# Study protocol

**A Single-Center, Single-Arm, and Open-Label Clinical Study of Anti-PD-1 Antibody SHR-1210 in Combination with Apatinib Mesylate for the Treatment of Advanced Mucosal Malignant Melanoma**

**Protocol Number:** SHR-1210-APTN-MM

**Compounds Name:** Recombinant Humanized Anti-PD-1 Monoclonal Antibody for Injection (SHR-1210)

Apatinib Mesylate Tablets

**Protocol Responsible Person:**

**Clinical Study Site:**

**Principal Investigator:**

**Sponsor:**

**Compound Sponsor:** Jiangsu Hengrui Pharmaceutical Co., Ltd.

No. 7, Kunlunshan Road, Economic and Technological Development Zone, Lianyungang City, Jiangsu Province, 222047, China

**Protocol Synopsis**

| | |
|---|---|
| Title | **A Single-Center, Single-Arm, and Open-Label Clinical Study of Anti-PD-1 Antibody SHR-1210 in Combination with Apatinib Mesylate for the Treatment of Advanced Mucosal Malignant Melanoma** |
| Protocol Number | SHR-1210-APTN-MM |
| Study Duration | January 2019 ~ January 2022 |
| Study Objectives | **Primary Objectives**<br>To evaluate the objective response rate (ORR) of SHR-1210 in combination with apatinib mesylate in the treatment of patients with advanced mucosal melanoma<br>**Secondary Objectives**<br>1. To observe and evaluate the progression-free survival (PFS), duration of response (DOR), time to response (TTR), disease control rate (DCR), overall survival (OS), and 6-month/9-month/12-month survival rates in patients with advanced mucosal melanoma treated with SHR-1210 in combination with apatinib mesylate<br>2. To evaluate the safety of SHR-1210 in combination with apatinib |

| | |
|---|---|
| | mesylate in the treatment of patients with advanced mucosal melanoma<br>**Exploratory Objectives**<br>1. To evaluate the predictive, prognostic, and pharmacodynamic exploratory biomarkers in archived and/or fresh tumor tissue and blood samples, and to assess the correlation between these biomarkers and disease progression<br>2. To evaluate the quality of life in patients with advanced mucosal melanoma treated with SHR-1210 in combination with apatinib mesylate |
| Study Endpoints | **Primary Study Endpoints**<br>Accessed ORR per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria<br><br>**Secondary Study Endpoints**<br>**Efficacy:**<br>Accessed PFS per RECIST 1.1 criteria<br>* Time to response (TTR)<br>* Duration of response (DOR)<br>* Disease control rate (DCR)<br>* 6-month survival rate<br>* 9-month survival rate<br>* 12-month survival rate<br>* Overall survival (OS) |

| | |
|---|---|
| | **Safety**<br>* Incidence and severity of adverse events (AEs) and serious adverse events (SAEs), abnormal laboratory values, determined according to the National Cancer Institute (NCI) - Common Terminology Criteria for Adverse Events (CTCAE) V4.03criteria<br>* Dose interruption rate, dose discontinuation rate due to AEs<br><br>**Exploratory Study Endpoints**<br>* To explore the relationship between programmed cell death ligand-1 (PD-L1) expression level, proportion of positive cells, and/or other biomarkers, such as tumor mutation burden (TMB) at baseline, and efficacy<br>* To explore the correlation between biomarkers in archived and/or fresh tumor tissue and blood samples and disease progression<br>* To evaluate the quality of life in patients with advanced mucosal melanoma treated with SHR-1210 in combination with apatinib mesylate |
| Study Subjects | 1. Patients with advanced mucosal malignant melanoma ineligible for radical surgery<br>2. Patients with advanced mucosal malignant melanoma experiencing recurrence and metastasis after radical surgery of the primary lesion |

| | |
|---|---|
| Study Design | As a single-arm, open-label, and single-center clinical study, this study aims to observe and evaluate the efficacy and safety of anti-PD-1 (programmed cell death receptor-1) antibody SHR-1210 in combination with apatinib mesylate in patients with advanced mucosal melanoma.<br>The study subjects will be the patients with advanced mucosal melanoma who cannot be cured.<br>The study will enroll approximately 30 patients with advanced mucosal melanoma using ORR as the primary efficacy endpoint.<br>After obtaining informed consent and signing the informed consent form (ICF), the eligible subjects will continuously receive apatinib 500 mg, orally, once daily, and SHR-1210 200 mg, intravenously (IV), every 2 weeks. The dose of apatinib will be adjusted according to the patient's tolerance, with a treatment cycle of 4 weeks, until the treatment discontinuation events specified in the protocol occur. After the end of treatment, subjects will undergo post-treatment safety visits and survival follow-up. For subjects who discontinue treatment due to reasons other than disease progression or death, tumor progression follow-up will also be conducted after the end of treatment.<br>After the subjects are enrolled in the study, safety visits will be conducted before the administration of SHR-1210 on Day 1 and Day 15 of each treatment cycle. Imaging examinations will be performed every 2 cycles during the first 12 treatment cycles to evaluate the efficacy, and every 3 cycles thereafter until the end of treatment, withdrawal of informed consent, or death.<br>The study will also explore predictive, prognostic, and |

| | |
|---|---|
| | pharmacodynamic exploratory biomarkers in archived and/or fresh tumor tissue and blood samples, and assess the correlation between these biomarkers and disease progression. For subjects who have signed the ICF for biomarker sample collection, biomarker blood samples and tumor samples will be collected at baseline period and during the study, including any potential tumor biopsies performed at baseline. |
| Study Drugs | Recombinant Humanized Anti-PD-1 Monoclonal Antibody for Injection (Drug No. "SHR-1210") (Manufacturer: Suzhou Suncadia Biopharmaceuticals Co., Ltd.)<br>Apatinib Mesylate Tablets (Manufacturer: Jiangsu Hengrui Pharmaceutical Co., Ltd.) |
| Mode of Administration | SHR-1210 will be administered via intravenous infusion (no prophylactic medication required) at a fixed dose of 200 mg, and 3 mg/kg for patients weighing < 50 kg at baseline. Each infusion will last for 30 minutes (no less than 20 minutes, no more than 60 minutes), and the drug will be administered once every 2 weeks, with 4 weeks for one cycle and the maximum cumulative treatment duration of 2 years.<br>Apatinib will be taken orally at a dose of 500 mg after a meal once daily. The dose of apatinib will be adjusted according to the patient's tolerance, with continuous administration and 4 weeks for one cycle. |
| Enrollment Criteria | Patients must meet all the following inclusion criteria to be enrolled in this study:<br>1. The patient voluntarily participates in the study and signs the ICF;<br>2. ≥ 18 years of age, male or female; |

| | |
|---|---|
| | 3. Clinically diagnosed or pathologically confirmed advanced mucosal malignant melanoma, with at least one measurable lesion that has not undergone local treatment (according to RECIST v1.1 requirements, the measurable lesion should have a long diameter of ≥ 10 mm or an enlarged lymph node should have a short diameter of ≥ 15 mm by a spiral computed tomography [CT] or magnetic resonance imaging [MRI] scan).<br>4. Can swallow tablets normally;<br>5. Eastern Cooperative Oncology Group (ECOG) score: 0 ~ 1;<br>6. Expected survival ≥ 12 weeks;<br>7. The function of vital organs must meet the following requirements (no use of any blood components, cell growth factors, or other corrective therapeutic drugs is allowed within 14 days prior to the first administration of the investigational drug):<br>● Absolute neutrophil count ≥ $1.5 \times 10^9$ /L;<br>● Platelets ≥ $80 \times 10^9$ /L;<br>● Hemoglobin ≥ 90 g/L;<br>● Serum albumin ≥ 30 g/L;<br>● Thyroid stimulating hormone (TSH) ≤ 1× upper limit of normal (ULN) (in case of abnormality, free triiodothyronine [FT3] and free thyroxine [FT4] levels should be evaluated simultaneously; if FT3 and FT4 levels are within the normal range, the subject can be included in the study);<br>● Bilirubin ≤ 1.5 × ULN (within 7 days prior to the first administration of the investigational drug); |

| | |
|---|---|
| | ● Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) ≤ 1.5 × ULN (within 7 days prior to the first administration of the investigational drug);<br>● Serum creatinine ≤ 1.5 × ULN;<br>8. For female patients who are non-surgically sterilized or of childbearing potential, they are required to use a medically approved contraceptive method (such as an intrauterine device, contraceptive medication, or condom) during the study treatment period and within 3 months after the end of the study treatment. Non-surgically sterilized women of childbearing potential must have a negative serum or urine human chorionic gonadotrophin (HCG) test within 72 hours prior to study enrollment, and must be non-lactating. For male patients with female partners of childbearing potential, effective contraception should be used during the study period and within 3 months after the last administration of SHR-1210. |
| Exclusion Criteria | Patients with any of the following conditions will be excluded from the study:<br>1. Patients who have any active autoimmune diseases or a history of autoimmune diseases (including, but not limited to: autoimmune hepatitis, interstitial pneumonia, uveitis, enteritis, hepatitis, hypophysitis, vasculitis, nephritis, hyperthyroidism, vitiligo, asthma (patients with asthma that has completely resolved in childhood requires no any medical intervention in adulthood can |

