~23	HR at bound	0.725	0.735
Final analysis	Z	-2.089	-2.000
Events：359	p (one-sided)	0.018	0.023
Months：~36	HR at bound	0.802	0.810

Note: Results were generated using the EAST® 6.4.1. software; HR=Hazard ratio (SHR-1210 + rivoceranib / Sorafenib) less than 1 indicates SHR-1210+rivoceranib group is superior than Sorafenib arm. The one-sided nominal significance level and stopping boundary will be determined by the actual percentage of events when the interim analysis is conducted.

If both PFS and OS endpoints are not significant, then α-reallocation will not perform. If both the PFS and OS endpoints are significant, ORR assessed by BIRC according to RECIST v1.1 may be tested at 0.025 one-sided. The graphical approach in Figure 8 shows the α-reallocation strategy for endpoints PFS and OS [28, 29]:

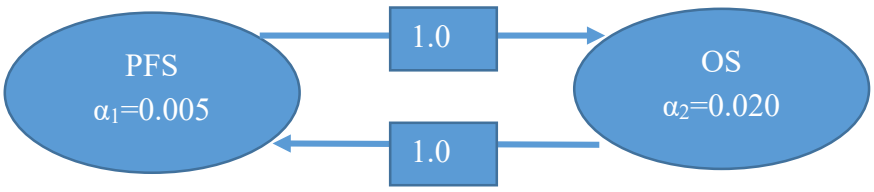


Figure 8. Type I error reallocation strategy for endpoints PFS and OS.

Above shows the initial one-sided α-allocation for each hypothesis in the ellipse representing the hypothesis. The weights for re-allocation from each hypothesis to another are represented in the rectangular boxes on the lines connecting hypotheses.

When there are less than 251 OS events at the planned PFS analysis at ~19 months, a nominal α (0.001%, independent of OBF approach to allocate alpha) will be used, but the trial will not stop based on this OS result at the time of the PFS analysis. The study will continue to the next planned OS interim analysis (70%) and could continue to the final analysis after ~251 OS events and ~359 OS events at ~23 and ~36 months, respectively, at the alpha level as determined by the OBF boundaries and the actual number of OS events observed. The nominal alpha (0.001%) is considered, as this has negligible impact on overall Type I error rate and the study will not stop early for a positive OS result at the time of the PFS analysis.

Any changes to the above strategy will be documented elsewhere, if not in a protocol amendment, at the earliest time before any formal analysis is being conducted.

10.4.13. Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, HR and 95% CI for the primary endpoints OS and PFS (assessed by BIRC based on RECIST v1.1) will be estimated and plotted within each category of the following classification variables:

- Age (<65 years vs. ≥ 65 years)
- Gender (male versus female)

- Geographic Region (Asia vs countries outside of Asia)
- Race (Asian vs non-Asian)
- Country (Greater China area [mainland China, Hong Kong and Taiwan] vs US vs Europe)
- BCLC stage (Stage B vs Stage C)
- Macrovascular invasion and/or extrahepatic spread (Presence vs. Absence)
- The underlying disease or medical condition related to etiology (HBV vs HCV vs others)
- AFP elevation at the baseline (<400 ng/mL vs ≥400 ng/mL)
- Involved disease sites (1 vs 2 vs ≥ 3)
- Previous local therapy (including radiotherapy) (yes vs no)
- Weight (<60 kg vs. ≥60 kg)
- ECOG-PS Score (0 vs. 1).

10.5. Blinded Independent Review Committee

A BIRC will be established to perform an independent review of all radiological images (imaging for tumor assessment will be provided by study centers to BIRC), and to determine all instances of response and disease progression on the basis of RECIST v1.1 and mRECIST criteria. If the investigator evaluates it as PD according to the RECIST v1.1 criteria, all radiological data must be submitted to BIRC, and PD will have to be confirmed by BIRC (Please refer to Figure 7 for PD confirmation process), and even if BIRC confirms PD per RECIST v1.1, the investigator needs to evaluate whether the subject continues to have benefit and meet the criteria for continued treatment beyond disease progression, and if so, the subject will continue the treatment and continue to be performed tumor radiological assessments.

The tumor assessment by BIRC will be used for the reporting of the study results. All decisions made during the performance of the study will be on the basis of the local investigator's assessment of radiographic images, clinical status, and relevant examination of the subjects. Sites will submit specific radiographic image files to the centralized data review facility during the study at an ongoing basis or at the sponsor's request. Detail rules and guidelines for radiographic radiological and tumor assessments by BIRC will be outlined separately in the DMC charter, Image Acquisition Guidelines, and Central Laboratory Manual.

10.6. Data Monitoring Committee

The study will establish an independent Data Monitoring Committee (DMC) to regularly assess safety data, and analysis will be conducted for assessment of efficacy and safety at the time of PFS analysis and OS interim analysis. The DMC will provide advice on the measures that must be taken for protection of subjects and overall safety evaluation to the sponsor.

The DMC is the consultant to the study team of the sponsor. The study team of the sponsor are responsible for overall conduction of the study, including management of

the exchange and communication of study data, analysis based on the advice from the DMC, and making decisions on continuation of, amendment to or termination of the study.

After the study is initiated, the DMC will hold meeting to evaluate safety data on a regular basis, as to ensure the subject's safety is carefully supervised. The sponsor can also consult the DMC in a retrospective manner based on the safety signals discovered, and hold retrospective safety review meetings as required. The DMC can make recommendations for continuing, revising or terminating the study based on observed safety or efficacy data. Prior to the meeting, the DMC will look up and review the study data acquired, including the characteristics of the study population, dose information, safety and efficacy data in PFS analysis.

The composition, responsibilities, frequency, format, operation and management of the DMC will be detailed in a separate DMC charter.

11. DATA MANAGEMENT METHODS

11.1. Recording of Data

Electronic data capture system (EDC) will be used for collection and management of clinical study data in this study.

11.1.1. Recording of Source Document

The source document should be completely maintained as the original document in clinical trial. They should be filled in and maintained by investigators. The subject's information on the cover of the source document should be checked firstly prior to filling in each time, the handwriting should be legible and easy to read, so that the monitor can check the data with eCRF.

11.1.2. Filling of eCRF

The data in eCRF comes from original documents such as medical record and laboratory examination report, and should be consistent with the original documents. Any observation and examination result during the trial should be filled in the eCRF promptly, correctly, completely, standardized and truthfully.

The reason for data modification needs to be filled in accordance with the system implication, when the data in eCRF are corrected.

11.1.3. eCRF Review

Investigators should fill in, save and submit the eCRF promptly after the end of each visit. The system logic verification program will check the integrity and logic of the data entered in EDC system, and query the problem data. The principal investigator or data entry personnel are allowed to modify or explain the problem data, and multiple queries can be raised until the problem data are resolved, when necessary. Monitors, data administrator and medical auditors will review eCRF data when necessary and query the doubtful data. Investigators should respond to the queries from the system and data auditors in time. After completion of data clearance, investigators will sign the

electronic signature of the completed eCRF.

11.2. Data Management

11.2.1. Establishment of EDC Database

Data administrator will establish study data collection system and database in accordance with the protocol, and provide on-line use prior to enrollment of the subject. All EDC users need to complete relevant training, fill in training records, and account application forms to obtain the corresponding account of the login system.

11.2.2. Data Review and Database Lock

Prior to database lock, the project team need to summarize all the events of deviation from protocol during the trial, and hold data review meeting. Any decision made during the data review meeting should be documented.

After all data have been reviewed, database lock will be confirmed by investigators, sponsor and statisticians. The data documents can not be modified after locking. Post-locking data need to be properly maintained for future reference.

11.2.3. Data Archiving

After completion of the study, subject's eCRF in a format of PDF should be generated in EDC system, and saved onto a CD-ROM, and submitted to sponsor and the organization to maintain the file for inspection.

The storage and management of study documents must be performed in accordance with the requirement of ICH-GCP, investigators should inform the sponsor in advance when destroying any document or data related with the trial. After marketing approval of the investigational drug in the last country or region, or if the trial was discontinued, the sponsor must keep the study documents for at least 15 years.

12. SOURCE DATA AND SOURCE DOCUMENT

According to the International Council for Harmonization (ICH) E6, relevant regulations and study centers' requirements for the protection of subjects' personal information, each study center must keep records of treatment and research related to this study properly. As one part of the study funded or involved by Jiangsu Hengrui Pharmaceuticals Co., Ltd., each study center should allow Jiangsu Hengrui Pharmaceuticals Co., Ltd. or its authorized representative and regulatory authorities to audit (replicate if allowed by the law) the clinical records, as to perform quality review and audit, as well as evaluation of safety, study progress and data verification.

The source data are all the information necessary to reconstruct and evaluate clinical study, and are the original record of clinical findings, observations or other activities. Examples of these source documents and data include, but are not limited to: hospital records, laboratory records, memoranda, subject's diaries, pharmacy dispensing records, recording of consultation meetings, recording data of automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X-rays, and records kept at the

pharmacy, at the laboratories and at medico-technical departments involved in the study.

13. QUALITY ASSURANCE AND QUALITY CONTROL

In order to ensure the quality of the trial, the clinical study plan is discussed and established by the sponsor and investigators prior to the official start of the trial. And they should confirm whether the personnel involved in the trial has received appropriate GCP training.

Each study site must manage the investigational drugs in accordance with SOP, including receiving, storage, dispensation, recovery and destroying (if applicable).

According to ICH-GCP guidelines, necessary procedures must be taken during the design and implementation of the study, to ensure that the collected data are accurate, consistent, complete and reliable. All the results and abnormal findings observed in the clinical trial should be verified and recorded promptly to ensure the reliability of data. The instruments, equipment, reagents and standard materials used in the clinical trial should have strict quality standards, and ensure that they are working under normal conditions.

