



Efficacy and Safety of Apatinib Mesylate Tablets Combined With PD-1 Antibody (SHR-1210) in Previous Treated Advanced Osteosarcoma: A Single-arm, Open label, Prospective, Single-center Clinical Trial

Protocol number: PKUPH-sarcoma 02
Trial phase: Phase 2
Compound name: Camrelizumab for Injection (SHR-1210 for Injection),
Apatinib Mesylate Tablets
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Version No.: 3.0
Version date: 02 Dec 2017

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Signature Page of Sponsor

I have read and confirmed this protocol of clinical trial (protocol number: PKUPH-sarcoma 02; version number: 3.0; version date: 02 Dec 2017). 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 Medicine Co., Ltd.

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| Quanren WANG | Quanren WANG 王 人 | 2017.12.2 |
| Study Director (Print Name) | Study Director (Signature) | Signing date (Day/Month/Year) |

Signature Page of Principal Investigator

I will fulfill investigator's responsibilities carefully in accordance with ICH-GCP provisions, participate in or directly instruct this clinical study by myself. I have received the investigator's brochure of the investigational product for this clinical study; I have known and read 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, Helsinki Declaration, China 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 the 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, as to make sure 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: Peking University People's Hospital

Wei GUO

Principal Investigator
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Principal Investigator
(Signature)

2017.12.2
Signing Date
(Day/Month/Year)

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SYNOPSIS OF PROTOCOL

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| Study Title | Efficacy and Safety of Apatinib Mesylate Tablets Combined With PD-1 Antibody (SHR-1210) in Previous Treated Advanced Osteosarcoma: A Single-arm, Open label, Prospective, Single-center Clinical Trial |
| Protocol Number | PKUPH-sarcoma 02 |
| Version Number | 3.0 |
| Principle Investigator | Professor Wei Guo |
| Study Centers | Peking University People's Hospital |
| Study Objectives | <p>Primary Study Objective:</p> <ul style="list-style-type: none"> To observe the Clinical Benefit Rate (CBR) and Progression Free survival Rate (PFR) of apatinib combined with SHR-1210 for patients with advanced osteosarcoma. <p>Secondary Study Objectives:</p> <ul style="list-style-type: none"> To compare the efficacy of apatinib combined with SHR-1210 for patients with advanced osteosarcoma, through evaluations of overall survival (OS), objective response rate (ORR), disease control rate (DCR), and duration of response (DoR); <p>Exploratory Study Objectives:</p> <ul style="list-style-type: none"> To evaluate the quality of life (QoL) of patients with advanced osteosarcoma who receive SHR-1210 combined with apatinib; To explore the correlation between biomarkers and the efficacy of combined therapeutic regimen; |
| Study Endpoints | <p>Primary Study Endpoints:</p> <ul style="list-style-type: none"> 6 months PFR; <p>Secondary Study Endpoints:</p> <p>Efficacy:</p> <ul style="list-style-type: none"> OS, PFS, ORR, DCR and DoR based on iRECIST v1.1; <p>Safety:</p> <ul style="list-style-type: none"> 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. <p>Exploratory Study Endpoints:</p> <ul style="list-style-type: none"> Average score and its change in the score from baseline in all the subscales of EORTC QLQ-C30; |

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| Study Subjects | Patients with incurable, locally advanced or metastatic osteosarcoma |
| Study Design | <p>This is a Single-arm, Open label, Prospective, Single-center Clinical Trial to evaluate the efficacy and safety of PD-1 antibody SHR-1210 plus Apatinib Mesylate Tablets in patients with advanced Osteosarcoma.</p> <p>Primary efficacy endpoint is 6 months PFR based on RECIST v1.1, and approximately 38 subjects who could be evaluated will be enrolled.</p> <p>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. SHR-1210, 200 mg, via intravenous infusion, once every two weeks (Q2W) + Apatinib Mesylate Tablets 500 mg, p.o., once per day (QD), continuously, 4 weeks (28 days) per cycle of therapy, until meeting the criteria for study treatment termination specified in the protocol. Subjects will continue to receive safety and survival follow-up after end of treatment. Subjects who discontinue treatment for reasons other than progression of disease will continue to receive regular radiological evaluation follow-up after end of treatment.</p> <p>Subjects will have safety visits on D1 of every 2 cycles; Radiological examination will be performed once every 8 weeks to evaluate efficacy until progression of disease is determined (non-pseudoprogression), start of a new anti-tumor therapy, withdrawal of informed consent, death, or termination of the study by the sponsor, whichever comes first.</p> |
| Study Drug | <p>SHR-1210 for Injection (Generic Name: Camrelizumab for Injection) (Manufacturer: Suzhou Suncadia Biopharmaceuticals Co., Ltd.)</p> <p>Apatinib Mesylate Tablets (Manufacturer: Jiangsu Hengrui Medicine Co., Ltd.)</p> |
| Route of Administration | <p>SHR-1210 200 mg will be infused intravenously (premedication is not required). Each infusion will be administered over 30 min (no less than 20 min, no more than 60 min), once every two weeks;</p> <p>Apatinib Mesylate Tablets 500 mg is administered orally after meals within 30 min, once per day, continuously.</p> |
| Inclusion Criteria | <p>Subjects can be enrolled in this study only when they meet all the inclusion criteria:</p> <ol style="list-style-type: none"> 1. Provided informed consent and sign the informed consent form; 2. ≥ 11 years old, male and female; |

3. Histopathologically or cytologically confirmed Advanced Osteosarcoma; (Local tumors and solitary pulmonary lesions must be confirmed by pathological diagnosis. Multiple pulmonary metastases need no pathological examination.)
4. Failed to receive chemotherapy for osteosarcoma (including HD-MTX, anthracyclines, DDP and IFO) are defined as those who progress within 6 months after adjuvant chemotherapy and chemotherapy for advanced osteosarcoma, and those who progress over 6 months require the consent of the subject or his legal representative.;
5. 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);
6. For subjects with progression after local regional therapy, the 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 prior to baseline radiological scanning, and any toxicity (except alopecia) induced by local regional therapy must have resolved to \leq Grade 1 in accordance with national cancer institute – common terminology criteria for adverse event version 4.03 (NCI-CTCAE v4.03);
7. ECOG-PS score 0-1;
8. With a life expectancy of ≥ 12 weeks;
9. The body surface area is over 1.2m^2 ;
10. 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 $\geq 0.75 \times 10^9/\text{L}$;
 - Platelet count $\geq 75 \times 10^9/\text{L}$;
 - Hemoglobin ≥ 80 g/L;
 - (2) Blood biochemistry: (no infusion of albumin within 14 days):

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| | <ul style="list-style-type: none"> • Serum albumin ≥ 25 g/L; • Serum total bilirubin $\leq 1 \times$ upper limit of normal (ULN); • Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (AKP) $\leq 2.5 \times$ULN; • Serum creatinine (Cr) $\leq 1.5 \times$ULN or Cr clearance > 50 mL/min (Cockcroft-Gault formula as below) Man: Cr clearance = $((140 - \text{age}) \times \text{weight}) / (72 \times \text{serum Cr})$ Woman: Cr clearance = $((140 - \text{age}) \times \text{weight}) / (72 \times \text{serum Cr}) \times 0.85$ Weight unit: kg; serum Cr unit: mg/mL; <p>11. Women of childbearing potential: must agree on abstinence (avoid heterosexual intercourse) or use of contraception methods with annual contraceptive failure rate of $< 1\%$ following the signature of informed consent form until at least 120 days after the last dose of study drug. The serum human chorionic gonadotropin (HCG) test must be negative within 7 days prior to enrollment in the study; and the subjects must not be in lactating period.</p> <p>If the female subject has menses, has not reached postmenopausal state (absence of menses for \geq 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.</p> |
| <p>Exclusion Criteria</p> | <p>Subjects who meet any one of the following criteria must not be enrolled in this study:</p> <ol style="list-style-type: none"> 1. Other active malignant tumor except advanced osteosarcoma 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. History of gastrointestinal hemorrhage within 6 months prior to the start of study treatment or clear tendency of gastrointestinal hemorrhage, for example, esophageal and fundal varices with hemorrhagic risk, locally active peptic ulcer, persistent fecal occult blood (+) (the fecal occult blood test can be repeated if it is positive at baseline, and gastroduodenoscopy |

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| | <p>[EGD] would be needed if it is still positive in repeated test; the patient can not be enrolled if the EGD shows esophageal and fundal varices with hemorrhagic risk);</p> <ol style="list-style-type: none"> 3. Abdominal fistula, gastrointestinal perforation or intraperitoneal abscess within 6 months prior to the start of study treatment; 4. Known genetic or acquired hemorrhage (e.g., coagulation dysfunction) or thrombotic tendency, for example, patient 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); 5. Current or recent (within 10 days prior to the start of study treatment) use of aspirin (> 325 mg/day) or dipyridamole, ticlopidine, clopidogrel and cilostazol; 6. 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; 7. 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 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 is abnormal, it can be detected for three times at an interval of 2 minutes and the average will be taken); 8. Hypertension that can not be well controlled through antihypertensive drugs (systolic blood pressure \geq140 mmHg or diastolic blood pressure \geq90 mmHg) (based on the average of BP readings acquired from \geq2 measurements), allowing to reach the above parameters by the use of antihypertensive therapy; previous hypertensive crisis or hypertensive encephalopathy; 9. Major vascular disease within 6 months prior to the start of study treatment (for example, aortic aneurysm |
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- requiring surgical repair or peripheral arterial thrombosis in recent days);
10. Serious, uncured or splitting wound and active ulcer or untreated bone fracture;
 11. Major surgical therapy within 4 weeks prior to the start of study treatment (except diagnosis), or expected major surgery during the study;
 12. Inability or unwilling to swallow tablets, malabsorption syndrome or any condition affecting gastrointestinal absorption;
 13. 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;
 14. Evidence on intraperitoneal pneumatosis that can not be explained by puncture or recent surgery;
 15. Previous or current presence of metastasis to central nervous system;
 16. Previous or present history of pulmonary fibrosis, organising pneumonia (e.g., obliterative bronchiolitis), interstitial pneumonia, pneumoconiosis, drug related pneumonitis, idiopathic pneumonia, or allowable previous radiation pneumonitis in the radiation area (fibrosis) for subjects with evidence on active pneumonia or serious pulmonary function impairment on thoracic computed tomography (CT) in screening period that may interfere with the detection and treatment of suspected drug related pulmonary toxicity; active tuberculosis;
 17. Any active autoimmune disease or history of autoimmune disease and expected recurrence (including but not limited to autoimmune hepatitis, interstitial pneumonia, uveitis, enteritis, hypophysitis, vasculitis, nephritis, hyperthyroidism, hypothyroidism [subjects that can be controlled with hormone replacement therapy only can be enrolled]); subjects with skin diseases that does no need systemic treatment, for example, leukoderma, psoriasis, alopecia, those with controlled type I diabetes by insulin or those with asthma that has been completely

- resolved in childhood and with no need of any intervention can be enrolled; while subjects with asthma who need bronchodilator for medical intervention can not be enrolled;
18. Current use of immunosuppressive medication, or systemic corticosteroid therapy to achieve the objective of immunosuppression (Prednisone at the dose of >10mg/day or equivalent), and continuous use within two weeks prior signing informed consent form;
 19. Use of strong CYP3A4/CYP2C19 inducers, including rifampicin (and its analogues) and St. John's Wort, or strong CYP3A4/CYP2C19 inhibitors within two weeks prior to the signature of informed consent form;
 20. Known history of serious allergy to any monoclonal antibody or targeted anti-angiogenic drug;
 21. 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 two weeks prior to the start of study treatment (for example, subjects who are given with preventive antibiotics for prevention of urinary tract infection or exacerbation of chronic obstructive pulmonary disease are eligible for participation in the study);
 22. Congenital or acquired immunodeficiency (e.g., HIV infection);
 23. Combined hepatitis B and hepatitis C co-infection;
 24. Previous treatment with other PD-1 antibody or other immunotherapy against PD-1/PD-L1, or previous use of other small molecules of anti-angiogenesis TKI drugs, such as pazopanib, sorafenib;
 25. Palliative radiotherapy for non-target lesions to control symptoms is allowed, but it must be completed at least 2 weeks prior to the start of study treatment, and the adverse event induced by radiotherapy must have resolved/improved to \leq CTCAE Grade 1;
 26. Treatment of other investigational product(s) within 28 days prior to the start of study treatment;
 27. 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

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| | examination abnormality, with family or social factors, that may affect subject's safety. |
| Criteria For Termination of Study Treatment | <p>Termination of study treatment does not represent withdrawal from the study. Subjects who terminate the study treatment must continue to complete the remaining study visits as required in the protocol. Subjects must terminate study treatment when any of the following conditions occurs:</p> <ul style="list-style-type: none"> • Subject requests termination of study treatment; • Efficacy evaluation shows progression of disease (evaluated by investigator), unless the subject meets the criteria for treatment beyond progression; • Pregnancy in female subject occurs during the study; • Subject can still not tolerate the toxicity after dose adjustment, or adverse event, laboratory examination abnormality or co-morbidities occur, and continued participation in the study is judged by investigators as violating the subject's optimal benefit; • Overall deterioration of health status, inability to continue participation in the trial; • Other reasons for inability to continue study treatment, as considered by investigators. |
| Criteria for Withdrawal From the Study | <p>The reasons for withdrawal from the study may include:</p> <ul style="list-style-type: none"> • Withdrawal of the informed consent on 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 detachment; • Lost to follow-up; • Death; • Termination of study by the sponsor or health authority. |
| Criteria for Study Termination | <p>The criteria for termination of this study include but not limited to the following:</p> <ul style="list-style-type: none"> • Discovery of unexpected, significant or unacceptable risk; • Low compliance with study requirements. |
| Safety Evaluation | <p>The severity of adverse events will be judged in accordance with CTCAE v4.03. Adverse event 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 adverse event.</p> |
| Efficacy | <p>To evaluate OS, subjects after study treatment termination will</p> |