| | |
|---|---|
| | be included; patients with asthma requiring medical intervention with bronchodilators cannot be included);<br>2. Patients who are receiving immunosuppressive agents or systemic hormonal therapy for immunosuppression (at doses > 10 mg/day prednisone or other equivalent hormonal therapy) and are still on treatment within 2 weeks prior to enrollment;<br>3. Severe allergic reactions to other monoclonal antibodies;<br>4. Patients with hypertension that cannot be well controlled with antihypertensives (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg);<br>5. Uncontrolled clinical symptoms or disease of the heart, such as:<br>● New York Heart Association (NYHA) grade 2 or higher heart failure<br>● Unstable angina<br>● Myocardial infarction within 1 year<br>● Clinically significant supraventricular or ventricular arrhythmias requiring treatment or intervention<br>● QTc > 450 ms (male); QTc > 470 ms (female);<br>6. Abnormal coagulation function (international normalized ratio [INR] > 2.0, prothrombin time [PT] > 16 s), with a bleeding tendency or currently receiving thrombolytic or anticoagulant therapy (the prophylactic use of low-dose aspirin and low molecular weight heparin is allowed);<br>7. Within 3 months prior to enrollment, subjects with significant clinically relevant bleeding symptoms or a clear bleeding |

| | |
|---|---|
| | tendency, such as hemoptysis (≥ 2.5 mL/day), gastrointestinal bleeding, esophageal and gastric varices with a risk of bleeding, hemorrhagic gastric ulcers, or vasculitis;<br>8. Arterial/venous thrombotic events within 6 months prior to enrollment, such as cerebrovascular accidents (including transient ischemic attacks, hemorrhage brain, cerebral infarction), deep vein thrombosis, and pulmonary embolism;<br>9. Known inherited or acquired bleeding and thrombophilia (such as hemophilia, coagulation disorders, and platelets decreased);<br>10. Urine protein ≥ ++ indicated by urinalysis and confirmed 24-hour urine protein amount > 1.0 g;<br>11. Patients who have previously received radiotherapy, chemotherapy, hormonal therapy, or surgery and have not completed the treatment (last administration) 4 weeks prior to the initiation of the investigational drug; patients who have received molecular targeted therapy (including other oral targeted drugs in clinical studies) within less than 5 drug half-lives prior to the first administration of the investigational drug, or patients whose AEs (except alopecia) caused by previous treatments have not recovered to ≤ CTCAE grade 1;<br>12. Patients with active infections, unexplained fever ≥ 38.5℃ within 7 days prior to medication, or baseline white blood cell count >$15\times10^9$/L; or those with purulent and chronic infections, and prolonged wound healing;<br>13. Patients with bone metastases who have received palliative |

| | |
|---|---|
| | radiotherapy to an area > 5% of the bone marrow area within 4 weeks prior to participating in this study;<br>14. Patients who have previously received anti-PD-1, anti-PD-L1, anti-PD-L2 therapy, or apatinib treatment;<br>15. Known allergy to recombinant humanized anti-PD-1 monoclonal antibody drugs or their components;<br>16. Patients with cutaneous melanoma, ocular melanoma, and melanoma of unknown primary origin;<br>17. Patients with severe local invasion of the primary lesion in mucosal malignant melanoma, and with a risk of organ leakage, major bleed, or perforation;<br>18. Pregnant or lactating women, or female patients of childbearing potential who have not taken contraceptive measures;<br>19. Patients with other malignant tumors at the same time;<br>20. Patients who participate in another clinical study at the same time;<br>21. Patients with positive human immunodeficiency virus (HIV) or hepatitis C virus (HCV); Individuals who are positive for HBsAg or HBcAb and have detectable hepatitis B virus (HBV) DNA copies (quantitative detection limit is 500 IU/mL);<br>22. Patients who have received live vaccine within 4 weeks prior to the initiation of treatment;<br>23. Other severe, acute, or chronic medical or mental diseases or laboratory abnormalities that may increase the risk associated with study participation or may interfere with the interpretation of |

| | |
|---|---|
| | study results as judged by the investigators. |
| Discontinuation Criteria | 1. The subject withdraws informed consent and requests withdrawal;<br>2. For patients identified with progressive disease by imaging:<br>● According to the RECIST v1.1 criteria, if disease progression is observed for the first time, confirmation is required 4 ~ 6 weeks later (except for rapid progression and significant clinical progression);<br>● Upon confirmation of disease progression in the subject, if the clinical symptoms are stable, the investigator may decide to continue treatment until further radiographic progression is observed;<br>● Stable clinical symptoms are defined as the following:<br>a. No significant clinical symptoms or changes in laboratory test indicators;<br>b. No change in performance status score (no worsening);<br>c. Rapid progression of non-tumor and tumor progression not involving vital organs/sites (such as spinal cord compression);<br>3. When the cumulative usage of SHR-1210 reaches 2 years (without radiographic progression) and the radiographic examination confirms a complete response (CR), the medication may be considered for discontinuation after completing 12 treatment cycles; |

| | |
|---|---|
| | 4. Intolerant of toxicity;<br>5. Poor subject compliance;<br>6. The subject is lost to follow-up or becomes pregnant;<br>7. Other circumstances that, in the opinion of the investigator, a withdrawal from the study is necessary. |
| Study Discontinuation Criteria | Discontinuation criteria for this study include, but are not limited to, the following:<br>1. Identify unexpected, significant, or unacceptable risks to patients;<br>2. Major errors in the protocol are found during the implementation of the study;<br>3. Investigational drug/therapy is ineffective, or continuing the study is meaningless;<br>4. The sponsor decides to terminate the study due to reasons such as severe delay in patient enrollment or frequent protocol deviations. |
| Safety Evaluation | The severity of AEs will be assessed according to the CTCAE v4.0.3 criteria. During the trial, the adverse event record form should be filled out truthfully, including the onset time, severity, causality with the study drug, duration, actions taken, and outcome of the AE. |
| Concomitant Medications and Therapies | During the study, the investigator is allowed to provide appropriate supportive therapy based on the clinical needs of subjects. the following Specific medications can be found in the following description of concomitant medications. The use of anti-tumor treatments not specified in the study protocol is prohibited during the treatment, except |

| | |
|---|---|
| | for medical interventions taken for life-threatening tumor emergencies.<br>1. Permitted concomitant medications<br>● All concomitant medications/treatments must be recorded in the case report form (CRF), including all prescriptions, over-the-counter drugs, traditional Chinese herbal medicines, intravenous medications, and fluids.<br>● If changes occur during the study, the drug dose, frequency, mode and date of administration should also be recorded in the CRF.<br>2. All concomitant medications/treatments must be recorded between 30 days before the first administration of the investigational drug and 30 days after the last administration in the study.<br>3. Prohibited concomitant medications<br>During the screening and treatment periods of the study, subjects are prohibited from receiving the following treatments:<br>● Systemic anti-tumor chemotherapy or biotherapy<br>● Immunotherapy not specified in this protocol<br>● Investigational drugs other than SHR-1210 and apatinib mesylate tablets<br>● Vaccination within 4 weeks prior to treatment administration and during the administration period. Examples of vaccines include, but are not limited to: measles, mumps, rubella, varicella, yellow fever, rabies, Bacillus of Calmette and Guérin, and typhoid (oral) vaccines. |

| | |
|---|---|
| | ● Use of any glucocorticoids other than the treatment of AEs caused by immunotherapy and anti-angiogenic therapy (Note: The physiological doses of steroids may be permitted after communication with the sponsor). |

| | |
|---|---|
| Study Visits | ● Screening / Baseline Period (Day -21 to Day 0)<br>Only after the subject signs the ICF approved by the Institutional Review Board (IRB), the screening and tumor assessment related to the clinical study can be initiated. During the screening period, the following tests will be performed: complete medical history, physical examination, height, weight, vital signs (blood pressure and heart rate), electrocardiogram (ECG), ECOG score, etc. Past medications and clinical laboratory tests, including urinalysis, hematology (differential blood count), blood chemistry, coagulation function, stool routine, myocardial zymogram, and lymphocyte subsets must be performed within one week before drug administration. Thyroid function, pituitary-adrenal axis function, virological parameters, and pregnancy test (only for women of childbearing potential) must be completed within 21 days before the first drug administration. Tumor assessment must be completed within 3 weeks before the administration of the study drug (additional nasopharyngeal MRI or CT for nasopharyngeal melanoma, additional oropharyngeal MRI or CT for oropharyngeal melanoma, colposcopy for female genital tract |

| | |
|---|---|
| | melanoma as needed, and colonoscopy for rectal melanoma as needed). Concurrently, pathological tissue and blood samples will be collected for pathological consultation and genetic testing.<br>● Treatment Period<br>The subjects will receive recombinant humanized anti-PD-1 monoclonal antibody injection in combination with apatinib according to the protocol. Treatment may be terminated in the event of recurrent disease metastases, intolerable toxicity, withdrawal of informed consent, or other criteria for treatment withdrawal.<br>At each visit, the concomitant medications and clinical symptom information of the subjects will be recorded, including any AEs. All subjects will undergo imaging assessments every 2 cycles during the first 12 treatment cycles, and every 3 cycles thereafter until the end of treatment, withdrawal of informed consent, or death. Cranial CT or MRI and bone scans will be performed annually (increase the frequency of imaging assessments if clinically indicated) until the end of the study.<br>● Visits After the End of Study Treatment:<br>After the termination of the study treatment, the subjects should undergo the following safety evaluations: physical examination, vital signs, ECOG, ECG, hematology, urinalysis, stool routine, blood chemistry, coagulation function, thyroid function, lymphocyte subsets, and pregnancy test (only for women of childbearing potential). The date and reason for termination of the |