The investigators input the required information into the eCRF, the monitors check the complete and accurate filling, and instruct the personnel at the study center for necessary modification and supplementation.

Regulatory Authorities, Institutional Review Board (IRB)/Independent Ethics Committee (IEC), the Sponsor's monitors and/or auditors may conduct a systematic review of the clinical trial-related activities and documents to assess whether the trial has been conducted in accordance with the trial protocol, SOP and the requirements of relevant laws and regulations, and whether the trial data are timely, truthfully, accurately and completely recorded. The audit should be performed by the personnel who are not directly involved in the clinical trial.

14. REGULATIONS, ETHICS, INFORMED CONSENT AND PROTECTION OF SUBJECTS

14.1. Considerations on Regulations

This study will be conducted completely in accordance with ICH E6 GCP guideline and the principle of Declaration of Helsinki, and national laws and regulations, as to provide the maximum protection for individuals. This study will comply with the requirements in ICH E2A guideline (clinical safety data management: definition and criteria of accelerated reporting).

Legal basis for design of this protocol:

1) Drug Registration Regulations;
2) Good Clinical Practice;
3) Technical Guidelines for Clinical Pharmacokinetics of Chemical drugs;

4) Based on the ethical principle and consensus in the international ethical guidelines, including Declaration of Helsinki and the international ethical guidelines by the Committee of International Organization in Medical Science (CIOMS);
5) ICH Guidelines;
6) Other applicable laws and regulations.

14.2. Ethics

Investigators will make sure this study will be performed completely in accordance with the requirement on protection of subjects specified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56 and/or ICH E6.

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

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

14.3. Independent Ethics Committee

The protocol, informed consent form, recruiting materials and all the subjects' materials will be submitted to the ethics committee for review and approval. The subjects can be enrolled only after approval of the protocol and informed consent form. Any amendment to the protocol can be implemented only after review and approval by the ethics committee. All the amendments to the informed consent form also have to be approved by the ethics committee, and it will be decided by the ethics committee whether the new version of informed consent form needs to be re-signed for the subjects who have signed the previous version.

14.4. Informed Consent

14.4.1. Written Information Required for Informed Consent Form and Subjects

The informed consent form will describe the investigational product and course of study in detail, and make a sufficient explanation of the risks of the study to subjects. The required informed consent form must be signed by the subject prior to conduct of any study related procedure.

The informed consent form must be in compliance with ICH-GCP, local regulatory requirements and legal requirements, including applicable privacy laws.

14.4.2. Course and Record of Informed Consent

The informed consent starts before subject's agreement on participation in the clinical study, and sustains throughout the clinical study. The risks and possible benefits of participation in the study will be discussed with subjects or their legal representatives carefully and adequately. Subjects (or LARs) will be asked to read and review the informed consent form that are approved by the ethics committee. Investigators will explain the clinical study to subjects (or LARs) and answer any question possibly proposed by subjects (or LARs). Only after the subject has signed the informed consent form he/she is able to enter the study. Throughout the course of the clinical study, subjects (or LARs) can withdraw their informed consent at any time. One copy of informed consent form will be kept by subjects. Even if consulted subjects (or LARs) refuse to participate in this study, their rights will still be fully protected, and the quality of their medical care will also not be affected.

14.5. Confidentiality of Subject's Information

The confidentiality of subject's information will be strictly maintained by investigators, study personnel involved, the sponsor and their representatives. The confidentiality covers the biological samples in addition to the clinical data. Thus, the study protocol, documents, data and all the other incurred information will be strictly kept in confidence. Without the prior written approval by the sponsor, all the relevant study or data information can not be revealed to any unauthorized third party.

Other authorized representatives of the sponsor, ethics committee/IRB, regulatory departments and representative of pharmaceutical company which supplies investigational product can check all the documents and records which are required to be maintained by investigators, including but not limited to medical records and subject's medication records. The study center should have the access to these records.

The subject's contact information will be stored at each study center safely and only provided for internal use during the study. At the end of study, all the records will continue to be stored in a secure place in accordance with the time limit specified by local ethics committee/IRB and regulations.

The study data collected for statistical analysis and scientific report should not include subject's contact information or identification information. Individual subjects and their study data will be given a separate study identification number. EDC and study administration system used in each clinical study center are confidential and protected by password. At the end of study, all the identification data in the database will be eliminated and archived at each clinical study center, respectively.

The sponsor will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

15. PUBLICATION OF STUDY RESULTS

Study results are the property of Jiangsu Hengrui Pharmaceuticals Co., Ltd. In order to protect confidential and/or patentable information, protect patient privacy, and ensure the accuracy of study results, Hengrui Medicine Co., Ltd., as the Sponsor, has the right

to review all planned publications, including articles in journals as well as abstracts, posters, and slides for oral presentations at academic conferences.

- The Investigator should provide full-text of all planned publications to Sponsor at least 30 days prior to submission.
- If Sponsor deems it necessary to apply for a patent to protect intellectual property, the Investigator should agree to delay the publication plan for no more than 60 days. Prior to the submission of planned publications, Sponsor shall have the right to request the Investigator to remove any undisclosed Confidential Information (except study results).

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APPENDIX 1. Barcelona Clinic Liver Cancer (BCLC) Classification

BCLC Stage	ECOG-PS Score	Tumor Status	Child-Pugh Class
0 (very early stage)	0	Single lesion <2 cm carcinoma in situ	A
A (early stage)	0	Single lesion or 3 nodules ≤3 cm	A-B
B (intermediate stage)	0	multinodular	A-B
C (advanced stage)	1-2	Portal vein invasion, N1, M1	A-B
D (terminal stage)	3-4	Any	C

Note: All the conditions need to be met for stages 0, A and B; any one of them just needs to be met for stage C and D (PS score or tumor status). N1: lymph node metastasis, M1: distant metastasis.

APPENDIX 2. Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) and Its Comparison with Immune-Modified RECIST (imRECIST) and Modified RECIST (mRECIST)

RECIST v1.1

1. Measurability of tumor at baseline

1.1 Definitions

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

Measurable

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement 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: To be considered pathologically enlarged and measurable, a lymph node must be 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with 10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible radiological techniques.

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 radiological techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional radiological 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 bone 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 non-cystic lesions are present in the same subject, 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 loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

1.2 Specifications by methods of measurements

Measurement of lesions

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

Method of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Radiological based evaluation should always be done rather than clinical examination unless the lesion being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and 10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and radiological, radiological 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, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are

clearly defined and surrounded by aerated lung.

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

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, 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 of CT in selected instances.

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

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a subject to be considered in 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 CA125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

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

2. Tumor response evaluation

2.1 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, taking as reference the baseline sum diameters.

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

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

2.2 Special notes on the assessment of target lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each 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 case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions 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 on treatment: When non-nodal lesions 'fragment', 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'.

2.3 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 nodes must be non-pathological in size (<10 mm short axis).

Non-complete Response or non-PD: Persistence of one or more non-target lesion 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 progression.

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

The concept of progression of non-target disease requires additional explanation as follows.

When the subject also has measurable disease: In this setting, 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, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. 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 subject has only non-measurable disease: This circumstance arises in some phase 3 trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. 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 subjects for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. 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 therapy'. If 'unequivocal progression' is seen, the subject 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.

2.5 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 new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in radiological modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the subject'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 in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the subject who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The subject's brain metastases are considered to be evidence of PD even if he/she did not have brain radiological at baseline.

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

While FDG-PET response assessments 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 radiological can be identified according to the following algorithm:

Negative FDG-PET at baseline, with a positivel 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, this is PD.

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 anatomic images, this is not PD.

2.6 Missing assessments and not evaluable designation

When no radiological/measurement is done at all at a particular time point, the subject is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion would not change the assigned time point response.

2.7 Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes 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 subjects with CR may not have a total sum of 'zero' on the case report form (CRF).

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

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such subjects is to be determined by evaluation of target and non-target disease as shown in Tables 1-3 below.

Conditions that define 'early progression, early death and inevaluability' are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade 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.

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

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD

Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

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

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Note: CR=complete response, PD=progressive disease, NE=not evaluable.
'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

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 assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

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

Overall response First time point	Overall response 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

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

a. If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease

meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the subject 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.

2.8 Confirmatory measurement/duration of response

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. In randomized trials (phase 2 or 3) 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. 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.

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 PD is objectively documented (taking as reference for PD the smallest measurements recorded on study). The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

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 subjects achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

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

2.9 Progression-free survival/proportion progression-free

Phase 3 trials in advanced cancers are increasingly designed to evaluate PFS or TTP as the primary outcome of interest. Assessment of progression is relatively straightforward if the protocol requires all subjects to have measurable disease. Increasingly, trials allow entry of both subjects with measurable disease as well as those with non-measurable disease only. In this circumstance, care must be taken to explicitly describe the findings which would qualify for PD for those subjects without measurable lesions. Because the

date of progression is subject to ascertainment bias, timing of investigations in study arms should be the same.

Comparison of imRECIST with RECIST v1.1

Source: *Hodi FS, Ballinger M, Lyons B, et al. Immune-Modified Response Evaluation Criteria In Solid Tumors (imRECIST): Refining Guidelines to Assess the Clinical Benefit of Cancer Immunotherapy. J Clin Oncol. 2018 Mar 20;36(9):850-858.*
Full text link: http://ascopubs.org/doi/abs/10.1200/JCO.2017.75.1644?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed

Briefly, immune-modified Response Evaluation Criteria in Solid Tumors (imRECIST) allows for collection of additional scans and for BOR to occur after radiologic PD assessment(s) in subjects continuing treatment (see Table 4 below). New lesions are added to the total tumor burden along with the sum of the target lesions when measurable; when not measurable, they are not factored into the PD assessment. In addition, progression in non-target lesions does not define PD. For analysis of imRECIST-defined PFS (imPFS), imRECIST PD or death is considered an event; however, an imRECIST PD is not considered an imPFS event if the time point response at the subsequent scan (≥ 4 weeks later) is imRECIST SD/PR/CR. An imRECIST PD followed by no additional assessments is considered an imPFS event.