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| <p>Evaluation</p> | <p>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.</p> <p>6 months PFR: defined as the progression free survival rate at 6 months after enrollment. Evaluations of PFR well as PFS, ORR, DCR and DoR will be performed based on RECIST v1.1 and iRECIST: The radiological evaluation will be performed once every 8 weeks; and can be performed in a real-time manner if new lesion is suspected; the efficacy must be confirmed in 4 weeks for the subjects who are firstly evaluated as PR/CR. The progression of disease that is suspected as pseudoprogression needs to be confirmed in subsequent radiological examinations, the time of the radiological examination for confirmation is at least 4 weeks after progression of disease is found or at the next scheduled time point (not exceeding 12 weeks), and prior to termination of study treatment. The patients who meet RECIST v1.1 criteria for progression will continue to receive tumor assessment until progression of disease (meeting the definition of iRECIST) or termination of study treatment, whichever occurs later. Once clinical progression occurs at any time, physical examination and immediate confirmation by imaging rather than waiting for the next scheduled imaging examination need to be done for the subject.</p> |
| <p>Sample Size Determination</p> | <p>The trial was designed to discard a PFS at 6 month of 37% (null hypothesis) aiming to reach a PFS at 6 month of 60% or higher (alternative hypothesis). Using Simon's optimum two-stage design and setting α-error at 0.05 and β-error at 0.10, the presence of at least six successes in the 12 patients enrolled in the first stage allowed the trial to proceed to the second stage in which 31 more patients were needed to be enrolled for the minimum total of 43 patients.</p> |
| <p>Data Analysis / Statistical Methods</p> | <p>Efficacy Analyses</p> <p>The two primary endpoints for the study are PFR (base on RECIST v1.1).</p> <p>PFR will be evaluated by stratified Log-rank test and the corresponding 95% confidence interval (CI) will be estimated in a stratified Cox proportional hazard model. The PFS and OS curves will be estimated using the Kaplan-Meier (KM) product-limit method. A 95% CI for median PFS and OS will be estimated by Brookmeyer-Crowley method.</p> <p>ORR and DCR will be assessed according to RECIST v1.1. ORR and DCR according to RECIST v1.1 will be performed using stratified Cochran-Mantel-Haenszel (CMH) test at 0.025 one-sided. Difference in proportions for ORR and DCR, and their 95% CI using normal approximation will be provided.</p> |

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| | <p>Overall response rates and their corresponding 95% exact CIs will be calculated by Clopper-Pearson method.</p> <p>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.</p> <p>For other binary variables, stratified CMH test will be used and two-sided 95% CI for treatment difference will be calculated using normal approximation.</p> <p>Safety Analyses</p> <p>Safety data including Adverse events (AEs) and laboratory results will be summarized descriptively using summary statistics.</p> <p>Other Analyses:</p> <p>Exploratory endpoints including average scores and its change from baseline obtained from EORTC QLQ-C30 will be summarized descriptively using summary statistics.</p> |
| End of Study | <p>For this study, end of study is defined as the date of the Last Patient's Last Visit (LPLV).</p> |
| Study Period | <p>Estimated enrollment for first subject in: Jan 2018</p> <p>Estimated enrollment for last subject in: Jan 2019</p> <p>Estimated end of study: Jun 2019</p> |

SCHEDULE OF ACTIVITIES

| Item/evaluation time | Screening period ^a | Treatment period | | Follow-up period | |
|---|-------------------------------|------------------|------------------------|-------------------------------------|------------------------|
| | | Treatment period | End-of treatment visit | Every 8 weeks in 36 weeks until PDb | End-of treatment visit |
| | | D1 | D15 | D8 | D29 |
| Signature of informed consent form | X | | | | |
| Determination of inclusion / exclusion criteria | X | | | | |
| Demographics | X | | X | | X |
| Physical examination ^d | X | X | X | | X |
| Vital signs ^d | X | X | X | | X |
| Body surface area (BSA) ^e | | X | | | X |
| ECOG PS | X | X | X | | X |
| EKG | X ^f | | X | | X |
| AE ^d | X | X | X | X | X |
| Concomitant medication | X | X | X | X | X |
| Quality of life ^l | X | | X | | X |
| Laboratory examination | | | | | |

SCHEDULE OF ACTIVITIES

| Item/evaluation time | Screening period ^a | Treatment period | Follow-up period | |
|--|-------------------------------|----------------------|---|--|
| | | Treatment period | Every 8 weeks in 36 weeks until PD ^b | End-of treatment visit |
| Hematology | X | D1 X ^h | D8 | D15 D22 D29 |
| Liver and kidney function, blood electrolyte | X | X ^h | | X X X |
| Urinary pregnancy test ^l | X | | | |
| Study treatment | | | | |
| Apatinib Mesylate Tablets 500mg | | X ^m | X ^m | X ^m X ^m X ^m |
| SHR-1210 200mg Q2W (for 36 weeks) | | X | | X |
| Curative effect | | | | |
| Tumor imaging evaluation | X ^b | | | X ^b X ^b X ^b |
| AE | X ^k | | | X ^k X ^k X ^k |

BSA = body surface area; ECG = electrocardiogram; PD = disease progression;

- The informed consent should be signed within 2 weeks before the medication. Screening evaluation should be completed within 2 weeks before medication.
- The disease was assessed using the same radioimaging techniques (CT scan or MRI), every 8 weeks during the treatment period and every 12 weeks during the follow-up period until the disease progressed, the subjects began follow-up anti-cancer treatment, the end of the study or the subjects died. Disease assessment should include enhanced CT or MRI of the primary tumor site, chest plain CT, ECT whole body bone imaging or whole body PET/CT examination.

- c. Subjects will continue to receive research medication until the disease progresses or unacceptable toxicity occurs. End-of-treatment visits should be conducted within 4 weeks of the last drug administration and adverse events within 4 weeks of the last drug administration should be recorded.
- d. The abnormal changes of clinically significant physical examination results (including vital signs and ECOG physical condition score) should be recorded as adverse events, and PD should not be reported as adverse events.
- e. does not need to recalculate BSA every cycle unless the research center guidelines require or subjects to gain or lose more than 10% of their original weight. For obese subjects (BMI > 30), BSA should be calculated using ideal body weight throughout the study period.
- f. To record adverse events within 4 weeks after the last administration of the drug. Drug-related grade 3 or 4 toxicity was monitored until it was reduced to grade 2 or below, or at least 24 weeks after the last drug administration, whichever was earlier. Liver or cardiac toxicity of grade 2 to 4 was monitored until it dropped to grade 1 or below, or at least 24 weeks after the last administration of the drug, whichever was earlier.
- g. Records only the date when new cancer treatments are initiated.
- h. Laboratory results must be obtained within 48 hours before administration.
- i. applies only to women of childbearing age who have sex.
- j. Survival status should be followed up at least every 12 weeks within 2 years after the last administration of the drug, and then every 24 weeks until the end of the clinical study.
- k. The formula of creatinine clearance was: $\text{Cr} = (140 - \text{age}) * \text{body weight}(\text{kg}) / [72 * \text{Scr}(\text{mg/dl})]$ or $\text{Cr} = [(140 - \text{age}) * \text{body weight}(\text{kg})] / [0.818 * \text{Scr}(\text{umol/L})]$. Women were calculated by the result *0.85

ABBREVIATIONS

| Abbreviations | Definition |
|------------------|---|
| AE | adverse event |
| ADA | antidrug antibody |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| AUC | area under the concentration time curve |
| BID | twice daily |
| BOR | best overall response |
| BUN | blood urea nitrogen |
| CK | creatinine kinase |
| C _{max} | maximum concentration |
| Cr | creatinine |
| CT | computed tomography |
| CTLA4 | cytotoxic T lymphocyte antigen 4 |
| D | Day |
| DCR | disease control rate |
| DNA | deoxyribonucleic acid |
| DoR | duration of response |
| eCRF | electronic case report form |
| ECOG-PS | Eastern Cooperative Oncology Group- Performance Status |
| EDC | electronic data capture |
| EORTC | European Organization for the Research and Treatment of Cancer |
| FAS | full analysis set |
| G-CSF | granulocyte colony-stimulating factor |
| GCP | Good Clinical Practice |
| GGT | γ-glutamyl transferase |
| GHS | general health status |
| 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 |
| ICC | intrahepatic cholangiocarcinoma |
| ICH | International Council for Harmonisation |
| DMC | Data Monitoring Committee |
| iRECIST | immune RECIST |
| INN | international nonproprietary name (for pharmaceutical substances) |
| INR | international normalized ratio |
| LEU | leukocytes in urine |
| LVEF | left ventricular ejection fraction |

| Abbreviations | Definition |
|-----------------|---|
| IU | international unit |
| LDH | lactate dehydrogenase |
| LSLV | last subject last visit |
| LYMPH | lymphocyte |
| MFD | maximum feasible dose |
| 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 |
| ORR | objective response rate |
| OS | overall survival |
| PD | progressive disease |
| PD-1 | programmed death-1 |
| PFS | progression free survival |
| PRO | patient reported outcome |
| PT | prothrombin time |
| QLQ-C30 | Quality of Life Questionnaire-Core 30 |
| RECIST v1.1 | Response Evaluation Criteria in Solid Tumors |
| RO | receptor occupancy |
| SAE | serious adverse event |
| SIE | AE of special interest |
| SS | safety set |
| TBIL | total bilirubin |
| TTD | time to deterioration |
| TTP | time to progression |
| 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 Advanced Osteosarcoma

Osteosarcoma is a malignant tumor arising from mesenchymal tissue, which is highly invasive and prone to hematogenous metastasis in the early stage. The most common site of metastasis is lung, followed by bone. With the development of high-dose methotrexate (HD-MTX)/cisplatin (DDP)/doxorubicin (ADM)/ifosfamide (IFO)-based neoadjuvant/adjuvant chemotherapy and limb salvage technology, the disease-free survival and overall survival of patients with high-grade osteosarcoma have been significantly improved in the past 30 years. However, 30-40% of primary non-metastatic osteosarcoma patients will suffer from distant metastasis. Although these patients have undergone resection of metastases, the prognosis is still very poor. The

total 5-year survival rate of patients with primary resectable metastases is 20%-30%, which tends to be 0 in patients with primary unresectable metastases.

Young patients with recurrent/metastatic osteosarcoma tend to have good physical conditions for second-line treatment. Currently, there is no high-level evidence-based second-line therapeutic regimen. The most common second-line chemotherapy regimens are as follows: First, for docetaxel and gemcitabine regimen, the effective rate (PR+SD) was 29%. Second, for cyclophosphamide and etoposide regimen, the 4-month disease-free survival rate and 1-year survival rate were 42% and 50%, respectively. Third, Ewing's sarcoma and rhabdomyosarcoma responded well to cyclophosphamide and topotecan regimen, while osteosarcoma was not sensitive to this regimen. Fourth, for high-dose intensive ifosfamide and etoposide regimen, the objective response rate was 30.8%. Fifth, for irinotecan with or without temozolomide regimen, the objective response rate was 30-60 in sarcoma, but less than 30% in osteosarcoma. The efficacy of conventional second-line therapeutic regimens was quite limited. Therefore, it is of vital importance to explore effective drugs which will bring new life to these patients in the second-line setting.

1.1.2. Advances in the Treatment of Advanced Osteosarcoma

In recent 20 years, the development of small molecule tyrosine kinase inhibitors (TKIs) has made great progress in the field of anti-cancer. Imatinib was first used in the treatment of chronic myelogenous leukemia and was subsequently shown to be effective in gastrointestinal stromal tumors (GIST). TKIs targeting EGFR (Epidermal Growth Factor Receptor), like gefitinib, have triggered a revolution in the treatment of lung cancer. In the field of sarcoma, the use of TKIs is still in the process of exploration. EORTC 62043, a phase II clinical trial of the European Organization for Research and Treatment of Cancer, confirmed that pazopanib (a multi-target TKI) significantly prolonged survival in patients with advanced soft tissue sarcoma.

Angiogenesis is considered to be an important step in the development of osteosarcoma. Pre-and post-chemotherapy matching studies have shown that chemotherapy can induce the expression of vascular endothelial growth factor receptor (VEGF receptor) in osteosarcoma. Basic experiments have shown that osteosarcoma cells have high expression of angiogenic factors and their receptors, including vascular endothelial growth factor (VEGF), vascular endothelial growth factor R1 (flt-1), VEGFR2 (KDR), VEGFR3 (flt-4) and so on.

In recent years, the study of TKIs targeting VEGFR in osteosarcoma has achieved exciting results, including sorafenib, sunitinib, pazopanib and so on. How to choose the appropriate TKI and delay the occurrence of drug resistance have become a hot topic of recent research. For example, for sorafenib monotherapy, the 4 months progression-free survival rate was 46% and the median survival was 7 months in patients with osteosarcoma. mTOR (Mammalian Target Of Rapamycin) inhibitor can also be used in

the treatment of sarcoma. Everolimus and sorafenib combined treatment exhibited a 6-month progression-free survival rate of 45% in patients with advanced osteosarcoma. The above findings suggest that anti-angiogenesis therapy has broad prospects in the treatment of osteosarcoma.

As early as 1971, Judah Folkman et al first proposed that tumor proliferation depends on the blood supply of pathological neovascularization. In 2014, when exploring the principle of primary and secondary drug resistance induced by anti-angiogenesis drugs, Rakesh K. Jain et al proposed that hypoxia and acidosis during the development of malignant tumors resulting in a decrease in PH value, thereby triggering a series of cellular signaling pathways and altering the local microenvironment. The above process could lead to immune escape, which further stimulates the formation of pathological neovascularization and promotes the proliferation of tumor cells. Hypoxia can directly up-regulate and activate HIF1alpha, and lead to the overexpression of PD-L1 on tumor surface. Low doses of anti-angiogenesis small molecule TKIs can normalize pathological blood vessels, thereby reducing tumor hypoxia and improving tumor microenvironment immune escape. High doses of TKIs can promote tumor hypoxia and further induce tumor immune escape resulting from hypoxia and acidosis (Fig. 1). In 2017, Rakesh R. Ramjiawan et al further pointed that since antiangiogenic drugs can promote tumor hypoxia and tumor immune escape in a dose- and time/intensity-dependent manner, and then induce the overexpression of PDL-1 on the surface of tumor cell, whether the immune escape can be prevented using the immune checkpoint inhibitors by inducing a sustained response, thereby avoiding secondary resistance of antiangiogenic drug?

A series of clinical trials of antiangiogenic drugs combined with immunotherapy have been carried out in solid tumors, some of which have reached phase III clinical stage. However, no definite conclusion has yet been reached yet. As for osteosarcoma, in SARC028 clinical trial published in 2017, osteosarcoma was a tumor with low mutation load, and the PD-1 immune response rate of osteosarcoma was only 5%. Because the number of cases is small, it is not enough to prove the effectiveness of immunotherapy of osteosarcoma. As early as 2014, Jacson K Shen et al found that expression level of PDL1 in osteosarcoma patients was up to 84.2% at mRNA level, especially in 24% of patients. Danielle M Lussier et al found that the combination of antibodies against CTLA-4 and PD-1 could effectively control metastatic osteosarcoma *in vitro* in 2015. In 2016, Pratistha Koirala et al found that the expression of PDL1 in osteosarcoma cells was significantly correlated with prognosis ($P = 0.002$), the 5-year survival rate of metastatic osteosarcoma infiltrated by dendritic cells and macrophages was significantly lower than that of non-infiltrated patients ($P=0.001$ and 0.031 , respectively). In the field of osteosarcoma, there is no registered clinical trial on combination of antiangiogenic drugs and immunotherapy. However, in 2016, L. Paoluzzi et al enrolled four patients with bone tumors treated by PD-1 antibodies and

pazopanib. The overall clinical benefit rate was 50% (6-month progression free survival rate). Of the three PR patients, one was dedifferentiated chondrosarcoma, one was epithelioid sarcoma, and one was mandibular osteosarcoma. The above evidences showed that immune checkpoint inhibitors had therapeutic potential in the field of bone tumors.