| | |
|---|---|
| | study treatment must be clearly recorded in the CRF for the termination of the study treatment.<br>All subjects who complete the study treatment or withdraw from the study will be followed up for safety through outpatient visits or telephone follow-ups within 90 days after the last administration of the investigational drug, or until the patient receives another anti-tumor treatment, whichever occurs first. |
| Statistical Analysis | The main results of this study will be presented using descriptive statistical methods. The mean, standard deviation, median, maximum, and minimum values will be listed for measurement data, while the frequency (proportion), rate, and confidence interval (CI) will be listed for counting data and ranking data. All statistical analyses will be programmed and calculated using SAS 9.4 or above.<br>● Safety Analysis:<br>The descriptive statistical analysis will be used for analyzing AEs, SAEs, and adverse reactions (adverse reactions are defined as AEs with the causality to the study drug as "definitely related/possibly related/not evaluable") occurring in various populations. The worst clinical grade will be described for the laboratory test results at baseline and post-baseline.<br>● Efficacy Analysis:<br>The point estimates will be performed for efficacy endpoints such as ORR and DCR, and their 95% CIs will be provided. The interval estimates will be performed using the Clopper-Pearson |

| | |
|---|---|
| | method.<br>PFS, DOR, OS, 6-month, 9-month and 12-month survival rates will be estimated using the Kaplan-Meier method, and 95% CIs will be calculated. TTR will be described using mean, standard deviation, median, maximum, and minimum values.<br>● Additional Analyses:<br>For the SHR-1210-related solid tumor biomarkers, such as PD-L1 or other biological markers levels in tumor tissues, descriptive statistics will be used for analysis. |

**List of Abbreviations and Related Terms**

| Acronyms / Abbreviations | Explanation |
|---|---|
| ADA | Anti-drug antibody |
| ADR | Adverse drug reaction |
| AE | Adverse events |
| ALP | Alkaline phosphatase |
| ALT (SGPT) | Alanine aminotransferase |
| APTT | Activated partial thromboplastin time |
| AST (SGOT) | Aspartate aminotransferase |
| ANC | Absolute neutrophil count |
| AUC | Area under the concentration-time curve |
| BUN | Blood urea nitrogen |
| CBC | Complete blood count |
| Cl- | Chlorine |
| CRP | C-reactive protein |
| CT | Computer-assisted tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DLT | Dose limiting toxicity |
| DSMB | Data and Safety Monitoring Board |
| EC | Ethics Committee |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |

| | |
|---|---|
| CRF | Case report form |
| EDC | Electronic data capture |
| FAS | Full analysis set |
| CFDA | China Food and Drug Administration |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |

| | |
|---|---|
| HIV | Human immunodeficiency virus |
| IC | Informed consent |
| ICF | Informed consent form |
| ICH | International Coordinating Organization |
| INR | International normalization ratio |
| IRB | Institutional Review Board |
| IV | Intravenous |
| $K^+$ | Potassium |
| Kd | Dissociation constant |
| kg | Kilogram |
| LDH | Lactate dehydrogenase |
| Mab | Monoclonal antibody |
| MedDRA | Medical Dictionary for Registration Projects |
| mg | Milligram |
| mL | Milliliter |
| MRI | Magnetic resonance imaging |
| MTD | Maximum tolerated dose |
| $Na^+$ | Sodium |
| NK | Natural killer |
| PBMC | Peripheral blood mononuclear cells |
| PBSCT | Peripheral blood stem cell transplantation |
| PD | Progressive disease |

| | |
|---|---|
| PK | Pharmacokinetics |
| PS | Performance status |
| PT | Prothrombin time |
| PLT | Platelets |
| RBC | Red blood cells |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RO | Receptor occupancy |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SOP | Standard operating procedure |
| $t_{1/2}$ | Half-life |
| TCR | Tissue cross-reactivity |
| WBC | White blood cells |

**Protocol Text**

## 1. Study Background

### 1.1 Introduction

Malignant melanoma originates from neural crest melanocytes and is characterized by a high degree of malignancy, early metastasis, and poor prognosis [1-2]. Compared with cutaneous melanoma, mucosal melanoma is the second most common subtype in the Asian population [3-4], but it is extremely rare in the Caucasian population, accounting for only 1.3% [5-6]. The prognosis of mucosal melanoma is worse than that of cutaneous melanoma, with a reported 5-year disease-free survival rate of 0% ~ 20% [7-10]. Therefore, it is more and more important to improve early diagnosis and effective adjuvant therapy. Early diagnosis and standardized surgical treatment are the only possibilities for achieving a cure for melanoma. For patients with mucosal melanoma at high risk of recurrence, it is crucial to receive systematic adjuvant therapy after surgery [11-12].

Multiple randomized studies have been conducted to evaluate adjuvant therapy for stage II/III melanoma, such as chemotherapy, nonspecific immunotherapy, or combination therapy. Apart from high-dose interferon (HD-IFN α-2b) being effective, all other treatments have yielded negative results [13-16]. Clinical studies of HD-IFN have shown that HD-IFN α-2b can significantly improve relapse-free survival and/or overall survival (OS) in patients with high-risk melanoma [15-16]. Therefore, it has been recommended by the National Comprehensive Cancer Network (NCCN) guidelines as the standard treatment for adjuvant therapy of melanoma at high risk of recurrence and metastasis [17-18].

In recent years, programmed cell death receptor-1 (PD-1) antibodies represented by pembrolizumab and nivolumab have achieved relatively good confirmatory

therapeutic effects in advanced melanoma. The immune regulation mechanism mediated by the PD-1/L1 pathway is currently a breakthrough point in tumor immunotherapy. Tumor cells can evade the immune surveillance of activated T cells through this pathway. PD-1 is expressed on the surface of activated T cells. Under healthy conditions, its normal function is to downregulate unnecessary or excessive immune responses, including autoimmune responses. PD-1 is a member of the immunoglobulin (Ig) superfamily, and it has been confirmed that when PD-1 binds to its ligands (programmed cell death ligand-1 [PD-L1] and/or programmed cell death ligand-2 [PD-L2]), it can negatively regulate antigen receptor signals [19-20]. Although normal organs can only express a small amount of PD-L1(if any), studies have confirmed that various tumor cells can express large amounts of this T cell inhibitor. It has been found that high expression of PD-L1 (lower levels of PD-L2) in tumor cells is associated with poor prognosis and survival in various tumors, including renal cell carcinoma, pancreatic cancer, hepatocellular carcinoma, ovarian cancer, and non-small cell lung cancer [21-24]. In addition, studies have found that PD-1 can regulate the expansion of tumor-specific T cells in melanoma patients [28]. This suggests that the PD-1/PD-L1 pathway plays an important role in tumor invasion and is therefore a highly regarded target for therapeutic intervention.

Recent data on anti-PD-1 antibodies (including nivolumab and pembrolizumab) indicate that PD-1 is a highly attractive target for clinical intervention, and anti-PD-1 monoclonal antibodies have validated this theory in the treatment of cutaneous melanoma [25-28]. Nivolumab has an objective response rate (ORR) of 28% in patients with cutaneous melanoma who have not previously received ipilimumab (IPI) treatment [27], while pembrolizumab has shown a better response rate (41%) in patients with cutaneous melanoma. Specifically, in patients with cutaneous melanoma

who have not previously received IPI treatment, the response rate of pembrolizumab is greater than 40% [29], which is significantly higher than the response rate of 11% ~ 15% observed in IPI registration trials. It should be noted that both nivolumab and pembrolizumab were well tolerated with longer duration of response. The median overall survival for nivolumab was 16.8 months, with 1-year and 2-year survival rates of 62% and 43%, respectively [29-30]. In the KEYNOTE-001 study of pembrolizumab, the median overall survival for cutaneous melanoma was not reached at the time of analysis, regardless of the overall study population or individual dose groups. For all subjects and dosing regimens, the proportion of patients alive at 1 year was approximately over 80%. However, the use of PD-1 monoclonal antibodies in mucosal melanoma lacks widely accepted data.

Although this category of therapy has achieved unprecedented success, it cannot be ignored that a large proportion of the patient population does not respond to this treatment. At present, combination therapy is expected to be one of the inevitable trends in the future development of tumor immunotherapy. How to conduct combination therapy is a problem that needs to be further addressed in the medical community.

Currently, many ongoing phase 1/2 clinical studies involve the combination of targeted therapies and immunotherapies. The fundamental rationale supporting these combination therapies is that the two therapies combine different immunological and tumor biological mechanisms to enhance anti-tumor activity. Moreover, some evidence suggests that targeted therapies can synergistically enhance certain steps of the "cancer-immune cycle" (such as tumor antigenicity and T-cell priming /trafficking/infiltration) in conjunction with immunotherapy. In particular, targeted therapies targeting the mitogen-activated protein kinase pathway and the vascular

endothelial growth factor (VEGF) pathway, represented by drugs such as sunitinib, not only have direct effects on tumor cell growth and tumor angiogenesis but also influence tumor cell antigenicity and intratumoral T-cell infiltration. The impact on immune response of patient goes beyond their scope of action on tumor biology, providing a strong basis for combination therapy. Therefore, the combination of PD-1 monoclonal antibody and anti-angiogenesis therapy is a direction of future studies.