Table 4 Comparison of RECIST 1.1 with imRECIST

Criterion	RECIST v1.1	irRC	imRECIST*
Tumor burden	Unidimensional Up to 5 target lesions/2 per organ	Bidimensional per WHO Up to 10 target lesions/ 5 per organ	Unidimensional, with other target lesion criteria (number, measurability) per RECIST v1.1
New lesions	Always represent PD	New lesions do not categorically define PD Measurable new lesions incorporated into the total tumor burden Non-measurable new lesions preclude CR	
Non-target lesions	Can contribute to defining CR or PD (unequivocal progression)	Non-target progression does not define PD Can only contribute to defining CR (complete disappearance required)	
PD	≥ 20% increase in the SLD (RECIST) and ≥ 5 mm increase compared with nadir, unequivocal progression in nontarget lesions, and/or appearance of new lesions	Determined only on the basis of measurable disease	
		Negated by subsequent non-PD assessment ≥ 4 weeks from the date first documented (lack of confirmation)	
		≥ 25% increase in the SLD compared with baseline/ nadir	≥ 20% increase in SLD (RECIST) compared with baseline/ nadir
	Confirmation of PD not required	Best response may occur before confirmed PD	Best response may occur after any number of PD assessments

Note: CR=complete response, imRECIST=immune-modified RECIST, irRC=immune-related response criteria, PD=progressive disease, RECIST=Response Evaluation Criteria in Solid Tumors, SLD=sum of longest diameters.
*imRECIST follows RECIST v1.1 convention unless otherwise stated.

ImRECIST is derived from RECIST v1.1 conventions and immune-related response criteria (irRC)[1]. When not otherwise specified, RECIST v1.1 conventions will apply.

Table 5 imRECIST and RECIST v1.1: Summary of Changes

	RECIST v1.1	imRECIST
New lesions after baseline	Define progression.	New measurable lesions are added into the total tumor burden and followed.
Non-target lesions	May contribute to the designation of overall progression.	Contribute only in the assessment of a CR.
Radiographic progression	First instance of ≥ 20% and ≥ 5mm increase in the sum of diameters or unequivocal progression in non-target disease.	Determined only on the basis of measurable disease.

Note: CR=complete response, imRECIST=immune-modified RECIST, RECIST=Response Evaluation Criteria in Solid Tumors.

Target Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

Non-Target Lesions

After baseline, changes in non-target lesions will contribute only in the assessment of CR (i.e., a CR is attained only with the complete disappearance of all tumor lesions, including non-target lesions) and will not be used to assess PD.

New Lesions

During the study, all new lesions identified and recorded after baseline must be assessed at all tumor assessment timepoints. New lesions will also be evaluated for measurability with use of the same criteria applied to prospective target lesions at baseline per RECIST, (e.g., non−lymph node lesions must be ≥ 10 mm; see note for new lymph node lesions below). Up to a maximum of 5 new lesions total (and a maximum of 2 lesions per organ), all with measurements at all timepoints, can be included in the tumor response evaluation. New lesion types that would not qualify as target lesions per RECIST cannot be included in the tumor response evaluation but can be used for CR exclusion.

New lesions that are not measurable at first appearance but meet measurability criteria at a subsequent timepoint will be measured from that point on and contribute to the sum of longest diameters (SLD), if the maximum number of 5 measurable new lesions being followed has not been reached.

[1] Wolchok et al. Clin Can Res 2009;15:7412−20; Nishino et al. J Immunother Can 2014;2:17; Nishino et al. Clin Can Res 2013;19:3936−43.

Calculation of Sum of the Diameters

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated as a measure of tumor burden.

The sum of the diameters is calculated at baseline and at each tumor assessment for the purpose of classification of tumor responses.

Sum of the Diameters at Baseline: The sum of the diameters for all target lesions identified at baseline prior to treatment on Day 1.

Sum of the Diameters at Tumor Assessment: For every on-study tumor assessment collected per protocol or as clinically indicated the sum of the diameters at tumor assessment will be calculated using tumor radiological scans. All target lesions selected at baseline and up to 5 new measurable lesions (with a maximum of 2 new lesions per organ) that have emerged after baseline will contribute to the sum of the diameters at tumor assessment. Hence, each net percentage change in tumor burden per assessment with use of modified RECIST accounts for the size and growth kinetics of both old and new lesions as they appear.

Note: In the case of new lymph nodes, RECIST v1.1 criteria for measurability (equivalent to baseline target lesion selection) will be followed. That is, if at first appearance the short axis of a new lymph node lesion ≥ 15 mm, it will be considered a measurable new lesion and will be tracked and included in the SLD. Thereafter, the lymph node lesion will be measured at subsequent timepoints and measurements will be included in the SLD, even if the short axis diameter decreases to <15 mm (or even <10 mm). However, if it subsequently decreases to < 10 mm, and all other lesions are no longer detectable (or have also decreased to a short axis diameter of < 10 mm if lymph nodes), then a response assessment of CR may be assigned.

If at first appearance the short axis of a new lymph node is ≥ 10 mm and < 15 mm, the lymph node will not be considered measurable but will still be considered a new lesion. It will not be included in the SLD unless it subsequently becomes measurable (short axis diameter ≥ 15 mm).

The appearance of new lymph nodes with diameter < 10 mm should not be considered pathological and not considered a new lesion.

Response Criteria

<u>Timepoint Response</u>

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table 6 provides a summary of the overall response status calculation at each timepoint for subjects who have measurable disease at baseline.

Complete Response (CR): Disappearance of all target and non-target lesions. Lymph nodes that shrink to <10 mm short axis are considered normal.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of all target and all new measurable lesions, taking as reference the baseline sum of diameters, in the absence of CR.

Note: the appearance of new measurable lesions is factored into the overall tumor burden but does not automatically qualify as PD until the sum of the diameters increases by ≥ 20% when compared with the sum of the diameters at nadir.

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

Progressive Disease (PD): At least a 20% increase in the sum of diameters of all target and selected new measurable lesions, taking as reference the smallest sum on study (nadir SLD; this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Impact of New Lesions on imRECIST

New lesions alone do not qualify as progressive disease. However, their contribution to total tumor burden is included in the sum of the diameters, which is used to determine the overall modified RECIST tumor response.

Missing Assessments and Not Evaluable Designation

When no radiological/measurement is done at all at a particular timepoint, the subject is considered not evaluable (NE) at that timepoint. If only a subset of lesion measurements is made at an assessment, usually the case is also considered NE at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint response. This would only happen in the case of PD. For example, if a subject had a baseline sum of 50 mm with 3 measured lesions and at follow-up only 2 lesions were assessed but those gave a sum of 80 mm, the subject will be assigned PD status, regardless of the contribution of the missing lesion.

Table 6 imRECIST Timepoint Response Definitions

% Change in Sum of the Diameters [a]	Non-Target Lesion Response Assessment	Overall Immune-Modified RECIST Timepoint Response
−100% from baseline [b]	CR	CR
−100% from baseline [b]	Non-CR or not all evaluated	PR
≤ −30% from baseline	Any	PR
> −30% to < +20%	Any	SD
Not all evaluated	Any	NE
≥ +20%from nadir SLD	Any	PD

Note: CR=complete response, NE= not evaluable, PD= progressive disease, PR= partial response, RECIST=Response Evaluation Criteria in Solid Tumors, SD= stable disease, SLD= sum of the longest diameter.

a. Percent change in sum of the diameters (including measurable new lesions when present).

b. When lymph nodes are included as target lesions, the % change in the sum of the diameters may not be 100% even if CR criteria are met, because a normal lymph node is defined as having a short axis of < 10 mm. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm in order to meet the definition of CR.

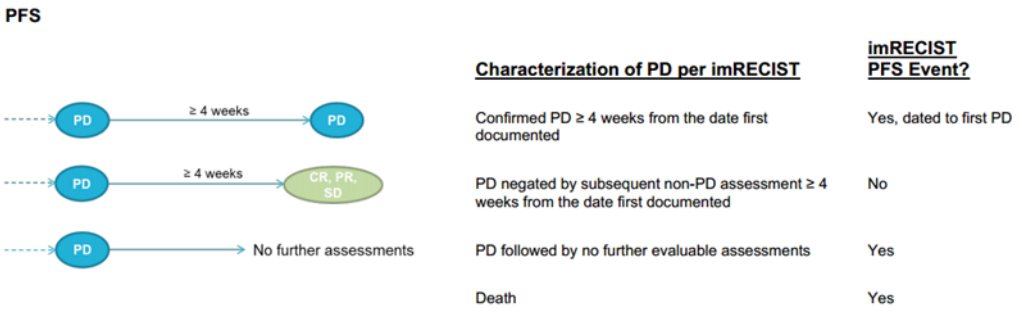


Figure 1 Definition of imPFS event and BOR

Comparison of mRECIST with Conventional RECIST

Source：*Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis. 2010 Feb;30(1):52-60.*

Note the following points regarding modified RECIST (mRECIST):

- mRECIST are recommended by American Association for the Study of Liver Diseases (AASLD) for the assessment of tumor response in HCC.
- Subjects can be followed with either contrast-enhanced spiral CT or contrast-enhanced dynamic MRI.
- In contrast-enhanced studies, it is mandatory to obtain a dual-phase radiological of the liver (high-quality arterial phase radiological obtained on the first run, and high-quality portal venous phase radiological obtained on the second run).

When assessing tumor response, the longest diameter of the target lesion (either viable or necrotic) is measured in conventional RECIST, whereas only viable target lesions are taken into account in mRECIST (see Table 7 below).