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 patient'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 patients 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 patients with hepatocellular carcinoma (HCC). 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.

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 [1] 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 [2]. 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

We tested the binding affinity of antibody SHR-1210 to human, monkey, and mouse antigens. The results are shown in Table 1.

Table 1. Binding Affinity of Antibody SHR-1210 to Human, Monkey, and Mouse PD-1 Antigens

| Stationary Phase | Mobile Phase | Binding Affinity (nM) |
|---------------------------|--------------------|--|
| SHR-1210 | Human PD-1 antigen | 6.9 |
| SHR-1210 | Mouse PD-1 antigen | Very weak signals, no detectable binding |
| Monkey PD1 antigen (-hFc) | SHR-1210 | 4.1 |

The results of the binding affinity assay showed that the affinity of antibody SHR-1210 to human and monkey PD-1 antigens was very similar, 6.9 nM and 4.1 nM, respectively, while no binding was detected to mouse PD1 antigen. 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-

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.

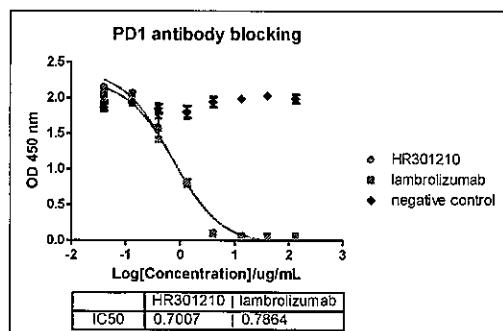


Figure 1. SHR-1210 and Pembrolizumab Blocking the Binding of PD-1/PD-L1

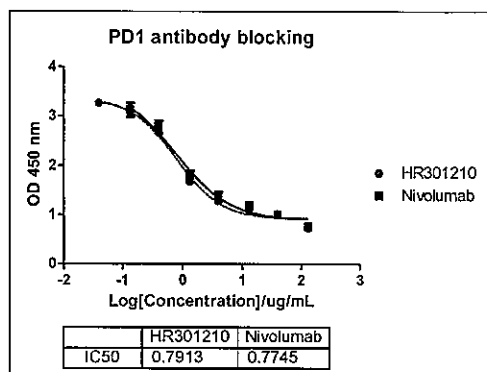


Figure 2. SHR-1210 and Nivolumab Blocking the Binding of PD-1 / PD-L1

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 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 acute toxicity in cynomolgus monkeys, male and female cynomolgus monkeys SHR-1210 was well tolerated when intravenously injected at 20, 50 and 100 mg / kg for 4 weeks (5 times) once a week. No changes in clinical signs associated with SHR-1210 were observed, including injection site irritation, 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 | T1/2 (h) | Tmax (h) | Cmax (µg/mL) | AUClast (h*µg/mL) | Vz (mL/kg) | Cl (mL/h/kg) | MRTlast (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 |
| | 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

1.2.2.2 Progress in Clinical Research of Apatinib Monotherapy for Advanced Osteosarcoma

Before the beginning of this study, the lab of Orthopaedic Oncology, Peking University People's Hospital had detected the mRNA expression of commonly used targeted drugs, such as VEGFR1-3, mTOR, PDGFR-alpha and PDGFR-beta, in fresh specimens of 29 patients with advanced sarcoma, and the paraffin specimens were analyzed by immunohistochemistry. In addition, VEGFR-2 was highly expressed and was positively correlated with the expression of PDGFR-beta. Through basic research, we also found that apatinib promoted autophagy and apoptosis in osteosarcoma cells through the VEGFR2/STAT3/BCL-2 signaling pathway.

A retrospective analysis of 63 consecutive cases of progressive sarcoma treated with

Apatinib Mesylate was carried out in the Peking University People's Hospital, Peking University Shougang Hospital and Peking University International Hospital from June 1, 2015 to December 1, 2016. The results showed that 56 patients with advanced sarcoma were eventually enrolled, the median age was 24.5 years (range, 9 to 63 years) and a median follow-up period was about 6 months (range, 1 to 18 months). The overall objective response rate of the final patients was 62.5% and 82.1% of the patients achieved stable disease. Overall progression free survival in April and June was 48.5% and 37.7% respectively. Overall duration of response (DR) was 3.2 months for osteosarcoma (95% CI, 2.3-4.1 months), 2.0 months for Ewing sarcoma (95% CI, 1.3-2.7 months), 5.2 months for synovial sarcoma (95% CI, 0.3-10.2 months), and 8.8 months for malignant peripheral neurilemmoma (95% CI, 4.3-11.5 months). While the median DR of the pleomorphic undifferentiated sarcoma was 5.6 months (95% CI, 1.3-9.8 months). Eight (14.3%) patients had grade 3 to 4 adverse events, the most common of which were hypertension, spontaneous pneumothorax, wound healing disorders, anorexia, rash and desquamation. This study proved that apatinib mesylate has a higher objective response rate in patients with advanced sarcoma, and the disease control time is no less than, but not significantly stronger than other anti-angiogenesis targeted drugs that have been verified in other large clinical trials.

Peking University People's Hospital also conducted a study on the efficacy and safety of apatinib mesylate in patients with advanced osteosarcoma (NCT02711007) who experienced progression after conventional chemotherapy in 2016-2017. At present, 37 subjects are in the process of data analysis. Preliminary results show that the objective response rate (ORR) and clinical benefit rate (6-month progression-free survival rate) were 44.4% and 19.4%, respectively. Patients with lung metastases are more sensitive to apatinib treatment than those with bone metastases. This suggests that apatinib mesylate is very effective in osteosarcoma and can significantly reduce the tumor size, compared with sorafenib monotherapy and sorafenib everolimus combined therapy. But how to effectively prevent apatinib resistance has become a new topic.

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

After obtaining the 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 patients with advanced solid tumors. As of February 28, 2018, three phase I studies included 258 patients 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 $\geq 10\%$ 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 $\geq 2\%$ 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 $\geq 10\%$ 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 $\geq 2\%$ 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 $\geq 2\%$ 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 patients 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 patients 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.

1.2.2.3 Preliminary Data of SHR-1210 Combined With Apatinib

1.2.2.3.1 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 Medicine Co., Ltd. suggested that SHR-1210 combined with apatinib 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 apatinib significantly enhanced the tumor growth inhibition of SHR-1210 without increasing significant toxicity (no significant change in animal body weight):

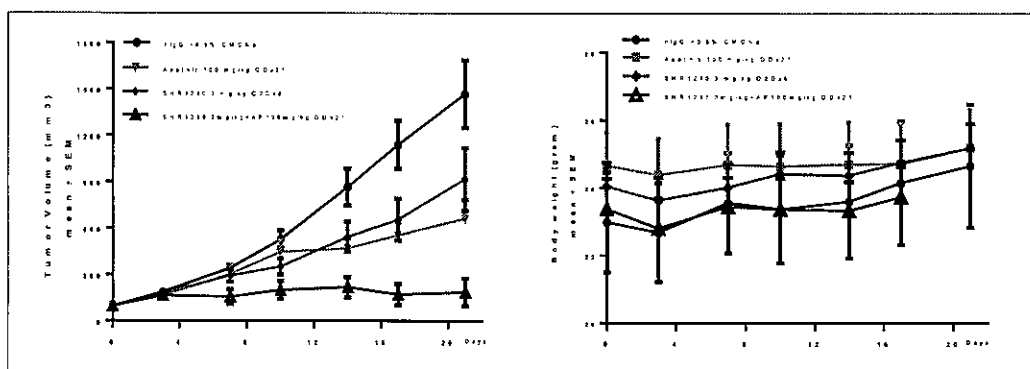


Figure 3. Evaluation of the Effect of SHR-1210 Combined With Apatinib on MC38 Colorectal Cancer in Tg Mice Expressing Human PD-1

Preclinical findings suggest that the use of SHR-1210 in combination with apatinib may increase the objective response rate of the tumor while preserving the efficacy and persistence of immunotherapy.

1.2.2.3.2 Exploration of Combination Administration in Preliminary Clinical Studies

Since October 2016, Jiangsu Hengrui Medicine Co., Ltd. has served as a funder or sponsor to conduct a number of clinical trials of SHR-1210 combined with apatinib 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 apatinib mesylate and the initial efficacy against a variety of tumors.

Preliminary results confirm: for SHR-1210 200mg fixed dose, once every two weeks (Q2W) combined with apatinib 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 case enrolled/case number | Registration Number of Clinical Trial |
|--|--|---------------------------------|---------------------------------------|
| Exploratory clinical study of PD-1 antibody SHR-1210 combined with apatinib 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 apatinib mesylate in the treatment of advanced non-small cell lung cancer | Dose-finding, dose expansion, phase II study | 2017-3/99 | NCT03083041 |
| Phase II clinical study of PD-1 antibody SHR-1210 combined with apatinib mesylate or chemotherapy in advanced primary liver cancer or extrahepatic cholangiocarcinoma | Dose-finding, dose expansion, phase II study | 2017-4/96 | NCT03092895 |
| One-arm, open-label, prospective, multicenter clinical study of the efficacy and safety of apatinib 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 | 2017-12/37 | NCT03359018 |
| Two-arm, open-label, investigator-initiated phase II clinical trial of anti-PD-1 antibody SHR-1210 in combination with apatinib mesylate in the treatment of recurrent metastatic triple-negative breast cancer | Two-arm, open-label, phase II study | 2017-12/23 | NCT03394287 |
| One-arm, open-label, phase II clinical trial of anti-PD-1 antibody SHR-1210 combined with apatinib mesylate in the treatment of advanced hepatocellular carcinoma | One-arm, open, phase II study | 2018-3/122 | NCT03463876 |
| Phase II clinical study of SHR-1210 combined with apatinib mesylate in the treatment of extensive-stage small cell lung cancer with first-line standard of care failure | phase II study | 2018-1/1 | NCT03359018 |

Cut-off date: 25 Aug 2018

1.3. Potential Risks and Benefits

As described above, current therapies have limited efficacy in advanced osteosarcoma. SHR-1210 is one humanized PD-1 antibody that is independently researched and developed by Jiangsu Hengrui Medicine 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 apatinib has achieved an encouraging preliminary result in treatment of advanced carcinoma. Participation in the phase II study to receive the study drug may bring clinical benefit to patients with advanced osteosarcoma and provide a useful therapeutic option for them.

1.3.1. Known Potential Risks

In the previous clinical studies for multiple solid tumors and hematological tumors, the most common ($\geq 10\%$) adverse reactions induced by SHR-1210 included: reactive cutaneous capillary endothelial proliferation (RCCEP), 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 patient'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, RCCEP 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 apatinib, the incidence of RCCEP was significantly reduced, which may be related to the anti-angiogenic effect of apatinib. 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, etc. Symptomatic treatment will be given in accordance with EMSO/NCCN guideline on management of immunotoxicity and can ensure the safety of patients during the trial. Please refer to the investigator's brochure for more details on adverse drug reactions associated with SHR-1210.

Apatinib 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 ($\geq 10\%$) adverse reactions of apatinib (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 apatinib 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 apatinib mesylate. Currently, the known safety information on apatinib 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 apatinib 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 apatinib 500 mg QD, overlapped adverse reactions that require the investigator's special attention include but not limited to: various rashes, hematological toxicity, abnormal liver function, diarrhea, anorexia, proteinuria and fatigue.

1.3.2. Known Possible Benefits

The osteosarcoma patients enrolled in this study may achieve partial or even complete response, and some patients may obtain sustained stable disease. The above trial data will provide a strong guidance for the clinical practice for osteosarcoma treatment and allow more patients to access and benefit from new therapeutic methods.

2. STUDY OBJECTIVES AND ENDPOINTS

| Primary Study Objective | Primary Study Endpoints |
|---|---|
| <ul style="list-style-type: none"> To observe the Clinical Benefit Rate (CBR) and Progression Free survival Rate (PFR) of mesylate apatinib combined with SHR-1210 as second/third-line therapy for patients with advanced osteosarcoma who have progressed upon chemotherapy. | <ul style="list-style-type: none"> Clinical Benefit Rate (CBR); Progression Free survival Rate (PFR) of 6 month evaluated by the blinded independent review committee (BIRC) based on RECIST v1.1. |
| Secondary Study Objectives | Secondary Study Endpoints |
| <ul style="list-style-type: none"> To compare the efficacy of mesylate apatinib combined with SHR-1210 in patients with advanced osteosarcoma, who have progressed upon chemotherapy, through evaluations of overall survival (OS), objective response rate (ORR), disease control rate (DCR), and duration of response (DoR); | <ul style="list-style-type: none"> Objective response rate (ORR), disease control rate (DCR), and duration of response (DoR) evaluated by BIRC based on RECIST v1.1; PFS, ORR, DCR and DoR evaluated by investigator based on RECIST v1.1; PFS, ORR, DCR and DoR evaluated by BIRC based on the immune-related response criteria (irRC). |
| <ul style="list-style-type: none"> To evaluate the safety of mesylate apatinib combined with SHR-1210 in patients with advanced osteosarcoma, who have progressed upon chemotherapy; | <ul style="list-style-type: none"> 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; |
| Exploratory Study Objectives | Exploratory Study Endpoints: |
| <ul style="list-style-type: none"> To evaluate the quality of life (QoL), including general health status (GHS), physical functioning and role functioning, of patients with advanced osteosarcoma who receive mesylate apatinib | <ul style="list-style-type: none"> Time to deterioration (TTD): defined as time from randomization to first deterioration, as determined by following subscales of European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire-Core 30 (QLQ-C30) (ie, a decreased in score by ≥ 10 |

| | |
|---|---|
| <p>combined with SHR-1210;</p> | <p>from baseline maintained for two consecutive time points, or one time-point followed by death [from any cause] within 3 weeks):</p> <ul style="list-style-type: none"> - Global health status - Physical Functioning - Role Functioning |
| <ul style="list-style-type: none"> • To explore the correlation between biomarkers and the efficacy of combined therapeutic regimen; | <ul style="list-style-type: none"> • Average score and its change in the score from baseline in all the subscales of EORTC QLQ-C30 (by 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 mesylate apatinib combined with SHR-1210 (including but not limited to PFS, ORR, OS); |

3. STUDY DESIGN

3.1. Overall Design

This is a Single-arm, Open label, Prospective, Single-center phase II trial to evaluate the efficacy and safety of PD-1 antibody SHR-1210 plus apatinib mesylate as seconde/third-line therapy in patients with advanced osteosarcoma.