This clinical study involves the recombinant humanized anti-PD-1 monoclonal antibody injection (SHR-1210), a therapeutic biological product in Category 1: innovative biological products developed by Jiangsu Hengrui Pharmaceutical Co., Ltd., which has not been marketed overseas and in China. The efficacy and safety of SHR-1210 have been confirmed in phase 1 studies. Currently, multiple studies on the use of PD-1 antibodies for the treatment of melanoma are ongoing.

This clinical study also involves apatinib mesylate (trade name: Aitan), a small molecule targeted drug developed by Jiangsu Hengrui Pharmaceutical Co., Ltd., which was marketed in 2014. Apatinib is a tyrosine kinase inhibitor of vascular endothelial growth factor receptor (VEGFR) and mainly exerts its anti-angiogenic effects by inhibiting VEGFR in the treatment of malignant tumors. Preclinical studies have shown that its anti-tumor activity is superior to that of similar drugs. In 2014, apatinib was approved for use in patients with advanced gastric adenocarcinoma or gastroesophageal junction adenocarcinoma who had progressed or relapsed after receiving at least two prior systemic chemotherapies.

This study explores novel combination therapies urgently needed in clinical practice, not only laying the foundation for subsequent studies, but also investigating tumor immune-related biomarkers, which have significant scientific and clinical value.

## 2. Study Objectives

### 2.1. Primary objectives

To evaluate the ORR of SHR-1210 in combination with apatinib mesylate in the treatment of patients with advanced mucosal melanoma.

### 2.2. Secondary objectives

1. To observe and evaluate the progression-free survival (PFS), duration of response (DOR), time to response (TTR), disease control rate (DCR), OS, and 6-month/9-month/12-month survival rates in patients with advanced mucosal melanoma treated with SHR-1210 in combination with apatinib mesylate.

2. To evaluate the safety of SHR-1210 in combination with apatinib mesylate in the treatment of patients with advanced mucosal melanoma.

### 2.3. Exploratory objectives

1. To evaluate the predictive, prognostic, and pharmacodynamic exploratory biomarkers in archived and/or fresh tumor tissue and blood samples, and to assess the correlation between these biomarkers and disease progression.

2. To evaluate the quality of life in patients with advanced mucosal melanoma treated with SHR-1210 in combination with apatinib mesylate.

## 3. Study Design

### 3.1. Overall design

As a single-arm, open-label, and single-center clinical study, this study aims to observe and evaluate the efficacy and safety of anti-PD-1 antibody SHR-1210 in combination with apatinib mesylate in patients with advanced mucosal melanoma. The study subjects will be the patients with advanced mucosal melanoma who cannot be cured. The study will enroll approximately 30 patients with advanced mucosal melanoma using ORR as the primary efficacy endpoint. After obtaining informed

consent and signing the informed consent form (ICF), the eligible subjects will continuously receive apatinib 500 mg, orally, once daily, and SHR-1210 200 mg, intravenously (IV), every 2 weeks (q2W). The dose of apatinib will be adjusted according to the patient's tolerance, with a treatment cycle of 4 weeks, until the treatment discontinuation events specified in the protocol occur. After the end of treatment, subjects will undergo post-treatment safety visits and survival follow-up. For subjects who discontinue treatment due to reasons other than disease progression or death, tumor progression follow-up will also be conducted after the end of treatment.

After the subjects are enrolled in the study, safety visits will be conducted before the administration of SHR-1210 on Day 1 and Day 15 of each treatment cycle. Imaging examinations will be performed every 2 cycles during the first 12 treatment cycles to evaluate the efficacy, and every 3 cycles thereafter until the end of treatment, withdrawal of informed consent, or death.

The study will also explore predictive, prognostic, and pharmacodynamic exploratory biomarkers in archived and/or fresh tumor tissue and blood samples, and assess the correlation between these biomarkers and disease progression. For subjects who have signed the ICF for biomarker sample collection, biomarker blood samples and tumor samples will be collected at baseline and during the study, including any potential tumor biopsies performed at baseline.

### 3.2. Methods to reduce bias

#### 3.2.1. Enrollment / randomization / blinding procedures

This study is a single-arm study with continuous enrollment, without randomization and not blinded.

#### 3.2.2. Blinded evaluation

Not applicable.

### 3.2.3. Unblinding

Not applicable.

## 4. Subject Selection and Withdrawal

### 4.1. Inclusion criteria

Patients must meet all of the following inclusion criteria to be enrolled in this study:

1. The patient voluntarily participates in the study and signs the ICF;
2. ≥ 18 years of age, male or female;
3. Clinically diagnosed or pathologically confirmed advanced mucosal malignant melanoma, with at least one measurable lesion that has not undergone local treatment (according to Response Evaluation Criteria in Solid Tumors [RECIST] v1.1 requirements, the measurable lesion should have a long diameter of ≥10 mm or an enlarged lymph node should have a short diameter of ≥15 mm by a spiral computed tomography [CT] or magnetic resonance imaging [MRI] scan);
4. Can swallow tablets normally;
5. Eastern Cooperative Oncology Group (ECOG) score: 0 ~ 1;
6. Expected survival ≥ 12 weeks;
7. The function of vital organs must meet the following requirements (no use of any blood components, cell growth factors, or other corrective therapeutic drugs is allowed within 14 days prior to the first administration of the investigational drug):
   - Absolute neutrophil count ≥ $1.5 \times 10^9$/L;
   - Platelets ≥ $80 \times 10^9$/L;
   - Hemoglobin ≥ 90 g/L;
   - Serum albumin ≥ 30 g/L;

- Thyroid stimulating hormone (TSH) ≤ 1× upper limit of normal (ULN) (in case of abnormality, free triiodothyronine [FT3] and free thyroxine [FT4] levels should be evaluated simultaneously; if FT3 and FT4 levels are within the normal range, the subject can be included in the study);
- Bilirubin ≤ 1.5 × ULN (within 7 days prior to the first administration of the investigational drug);
- Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) ≤ 1.5 × ULN (within 7 days prior to the first administration of the investigational drug);
- Serum creatinine ≤ 1.5 × ULN;

8. For female patients who are non-surgically sterilized or of childbearing potential, they are required to use a medically approved contraceptive method (such as an intrauterine device, contraceptive medication, or condom) during the study treatment period and within 3 months after the end of the study treatment. Non-surgically sterilized women of childbearing potential must have a negative serum or urine human chorionic gonadotrophin (HCG) test within 72 hours prior to study enrollment, and must be non-lactating. For male patients with female partners of childbearing potential, effective contraception should be used during the study period and within 3 months after the last administration of SHR-1210.

**4.2. Exclusion criteria**

Patients with any of the following conditions will be excluded from the study:

1. Patients who have any active autoimmune diseases or a history of autoimmune diseases (including, but not limited to: autoimmune hepatitis, interstitial pneumonia, uveitis, enteritis, hepatitis, hypophysitis, vasculitis, nephritis, hyperthyroidism, vitiligo, asthma (patients with asthma that has completely

resolved in childhood and requires no any medical intervention in adulthood can be included; patients with asthma requiring medical intervention with bronchodilators cannot be included);

2. Patients who are receiving immunosuppressive agents or systemic hormonal therapy for immunosuppression (at doses > 10 mg/day prednisone or other equivalent hormonal therapy) and are still on treatment within 2 weeks prior to enrollment;
3. Severe allergic reactions to other monoclonal antibodies;
4. Patients with hypertension that cannot be well controlled with antihypertensives (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg);
5. Uncontrolled clinical symptoms or disease of the heart, such as:
   - New York Heart Association (NYHA) grade 2 or higher heart failure
   - Unstable angina
   - Myocardial infarction within 1 year
   - Clinically significant supraventricular or ventricular arrhythmias requiring treatment or intervention
   - QTc > 450 ms (male); QTc > 470 ms (female);
6. Abnormal coagulation function (international normalized ratio [INR] > 2.0, prothrombin time [PT] > 16 s), with a bleeding tendency or currently receiving thrombolytic or anticoagulant therapy (the prophylactic use of low-dose aspirin and low molecular weight heparin is allowed);
7. Within 3 months prior to enrollment, subjects with significant clinically relevant bleeding symptoms or a clear bleeding tendency, such as hemoptysis (≥ 2.5 mL/day), gastrointestinal bleeding, esophageal and gastric varices with a risk of bleeding, hemorrhagic gastric ulcers, or vasculitis. If fecal occult blood is

positive at baseline, it can be retested. If it remains positive after retesting, a gastroscopy is required. Patients with severe esophageal and gastric varices indicated by gastroscopy cannot be enrolled (except for those who have undergone gastroscopy within 3 months prior to enrollment to exclude such conditions);