Table 7 Comparison of mRECIST with Conventional RECIST

Conventional RECIST	mRECIST
CR=Disappearance of all target lesions.	CR=Disappearance of any intratumoral arterial enhancement in all target lesions.
PR=At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of the diameters of target lesions.	PR=At least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions.
SD=Any cases that do not qualify for either PR or PD.	SD=Any cases that do not qualify for either PR or PD.
PD=An increase of at least 20% in the sum of the diameters of target lesions, taking as reference the smallest sum of the diameters of target lesions recorded since treatment started.	PD=An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started.

Note: mRECIST=modified RECIST, CR=complete response, PR=partial response, RECIST=Response Evaluation Criteria in Solid Tumors, SD=stable disease, PD=progressive disease.

APPENDIX 3. Child-Pugh Classification Criteria for Liver Function

Measure	Score		
	1 point	**2 points**	**3 points**
Hepatic encephalopathy	None	Grade 1 or 2	Grade 3 or 4
Ascites	None	Mild	Moderate and above
Prolongation of prothrombin time (s) **OR** international normalized ratio (INR)	<4 seconds **OR** ＜1.7	4-6 seconds **OR** 1.7-2.3	＞6 seconds **OR** >2.3
Total bilirubin (μmol/L)	＜34	34-51	＞51
Serum albumin (g/L)	＞35	28-35	＜28

Note: 5～6 points for Grade A; 7～9 points for Grade B and 10～15 points for Grade C.

APPENDIX 4. Criteria for Eastern Cooperative Oncology Group - Performance Status (ECOG-PS) Score

ECOG-PS Score	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 housework, 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 more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

APPENDIX 5. New York Heart Association (NYHA) Cardiac Function Classification

The severity of heart failure is poorly related with ventricular function, but clearly related with the survival rate, and subjects with mild symptom may still have a high absolute risk for hospitalization and death.

Grade	Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath)
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath)
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea
IV	Symptom of heart failure at rest. If any physical activity is undertaken, discomfort increases. In case of no intravenous administration, those who can move indoors or at bedside are classified as Grade IVa and those who can not get out of bed and need intravenous support are classified as Grade IVh

APPENDIX 6. Recommended Treatment Procedures for Common Immune-Related Adverse Events

When dealing with immune-related AEs, the investigator may refer to the following treatment procedures for common immune-related AEs. These procedures are recommended based on *Management of Toxicities From Immunotherapy: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-Up* (Annals of Oncology 28 (supplement 4):iv119-iv142, 2017)" in combination with this study protocol.

The general principle is that AEs should go through careful assessment and differential diagnosis in accordance with medical standards; non-inflammatory causes should be considered and properly managed.

Corticosteroids are the main therapeutic agents for Immuno-Oncology (I-O) drug related AEs. Subjects with low-grade toxicities who can walk around may consider oral doses equivalent to recommended intravenous doses. If the equivalent dose of oral corticosteroids is changed, the lower bioavailability of oral corticosteroids should be considered.

It is recommended to consult with physicians or surgeons, especially prior to invasive diagnosis or treatment.

1. Rules for management of gastrointestinal adverse event

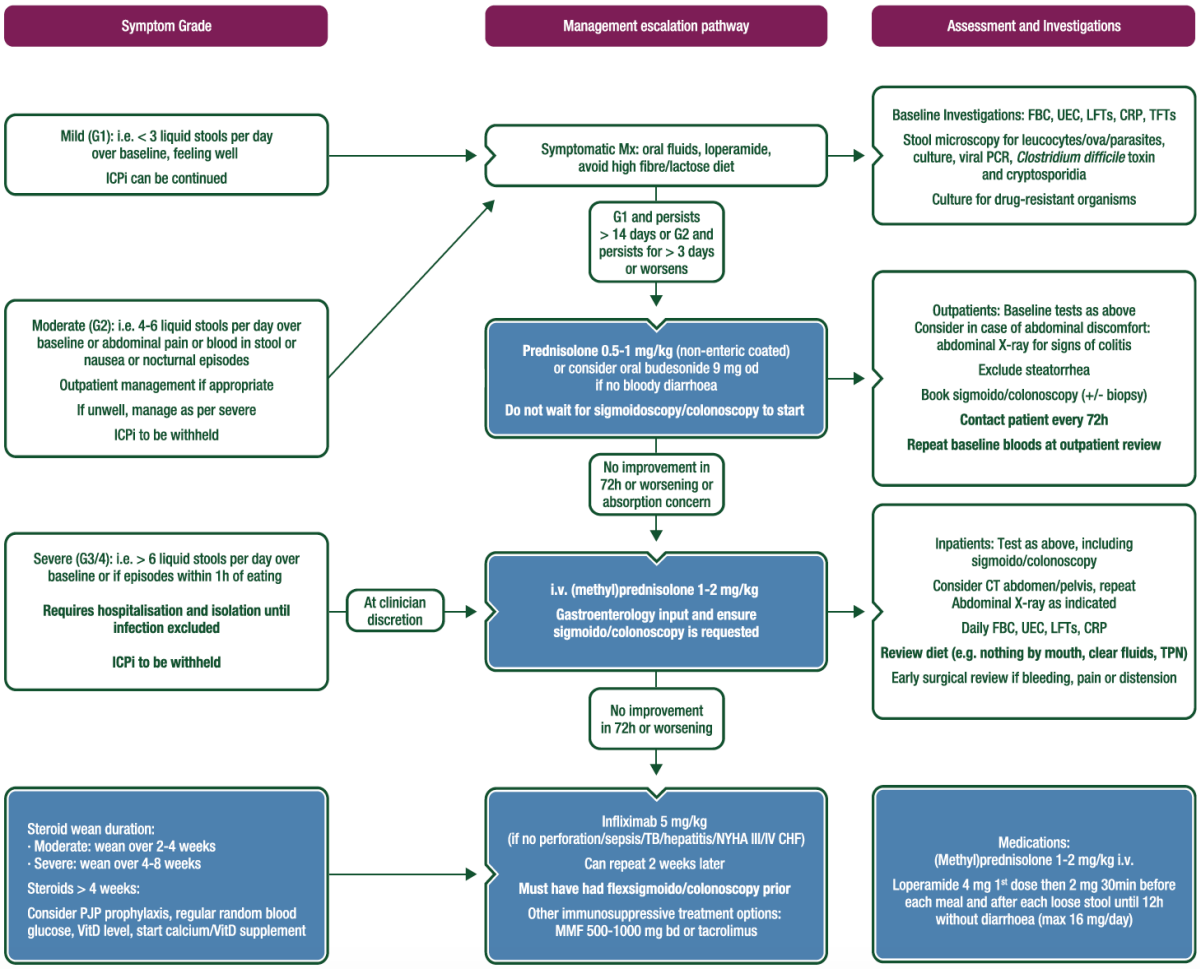


Figure 1. ICPi-Related Toxicity: Management of Diarrhoea and Colitis

BID=twice daily, CHF=congestive heart failure, CRP=C-reactive protein, CT=computed tomography, FBC=full blood count, ICPi=immune checkpoint inhibitor, i.v.=intravenous, LFTs=liver function tests, MMF=mycophenolate mofetil, NYHA=New York Heart Association, QD=once daily, PCR=polymerase chain reaction, PJP=Pneumocystis jiroveci pneumonia, TB=tuberculosis, TFTs=thyroid function tests, TPN=total parenteral nutrition, UEC=urea/electrolytes/creatinine.