The study will be conducted in subjects with incurable, locally advanced or metastatic osteosarcoma who had progressed upon first-line/second-line chemotherapy including high-dose methotrexate, doxorubicin, cisplatin with or without ifosfamide. Primary efficacy endpoints include both CBR and PFS evaluated by the BIRC based on RECIST v1.1, and approximately 43 subjects will be enrolled. Eligible subjects will receive SHR-1210 combined with apatinib mesylate (experimental arm).

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) + apatinib mesylate 500 mg, p.o., once per day (QD), continuously, 4 weeks (28 days) per cycle of therapy, until meeting the criteria for study treatment termination specified in the protocol. Subjects will continue to receive safety and survival follow-up after end of treatment. Subjects who discontinue treatment for reasons other than progression of disease will continue to receive regular radiological evaluation follow-up after end of treatment.

The subject will continue to receive study treatment until intolerable toxicity occurs, or until 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 until the subject voluntarily withdraws from study treatment, whichever comes first.

Following disease progression in accordance with RECIST v1.1 (evaluated by investigator), subjects may continue treatment with SHR-1210 monotherapy or in combination with apatinib, if they can still clinically benefit from and tolerate study treatment as determined by investigator (see Section 6.6 for treatment criteria after disease progression).

Subjects will have safety visits on D1 and D15 of each cycle of therapy within the first 3 cycles for both arms. Beginning from the 4th cycle, 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. Radiological examination will be performed once every 8 weeks to evaluate efficacy for the first 33 cycles, and once every 12 weeks thereafter, until progression of disease is determined (non-pseudoprogression), start of a new anti-tumor therapy, withdrawal of informed consent, death, or termination of the study by the sponsor, whichever comes first. The study design is shown in Figure 4.

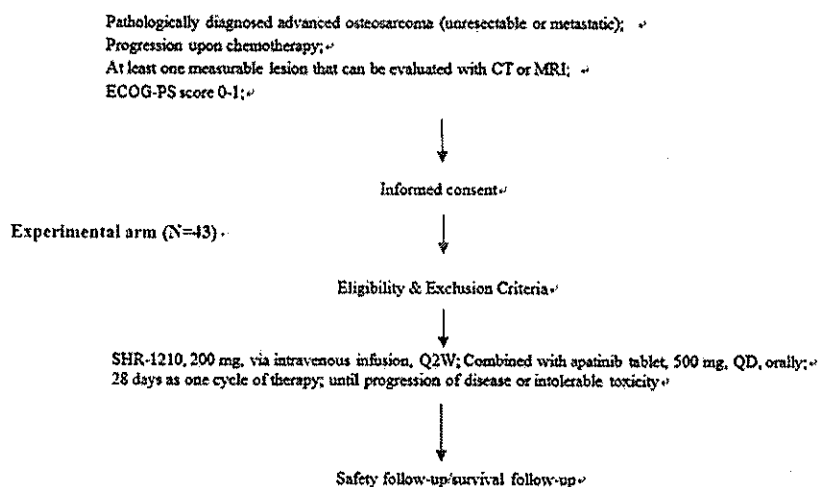


Figure 4. Study Design Chart

4. SELECTION AND WITHDRAWAL OF SUBJECTS

Subjects can be allowed to participate in this study only when they meet the following criteria. All the medical and non-medical conditions of each subject are 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. ≥ 11 years old, male and female;
3. Histopathologically or cytologically confirmed Advanced Osteosarcoma; (Local tumors and solitary pulmonary lesions must be confirmed by pathological diagnosis. Multiple pulmonary metastases need no pathological examination.)
4. Failed to receive chemotherapy for osteosarcoma (including high-dose methotrexate, anthracyclines, cisplatin and ifosfamide) are defined as those who progress within 6 months after adjuvant chemotherapy and chemotherapy for advanced osteosarcoma, and those who progress over 6 months require the consent of the subject or his legal representative.;
5. 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);
6. For subjects with progression after local regional therapy, the 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 prior to baseline radiological scanning, and any toxicity (except alopecia) induced by local regional therapy must have resolved to \leq Grade 1 in accordance with national cancer institute – common terminology criteria for adverse event version 4.03 (NCI-CTCAE v4.03);
7. ECOG-PS score 0-1(see APPENDIX 2);
8. With a life expectancy of ≥ 12 weeks;
9. The body surface area is over 1.2m^2 ;
10. Have the required screening laboratory values including the following parameters (within 7 days prior to the start of study treatment):
11. 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 $\geq 0.75 \times 10^9/\text{L}$;
 - Platelet count $\geq 75 \times 10^9/\text{L}$;
 - Hemoglobin ≥ 80 g/L;
 - Blood biochemistry: (no infusion of albumin within 14 days):
 - Serum albumin ≥ 25 g/L;
 - Serum total bilirubin $\leq 1 \times$ upper limit of normal (ULN);
 - Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (AKP) $\leq 2.5 \times$ ULN;
12. Serum creatinine (Cr) ≤ 1.5 ULN or Cr clearance >50 mL/min (Cockcroft-

Gault formula as below)

Man: Cr clearance = $((140 - \text{age}) \times \text{weight}) / (72 \times \text{serum Cr})$

Woman: Cr clearance = $((140 - \text{age}) \times \text{weight}) / (72 \times \text{serum Cr}) \times 0.85$

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

13. Women of childbearing potential: must agree on abstinence (avoid heterosexual intercourse) or use of contraception methods with annual contraceptive failure rate of < 1% following the signature of informed consent form until at least 120 days after the last dose of study drug. The serum human chorionic gonadotropin (HCG) test must be negative within 7 days prior to enrollment in the study; and the subjects must not be in lactating period.
14. If the female subject has menses, has not reached postmenopausal state (absence of menses for \geq 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.

4.2. Exclusion Criteria

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

1. Other active malignant tumor except advanced osteosarcoma within 5 years or simultaneously. Cured localized tumor, for example, basal cell carcinoma of skin, squamous cell carcinoma of skin, superficial bladder cancer, carcinoma in situ of prostate, carcinoma in situ of cervix, breast cancer in situ may be enrolled;
2. Abdominal fistula, gastrointestinal perforation or intraperitoneal abscess within 6 months prior to the start of study treatment;
3. Known genetic or acquired hemorrhage (e.g., coagulation dysfunction) or thrombotic tendency, for example, patient 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);
4. Current or recent (within 10 days prior to the start of study treatment) use of aspirin (> 325 mg/day) or dipyridamole, ticlopidine, clopidogrel and cilostazol;
5. 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;
6. 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 3) 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 detected for three times at an interval of 2 minutes and the average will be taken);

7. 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;
8. 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);
9. Serious, uncured or splitting wound and active ulcer or untreated bone fracture;
10. Major surgical therapy within 4 weeks prior to the start of study treatment (except diagnosis), or expected major surgery during the study;
11. Inability or unwilling to swallow tablets, malabsorption syndrome or any condition affecting gastrointestinal absorption;
12. 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;
13. Evidence on intraperitoneal pneumatosis that can not be explained by puncture or recent surgery;
14. Previous or current presence of metastasis to central nervous system;
15. Previous or present history of pulmonary fibrosis, organising pneumonia (e.g., obliterative bronchiolitis), interstitial pneumonia, pneumoconiosis, drug related pneumonitis, idiopathic pneumonia, or allowable previous radiation pneumonitis in the radiation area (fibrosis) for subjects with evidence on active pneumonia or serious pulmonary function impairment on thoracic computed tomography (CT) in screening period that may interfere with the detection and treatment of suspected drug related pulmonary toxicity; active tuberculosis;
16. Any active autoimmune disease or history of autoimmune disease and expected recurrence (including but not limited to autoimmune hepatitis, interstitial pneumonia, uveitis, enteritis, hypophysitis, vasculitis, nephritis, hyperthyroidism, hypothyroidism [subjects that can be controlled with hormone replacement therapy only can be enrolled]); subjects with skin diseases that does no need systemic treatment, for example, leukoderma, psoriasis, alopecia, those with controlled type I diabetes by insulin or those with asthma that has been completely resolved in childhood and with no need of any intervention can be enrolled; while subjects with asthma who need bronchodilator for medical intervention can not be enrolled;
17. Current use of immunosuppressive medication, or systemic corticosteroid therapy to achieve the objective of immunosuppression (Prednisone at the dose

- of >10mg/day or equivalent), and continuous use within two weeks prior to enrollment;
18. Use of strong CYP3A4/CYP2C19 inducers, including rifampicin (and its analogues) and St. John's Wort, or strong CYP3A4/CYP2C19 inhibitors within two weeks prior to signing informed consent form;
 19. Known history of serious allergy to any monoclonal antibody or targeted anti-angiogenic drug;
 20. 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 two weeks prior to the start of study treatment (for example, subjects who are given with preventive antibiotics for prevention of urinary tract infection or exacerbation of chronic obstructive pulmonary disease are eligible for participation in the study);
 21. Congenital or acquired immunodeficiency (e.g., HIV infection);
 22. Combined hepatitis B and hepatitis C co-infection;
 23. Previous treatment with other PD-1 antibody or other immunotherapy against PD-1/PD-L1, or previous use of apatinib or sorafenib;
 24. Palliative radiotherapy for non-target lesions to control symptoms is allowed, but it must be completed at least 2 weeks prior to the start of study treatment, and the adverse event induced by radiotherapy must have resolved/improved to \leq CTCAE Grade 1;
 25. Attenuated live vaccine therapy administered within 28 days prior to the start of study treatment, or needed administration of such vaccines during SHR-1210 treatment or within 60 days after the last dose of SHR-1210;
 26. Treatment of other investigational product(s) within 28 days prior to the start of study treatment;
 27. 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. Lifestyle Requirements

4.3.1. Contraception

At least two highly effective contraceptive methods must be used for female subjects of childbearing potential and male subjects whose partners are those women of childbearing potential. Highly effective contraceptive method is defined as the method used alone or combined with other methods continuously and properly, with annual failure rate of <1%. Highly effective contraceptive methods include the following:

- Generally used hormone contraceptive method related with inhibition of ovulation (e.g., oral, insertion, injection, implantation, percutaneous), which needs to meet: the female subject or the partner of male subject has used this

method for a period continuously that is demonstrated as effective, and plans to use the method continuously and properly throughout the study.

- intra-uterine contraceptive device is correctly placed.
- Male/female condom concurrently with spermicide for external use (i.e., foam, gel, film, cream or suppository).
- Vasectomy for sterilization for males.
- Ligation of bilateral fallopian tubes/bilateral salpingectomy or occlusion of bilateral fallopian tubes (the occlusion has been demonstrated as effective by relevant instruments).

Investigators or their designated personnel must assist subjects in selection of two suitable methods from the above highly effective contraceptive methods, and must confirm the subject is aware of how to use the selected methods properly and continuously. 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.

For female subjects of childbearing potential, duration of the highly effective contraception will be the whole administration period and 120 days after the last dose (based on the last subject who discontinues the administration); for male subjects whose partners are women of childbearing potential, duration of the highly effective contraception will be the whole administration period and 120 days after the last dose (based on the last subject who discontinues the administration).

4.4. Subjects' Withdrawal From the Study or Termination of Study Treatment

4.4.1. Criteria for Termination of Study Treatment

Termination of study treatment does not represent withdrawal from the study. Subjects who terminate the study treatment should continue to complete the remaining study visits as required in the protocol. Subjects should terminate study treatment when any of the following conditions occurs:

- Subject requests termination of study treatment;
- Efficacy evaluation shows progression of disease (evaluated by investigator), unless the subject meets the criteria for treatment beyond progression (see Section 6.6 of the protocol);
- Pregnancy in female subject occurs during the study;
- Subject can still not tolerate the toxicity after dose adjustment, or adverse event, laboratory examination abnormality or co-morbidities occur, when continued participation in the study is judged by investigators as violating the subject's optimal benefit;
- Overall deterioration of health status, inability to continue participation in the trial;
- Ineligibility or other significant deviation from protocol after enrollment (following confirmation by the sponsor);

- Termination of study by the sponsor, or health authority;
- Other reasons for inability to continue study treatment, as considered by investigators.

4.4.2. 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, as discreted by investigator. E.g., subject's loss of the ability to express his/her wishes freely due to imprisonment or detachment;
- Lost to follow-up;
- Death;
- Termination of study by the sponsor or health authority.

4.4.3. The Procedures of Withdrawal From the Study or Termination of Study Treatment

Subjects should comply with the follow-up schedule specified in the protocol after termination 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 patients.

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.

4.4.4. 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 the 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.

4.5. 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 Medicine 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 National Medical Products Administration (NMPA), or the local regulatory authority, the study can proceed.

4.6. Definition of End of Study

Definition of end of study is as follows:

The last visit of the last subject (LSLV) (approximately 18 months after the last subject is enrolled).

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 recovered, and the two sides need to sign the drug recovery list. The dispensation and recovery of each 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 and apatinib mesylate tablets are as below:

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 tentatively

Storage: protected from light at 2-8°C, must not be frozen

Experimental arm: apatinib mesylate tablets

Manufacturer: Jiangsu Hengrui Medicine Co., Ltd.

Dosage form: tablet

Strength: 0.25 g/tablet

Package: 10 tablets/plate/box

Administration: oral

Validity: 24 months

Storage: stored in sealed container, protected from light at below 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.

Once any deviation from the conditions on the product label appears, it should be reported promptly when it is found. 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 4.

Table 4. Dosing Regimens for Each Treatment Cycle

| | | |
|--|-------------------|---|
| Experimental arm: SHR-1210 combined with apatinib | 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), 4 weeks (28 days) as one treatment cycle. The interval between two doses should not be less than 12 days. |
| | Apatinib mesylate | 500 mg, once per day (QD) orally, after meals within 30 min, for continuous administration, 4 weeks (28 days) is one cycle. |

If a subject in the experimental arm (SHR-1210 in combination with apatinib) develops a treatment-related AE that leads to permanent discontinuation of apatinib 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 termination 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 apatinib, the subject may continue to receive monotherapy, and the combination therapy can be resumed only after the toxicity resolves.

≥7 days later after the scheduled date of administration of SHR-1210 will be considered as a dose delay. The subsequent drug administration time will be calculated from the actual date of the previous dose. Subjects will be given the study drug until meet the criteria for termination of study treatment specified in the protocol.