8. Arterial/venous thrombotic events within 6 months prior to enrollment, such as cerebrovascular accidents (including transient ischemic attacks, hemorrhage brain, cerebral infarction), deep vein thrombosis, and pulmonary embolism;
9. Known inherited or acquired bleeding and thrombophilia (such as hemophilia, coagulation disorders, and platelets decreased);
10. Urine protein ≥ ++ indicated by urinalysis and confirmed 24-hour urine protein amount > 1.0 g;
11. Patients who have previously received radiotherapy, chemotherapy, hormonal therapy, or surgery and have not completed the treatment (last medication) 4 weeks before the initiation of the investigational drug; patients who have received molecular targeted therapy (including other oral targeted drugs in clinical studies) within less than 5 drug half-lives prior to the first administration of the investigational drug, or patients whose AEs (except alopecia) caused by previous treatments have not recovered to ≤ CTCAE grade 1;
12. Patients with active infections, unexplained fever ≥ 38.5℃ within 7 days prior to medication, or baseline white blood cell count > $15\times10^9$/L; or those with purulent and chronic infections, and prolonged wound healing;
13. Patients with bone metastases who have received palliative radiotherapy to an area > 5% of the bone marrow area within 4 weeks prior to participating in this study;

14. Patients who have previously received anti-PD-1, anti-PD-L1, anti-PD-L2 therapy or apatinib treatment;
15. Known allergy to recombinant humanized anti-PD-1 monoclonal antibody drugs and their components;
16. Patients with cutaneous melanoma, ocular melanoma, and melanoma of unknown primary origin;
17. Patients with severe local invasion of the primary lesion in mucosal malignant melanoma, and with a risk of organ leakage, major bleed, or perforation;
18. Pregnant or lactating women, or female patients of childbearing potential who have not taken contraceptive measures;
19. Patients with other malignant tumors at the same time;
20. Patients who participate in another clinical study at the same time;
21. Patients with positive human immunodeficiency virus (HIV) or hepatitis C virus (HCV); Individuals who are positive for HBsAg or HBcAb and have detectable hepatitis B virus (HBV) DNA copy number (quantitative detection limit is 500 IU/mL);
22. Patients who have received live vaccine within 4 weeks prior to the initiation of treatment;
23. Other severe, acute, or chronic medical or mental diseases or laboratory abnormalities that may increase the risk associated with study participation or may interfere with the interpretation of study results as judged by the investigators.

### 4.3. Withdrawal from the study or termination of study treatment

#### 4.3.1. Discontinuation criteria

1. The subject withdraws informed consent and requests withdrawal;
2. For patients identified with progressive disease by imaging:
3. According to the RECIST v1.1 criteria, if disease progression is observed for the first time, confirmation is required 4 ~ 6 weeks later (except for rapid progression and significant clinical progression);
4. Upon confirmation of disease progression in the subject, if the clinical symptoms are stable, the investigator may decide to continue treatment until further radiographic progression is observed;
5. Stable clinical symptoms are defined as the following:

a. No significant clinical symptoms or changes in laboratory test indicators;

b. No change in performance status score (no worsening);

c. Rapid progression of non-tumor and tumor progression not involving vital organs/sites (such as spinal cord compression);

6. When the cumulative usage of SHR-1210 reaches 2 years (without radiographic progression) and the radiographic examination confirms a complete response (CR), the medication may be considered for discontinuation after completing 12 treatment cycles;
7. Intolerant of toxicity;
8. Poor subject compliance;
9. The subject is lost to follow-up or becomes pregnant;
10. Other circumstances that, in the opinion of the investigator, a withdrawal from the study is necessary.

**4.3.2. Procedures for withdrawal from the study or termination of study treatment**

It is essential to diligently complete the efficacy and safety assessments specified in

the protocol when withdrawing from the study, as well as to complete the safety follow-up period, and comprehensively record AEs and their outcomes.

The investigator may suggest or provide new or alternative treatment methods to the study subjects based on their actual conditions.

Patients without disease progression should continue to be followed up for radiological evaluation until the subject starts a new anti-tumor treatment or disease progression. If a subject refuses to come to the study site for further visits, his/her survival status should still be followed up, unless the subject withdraws consent for further disclosure of information or further contact. In such cases, no further study evaluations should be conducted, and no additional data should be collected. The sponsor may retain and continue to use all data collected before the subject withdraws his/her informed consent, unless the subject requests the withdrawal of the already collected information.

**4.4. Premature termination or suspension of the study**

Discontinuation criteria for this study include, but are not limited to, the following:

1. Identify unexpected, significant, or unacceptable risks to patients;
2. Major errors in the protocol are found during the implementation of the study;
3. Investigational drug/therapy is ineffective, or continuing the study is meaningless;
4. The sponsor decides to terminate the study due to reasons such as severe delays in patient enrollment or frequent protocol deviations.

**4.5. Definition of end of study**

Six months after the last patient's first administration of the investigational drug, the study will be ended, and statistical analysis will be conducted on the primary and secondary endpoints of the study.

All patients will be followed up until 12 ~ 24 months after the last patient has received

the medication, and a supplementary analysis will be conducted on the primary and secondary endpoints of the study after the follow-up is completed.

After the completion of the study, if the patient continues to benefit, they may continue to use the investigational drug until they meet the treatment discontinuation criteria. The serious adverse events (SAEs) will be collected and recorded during the medication period and after the last administration in accordance with the protocol.

## 5. Study Medication

### 5.1. Overview of investigational product

#### 5.1.1. Methods of access to study drugs

The investigational product, SHR-1210 for injection, is produced by Suzhou Suncadia Biopharmaceuticals Co., Ltd., and is uniformly packaged and has passed inspection (see corresponding certificate of analysis).

Apatinib is produced by Jiangsu Hengrui Pharmaceutical Co., Ltd., and is uniformly packaged and has passed inspection (see corresponding certificate of analysis).

Concomitant medications for AEs and prophylactic medications are non-investigational drugs and are not provided by the sponsor. These drugs are marketed products purchased by the study site and are stored according to the package insert or summary of product characteristics.

#### 5.1.2. Dosage form, appearance, packaging, and labeling of the investigational product

Investigational product: SHR-1210 for Injection

Manufacturer: Suzhou Suncadia Biopharmaceuticals Co., Ltd.

Dosage form: Lyophilized powder

Strength: The tentative strength for this product is 200 mg, packaged in a 20 mL vial.

Batch No.: See drug label

Usage: Intravenous infusion

Expiry date: The shelf life is tentatively set for 2 years from the date of manufacture.

Storage conditions: sealed, protected from light, and stored in a medical refrigerator at 2~ 8℃, and the product should not be frozen.

Dispensing strength and quantity of SHR-1210 drug: 200 mg/20 mL vial, 1 vial per small box, 20 small boxes per large box.

The labeling of the investigational product will be conducted in accordance with the Good Clinical Practice (GCP) guidelines. The content of the label should include, but not be limited to: clinical approval number, study title, drug name, drug code, packaging strength, manufacturing batch number, expiration date, dosage and administration, drug storage conditions, and the statement "For Clinical Study Use Only".

Investigational Product Label (for illustration purposes only, subject to the actual label):

A Clinical Study of Anti-PD-1 Antibody SHR-1210 in Combination with Apatinib Mesylate for the Treatment of Advanced Mucosal Malignant Melanoma

For clinical study use only

Drug Name: SHR-1210 for Injection

Clinical Study Number: SHR-1210-APTN-MM

Clinical Study Approval Number: 2016L01455

Indication: Advanced mucosal malignant melanoma

Strength: Lyophilized powder for injection, 200 mg/vial

Usage: Configured in accordance with the Pharmacy Manual, for intravenous use only

Drug Number _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

Storage: store at 2 ~ 8℃, protected from light. Batch number: Expiration date: 20XX (year) XX (month) XX (day)

Manufacturer: Suzhou Suncadia Biopharmaceuticals Co., Ltd.

### 5.1.3. Storage and stability of study drugs

The investigator, or his/her authorized representative (e.g., pharmacist), will ensure that all study drugs are stored in a secure area with controlled access, in compliance with storage conditions, and in accordance with applicable regulatory requirements.

The investigational drug should be stored in its original container and as indicated on the drug label. If the storage conditions on the label and in other materials of the investigational drug (such as the Pharmacy Manual) are inconsistent, the storage conditions on the label shall prevail.

The study site must be able to measure and record the daily maximum and minimum temperatures at all storage locations (such as frozen, refrigerated, or room temperature). The recording period should start from the receipt of the investigational drug until the end of the study. Even with continuous monitoring system in place, the study site should maintain a record log to ensure proper storage temperatures. Temperature monitoring devices and storage devices (such as refrigerators) should be regularly inspected to ensure proper functioning.

Once any deviation from the conditions on product label occurs, it should be reported promptly upon discovery. The investigator should actively take measures to return the investigational drug to the storage conditions described on the label as soon as possible. Meanwhile, the temperature deviation and the measures taken should be reported to the sponsor.

Investigational drugs affected by temperature deviations must be temporarily separated until permission is granted by the sponsor to continue their use, and this will not be considered as a protocol deviation. If the affected investigational drugs are used without the sponsor's permission, it is considered a protocol deviation. The sponsor will provide the study site with specific procedures for reporting temperature

deviations.

### 5.1.4. Preparation of study drugs

SHR-1210 should be prepared by qualified or experienced investigators, such as physicians, pharmacists, or medical assistants (as permitted by national or institutional operating guidelines), based on the pharmacy manual and package insert of commercially available drugs. For the mixing method and concentration (preparation) of the dosing solution and its usage, please refer to the SHR-1210 Pharmacy Manual. Since this product does not contain any preservatives or antimicrobial agents with antimicrobial activity, it is essential to be cautious and ensure that the prepared solution is sterile.