2. Rules for management of pulmonary adverse events

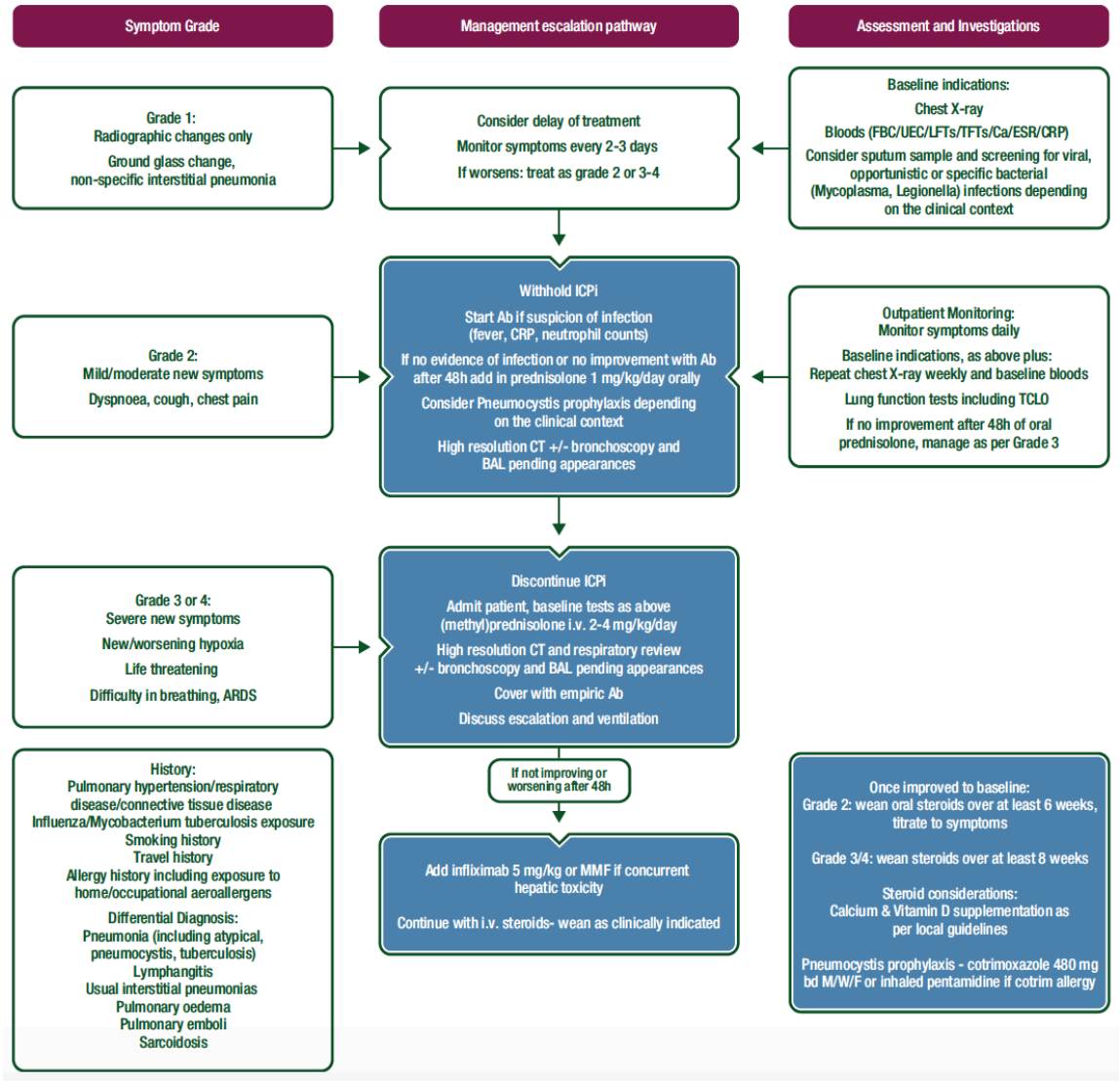


Figure 2. ICPi-Related Toxicity: Management of Pneumonitis

ARDS=acute respiratory distress syndrome, ICPi=immune checkpoint inhibitor, MMF=mycophenolate mofetil, FBC=full blood count, UEC=urea/electrolytes/creatinine, LFT=liver function tests, TFT=thyroid function tests, ESR=erythrocyte sedimentation rate, CRP=C-reactive protein, TCLO=transfer factor for carbon monoxide.

3. Rules for management of renal adverse events

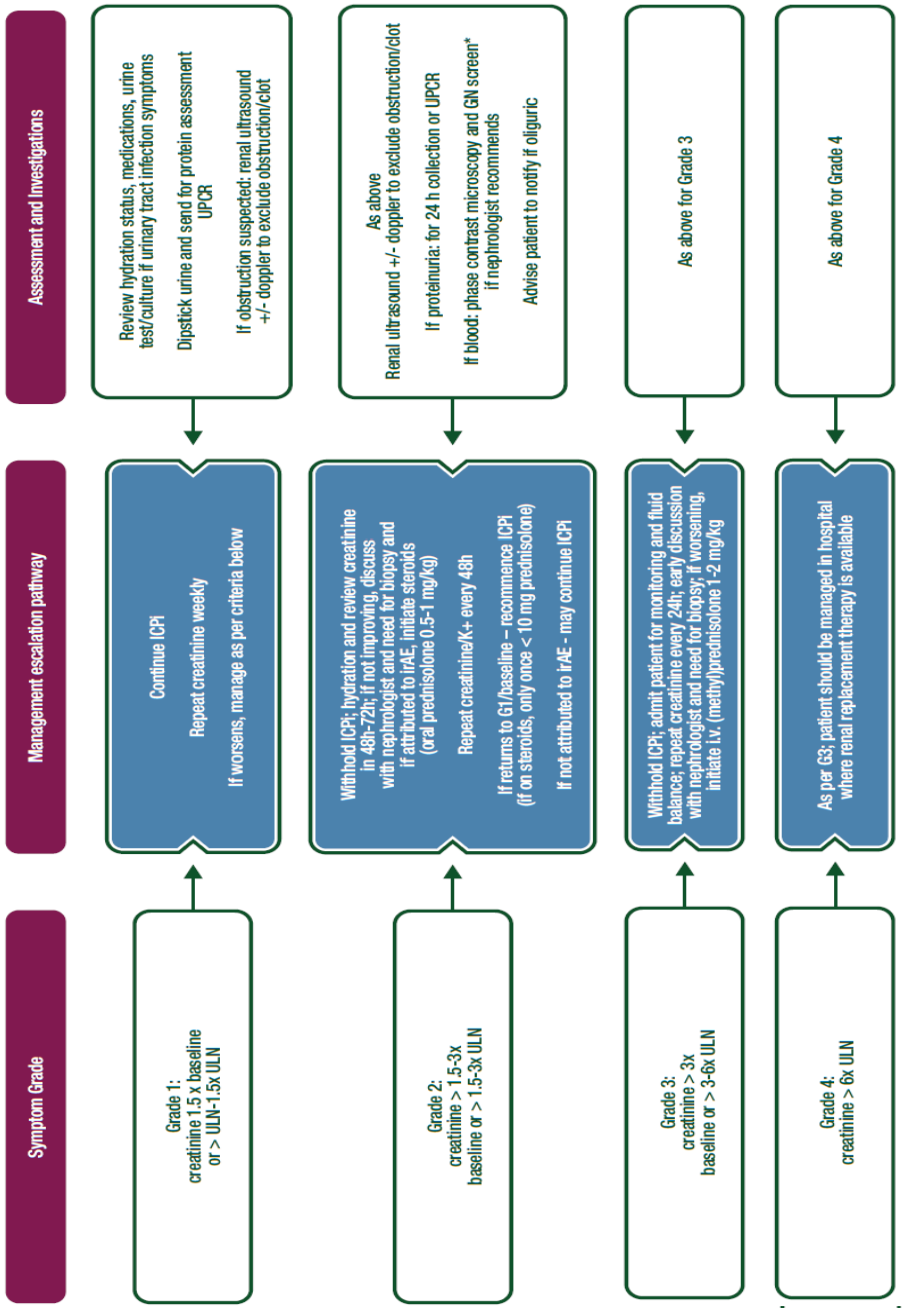


Figure 3. ICPi-Related Toxicity: Management of Nephritis

Renal injury occurs in around 1%-4% of subjects treated with ICPi, usually a pattern of acute tubule-interstitial nephritis with a lymphocytic infiltrate. Attention needs to be paid to the subject's baseline creatinine, not just abnormal results per biochemistry upper limit of normal (ULN). Confounding diagnoses include dehydration, recent i.v. contrast, urinary tract infection, medications, hypotension, or hypertension. Early consideration for renal biopsy is helpful which may negate the need for steroids and determine whether renal deterioration is related to ICPi or other pathology. Oliguria should prompt insubject admission for careful fluid balance and plan for renal replacement therapy. Steroid wean: begin to wean once creatinine Grade 1; Grade 2 severity episode-wean steroids over 2-4 weeks; Grade 3/4 episode-wean over ≥ 4 weeks. If on steroid for >4 weeks-Pneumocystis jiroveci pneumonia (PJP) prophylaxis, calcium/vitamin D supplementation, gastric protection and check afternoon glucose for hyperglycaemia. *GN screen:

ANA, complement C3, C4, ANCA, anti-GBM, hepatitis B and C, HIV, immunoglobulins and protein electrophoresis.

ANA=antinuclear antibody, ANCA=anti-neutrophil cytoplasmic antibody, GBM= glomerular basement membrane, GN=glomerulonephritis, HIV=human immunodeficiency virus, ICPi=immune checkpoint inhibitor, irAE=immune-related adverse event; i.v.=intravenous.