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 \geq 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 $>3\times$ ULN;
 - AST or ALT at baseline elevates no greater than Grade 1, and drug-related elevated AST or ALT reaches $>5\times$ 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 $>8\times$ ULN (whichever is lower);
 - Total bilirubin at baseline is within the normal range, and drug-related elevated total bilirubin reaches $>2\times$ 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 Grade 3 and above reactive capillary endothelial proliferation occurs during the trial, the administration of SHR-1210 needs to be temporarily interrupted until the toxicity is recovered to Grade 2 or below.
- If subjects have fever ($>38^{\circ}\text{C}$) 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 given according to the subsequent schedule 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 when clinically indicated. It is recommended to monitor liver function every three days, until the highest value of AST or ALT starts to decrease. When meeting the criteria for resumption of medication (see Section 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 at least once every 6 weeks, or more frequently when clinically indicated.

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 can be resumed, except the following:

- The therapy can be resumed for the subjects with Grade 2 fatigue that has not been recovered;
- The therapy can be continued for Grade 2 cutaneous AE;
- 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;
- 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 4 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 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 than 7 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 sequelae 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 terminated.
- The study treatment must be terminated 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, the tumor assessment should continue as required by the protocol. Safety visits and laboratory tests should also be performed at the original frequency (at least once every 6 weeks) or more frequently when clinically indicated;
 - SHR-1210 delay for >12 weeks due to non-drug related reasons must be discussed with the sponsor prior to resuming administration. During the dose delay, the tumor evaluation should still proceed as required in the protocol. Safety visits and laboratory examinations should also be performed at least once every 6 weeks, or more frequently when clinically indicated;
- 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 \geq Grade 3 (\geq Grade 2 for pneumonia) reoccurs, termination 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 evaluated by investigators in accordance with RECIST v1.1 (see APPENDIX 1 for details) (unless the subject meets the criteria for treatment beyond progression in Section 6.6).

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

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

5.1.6.1.5. Criteria for Dose Modification of Apatinib

Dose modification methods resulted from apatinib-related toxicities include dose interruption, adjustment of administration schedule (first adjustment: 250mg orally daily; re-adjustment: 500 mg orally daily and termination of apatinib. After the administration schedule of apatinib is adjusted during the study, will not allow going back to initial administration schedule.

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

Referring to the experience in phase II clinical studies, it is advisable to interrupt the dose of SHR-1210 and apatinib at the same time, for the immune-related toxicities during the trial, in particular immune pneumonia, hepatitis, colitis and so on, the dose can be resumed when the toxicity is recovered to \leq Grade 1 or baseline level (for patients with abnormal ALT/AST and TBIL during baseline). It is recommended to resume SHR-1210 firstly, followed by apatinib when no significant abnormality is seen after administration of SHR-1210, and observe for 7-14 days. The subsequent administration schedule for apatinib will be adjusted (first adjustment: 250 mg daily; re-adjustment: 125 mg daily).

Changes in the blood pressure should be monitored routinely during apatinib administration. It is advisable to interrupt the dose of apatinib firstly in case Grade 3 elevated blood pressure occurs (systolic blood pressure \geq 160mmHg or diastolic blood pressure \geq 100mmHg or more than one antihypertensive agent is needed), and perform antihypertensive therapy under specialist's instructions. Apatinib can be resumed when the blood pressure is decreased to normal range (systolic blood pressure \leq 140 mmHg and diastolic blood pressure \leq 90mmHg). If there is still hypertension, the administration schedule of apatinib must be adjusted. For patients with hypertensive

crisis (systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 120 mmHg, and/or with progressive insufficiency of target organs), the apatinib should be terminated immediately and symptomatic treatment should be given actively (antihypertension, dehydration, anti-convulsion and so on).

Dose interruption use and adjustment of administration schedule of apatinib is needed for \geq Grade 3 hematological toxicities or \geq 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 ($<38^{\circ}\text{C}$), 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 5. Dose Adjustment Plan of Apatinib

| Drug-related toxicity | Grade | Dose interruption of apatinib (Yes or No) | Criteria on dose resumption of apatinib | Dosage modification method of apatinib | Criteria on termination of apatinib |
|--------------------------------|--------------------------------------|---|--|--|---|
| Hematologic toxicities | Grade 1, Grade 2 | No | — | — | — |
| | Grade 3 | Yes (except lymphocyte count decreased) | When the toxicity is recovered to \leq 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 apatinib must be discontinued. |
| | Grade 4 | Yes | When the toxicity is recovered to \leq 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 ≥ 7 d) | Yes | When the toxicity is recovered to \leq Grade 1 | Original dose | —; |
| | Grade 3 | Yes | When the toxicity is recovered to \leq Grade 1 | 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, apatinib must be discontinued*. |
| Hypertension | Grade 3 (after corrective treatment) | Yes | When the toxicity is recovered to \leq 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, apatinib must be discontinued. |

| Drug-related toxicity | Grade | Dose interruption of apatinib (Yes or No) | Criteria on dose resumption of apatinib | Dosage modification method of apatinib | Criteria on termination of apatinib |
|---|--|---|--|--|---|
| | Hypertensive crisis | Yes | — | Permanently discontinue apatinib | Terminated administration of apatinib |
| Proteinuria (without significantly elevated serum 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, apatinib 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, apatinib 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, apatinib 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, apatinib 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.

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 apatinib 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 apatinib after dose interruption and recovery of the toxicity.

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; imaging (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 patients who do not respond to immunosuppressive agents.

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

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 \geq 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) Serum 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 imaging;
- 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 4 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. The following provides the recommendations on management of immune-related adverse events (see Table 6), for reference. Recommended treatment procedures for common immune-related adverse events are detailed in APPENDIX 4 (Note that the rules for management of hepatic irAEs have been amended in this protocol [see Section 5.1.6.2.3 below]).

Table 6. Recommendations on Management of Immune-Related Adverse Events

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

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 24h, 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 7.

Table 7. 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. <ul style="list-style-type: none"> 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 Apatinib

Management of apatinib-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 patients during chemotherapies or molecular targeted therapies. HFSR is characterized by numbness, hypoesthesia, paresthesia, stabbing pain, analgesia or swelpain, 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 patient's daily life.

Grade 3: moist desquamation, ulcer, blister or serious pain of hand and/or foot and/or serious discomfort that makes patient 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 \geq Grade 3 hand-foot syndrome occurs for consecutive three times, with an aggravating tendency, the administration of apatinib 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:

The blood pressure should be monitored everyday (based on the average of BP readings acquired from ≥ 2 measurements) after the initiation of apatinib 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.

Subjects are required to keep a detailed record of their daily blood pressure in 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. Apatinib mesylate should be discontinued in patients with hypertensive crisis.

3. Proteinuria

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

Note: Apatinib 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

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

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

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 (such as Thymalfasin, interferon, interleukin-2 and other immunologic agents) simultaneously during the treatment period of this study (except management on the treatment-related

adverse events).

Systemic corticosteroid can be used at the dose of >10mg/day (Prednisone or equivalent), except for treatment-related AEs treatments or short-term preventive therapies.

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 Apatinib During the Study

In vitro studies have shown that apatinib is mainly metabolized by the liver P450 enzyme CYP3A4, strong inhibitors and inducers of CYP3A will significantly increase or decrease clearance of apatinib with increased or decreased exposures of apatinib. Therefore, the strong inhibitors and inducers of CYP3A will be prohibited (see below lists of the strong inhibitors and inducers of CYP3A). When combined with other drugs, it is recommended to choose alternative drugs that have no inhibition or induction of CYP3A4 enzyme. If CYP3A4 enzyme strong inhibitors or inducers must be used simultaneously, dosage adjustment should be considered in combination with clinical observations. And apatinib has strong inhibitory effect on CYP3A4 and CYP2C9, moderate inhibitory effect on CYP2C19.

- The drugs interfering with hepatic P450 enzymes:
 - (prohibited) strong inducers of CYP3A4: dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital and rifapentine, etc;
 - (prohibited) strong inhibitors of CYP3A4: itraconazole, clarithromycin, voriconazole, telithromycin, saquinavir, ritonavir, etc.;
 - (prohibited) strong inducers of CYP2C19: rifampicin, ritonavir, etc.;
 - (prohibited) strong inhibitors of CYP2C19: fluconazole, fluvoxamine, ticlopidine, fluoxetine, etc.;
 - (used cautiously) drugs metabolized via CYP3A4: benzodiazepines, dihydropyridine, calcium antagonists nisoldipine and lercanidipine, HMG-COA reductase inhibitors such as simvastatin, lovastatin, and midazolam, etc.;
 - (used cautiously) drugs metabolized via CYP2C9: warfarin, phenytoin and some sulfonylureas anti-hyperglycemic agents, such as glibenclamide; dose reduction should be considered with close monitoring in case of warfarin is used for anticoagulation therapy during the trial, and discontinuation of the investigational products can be considered if necessary.
 - (used cautiously) drugs metabolized by CYP2C19 with narrow therapeutic index: such as S-mephenytoin and sensitive substrates of CYP2C19 clobazam, lansoprazole, omeprazole, etc.;
- Due to the toxic and side effects of similar drugs in prolonging the QTc interval, it is necessary to use drugs that prolong the QT interval carefully and observe ECG closely during the study period, including antibiotics, fluoroquinolones, macrolides, and anti-arrhythmics, angina relieving drugs, antipsychotic drugs,

antifungal drugs, antimalarial drugs, antihistamines, gastrointestinal antiemetic and promoting drugs, and antidepressants, etc.;

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:

Patients 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; the drug must be replaced by Entecavir if the virus is not satisfactorily controlled, and patients can be enrolled when HBV-DNA is <500 IU/mL; patients with newly discovered HBV infection in screening period can start Entecavir therapy immediately and can be enrolled when HBV-DNA is <500 IU/mL.

Patients with HCV infection, if HCV-RNA is positive, patients 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 can not be target lesions;

- Patients 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 apatinib, it is advised to interrupt the dose of apatinib 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 palliative radiotherapy, prior to treatment and at least 14 days after the end of radiotherapy in this protocol, the dose resumption in the subjects receiving operation needs to depend 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 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 imaging (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 history of other diseases);
- Collect concomitant medications/therapies;
- Collect AE;
- Tumor imaging 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), irRECIST (evaluated by investigator only). All the measurable and evaluable tumor lesions should be evaluated and recorded, including CT scan of thorax, abdomen, pelvis and site of lesions, brain MRI or enhanced CT scan (excluding intracranial metastasis); bone scan should be performed once every 24 weeks and PET/CT 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 2 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, 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;

- Serum ALP test;
- Thyroid function (FT3, FT4, TSH);
- 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:

- 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 $\geq 2+$, 24h urine protein quantification must be added;
- Blood biochemistry: including ALT, AST, total bilirubin, γ -glutamyl transferase (GGT), direct bilirubin, indirect bilirubin, ALP, LDH, albumin, blood urea nitrogen (BUN) or serum 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);
- Serum 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 recovery 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 questionnaires.

The following information must be collected within 72h 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 $\geq 2+$, 24h urine protein quantification must be added;
- Blood biochemistry: including ALT, AST, total bilirubin, γ -glutamyl transferase (GGT), direct bilirubin, indirect bilirubin, ALP, LDH, albumin, blood urea nitrogen [BUN] or serum 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 2 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, blood pressure, pulse rate and respiratory frequency;

The test items at correspondingly scheduled visits should be consistent with the actual time of administration in case of dose delay. When the dose is delayed for a long time, the interval of test frequency can not exceed 6 weeks, or the test can be performed more frequently when clinically indicated. In addition, echocardiography and serum HCG test can be monitored at any time, if necessary. Also, in accordance with RECIST v1.1 (investigator and BIRC evaluation), irRECIST (only for investigator evaluation), the evaluation during treatment, 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 determined progression of disease, tumor evaluation should be continued, regardless of termination 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 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. The progression of disease that is suspected as pseudoprogression

needs to be confirmed in subsequent radiological examinations, the confirmed radiological examination should be performed at least 4 weeks after progression of disease is found or at the next scheduled time point (not exceeding 12 weeks), and prior to termination of study treatment.

Patients with progression can continue to use SHR-1210 monotherapy or combination with apatinib (experimental arm) if they meet the criteria defined in Section 6.6.

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 2 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, blood pressure, pulse rate and respiratory frequency;
- Intravenous infusion of SHR-1210 (experimental arm);
- Oral administration of apatinib (experimental arm) (daily, continuously);
- Distribution of subject's diary;
- Subject's self-evaluation results: all the subjects will complete EORTC QLQ-C30 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, 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 $\geq 2+$, 24h urine protein quantification must be added;
- Blood biochemistry: including ALT, AST, total bilirubin, γ -glutamyl transferase (GGT), direct bilirubin, indirect bilirubin, ALP, LDH, albumin, blood urea nitrogen [BUN] or serum 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);
- Collect concomitant medications/therapies;
- Collect AE;
- Intravenous infusion of SHR-1210 (experimental arm);
- Oral administration of apatinib (experimental arm) (daily, continuously);
- Distribution, verification and recovery 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 2 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, 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 $\geq 2+$, 24h urine protein quantification must be added;
- Blood biochemistry: including ALT, AST, total bilirubin, γ -glutamyl transferase (GGT), direct bilirubin, indirect bilirubin, ALP, LDH, albumin, blood urea nitrogen or serum 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;
- Thyroid function (only performed on C3D1, TSH, FT3, FT4);
- 12-lead ECG (performed after sitting still for at least 5 minutes): heart rate and QTc interval (calculated using Fridericia's formula);
- Immunogenicity and drug concentration: the blood sample will be collected only from SHR-1210 experimental arm (including SHR-1210 combined with apatinib and SHR-1210 alone), 0.5h prior to administration of SHR-1210 on Day 1 of Cycle 2 and 3 (C2D1, C3D1) (the administration time of apatinib needs to be provided by the patient, and it must occur on the same day earlier than SHR-1210 administration).
- Intravenous infusion of SHR-1210 (experimental arm);
- Oral administration of apatinib (experimental arm) (daily, continuously)
- Distribution, verification and recovery of subject's diary;
- Subject's self-evaluation results: it will only performed on C3D1, all the subjects will complete EORTC QLQ-C30 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, 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 $\geq 2+$, 24h urine protein quantification must be added;
- Blood biochemistry: including ALT, AST, total bilirubin, γ -glutamyl transferase (GGT), direct bilirubin, indirect bilirubin, ALP, LDH, albumin, blood urea nitrogen or serum 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 apatinib (experimental arm) (daily, continuously);
- Distribution, verification and recovery 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 2 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, 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 $\geq 2+$, 24h urine protein quantification must be added;
- Blood biochemistry: including ALT, AST, total bilirubin, γ -glutamyl transferase (GGT), direct bilirubin, indirect bilirubin, ALP, LDH, albumin, blood urea nitrogen [BUN] or serum 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;
- Thyroid function (once every two cycles, for example, C5D1, C7D1, TSH, FT3, FT4);
- 12-lead ECG (performed after sitting still for at least 5 minutes): heart rate and QTc interval (calculated using Fridericia's formula);
- Intravenous infusion of SHR-1210 (experimental arm);

- Oral administration of apatinib (experimental arm) (daily, continuously);
- Distribution, verification and recovery 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: (once every two cycles in the first 12 cycles of therapy, for example, C5D1, C7D1, once every three cycles afterwards). All the subjects will complete EORTC QLQ-C30 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 (only in experimental arm): 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, only in experimental arm): including temperature, blood pressure, pulse rate and respiratory frequency;
- Collect concomitant medications/therapy;
- Collect AE;
- Intravenous infusion of SHR-1210 (experimental arm);
- Oral administration of apatinib (experimental arm) (daily, continuously);
- Distribution, verification and recovery 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 (premanent discontinuation of both of the drugs (SHR-1210 and apatinib) 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 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 $\geq 2+$, 24h urine protein quantification must be added;

- Blood biochemistry: including ALT, AST, total bilirubin, γ -glutamyl transferase (GGT), direct bilirubin, indirect bilirubin, ALP, LDH, albumin, blood urea nitrogen or serum 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 2 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, blood pressure, pulse rate and respiratory frequency;
- Fecal occult blood test;
- Thyroid function (FT3, FT4, TSH);
- Coagulation parameters: including INR and/or PT (if INR can not be collected, PT will be used as the basis for judgment);
- Serum human chorionic gonadotropin (HCG) test for female subjects of childbearing potential;
- Collect concomitant medications/therapies;
- Collect adverse events;
- Tumor imaging evaluation;
- Verification and recovery of subject diary.