The total storage period for prepared SHR-1210 solution (total time stored in the refrigerator and at room temperature) must not exceed 24 hours after preparation. For detailed information on the storage and use time of the prepared drug solution at room temperature/light exposure and in the refrigerator, please refer to the Pharmacy Manual. Expired or remaining drug solution must be discarded.

### 5.1.5. Method of use of study drugs

SHR-1210 is an intravenous injection, which must be administered by qualified or experienced study personnel in the outpatient department or ward of the study site. It is not allowed to be taken out of the study site for use.

Within 72 hours prior to each administration, except for imaging examinations, the subjects must complete all necessary clinical examinations to assess the tolerability of further medication use.

SHR-1210 will be administered via intravenous infusion for 30 minutes (not less than 20 minutes and not more than 60 minutes, including the flushing phase).

Intravenous and rapid bolus injections should not be allowed.

Intravenous will be performed through a medical infusion bag using an infusion set with an online filter (0.2 μM).

Before and after the infusion, do not administer other medications through the infusion pathway.

Apatinib mesylate tablets are an oral formulation. The investigator will prescribe them for the patients, who will be responsible for obtaining their own supply. The tablets should be taken orally after a meal, as detailed in the dosing regimen.

**5.1.6. Precautions for special dosing equipment**

The study site must also obtain intravenous infusion bags, diluents, and micron-level filters in the infusion lines (i.e., 0.2/1.2 μm); the required filters are detailed in the Pharmacy Manual.

**5.2. Dosing regimen**

SHR-1210 will be administered via intravenous infusion (no prophylactic medication required) at a fixed dose of 200 mg, and 3 mg/kg for patients weighing < 50 kg at baseline. Each infusion will last for 30 minutes (no less than 20 minutes, no more than 60 minutes), and the drug will be administered once every 2 weeks, with 4 weeks for one cycle and the maximum cumulative treatment duration of 2 years.

During the study period, SHR-1210 will be administered once every 2 weeks, with a dosing window of ±3 days from the scheduled dosing time. If the administration of SHR-1210 is delayed by more than 3 days from the scheduled dosing time, the dose will not be given for that time, and the original dose will be given at the next scheduled dosing time.

Apatinib will be taken orally after a meal, once daily, with 2 tablets per dose (250 mg per tablet). The dose of apatinib will be adjusted according to the patient's tolerance, with continuous administration and 4 weeks for one cycle.

Definition of "Administration after a meal": Administration within 30 minutes of the end of meal.

Patients will receive the investigational drug until the treatment discontinuation criteria specified in the protocol are met.

**5.3. Dose modifications**

During the study period, dose modifications of the investigational drug can be made based on its toxic side effects, including: dose interruption, dose reduction, modification of administration mode, and dose termination.

Dose interruption is allowed for SHR-1210, with a maximum allowable drug interruption of 12 weeks.

In addition to dose interruption, for subjects whose weight decreases to below 50 kg during the treatment period, the dose of SHR-1210 may be down-titrated to 3 mg/kg q2w, as appropriate.

Dose modifications due to apatinib-related toxicity include: dose interruption, dose reduction, modification of administration mode (first modification: 5 days on treatment and 2 days off; second modification: 7 days on treatment and 7 days off), and dose termination. During the study, after adjusting the administration mode of apatinib, the recovery of dose mode will not be allowed.

During the study, if definite apatinib-related AEs occur, such as hypertension, proteinuria, hand and foot syndrome (HFS), apatinib administration may be down-titrated or interrupted. After toxicity recovery, the original dose, adjusting the administration method, or terminating the dose may be given as appropriate. After discontinuing apatinib, the study subjects may continue to receive SHR-1210 monotherapy.

During the study, if immune-related toxicities occur, such as immune pneumonia,

hepatitis, enteritis, the administration of SHR-1210 and apatinib should be suspended as appropriate. Once the toxicity has recovered to ≤ grade 1 or baseline levels (for the increase of laboratory parameters such as ALT/AST and total bilirubin [TBIL]), the medication can be resumed. The administration of SHR-1210 should be resumed first, and after 14 days of observation without significant abnormalities, the administration of apatinib can be initiated and the mode of subsequent administration of apatinib will be adjusted.

During the study, if ≥ grade 3 immune pneumonia, ≥ grade 3 TBIL increased, grade 4 ALT/AST increased, or other grade 4 immune-related toxic reactions, grade 4 injection reactions occur, or if the immune-related toxicity causes a temporary suspension of SHR-1210 administration for more than 12 weeks and still cannot recover to ≤ grade 1 or baseline level, SHR-1210 must be permanently discontinued.

During the study, if ≥ grade 3 capillary hyperplasia occurs, no dose modifications are required for apatinib, and SHR-1210 should be suspended until the toxicity recovers to ≤ grade 2.

During the study, if the subject exhibits abnormal symptoms/signs or laboratory indicators, symptomatic treatment should be taken promptly, and it is recommended to refer to the following table for corresponding dose modifications:

**Table 1 Dose Modifications**

| Drug-related Toxicity | | Grading | Dose Interrupted or Not | | Criteria for Resumption of Dosing | Dose Modification Methods for Apatinib | Discontinuation Criteria |
|---|---|---|---|---|---|---|---|
| | | | SHR-1210 | Apatinib | | | |
| SHR-1210 and apatinib-related toxicities | Hematologic toxicity | Grade 1 and 2 | No | No | - | - | - |
| | | Grade 3 | Yes | Yes | When toxicity recovers to ≤ grade 2 | Original dose | After two modifications, if ≥ grade 3 hematologic toxicity occurs again, the administration of apatinib will be terminated. |
| | | Grade 4 | Yes | Yes | When toxicity recovers to ≤ grade 2 | First modification: Adjust to 5 days on treatment and 2 days off; Second modification: Adjust to 7 days on treatment and 7 days off; | |
| | Immune-rel | Grade 2 | Yes | No | When toxicity recovers | First modification: Resume | Unable to recover to ≤ grade |

| Drug-related Toxicity | Grading | Dose Interrupted or Not | | Criteria for Resumption of Dosing | Dose Modification Methods for Apatinib | Discontinuation Criteria |
|---|---|---|---|---|---|---|
| | | SHR-1210 | Apatinib | | | |
| ated pneumonia | | | | to ≤ grade 1 | at original dose<br>Second modification: Adjust to 5 days on treatment and 2 days off;<br>Third modification: Adjust to 7 days on treatment and 7 days off | 1 after > 12 weeks of discontinuation |
| ALT/AST and TBIL increased (after receiving | Grade 2 ALT or AST increased<br>Grade 2 bilirubin | Yes | Yes | When toxicity returns to baseline | First modification: Adjust to 5 days on treatment and 2 days off;<br>Second modification: Adjust to 7 days of on treatment | 1. If discontinuation of the drug for >12 weeks still does not result in recovery to baseline levels, then terminate the use of |

| Drug-related Toxicity | Grading | Dose Interrupted or Not | | Criteria for Resumption of Dosing | Dose Modification Methods for Apatinib | Discontinuation Criteria |
|---|---|---|---|---|---|---|
| | | SHR-1210 | Apatinib | | | |
| hepatoprotective treatment) | increased | | | | and 7 days off; | SHR-1210. |
| | Grade 3 ALT / AST increased | Yes | Yes | When toxicity returns to baseline | First modification: Adjust to 7 days on treatment and 7 days off;<br>Second modification: Permanently discontinue apatinib | 1. If discontinuation of the drug for >12 weeks still does not result in recovery to baseline levels, then terminate the use of SHR-1210.<br>2. If grade 3 ALT/AST increased occurs again, then terminate the use of |

| Drug-related Toxicity | | Grading | Dose Interrupted or Not | | Criteria for Resumption of Dosing | Dose Modification Methods for Apatinib | Discontinuation Criteria |
|---|---|---|---|---|---|---|---|
| | | | SHR-1210 | Apatinib | | | |
| | | | | | | | SHR-1210. |
| | Other nonhematologic toxicities | Grade 1 | No | No | - | - | - |
| | | Grade 2 (lasting for ≥ 7 days) | Yes | Yes | When toxicity recovers to ≤ grade 1 | Original dose | Unable to recover to ≤ grade 1 after > 12 weeks of discontinuation |
| | | Grade 3 | Yes | Yes | When toxicity recovers to ≤ grade 1 | First modification: Adjust to 5 days on treatment and 2 days off; Second modification: Adjust to 7 days on treatment and 7 days off; | |
| SHR-1210 | Capillary | Grade 3 | Yes | No | When toxicity recovers | Original dose | > 12 weeks of SHR-1210 |

| Drug-related Toxicity | | Grading | Dose Interrupted or Not | | Criteria for Resumption of Dosing | Dose Modification Methods for Apatinib | Discontinuation Criteria |
|---|---|---|---|---|---|---|---|
| | | | SHR-1210 | Apatinib | | | |
| -related toxicities | hemangioma | | | | to ≤ grade 2 | | discontinuation |
| Apatinib-related toxicities | Hypertension | Grade 3 (After corrective treatment) | No | Yes | When toxicity recovers to ≤ grade 1 | First modification: Resume at original dose<br>Recurrent grade 3 hypertension: Adjust to 5 days on treatment and 2 days off for apatinib.<br>The third occurrence of grade 3 hypertension: Adjust to 7 days on treatment and 7 days off for apatinib. | After two modifications, grade 3 hypertension occurs again, and the administration of apatinib will be terminated. |