4. Rules for management of endocrine adverse event

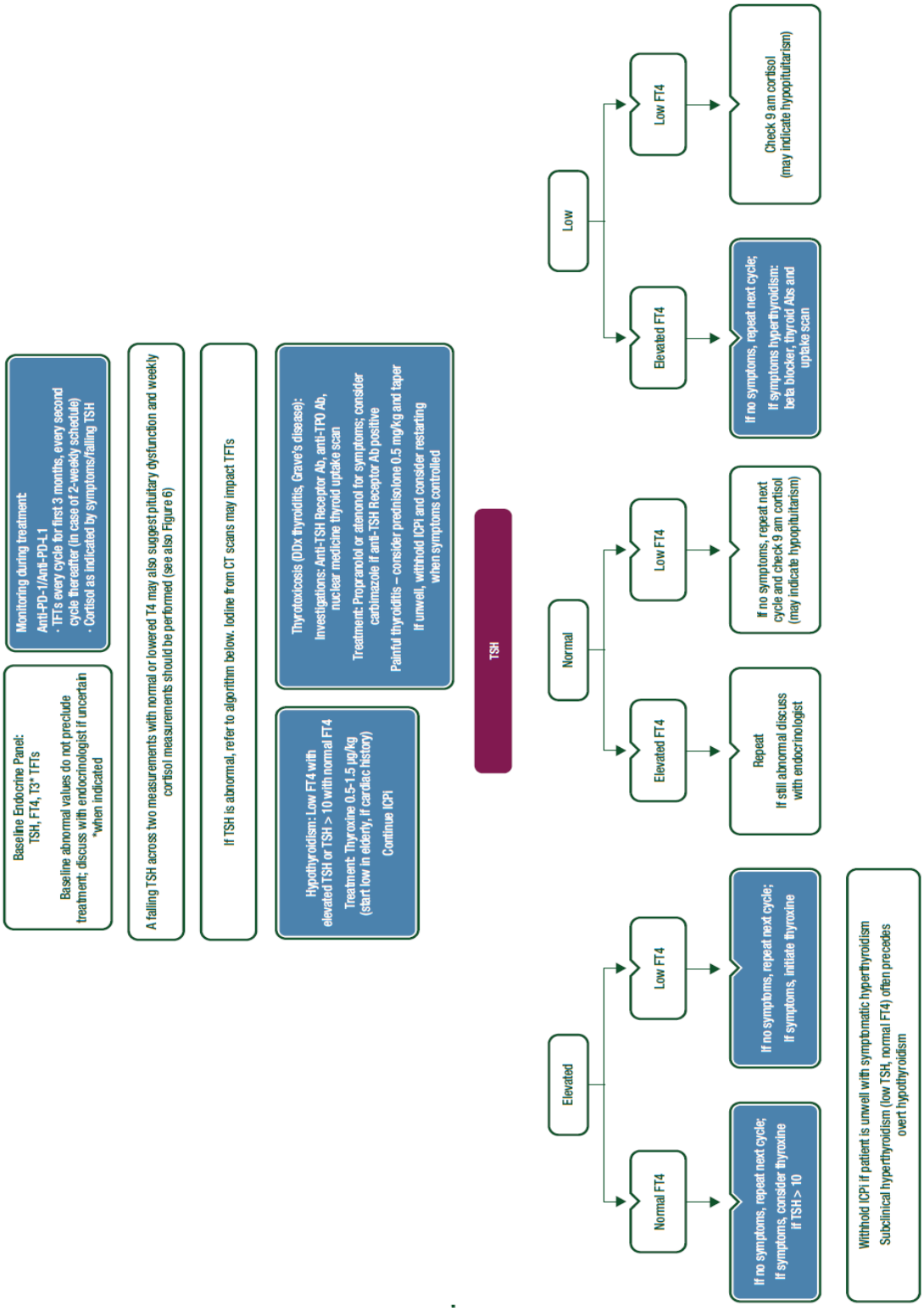


Figure 4. ICPi-Related Toxicity: Thyroid Function

CT=computed tomography, CTLA4=cytotoxic T-lymphocyte associated antigen 4, DDx=differential diagnosis, FT4=free thyroxine, ICPi=immune checkpoint inhibitor, PD-1=programmed death 1, PD-L1=programmed death ligand 1, T3=triiodothyronine,

T4=thyroxine, TFTs=thyroid function tests, TPO=thyroid peroxidase, TSH=thyroid-stimulating hormone.

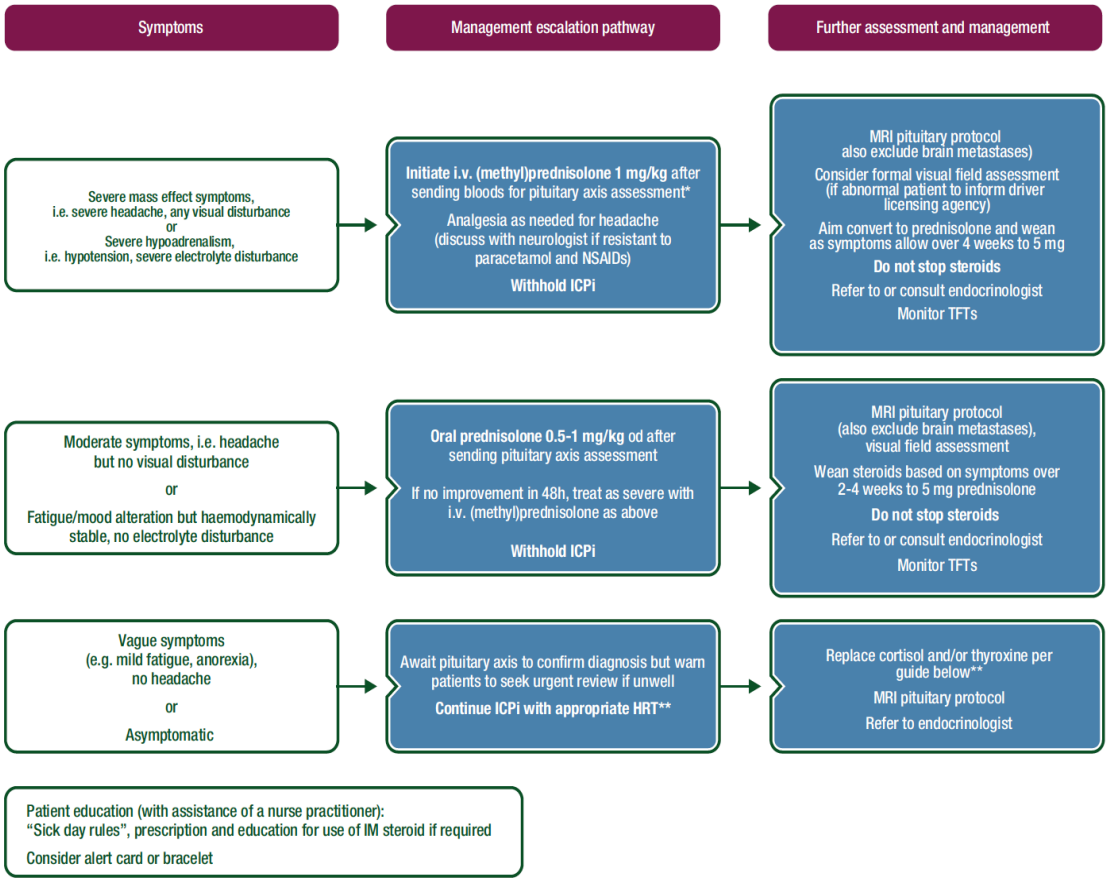


Figure 5. ICPi-Related Toxicity: Management of Hypophysitis

*Pituitary Axis bloods: 9 am cortisol (or random if unwell and treatment cannot be delayed), ACTH, TSH/FT4, LH, FSH, oestradiol if premenopausal, testosterone in men, IGF-1, prolactin. Mineralocorticoids replacement is rarely necessary in hypopituitarism.

**Initial replacement advice for cortisol and thyroid hormones:

- If 9 am cortisol < 250 or random cortisol < 150 and vague symptoms:
  - Replace with hydrocortisone 20/10/10 mg
  - If TFTs normal, 1–2 weekly monitoring initially (always replace cortisol for 1 week prior to thyroxine initiation)
- If falling TSH +/- low FT4
  - Consider need for thyroxine replacement (guide is 0.5-1.5 mg/kg) based on symptoms +/- check 9 am weekly cortisol
  - See Thyroid Guidelines for further information regarding interpretation of an abnormal TSH/T4

ACTH=adrenocorticotropic hormone, FSH=follicle-stimulating hormone, FT4=free thyroxine, HRT=hormone replacement therapy, ICPi=immune checkpoint inhibitor, IGF-1=insulin-like growth factor-1, i.v.=intravenous, LH=luteinizing hormone, MRI=magnetic resonance radiological, NSAIDs=nonsteroidal anti-inflammatory drugs, od=once daily, TSH=thyroid-stimulating hormone, TFTs=thyroid function tests.

5. Rules for management of cutaneous adverse events

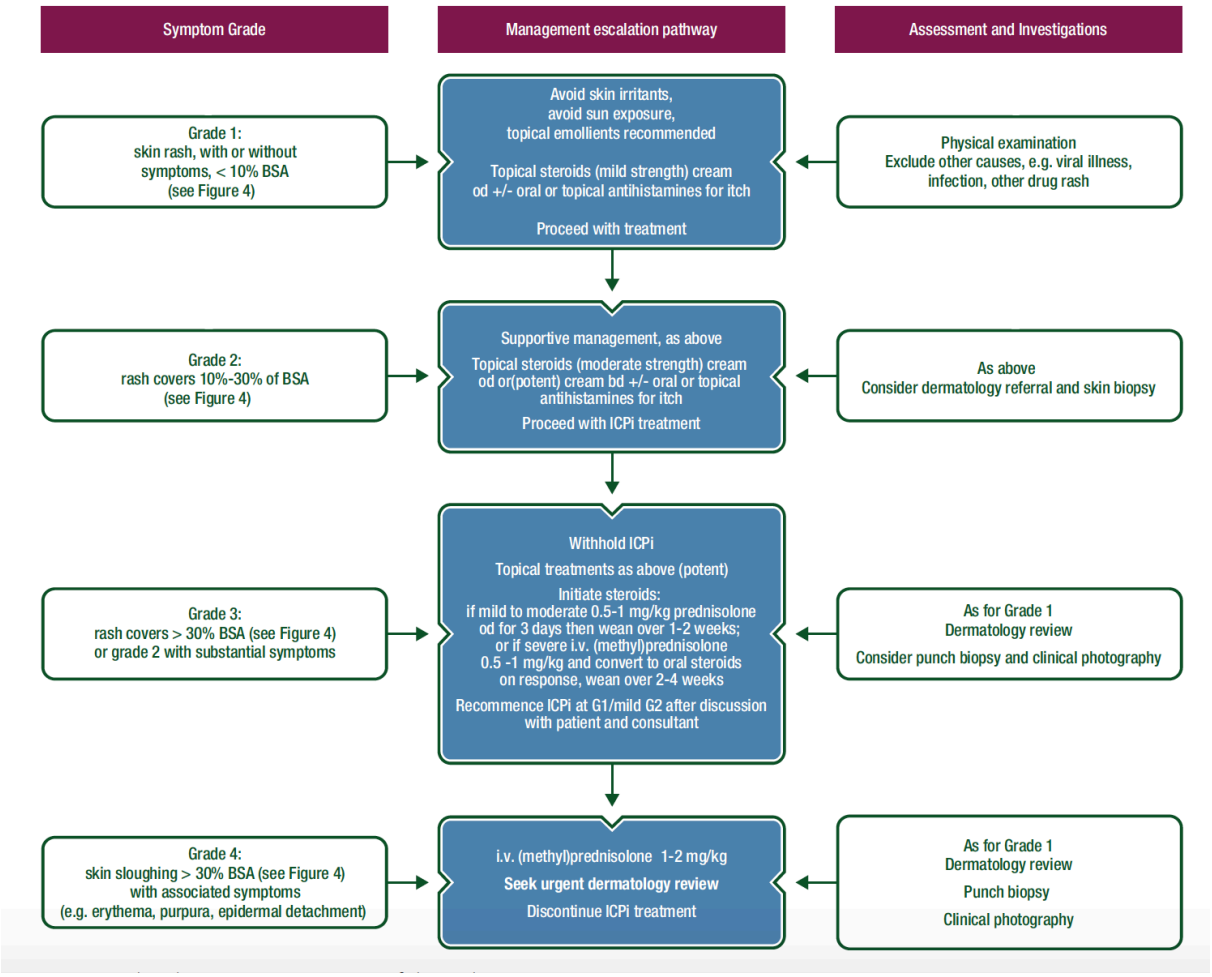


Figure 6. ICPi-Related Toxicity: Management of Skin Rash/Toxicity

Recognised skin AEs include: (1) most common: erythema, maculopapular and pustulopapular rash; (2) rare: toxic epidermal necrolysis, Steven-Johnson syndrome and DRESS; (3) vasculitis may also be present with purpuric rash.
BSA, body surface area; DRESS, drug rash with eosinophilia and systemic symptoms; ICPi, immune checkpoint inhibitor.