If 12-lead ECG, routine laboratory tests (including hematology, urinalysis, serum biochemistry, serum electrolyte, coagulation parameters, thyroid function, fecal occult blood and virology tests, AFP) are completed within 7 days before withdrawal, these tests 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. If the subject could not resume study drug for AE, the latest date of

administration is used as the date of last dose. If the date has exceeded 30 days (+7 days) over the date when the subject needs to be withdrawn from the study treatment by judgment, the situation does not need to be recorded as deviation from protocol but the subject is recommended to return to the study site as soon as possible for safety visit.

- 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 $\geq 2+$, 24h urine protein quantification must be added;
- Blood biochemistry: including ALT, AST, total bilirubin, γ -glutamyl transferase (GGT), direct bilirubin, indirect bilirubin, ALP, LDH, albumin, blood urea nitrogen [BUN] or serum 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 2 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, blood pressure, pulse rate and respiratory frequency;
- Thyroid function (FT3, FT4, TSH);
- Coagulation parameters: including INR and/or PT (if INR can not be collected, PT will be used as the basis for judgment);
- Serum human chorionic gonadotropin (HCG) test for female subjects of childbearing potential;
- Collect concomitant medications/therapies;
- Collect adverse events;
- Tumor imaging 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. 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, 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 imaging 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 as defined in RECIST v1.1, he/she still can continue SHR-1210 alone or combined with apatinib (experimental arm) when he/she can still clinically benefit from and tolerate study treatment, as evaluated by investigators.

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

A part of patients 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 patient may benefit under this circumstance. After progression of disease as defined by RECIST v1.1, subjects meeting all of the following criteria may continue with the study treatment. If the disease progression defined by irRECIST is confirmed in a subsequent radiological evaluation, the study treatment will be terminated, unless the investigator considers that the subject can continue to benefit clinically (which has to be further discussed

with and agreed by the sponsor); in the latter case, the subject may continue with the study treatment until the investigator determines that the subject can no more benefit clinically from the study treatment. Subjects who continue the dose following PD will receive periodic visit and efficacy evaluation according to the visit schedule specified in the trial.

- Investigators judge continuation of study treatment meets the best interest 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. Other Precautions for Post-Progression Continuation of Treatment

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

If a decision 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).

7. EVALUATION

7.1. Efficacy Evaluation

The efficacy endpoints include:

- Progression-free survival (PFS): defined as the length of time from the date of randomization to the first occurrence of progression or death, whichever comes first, evaluated by the BIRC or investigator based on RECIST v1.1 or irRECIST.
- Overall survival time (OS): defined as the length of 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) and investigator based on the immune-related RECIST (irRECIST):

- Objective response rate (ORR): defined as the percentage of subjects with complete remission (CR) or partial remission (PR) evaluated by the BIRC or investigator based on RECIST v1.1, or irRECIST.
- Disease control rate (DCR): defined as the percentage of subjects with complete remission, partial remission or stable disease (SD) ≥ 8 weeks evaluated by the BIRC or investigator based on RECIST v1.1, or irRECIST.
- Duration of response (DoR): defined as the length of time from the date of first record of objective response (CR or PR) to the first occurrence of progression or death, whichever comes first, evaluated by the BIRC or investigator based on RECIST v1.1, or irRECIST.
- 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.

7.2. Tumor Imaging Evaluation

7.2.1. Tumor Evaluation Based on RECIST v1.1, and irRECIST.

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

The tumor evaluation in screening period (at baseline) should include the enhanced CT 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 randomization), 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: if there are no more than two 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 determined progression of the disease, tumor evaluation should be continued, regardless of whether the subject has terminated the study, until the subject dies, withdraws the informed consent, initiates subsequent antitumor therapy or terminated the study by sponsor, whichever comes first. Tumor evaluation during treatment includes CT scan of thorax, abdomen, pelvis and site of lesions; cranial 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 remission (complete remission or partial remission) for the first time need to be confirmed through the next scheduled evaluation or repeated evaluation ≥ 4 weeks after the first evaluation. The progression of disease that is suspected as pseudoprogression must be confirmed in subsequent radiological examinations, the time of the radiological examination for confirmation is at least 4 weeks after disease progression is detected or at the next scheduled time point (not exceeding 12 weeks), and prior to the termination of study treatment. Patients who meet RECIST v1.1 criteria for progression will continue to receive tumor evaluation, until progression of disease (in accordance with the irRECIST definition) or end of study treatment, whichever comes later.

Once progressive disease occurs, a physical examination of the subject and imaging confirmation is required at all times, rather than waiting for the next planned imaging examination. If the unplanned imaging 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 imaging 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).

7.3. Safety Evaluation

7.3.1. Pregnancy Testing

Serum pregnancy test will be performed within 7 days prior to the start of administration 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.

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 8.

Table 8. 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 and indirect bilirubin), renal function (BUN or serum 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 72h prior to administration at each visit. If urine protein is $\geq 2+$, 24h urine protein quantification must be added. |
| Thyroid Function | TSH, FT3, FT4 |
| Virology | HIV-Ab, HBV and HCV infection test. Requirement for HBV test: HBV five serological markers (HBsAg, HBsAb, HBcAb, HBeAg, HBeAb) will be detected, if HBsAg or HBcAb is positive, HBV-DNA will be quantified. Requirement for HCV test: HCV-Ab will be detected as to determine the presence of HCV infection, if HCV-Ab is positive, HCV-RNA will be quantified. |

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, 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 2.

7.4. Patient Reported Outcomes (PRO)

All the subjects will complete EORTC QLQ-C30 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 two cycles in the first 12 cycles, and Day 1 of every three cycles afterwards, until end-of-treatment visit (inclusive). 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 the 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.

7.4.1. EORTC QLQ-C30

EORTC QLQ-C30 is a core scale in the quality of life measurement questionnaire system for all cancer patients that is systematically developed by European Organization for Research and Treatment of Cancer, and used for measurement of quality of life in all the cancer patients (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 samples of EORTC QLQ-C30 (version 3.0) in this study is seen in APPENDIX 5.

In this study, EORTC QLQ-C30 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 patients with advanced osteosarcoma who receive SHR-1210 combined with apatinib mesylate. The following endpoints are included:

- TTD, defined as time from enrollment to first deterioration, as determined by

following subscales of EORTC QLQ-C30 subscales (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 three 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 (by cycle);

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.

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 9 if any AE is unlisted in NCI-CTCAE v4.03.

Table 9. 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 a risk of immediate death);
- Events requiring hospitalization or prolonged hospitalization;
- Events that result in persistent or severe disability / dysfunction / limiting working ability;
- Congenital abnormalities or birth defects;

- Other significant medical events (defined as the event threatens the safety of the subject, or requires intervention measures for the prevention of any of the above conditions).

8.2.2. Hospitalization

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

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 which are unrelated to the exacerbation of adverse events will not be considered as serious adverse events. For example,

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

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

dysfunction / limiting work ability, congenital abnormalities or birth defects 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.

The word “disease progression” should not be reported as an AE or SAE term as disease progression is an expected occurrence in the study population. If any 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.

All cases of death that occur during the study period must be reported as SAEs, whether or not the subject has received other antitumor therapy (see Section 8.3). The death resulted from the symptom and sign of progression of disease should be recorded in eCRF and reported as a SAE. 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, record “unexplained death.”

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 “serious adverse event 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 serious adverse event 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 serious adverse event 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: bonetumor@163.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. An AE/SAE will be followed up until it is resolved, returns to the baseline level or \leq 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 best 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.

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 "Adverse Event of Special Interest Report Form in Hengrui Clinical Study" within 24h after the event is known, and report to the sponsor. If it is SAE at the same time, please also fill in "Serious Adverse Event Report Form".

- \geq Grade 3 infusion reaction
- \geq 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 are considered important medical events and should always be reported as SIEs.

- 1) ALT or AST $\geq 3 \times$ ULN (normal at baseline), ALT or AST $\geq 3 \times$ baseline value (abnormally elevated at baseline)
- 2) TBIL $\geq 2 \times$ ULN (normal at baseline), TBIL $\geq 2 \times$ 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 and indirect 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 patients, 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 the female subject is 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 24h after investigator awareness, and report to the ethics committee in time.

The investigator should follow up the pregnancy result, until one month after delivery, and will report the result 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 in accordance with SAE reporting requirements.

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

9. 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

According to our previous phase II trial of single agent of apatinib on advanced osteosarcoma, the 4-m PFS rate was 56.76% (95% CI 39.43%–70.84%) and the 6-m PFS rate was 36.77% (95% CI 21.48%–52.16%). 9/37 (24.32%) patients was progression free at 6 months. Median PFS and OS were 4.44 (95% CI 3.12–7.08) and 8.77 (95% CI 6.73–16.70) months, respectively. This trial was designed to discard a PFS at 6 month of 37% (null hypothesis) aiming to reach a PFS at 6 month of 60% or higher (alternative hypothesis). Using Simon’s optimum two-stage design and setting α -error at 0.05 and β -error at 0.10, the presence of at least six successes in the 12 patients enrolled in the first stage allowed the trial to proceed to the second stage in which 31 more patients were needed to be enrolled for the minimum total of 43 patients. 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 CBR and PFS evaluated by the BIRC based on RECIST v1.1 in one experimental arm (SHR-1210 in combination with apatinib).

Null Hypothesis: SHR-1210 in combination with apatinib PFS at 6 month of 37%.

Alternative Hypothesis: SHR-1210 in combination with apatinib PFS at 6 month of 60% or higher.

10.2.2. Key Secondary Objectives and Statistical Hypotheses

Objective: To compare the OS (assessed by BIRC according to RECIST) of SHR-1210 in combination with apatinib.

Hypothesis: The OS (assessed by BIRC according to irRECIST) of SHR-1210 combined with Apatinib Mesylate tablets (experimental arm) is superior to Apatinib (previous study).

10.3. Analysis Populations

- **Full Analysis Set (FAS):** In line with the Intention-to-Treat (ITT) principle, this population will include all randomized subjects who receive at least 1 dose of study treatment. 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 apatinib and had at least 1 ADA measurement.

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% confidence intervals.

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, 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 CBR and PFS (assessed by BIRC base on RECIST v1.1). Using Simon's optimum two-stage design and setting α -error at 0.05 and β -error at 0.10, the presence of at least six successes in the 12 patients enrolled in the first stage allowed the trial to proceed to the second stage in which 31 more patients were needed to be enrolled for the minimum total of 43 patients.

The hypothesis testing of OS and PFS will be evaluated by comparing SHR-1210 plus apatinib in FAS using a stratified Log-rank test (based on randomization stratification factors). The PFS and OS curves for experimental arm will be estimated using the Kaplan-Meier (KM) product-limit method. A 95% CI for median OS will be estimated by Brookmeyer-Crowley method. The analysis of OS will be repeated without the stratification factors included in the analysis. Wilcoxon test will also be performed, as well as other methods, if needed.

Detail of multiplicity control can be found in Section 10.4.10.

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. 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 at 0.025 one-sided. 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.

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. 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 apatinib 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 RECIST v1.1 will be evaluated using the same analytical methods for the secondary endpoints.

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

10.4.8. 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.

10.4.9. Safety Analyses

10.4.9.1. 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 $\geq 5\%$, SAE with incidence $\geq 5\%$, 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.

10.4.9.2. Laboratory Tests Results

Clinical laboratory (eg, 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. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) for laboratory parameters and their changes from baseline will be calculated. Laboratory values will be summarized by visit and by worst post baseline visit.

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.

10.4.9.3. Others

The analyses of vital signs will include summary statistics of change from baseline over time by experimental arm.

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.

10.4.10. Multiplicity

PFS hypothesis will be tested at $\alpha=0.005$ (one-sided) and OS hypothesis will be tested at $\alpha=0.02$ (one-sided). If either hypothesis is significant at its initial one-sided α level, its α will be re-allocated to the other endpoint to be tested at $\alpha=0.025$ one-sided. A nominal alpha of 0.01% will be spent on testing the OS hypothesis at the time of the planned PFS analysis. For the interim analysis (70% events) and final analysis of OS endpoint, the Lan-DeMets O'Brien-Fleming spending function was used to control the type I error.

When both the PFS analysis and OS (interim or final) analysis tests are significant, ORR assessed by BIRC according to RECIST v1.1 may be tested at 0.025 one-sided (alpha re-allocation).

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.

10.4.11. 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 base on RECIST v1.1) will be estimated and plotted within each category of the following classification variables:

- Age (<40 years vs. ≥ 40 years)
- Locations (extremities vs. axial skeleton)
- Gender (male versus female)
- Involved disease sites (1 vs 2 vs ≥ 3)
- Previous local therapy (including radiotherapy) (yes vs no)
- ECOG-PS Score (0 vs. 1).

10.5. Data Monitoring Committee

The study will establish a 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, 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 from the sponser 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 submission of 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 as well, 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 the EDC users need to complete relevant trainings, fill in the 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 lock of database, 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, lock of database 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 save it on in CD-ROM, and submit it to the sponsor and the organization to keep the file for inspection.