| Drug-related Toxicity | Grading | Dose Interrupted or Not | | Criteria for Resumption of Dosing | Dose Modification Methods for Apatinib | Discontinuation Criteria |
|---|---|---|---|---|---|---|
| | | SHR-1210 | Apatinib | | | |
| | Hypertensive crisis | Yes | Yes | When toxicity recovers to ≤ grade 1 | Permanently discontinue apatinib | Discontinue apatinib |
| Proteinuria (Without significant increase in blood creatinine) | Grade 3 (24-h urine protein quantitation) | No | Yes | When toxicity recovers to ≤ grade 2 | Adjust to 5 days on treatment and 2 days off for apatinib; Recurrence of grade 3 proteinuria: Adjust to 7 days on treatment and 7 days off for apatinib. | After two modifications, grade 3 proteinuria occurs again, and the administration of apatinib will be terminated. |
| Hand and foot syndrome | Grade 3 | No | Yes | When toxicity recovers to ≤ grade 1 | Adjust to 5 days on treatment and 2 days off for apatinib; Recurrence of | After two modifications, grade 3 hand and foot syndrome occurs again, and |

| Drug-related Toxicity | | Grading | Dose Interrupted or Not | | Criteria for Resumption of Dosing | Dose Modification Methods for Apatinib | Discontinuation Criteria |
|---|---|---|---|---|---|---|---|
| | | | SHR-1210 | Apatinib | | | |
| | | | | | | grade 3 hand and foot syndrome: Adjust to 7 days on treatment and 7 days off for apatinib. | the administration of apatinib will be terminated. |
| | Headache | After symptomatic treatment, the duration of grade 2 headache is ≥7 days, or grade 3 | No | Yes | When toxicity recovers to ≤ grade 1 | Adjust to 5 days on treatment and 2 days off for apatinib; Recurrence: Adjust to 7 days on treatment and 7 days off for apatinib | Recurrence after two modifications, discontinue apatinib |

| Drug-related Toxicity | | Grading | Dose Interrupted or Not | | Criteria for Resumption of Dosing | Dose Modification Methods for Apatinib | Discontinuation Criteria |
|---|---|---|---|---|---|---|---|
| | | | SHR-1210 | Apatinib | | | |
| | | headache | | | | | |

During the study, if a subject experiences significant toxicity that persists after symptomatic treatment, including grade 2 non-hematologic toxicity lasting for 2 weeks or more (excluding asymptomatic grade 2 hypertension) and abnormal laboratory test results (excluding proteinuria < 2 g/24 h), the investigator may consider, based on the subject's tolerance, to temporarily discontinue the medication and, after toxicity recovery, to choose a reduced dose of apatinib or adjust the administration mode of apatinib in subsequent study stages.

During the study, the investigator may make appropriate dose modifications in accordance with the above-mentioned dose modifications, taking into account the occurrence of drug-related toxicities in the subjects. For example, if a subject experiences multiple grade 2 drug-related toxicities and has poor tolerance to the study drug, the investigator may adjust the administration mode or reduce the dose of apatinib after temporarily discontinuing the drug and the toxicities have resolved.

During the study, if a subject experiences fever (> 38℃, requiring corrective treatment), or significant symptoms of gasping, polypnoea, breathlessness, the administration of SHR-1210 will not be given at the current or next scheduled dose time until the symptoms have resolved. After the symptoms have relieved and stabilized for more than 7 days, the administration of SHR-1210 will be resumed according to the subsequent planned schedule. If necessary, pneumonia should be ruled out by imaging examination before administration.

During the study period, if any of the following occurs: hypertensive crisis, hemorrhage brain, ≥ grade 2 pulmonary hemorrhage, ≥ grade 3 other hemorrhages, arterial thrombosis, grade 4 venous thrombosis, leukoencephalopathy syndrome, or gastrointestinal perforation, the administration of apatinib should be terminated, and the administration of SHR-1210 should be suspended. Active symptomatic treatment

should be provided, and the decision to continue SHR-1210 treatment will be based on the recovery status of the toxicity in the subject.

### 5.4. Management, dispensing and recovery of study drugs

In this study, the management, dispensing, and recovery of the study drugs are the responsibility of the designated study nurse at the study site. The investigator must ensure that all study drugs are used only for subjects in this study, and their dosage and administration should follow the study protocol. The expired or remaining drug solutions should be disposed of according to medical waste standards. It is prohibited to hand over the study drugs to any person not participating in the clinical study. The study drugs should be stored as per the label requirements. The investigator is responsible for monitoring the supply, use, storage of study drugs, and the disposal of remaining drugs in the clinical study.

### 5.5. Concomitant therapies

Concomitant therapies refer to the treatments other than the study treatment, given at the discretion of the investigator for the purpose of a subject's interests.

The concomitant medications and therapies received by the subjects within 30 days prior to the initiation of the study drugs and during the study period should be recorded in the case report form (CRF) in strict accordance with GCP requirements.

Only concomitant medications and concomitant therapies used for newly occurring or unresolved AEs related to the study treatment should be recorded if a subject discontinues the study treatment. The recording should be made until at least 30 days after the last administration.

#### 5.5.1. Other anti-tumor / anti-cancer drugs or study drugs

During the administration of the investigational drug, the study subject will not be

allowed to receive any other anti-tumor treatments.

Concurrent use of the listed anti-tumor traditional Chinese medicines is not allowed: Huatan Huisheng tablets, Yadanziyou soft capsules, Zhemu sugar syrup, Banmao, Huachansu, Chansu, Kang'ai injection, Kanglaite, Zhongjiefeng injection, Aidi injection, Awei Huapi plaster, Kangaiping pills, Fukang capsules, Xiaoaiping, Pingxiao capsules, Pingxiao tablets, Candan Sanjie capsules, Ankangxin capsules, Bosheng Aining, zedoary turmeric oil and glucose injection, Kanglixin capsules, Cidan capsules, Huaier granules, Delisheng injection, and other traditional Chinese medicine preparations that explicitly state "anti-tumor" effects in their package inserts.

#### 5.5.2. Supportive care

Palliative and supportive care for disease-related symptoms will depend on the investigator's judgment and relevant guidelines.

During the treatment period, the subjects should be given the best supportive care. The clinical comorbidities and various adverse reactions should be actively treated and managed, especially for the immune-related adverse reactions.

#### 5.5.3. Immunologic agents

Concurrent use of thymalfasin, interferon, interleukin-2, and other immunologic agents is not permitted in this study.

#### 5.5.4. Drugs with potential drug-drug interactions with apatinib

*In vitro* studies have shown that apatinib is primarily metabolized by the hepatic P450 enzyme CYP3A4 and has strong inhibitory effects on CYP3A4 and CYP2C9, as well as moderate inhibitory effects on CYP2C19. During treatment, the CYP3A4 inducers (dexamethasone, carbamazepine, rifampin, and phenobarbital) should be used with caution and strong CYP3A4 inhibitors (ketoconazole, itraconazole, erythromycin, and clarithromycin) should be prohibited.

During the study period, prohibited CYP3A4 substrates (drugs with a narrow safety window and potentially severe adverse reactions when metabolism is affected) include, but are not limited to:

- Hypoglycemic agents: tolbutamide, chlorpropamide
- Ergot derivatives: dihydroergotamine, ergometrine, ergotamine, methylergonovine (potential risk of ergotism, including peripheral and cerebral ischemia caused by severe vasospasm)
- Antipsychotic drugs: pimozide (potential increased risk of QT interval prolongation)
- Antiarrhythmic drugs: amiodarone (prohibited for 6 months prior to randomization), bepridil, flecainide, lidocaine, mexiletine, quinidine, propafenone
- Immunomodulators: cyclosporine, tacrolimus, sirolimus (potential increased risk of nephrotoxicity and neurotoxicity)
- Miscellaneous: quetiapine, risperidone, clozapine, atomoxetine hydrochloride

During the study period, if warfarin is used for anticoagulation, the dosage should be considered for reduction, and close monitoring should be conducted. If necessary, discontinuation of the study drugs should be considered.

#### 5.5.5. Drugs causing QT interval prolongation

Due to the toxic and side effects of prolonging the QT interval of tinib drugs in clinical use, drugs that prolong the QT interval should be used with caution during the study. This mainly includes, but is not limited to, the following categories of drugs:

- Antibiotics: fluoroquinolones: sparfloxacin, gatifloxacin, levofloxacin, moxifloxacin, ofloxacin, ciprofloxacin; macrocyclic lipids: erythromycin, clarithromycin, telithromycin, azithromycin, roxithromycin, metronidazole
- Antiarrhythmic drugs: quinidine, procainamide, disopyramide, flecainide,

propafenone, amiodarone, dronedarone, sotalol, dofetilide, ibutilide

- Angina pectoris relievers: ranolazine, ivabradine
- Antipsychotic drugs: risperidone, fluphenazine, droperidol, haloperidol, thioridazine, pimozide, olanzapine, clozapine
- Antifungals: voriconazole, posaconazole
- Antimalarials: mefloquine, chloroquine
- Antihistamines: terfenadine, astemizole, hydroxyzine
- Gastrointestinal drugs: antiemetics: ondansetron, granisetron, dolasetron, droperidol (0.625 to 1.25 mg may be a safe dose), hydroxyzine; prokinetic drugs: cisapride, domperidone, metoclopramide
- Antidepressants: amitriptyline, imipramine, clomipramine, dosulepin, doxepin

**6. Study Procedures**

Before initiating the study, patients must read and sign the currently approved ICF by the Ethics Committee (EC). All tests and study procedures will be performed according to the Study Flow Chart and will not be affected by the duration of drug discontinuation. However, changes within the test window are allowed due to festivals, holidays, or other administrative reasons.