6. General recommendations for immunization related toxicity treatment

Management of skin rash/toxicity:

- For Grade 1–2 skin AEs, continue (at least 1 week) with ICPis. Start topical emollients, antihistamines in the case of pruritus and/or topical (mild strength) corticosteroid creams. Reinitiate ICPi when ≤ Grade 1.
- For Grade 3 skin AEs, interrupt ICPi and start immediate treatment with topical emollients, antihistamines and high strength corticosteroid creams. [II, B]
- For Grade 4 skin AEs, discontinue ICPi (permanently), consider admitting subject and always consult dermatologist immediately. Start i.v. corticosteroids [1–2 mg/kg (methyl) prednisone] and taper based on response of AE. [II, B]
- Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but life-threathening severe cutaneous adverse reaction. Patients with SJS/TEN usually develop mucosal erosions or ulcers with variable extents of skin detachment after immunotherapy for a period of 1-3 weeks, it also may occur several months after treatment initiation. SJS and TEN are thought be a spectrum of the same disease. SJS, overlapping SJS/TEN, and TEN are characterized by separation of the dermis involving <10%, 10%-30%, and >30% body surface area (BSA). The management of Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) is detailed in below Table 16.

Table 16 SJS/TEN management and treatment

Early identification and management
·Inform patients of the symptoms and signs of SJS/TEN; advise patients to promptly notify investigator if signs of SJS/TEN occur ·Consider withhold study drugs (SHR-1210 and rivoceranib) and monitor patients closely every 3 days with Grade 2 immune-related rash for progression to involvement of greater BSA and/or mucous membrane involvement. Initiate therapy with topical corticosteroids. Consider initiation of prednisone (or equivalent) 0.5-1 mg/kg tapered over at least 4 weeks ·In cases of suspected SJS, withhold study drugs and consider early admission for further monitoring and treatment.
Initial assessment on presentation
·Review patient history, and a full list of patient medications ·Total body skin examination with attention to ALL mucous membranes as well as a complete review of systems ·Rule out any other etiology of the skin problem, such as an infection, another drug, or a skin condition linked to another systemic disease ·Perform skin biopsies for full-thickness epidermal necrosis to confirm the diagnosis

of SJS/TEN.
Treatment for SJS/TEN
·Should permanently discontinue SHR-1210 and rivoceranib once SJS/TEN is confirmed ·Should admit patient immediately with urgent consultation with dermatologist ·Initiate IV (methyl) prednisolone (or equivalent) 1-2 mg/kg, wean over at least 4 weeks when toxicity resolves to Grade ≤1. May consider intravenous immunoglobulin (IVIG) or cyclosporine as an alternative or in corticosteroid-refractory cases ·For mucous membrane involvement of SJS or TEN, seek urgent dermatology, ophthalmology, and urology consultation to prevent sequelae from scarring ·Supportive care should include assessment and management of skin wounds, fluid and nutrition status, electrolyte balance, renal and airway function, preventing infection, and adequate pain control ·Seek infectious disease consultation if patient might have secondary cellulitis or if patient has other infection risk factors, such as neutropenia, etc.

Immune-related endocrinopathies

- For subjects with Grade 2 symptomatic hyperthyroism, interrupt ICPi, start beta-blocker therapy (propranolol or atenolol/metoprolol). Restart ICPi when asymptomatic [IV–V, B].
- In the case of hypothyroidism, rarely>Grade 2, start HRT depending on the severity (50–100 lg/day). Increase the dose until TSH is normal. In the case of inflammation of the thyroid gland, start prednisone orally 1 mg/kg. Taper based on recovery of clinical symptoms. Consider interruption of ICPi treatment when symptomatic [IV–V, B].
- In the case of hypophysitis (rarely>Grade 2), when headache, diplopia or other neurological symptoms are present, start (methyl) prednisone 1 mg/kg orally and taper over 2–4 weeks. Start HRT depending on the affected hormonal axis (levothyroxine, hydrocortisol, testosterone) [V, B].
- In subjects with type I DM Grade 3 to 4 [ketoacidotic (sub)coma], admit to hospital immediately and start treatment of newly onset type I DM [I, A]. Role of corticosteroids in preventing complete loss of insulin producing cells is unknown and not recommended.

Gastrointestinal hepatotoxicity

- In subjects with non-severe diarrhoea (Grade 1), ICPi can be continued. Treatment with antidiarrhoeal medication (e.g. loperamide) should be prescribed [IV–V, B].

- In Grade 2 diarrhoea, ICPi should be interrupted and the subject should start with corticosteroids depending on the severity and other symptoms (either budesonide or oral corticosteroids 1 mg/kg). In the case of no improvement within 3–5 days, colonoscopy should be carried out and, in the case of colitis, infliximab 5 mg/kg should be administered [IV–V, B].

- In subjects with severe diarrhoea (Grade 3 to 4), permanently discontinue ICPi. Admit subject to the hospital and initiate (methyl) prednisone 2 mg/kg i.v. Add MMF if improvement is observed within 2–3 days. Consult a hepatologist if no improvement under double immunosuppression. Other immunosuppressive drugs to consider are ATG and tacrolimus. Consult or refer subject to an experienced center. Taper over 6 weeks under close monitoring of liver tests [IV–V, B].

Immune-related pneumonitis

- For subjects with Grade 2 pneumonitis, interrupt ICPi therapy, try to rule out infection and start with prednisone 1–2 mg/kg orally. Taper over 4–6 weeks [IV–V, B].
- In Grade 3 and 4 pneumonitis, discontinue ICPi permanently, admit the subject to the hospital, even ICU if necessary and immediately start high-dose (methyl) prednisone 2–4 mg/kg i.v. Add infliximab, MMF or cyclophosphamide in the case of deterioration under steroids. Taper over a period of 4–6 weeks [IV–V, B].

Cardiac toxicity

- When a myocarditis is suspected, admit the subject and immediately start high-dose (methyl) prednisone (1–2 mg/kg). In the case of deterioration, consider adding another immunosuppressive drug (MMF or tacrolimus) [V, B].

Rheumatological toxicity

- For mild arthralgia, start NSAIDs, and in the case of no improvement, consider low -dose steroids (10–20 mg prednisone). In the case of severe polyarthritis, refer subject to or consult a rheumatologist and start prednisone 1 mg/kg. Sometimes infliximab or another anti-TNFa drug is required for improvement of arthritis [V, B].

Renal toxicity

- In case of nephritis, rule out other causes of renal failure first. Interrupt or permanently discontinue ICPi depending on the severity of the renal insufficiency. Stop other nephrotoxic drugs. Start (methyl) prednisone 1–2 mg/kg. Consider renal biopsy to confirm diagnosis [V, B].

Notes: ALT=alanine transaminase, AST=aspartate transaminase, ATG=anti-thymocyte globulin, DM=diabetes mellitus, HRT=hormone replacement therapy, ICPi=immune checkpoint inhibitor, ICU=intensive care unit, Ig=immunoglobulin, MMF=mycophenolate mofetil, MRI=magnetic resonance radiological, NSAIDs=nonsteroidal anti-inflammatory drugs, TNFa=tumor necrosis factor alpha, TSH=thyroid-stimulating hormone.

For other rules that are not listes in this protocol, you may refer to the full text of *Management of Toxicities From Immunotherapy: ESMO Clinical Practice Guidelines*

for Diagnosis, Treatment and Follow-Up (Annals of Oncology 28 (supplement 4):iv119-iv142, 2017) or discuss with the clinical research associate from the sponsor.

Source: *Management of Toxicities From Immunotherapy: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-Up. Haanen JBAG, Carbonnel F, Robert C, et al. on behalf of the ESMO Guidelines Committee. Ann Oncol. 28 (Supplement 4): iv119–iv142, 2017.*

APPENDIX 7. Grade and Management of Reactive Capillary Endothelial Proliferation (RCEP)

RCEP mostly occurs on the surface of the skin, a small number can be found in the oral mucosa, nasal mucosa and orbital conjunctiva. RCEP occurring in the skin, initially expressed as a bright red spot on the body surface, diameter ≤ 2 mm, with the increase of medication times, the lesion range can be gradually increased, mostly nodular, also patchy, the color is bright red or dark red, need to observe the clinical symptoms and signs. It can be treated according to the following grading standards and treatment recommendations:

Grade	Clinical Manifestation	Treatment Suggestions
Grade 1	Single or multiple, nodule with longest diameter ≤10 mm, with or without rupture bleeding	Continue administration, enhance local treatment for those with rupture and bleeding to prevent infection
Grade 2	Single or multiple, nodule with longest diameter >10mm, with or without rupture bleeding	Continue the study treatment. Conduct local therapy such as laser or surgical resection if needed. Strengthen local treatment and prevent infection for subjects with rupture bleeding.
Grade 3	Widespread nodules, complicated by skin infections, maybe need hospitalization	Interrupt the study treatment until resolution of the AE to Grade 1. Conduct local therapy such as laser or surgical resection if needed. Conduct anti-infection treatment for subjects with concurrent infection.
Grade 4‡	Multiple and widespread nodule, life threatening	Discontinue the study treatment
Grade 5‡	Death	Discontinue the study treatment
† Grading is based on <Management of Immune Checkpoint Inhibitor-Related Toxicity-Guidelines of Chinese Society of Clinical Oncology (CSCO) 2019>. ‡Grade 4 life threatening and Grade 5 death have not occured in the study.		