The storage and management of study documents must be performed in accordance with the requirement of GCP, investigators should inform the sponsor in advance when destroying any document or data related with the trial. The sponsor should keep the study documents until at least 5 years after approval of the investigational drug.

12. SOURCE DATA AND SOURCE DOCUMENT

According to the International Council for Harmonisation (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 Medicine Co., Ltd., each study center should allow Jiangsu Hengrui Medicine 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 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.

Drug 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, or 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).

Secondly, in accordance with the requirements in domestic relevant regulations, new drug clinical trial need to be applied to NMPA prior to its conduction, and can be conducted only after getting the approval document. The approval number of SHR-1210 is 2016L01455.

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/institutional review board. 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/institutional review board 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 patient 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 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 and answer any question possibly proposed by subjects. Only after the subject has signed the informed consent form he/she is able to enter the study. In the whole course of the clinical study, subjects can withdraw the informed consent at any time. One copy of informed consent form will be kept by subjects. Even the consulted patients refuse to participate in this study, their rights will also 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 conducted by investigators, study personnel involved, the sponsor and their representatives. The confidentiality covers the biological samples and gene tests besides the clinical data at the same time. Thus, the study protocol, documents, data and all the other incurred information will be strictly keep in secret. Without the prior written approval by the sponsor, all the relevant study or data information can not be revealed to any unauthorized 3rd party.

Other authorized representatives of the sponsor, 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 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 patients' personal data consistent with applicable privacy laws.

15. PUBLICATION OF STUDY RESULTS

Study results are the properties of Peking University People's Hospital. If the

investigators intend to publish any study-related data and information, they should not provide any materials to the Jiangsu Hengrui Pharmaceutical Company.

16. PROGRESSION IN CLINICAL STUDY

Estimated enrollment for first subject in: Jan 2018

Estimated enrollment for last subject in: Jan 2019

Estimated end of study: Jun 2019

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APPENDIX 1. Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) and Its Comparison With Immune-Modified RECIST (irRECIST) and Modified RECIST (irRECIST)

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 imaging 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 imaging 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 imaging 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 patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other 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. Imaging 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 imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, 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 patient 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-progressive Disease: 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 patient 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 qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease: This circumstance arises in some phase III trials when it is not a criterion of study 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 patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: 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 patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

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 imaging 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 patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

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

If a new lesion is equivocal, for example because of its small size, continued 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 imaging can be identified according to the following algorithm:

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

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

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

When no imaging/measurement is done at all at a particular time point, the patient 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 patients 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 patient with time point responses of PR-NE-PR as a confirmed response.

Patients 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 patients 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: patients 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=inevaluable.

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

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

Note: CR=complete response, PD=progressive disease, NE=inevaluable.

'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 |

| Overall response First time point | Overall response Subsequent time point | BEST overall response |
|--------------------------------------|---|---|
| | | 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=inevaluable.

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 patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

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 II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. 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 progressive disease is objectively documented (taking as reference for progressive disease 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 patients 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 duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The

frequency should take into account many parameters including disease types and stages, treatment periodicity and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

2.9 Progression-free survival/proportion progression-free

Phase III trials in advanced cancers are increasingly designed to evaluate progression-free survival or time to progression as the primary outcome of interest. Assessment of progression is relatively straightforward if the protocol requires all patients to have measurable disease. Increasingly, trials allow entry of both patients 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 progressive disease for those patients 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 irRECIST With RECIST v1.1

Source: Hodi FS, Ballinger M, Lyons B, et al. Immune-Modified Response Evaluation Criteria In Solid Tumors (irRECIST): 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&rft_id=ori:rid:crossref.org&rft_dat=cr_pub%3dpubmed

Briefly, immune-modified Response Evaluation Criteria in Solid Tumors (irRECIST) allows for collection of additional scans and for BOR to occur after radiologic PD assessment(s) in patients 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 irRECIST-defined PFS (impFS), irRECIST PD or death is considered an event; however, an irRECIST PD is not considered an impFS event if the time point response at the subsequent scan (≥ 4 weeks later) is irRECIST SD/PR/CR. An irRECIST PD followed by no additional assessments is considered an impFS event.

Table 4 Comparison of RECIST 1.1 With irRECIST

| Criterion | RECIST v1.1 | irRC | irRECIST* |
|--------------------|---|---|---|
| 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 | $\geq 20\%$ 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) | |
| | | $\geq 25\%$ increase in the SLD compared with baseline/ nadir | $\geq 20\%$ 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, irRECIST=immune-modified RECIST, irRC=immune-related response criteria, PD=progressive disease, RECIST=Response Evaluation Criteria in Solid Tumors, SLD=sum of longest diameters.

*irRECIST follows RECIST v1.1 conventions unless otherwise stated.

IrRECIST 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 irRECIST and RECIST v1.1: Summary of Changes

| | RECIST v1.1 | irRECIST |
|----------------------------|--|--|
| 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 $\geq 20\%$ and $\geq 5\text{mm}$ 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, irRECIST=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 progressive disease.

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 $\geq 10\text{ mm}$; 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.

Calculation of Sum of the Diameters

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.

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 imaging 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

Timepoint Response

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 patients 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 progressive disease until the sum of the diameters increases by $\geq 20\%$ 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 irRECIST

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 imaging/measurement is done at all at a particular timepoint, the patient is considered not evaluable (NE) at that timepoint. If only a subset of lesion measurements are 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 patient 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 patient will be assigned PD status, regardless of the contribution of the missing lesion.

Table 6 irRECIST 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.

Comparison of irRECIST With Conventional RECIST

Source: *Lencioni R, Llovet JM. Modified RECIST (irRECIST) assessment for hepatocellular carcinoma.*

Semin Liver Dis. 2010 Feb;30(1):52-60.

Note the following points regarding modified RECIST (irRECIST):

- irRECIST are recommended by American Association for the Study of Liver Diseases (AASLD) for the assessment of tumor response in HCC.
- Patients 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 imaging of the liver (high-quality arterial-phase imaging obtained on the first run, and high-quality portal venous-phase imaging 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 irRECIST (see Table 7 below).

Table 7 Comparison of irRECIST With Conventional RECIST

| Conventional RECIST | irRECIST |
|---|---|
| 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: irRECIST=modified RECIST, CR=complete response, PR=partial response, RECIST=Response Evaluation Criteria in Solid Tumors, SD=stable disease, PD=progressive disease.

APPENDIX 2. 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 3. 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 patients 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 IVb |

APPENDIX 4. 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. Patients 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

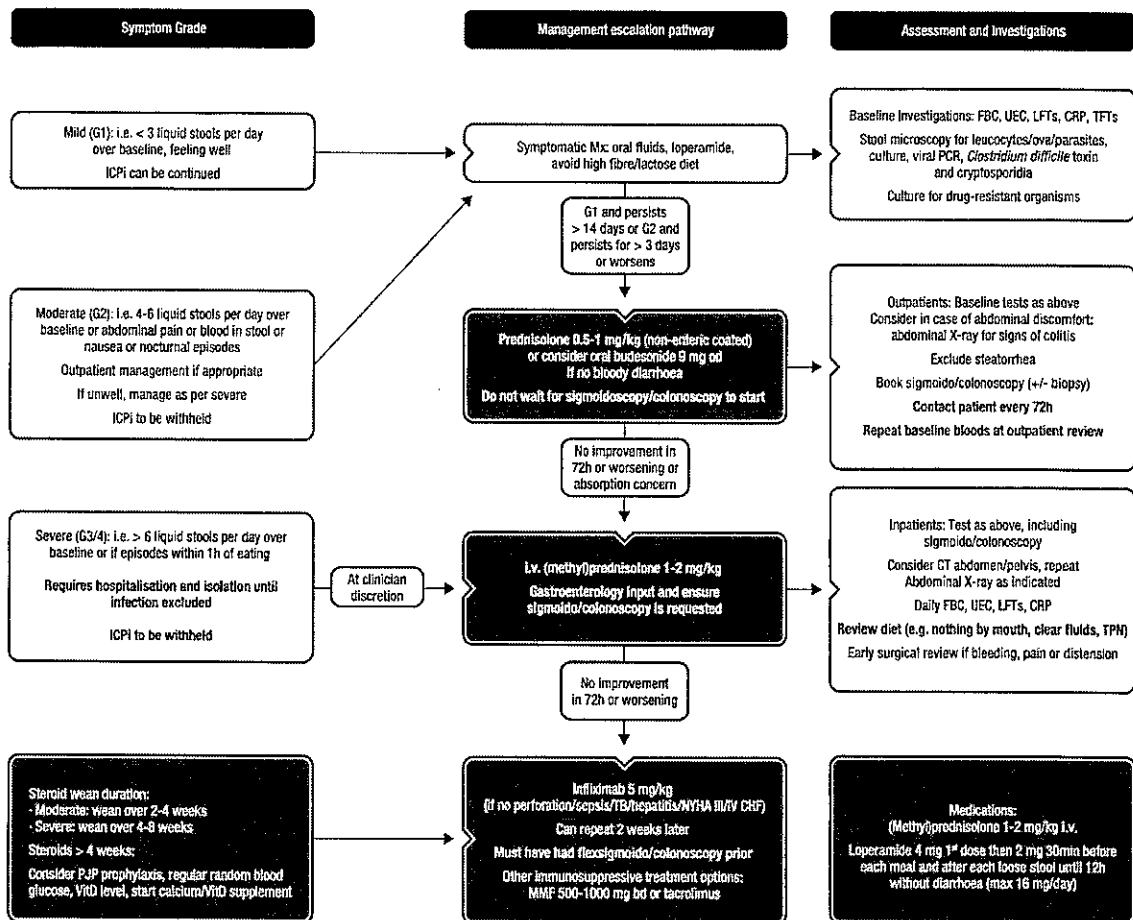


Figure 1. ICPi-Related Toxicity: Management of Diarrhoea and Colitis

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

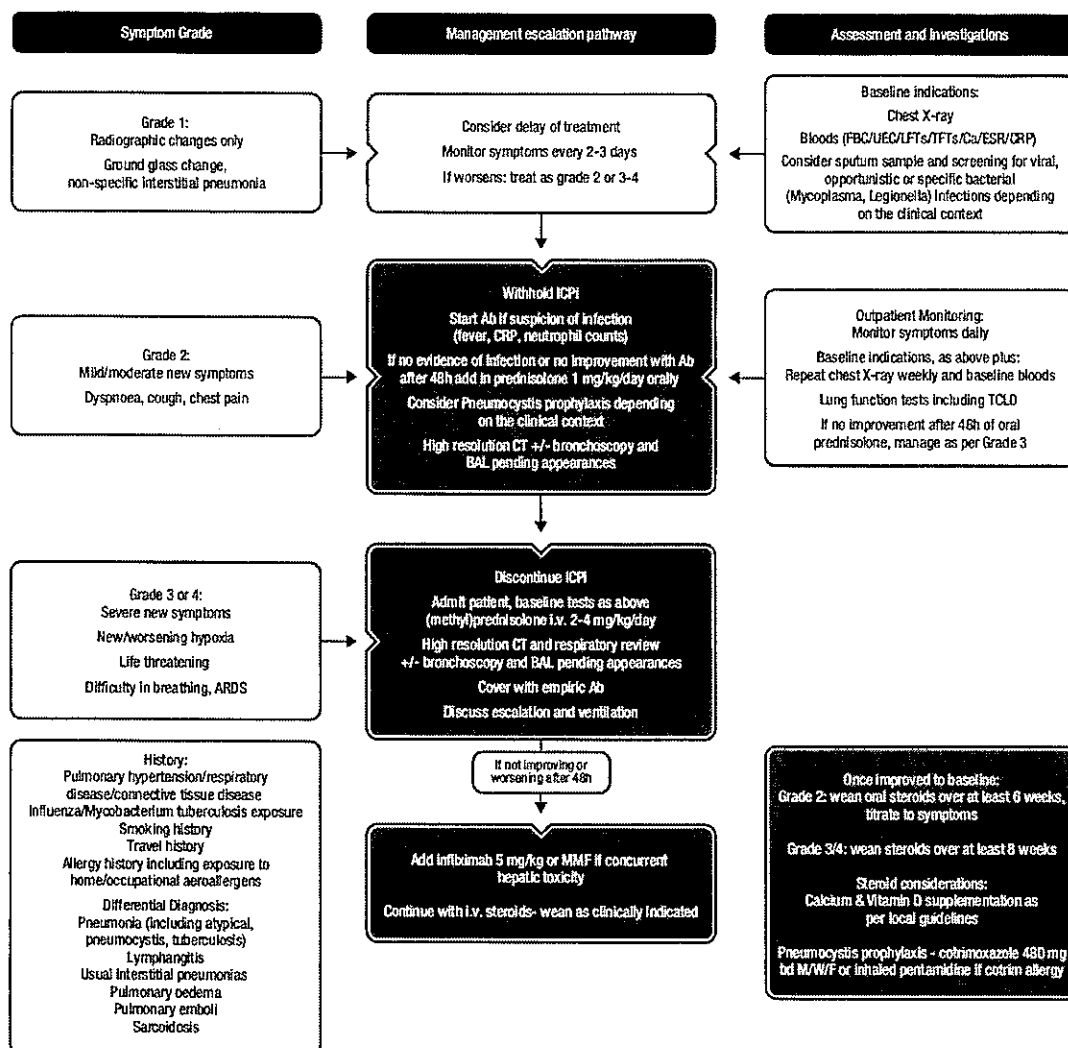


Figure 2. ICPI-Related Toxicity: Management of Pneumonitis

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

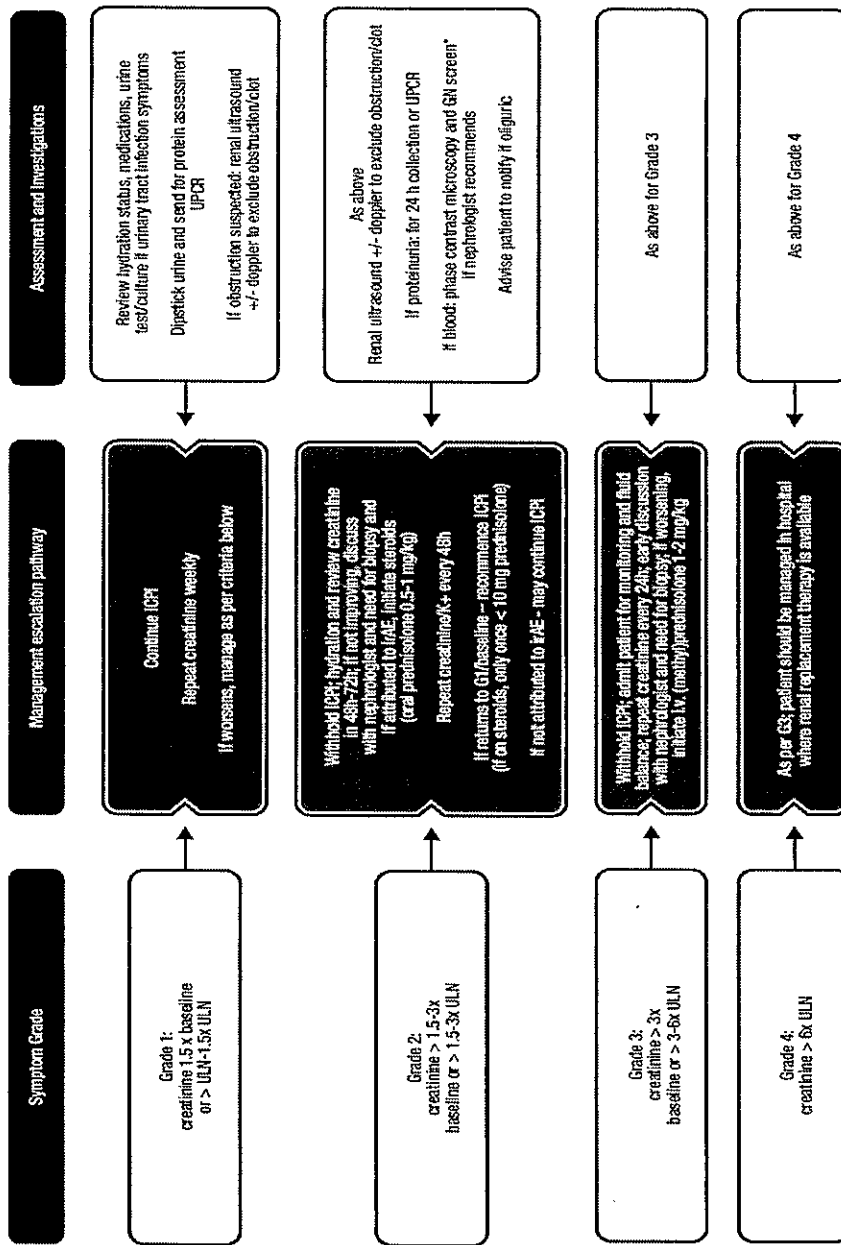


Figure 3. ICPI-Related Toxicity: Management of Nephritis

Renal injury occurs in around 1%-4% of patients treated with ICPI, usually a pattern of acute tubule-interstitial nephritis with a lymphocytic infiltrate. Attention needs to be paid to the patient'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 inpatient 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

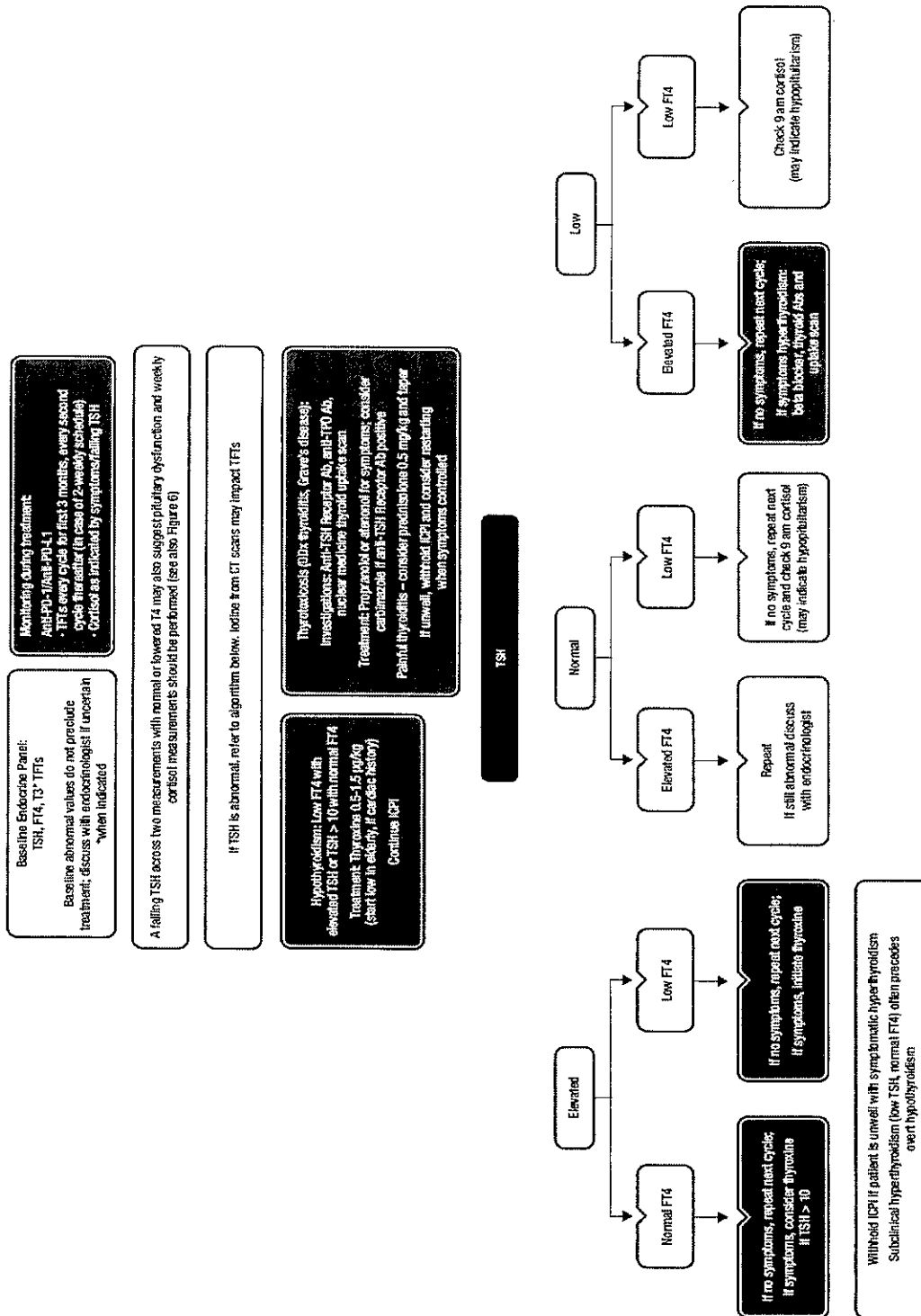


Figure 4. ICPI-Related Toxicity: Thyroid Function

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.

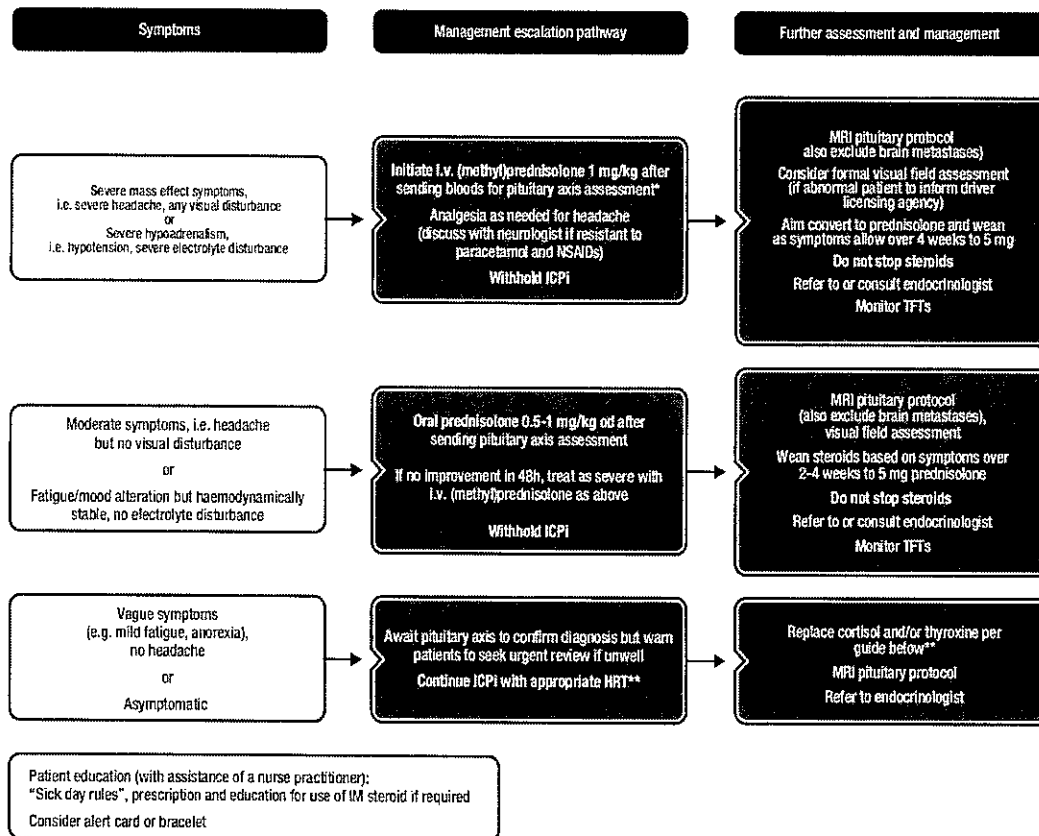


Figure 5. ICPI-Related Toxicity: Management of Hypophysitis

*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 imaging, NSAIDs=nonsteroidal anti-inflammatory drugs, od=once daily, TSH=thyroid-stimulating hormone, TFTs=thyroid function tests.

5. Rules for management of cutaneous adverse events

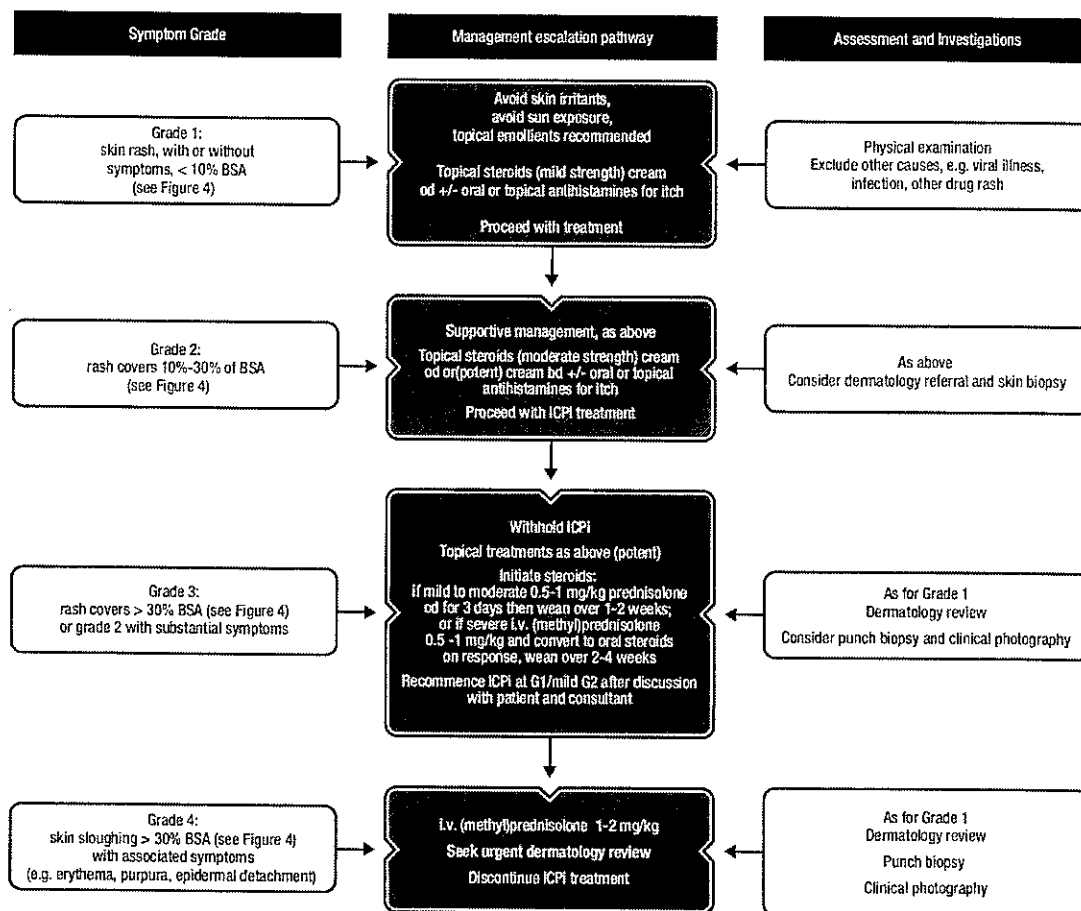


Figure 6. ICPI-Related Toxicity: Management of Skin Rash/Toxicity

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 ICPi. Start topical emollients, antihistamines in the case of pruritus and/or topical (mild strength) corticosteroid creams. Reinitiate ICPi when \leq 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 patient and always consult dermatologist immediately. Start i.v. corticosteroids [1–2 mg/kg (methyl) prednisone] and taper based on response of AE. [II, B]

Immune-related endocrinopathies

- For patients with Grade 2 symptomatic hyperthyroidism, 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 μ g/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 patients 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 patients 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 patient 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 patients with severe diarrhoea (Grade 3 to 4), permanently discontinue ICPi. Admit patient 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 patient to an experienced

centre. Taper over 6 weeks under close monitoring of liver tests [IV–V, B].

Immune-related pneumonitis

- For patients 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 patient 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 patient 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 (10–20mg prednisone). In the case of severe polyarthritis, refer patient to or consult a rheumatologist and start prednisone 1 mg/kg. Sometimes infliximab or another anti-TNF α 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 imaging, NSAIDs=nonsteroidal anti-inflammatory drugs, TNF α =tumor necrosis factor alpha, TSH=thyroid-stimulating hormone.

For other rules that are not listed 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, Carbone F, Robert C, et al. on behalf of the ESMO Guidelines Committee. *Ann Oncol*. 28 (Supplement 4): iv119–iv142, 2017.

APPENDIX 5. 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 <u>long</u> walk? | 1 | 2 | 3 | 4 |
| 3. Do you have any trouble taking a <u>short</u> 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

| 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 |

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¹ Ishida Y, Agata Y, Shibahara K, et al. Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. *EMBO J.* 1992;11(11):3887-95.

² Huang CY, Wang Y, Luo GY, Han F, Li YQ, Zhou ZG, Xu GL: Relationship between pd-1l expression and cd8+ t-cell immune responses in hepatocellular carcinoma. *Journal of immunotherapy (Hagerstown, Md : 1997)* 2017.

³ S. Champiat, O. Lambotte, E. Barreau, et al. Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper. *Annals of Oncology* 27: 559-574, 2016.