Avoid scratch or friction when adverse reaction occurs. Protect easily rubbing parts by gauze to avoid bleeding and contact the doctor in charge for appropriate treatment suggestions. Hemostasis by local compression or local treatment such as laser or surgical excision can be used in subjects with ruptured hemorrhage. Anti-infective treatment should be given to those complicated with infection. RCEP may occur in tissues other than skin (including visceral organs). Related medical examinations such as fecal occult blood, endoscopy and radiological should be performed if necessary.

APPENDIX 8. EORTC QLQ-C30 (Version 3.0)

English specimen of EORTC QLQ-C30 (version 3.0) is as below. The local language edition will be provided for the subjects in the trial.

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊_⌊_⌊_⌊_⌋

Your birthdate (Day, Month, Year): ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

Today's date (Day, Month, Year): 31 ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

APPENDIX 9. EORTC QLQ-HCC18

English specimen of EORTC QLQ-HCC18 is as below. The local language edition will be provided for the subjects in the trial.

ENGLISH

EORTC QLQ – HCC18

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	**Not at all**	**A little**	**Quite a bit**	**Very much**
31. Did you feel thirsty?	1	2	3	4
32. Have you had problems with your sense of taste?	1	2	3	4
33. Have you lost muscle from your arms or legs?	1	2	3	4
34. Have you had abdominal swelling?	1	2	3	4
35. Have you been concerned by the appearance of your abdomen?	1	2	3	4
36. Have you been concerned by your skin or eyes being yellow (jaundiced)?	1	2	3	4
37. Have you had itching?	1	2	3	4
38. Have you had pain in your shoulder?	1	2	3	4
39. Have you had abdominal pain?	1	2	3	4
40. Have you had fevers?	1	2	3	4
41. Have you had chills?	1	2	3	4
42. Have you worried about getting enough nourishment?	1	2	3	4
43. Have you felt full up too quickly after beginning to eat?	1	2	3	4
44. Have you worried about your weight being too low?	1	2	3	4
45. Have you been less active than you would like to be?	1	2	3	4
46. Have you found it difficult to finish things?	1	2	3	4
47. Have you needed to sleep during the day?	1	2	3	4
During the past four weeks:				
48. Has the disease or treatment had any effect on your sex life?	1	2	3	4

APPENDIX 10. EQ-5D-5L

English specimen of EQ-5D-5L is as below. The local language edition will be provided for the subjects in the trial.

(English version for the UK)

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

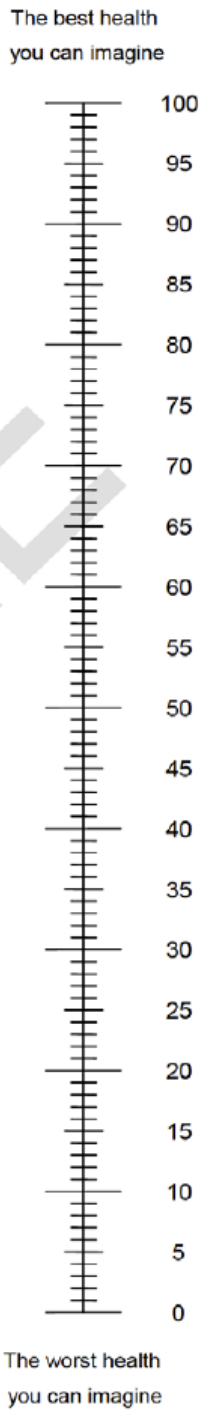
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



APPENDIX 11. Information Regarding Concomitant Use of Drugs Effecting CYP Enzymes and Acid Reducing Agents

Cytochrome P450 (CYP) isoforms

Lists of prohibited strong inhibitors and inducers for CYP isoformsinvolved in rivoceranib metabolism, prohibited substrates with narrow therapeutic index of CYP isoforms may potentially be affected by rivoceranib, and sensitive substrates to be used with caution of CYP isoforms may potentially be affected by rivoceranib.

Enzyme	Way to interfer	Compound	Notification
CYP1A2	Sensitive substrates	alosetron, caffeine, duloxetine, melatonin, ramelteon, tasimelteon, theophylline, tizanidine	Use with caution
	Strong inhibitors	ciprofloxacin, enoxacin, fluvoxamine, zafirlukast	Prohibited
CYP2B6	Sensitive substrates	bupropion	Use with caution
	Strong inducer	carbamazepine	Prohibited
CYP2C8	Sensitive substrates	repaglinide	Use with caution
	Strong inhibitors	clopidogrel, gemfibrozil	Prohibited
CYP2C9	Sensitive substrates	celecoxib	Use with caution

CYP2C19	Sensitive substrates	S-mephenytoin, omeprazole	Use with caution
	Strong inhibitors	fluconazole, fluoxetine, fluvoxamine, ticlopidine	Prohibited
	Strong inducer	rifampin, ritonavir	Prohibited
CYP2D6	Sensitive substrates	atomoxetine, desipramine, dextromethorphan , eliglustat, nebivolol, nortriptyline, perphenazine, tolterodine, venlafaxine	Use with caution
	Strong inhibitors	bupropion, fluoxetine, paroxetine, quinidine, terbinafine	Prohibited
CYP3A	Sensitive substrates	alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir, ebastine, everolimus, ibrutinib, lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, sirolimus, tacrolimus, tipranavir, triazolam, vardenafil,budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir, lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolvaptan	Use with caution
	Strong inhibitors	boceprevir, cobicistat, conivaptan, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, voriconazole, clarithromycin, diltiazem, idelalisib, nefazodone, nelfinavir	Prohibited
	Strong inducer	carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John’s wort	Prohibited

Acid Reducing Agents

The results of DDI study with acidic modifiers are unavailable at present, subjects should be advised to restrict use of proton pump inhibitors (PPIs) as listed in the table. Subjects should be encouraged to avoid concomitant administration of the studied drug with acidic neutrolizers or H2 blockers as listed in the table. If these medicines are needed, they should be taken 5 hours after the studied drug administration.

	Generic name	**Found in brand name(s)**	
Proton pump inhibitor (PPI)	dexlansoprazole	Dexilant	Prohibited
	esomeprazole magnesium	Nexium	
	esomeprazole magnesium and naproxen	Vimovo	
	lansoprazole	Prevacid	
	omeprazole	Prilosec	
	omeprazole and Sodium bicarbonate	Zegerid	
	pantoprazole sodium	Protonix	
	rabeprazole sodium	AcipHex	
	lansoprazole	Prevacid 24HR	
	omeprazole magnesium	Prilosec OTC	
	omeprazole and sodium bicarbonate	Zegerid OTC	
	omeprazole	Omeprazole	
	lansoprazole	Prevacid 24HR	
	omeprazole magnesium	Prilosec OTC	
	omeprazole and sodium bicarbonate	Zegerid OTC	
	omeprazole	Omeprazole	

H2 blocker	cimetidine	Tagamet	Avoid concomitant administration with the study drug If these medicines are needed, they should be taken 5 hours after the study drug administration.
	famotidine	Pepcid, Duexis	
	nizatidine	Axid, Nizatidine	
	ranitidine	Zantac, Tritec	

Transporters

The transporter inhibitors are reported to increase transporter substrates AUC by ≥1.5 to ≥2 fold, and thus fall into the catergory of moderate inhibitors. They are to be advised used with caution

Transporter	**Gene**	**Inhibitor**
P-gp[(a)]	ABCB1	amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil
BCRP	ABCG2	curcumin, cyclosporine A, eltrombopag
OATP1B1, OATP1B3	SLCO1B1, SLCO1B3	atazanavir and ritonavir, clarithromycin, cyclosporine, erythromycin, gemfibrozil, lopinavir and ritonavir, rifampin (single dose), simeprevir
OAT1, OAT3	SLC22A6, SLC22A8	p-aminohippuric acid (PAH)[(b)], probenecid, teriflunomide
MATE1, MATE2-K	SLC47A1, SLC47A2	cimetidine, dolutegravir, isavuconazole, ranolazine, trimethoprim, vandetanib

(FDA's Web site on Drug Development and Drug Interactions
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm)

Prohibited substrates with narrow therapeutic index for transporters

Transporter	**Gene**	**Substrate**
P-gp	ABCB1	dabigatran, digoxin
MATE1, MATE-2K, OCT2	SLC47A1, SLC47A2, SLC22A2	dofetilide

FDA's Web site on Drug Development and Drug Interactions
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

Drug bank for narrow therapeutic index

https://www.drugbank.ca/categories/DBCAT003972

APPENDIX 12. Schedule of Activities: Extension Phase

Assessment	Study period/Visit	
	Subject receive study treatment	Follow-up period
Study drug accountability	Every time study drug is dispensed	√[1]
Study treatment [2]	SHR-1210: 200 mg, once every two weeks (Q2W) Rivoceranib: 250 mg, once per day (QD) OR Sorafenib[3]: 400 mg, twice per day (BID)	-
Safety assessment	Frequency per standard of care	√[4]
Reporting of SAEs and pregnancy	Reports to Sponsor by email [5].	
Tumor assessments	Frequency per standard of care	-

[1]. Subjects should return all unused study medication.

[2]. Study treatment may continue until they are no longer benefiting from treatment as assessed by investigator's clinical judgment.

[3]. Sorafenib can be sourced either locally or centrally which can comply with the local regulatory and ethics requirement.

[4]. Safety evaluation should be based on standard of care and investigator's clinical judgement.

[5]. The sponsor's email to receive safety reports (SAEs and pregnancy) in this study: hengrui_drug_safety@hengrui.com.