**6.1. Screening (D-21 to D-1)**

Unless specifically indicated, the following screening procedures must be completed within 21 days prior to the first administration of the study drug:

[Signing Informed Consent] Before conducting any clinical study procedures, written consent must be obtained in advance.

[Demographic Data] Gender, date of birth, ethnicity, height, weight.

[Tumor History]

(1) Tumor diagnosis: Clinical diagnosis before enrollment, date of first pathological

confirmation, first pathological diagnosis, pathological grade, and clinical stage;

(2) The investigator will obtain the details of the subject's past and current melanoma disease. The CKIT/BRAF/NRAS/PDGFR gene status of the subject's tumor must be collected. If the study site cannot provide this information, the CKIT/BRAF/NRAS/PDGFR gene status of the tumor will be tested during the screening period at the study site or central laboratory.

[Past Medical History] Disease name, diagnosis date, treatment drug name, whether it is ongoing, and history of tumors other than malignant melanoma.

[Concomitant Medications] The concomitant medications and therapies will be recorded within 30 days prior to the initiation of the study drug and during the study period. Only concomitant medications and concomitant therapies used for newly occurring or unresolved AEs related to the study treatment should be recorded if a subject discontinues the study treatment. The recording should be made until at least 30 days after the last administration. If a new anti-tumor treatment is initiated within 30 days, only concomitant medications used for AEs related to the study drug should be recorded.

[Thyroid Function] FT3, FT4 and TSH.

[Pituitary-Adrenal Axis Assessment] includes adrenocorticotropic hormone, cortisol, and follicle-stimulating hormone.

[HIV Test] HIV antibody test.

[Hepatitis Panel] Hepatitis B "two half-and-half" examination: If the test results are abnormal, HBV DNA quantification and HBsAg quantitative tests should be performed; hepatitis C virus antibody (anti-HCV): For those with positive anti-HCV antibodies, HCV RNA testing must be conducted; For subjects with abnormal baseline HBsAg, HBV DNA quantification and HBsAg quantitative tests should be performed

on Day 1 ± 7 days every 2 cycles and at the end of the study.

[Pregnancy Test] The women of childbearing potential are required to undergo serum or urine pregnancy testing.

[Adverse Events] AEs should be recorded from the time of signing the informed consent until at least 30 days after the last administration of the drug, and followed up until the AE is resolved or stabilized. It is necessary to follow up on SAEs and immune-related adverse events (irAEs) within 90 days after the last administration of SHR-1210. If the patient starts a new anti-tumor treatment, follow-up should be performed until the initiation of the anti-tumor treatment (if it starts within 30 days after the last administration, follow-up should be performed for at least 30 days after the last administration; if it starts after 30 days, follow-up should be performed until the initiation of the anti-tumor treatment).

[Imaging Examination] The investigator will conduct imaging examinations based on the patient's condition, including enhanced CT or MRI of the lesion site, chest, abdomen, and pelvis. During the screening, subjects must undergo enhanced MRI or CT of the brain. The baseline tumor assessment during the screening can be extended to within 3 weeks before treatment. CT/MRI results obtained before signing the informed consent, as long as they meet the requirements, can be used for tumor assessment at screening. A bone scan examination is required when there is clinical suspicion of bone metastasis.

[Samples Collection for Biomarkers Analyses] The existing paraffin-embedded tumor tissue samples or the fresh biopsy specimens (soybean-sized) will be collected. At least 10 sections should be prepared, among which 3 ~ 5 sections of 3 ~ 5 μm thickness will be used for PD-L1 determination, and 5 ~ 8 paraffin sections of 8 ~ 10 μm thickness (no cell slides are acceptable, and paraffin rolls can be collected directly )

or fresh biopsy specimens (soybean-sized) will be used for the determination of biomarkers such as tumor mutational burden (TMB). For tumor sample collection and handling methods, please refer to the Laboratory Manual.

Unless specifically indicated, the following screening procedures must be completed within 7 days prior to the first administration of the study drug:

[Hematology] white blood cell count (WBC), absolute neutrophil count (ANC), lymphocyte count (LYM), hemoglobin (Hb), platelet count (PLT);

[Urinalysis] Urine protein and occult blood; if the semi-quantitative results show protein 2+ for two consecutive times, a 24-hour urine protein quantitative test should be performed;

[Stool Routine] If fecal occult blood is positive, a re-examination is required. If fecal occult blood remains positive after re-examination, a gastroscopy is required;

[Blood Chemistry] ALT, AST, AKP, γ-GT, LDH, creatinine, potassium, sodium, blood lipase (only performed during the screening period and when abdominal pain, bloating, or other suspected pancreatitis symptoms occur), blood amylase (only performed during the screening period and when abdominal pain, bloating, or other suspected pancreatitis symptoms occur);

[Coagulation Function] includes INR, APTT, PT, and FIB;

[Myocardial Zymogram Examination] includes CK, CK-MB, α-hydroxybutyrate dehydrogenase, LDH, AST;

[Lymphocyte Subsets] include T cell subsets (CD3+, CD4+, CD8+), natural killer cells (CD16/56+), immunoglobulins (IgG, IgA, IgM); complement (C3) (to be performed within 14 days prior to treatment);

[Vital Signs] temperature, pulse, respiratory rate, blood pressure;

[Blood Pressure Monitoring] During the screening period, the investigator or study

nurse will measure blood pressure for patients. For each blood pressure measurement, smoking and coffee consumption are prohibited within 30 minutes prior to the measurement, and the patient should rest quietly for at least 10 minutes. The measurement should be taken in a seated position, with the elbow at the same level as the heart, and blood pressure should be measured on the same side each time.

[Physical Examination] General condition, head and face, skin, lymph nodes, eyes (sclera, pupils), ears, nose, throat, oral cavity, respiratory system, cardiovascular system, abdomen (including liver and spleen), reproductive-urinary system, musculoskeletal system, nervous system, and mental status; Note: A comprehensive physical examination must be conducted during the study period, and only abnormal findings need to be recorded in the CRF. If there is no change compared with the screening period, there is no need to repeat the recording.

[ECOG Score]

[12-Lead Electrocardiogram] If any abnormalities are identified, two additional confirmations must be performed, or other necessary examinations should be conducted based on the investigator's judgment.

[Echocardiography]

[Blood Collection for Biomarkers Analyses] Ten (10) mL of patient’s blood samples will be collected at baseline, processed and sent according to the Laboratory Manual. The eligibility must be rechecked, patients can only be included in the study if they meet all inclusion criteria and do not meet any exclusion criteria.

**6.2. Study Period**

Cycle 1 Day 1: [Vital Signs] [Physical Examination and Body Weight Measurement] [SHR-1210 Intravenous Infusion] [Apatinib Administration]

Within 24 hours after the first administration of SHR-1210, acute allergic reactions

should be closely monitored. If any occur, treatment should be carried out in accordance with the medical practices and relevant guidelines of this institution.

To improve patient compliance, on Day 1 of the first cycle, only SHR-1210 administration can be performed, and oral apatinib can be initiated on Day 2. The dose of apatinib can be adjusted according to the patient's tolerance, and it should be taken continuously, with 4 weeks for one cycle.

Cycle 1 Day 15: [Hematology] [Blood Chemistry] [Urinalysis] [Stool Routine] [Coagulation Function] [Vital Signs] [Physical Examination and Body Weight Measurement] [Electrocardiogram] [SHR-1210 Intravenous Infusion] [Adverse Events] [Concomitant Medications]

Day 1 in Subsequent Cycles: - [Hematology] [Blood Chemistry] [Urinalysis] [Stool Routine] – [Coagulation Function] [Vital Signs] [Physical Examination and Body Weight Measurement] [ECOG Score] [Electrocardiogram] [SHR-1210 Intravenous Infusion] [Adverse Events] [Concomitant Medications] [Recovery/Dispensing of Apatinib]

Day 15 in Subsequent Cycles: [Hematology] [Blood Chemistry] [Urinalysis] [Vital Signs] [Physical Examination and Body Weight Measurement] [SHR-1210 Intravenous Infusion] [Adverse Events] [Concomitant Medications]

A ±3-day window period will be set, and the intravenous infusion of SHR-1210 should be performed after completing the assessments of examinations and tests specified in the flowchart.

[Imaging Assessment] During the treatment period, imaging examinations should be conducted under the same conditions as the baseline examination (scan thickness, use of contrast agents, etc.). The lesions identified at baseline should be examined every 2 cycles during the first 12 treatment cycles (bone scans should be performed when

bone progression is suspected or CR confirmation is needed), and every 3 cycles thereafter. If new lesions are suspected, timely examinations can be performed. The first partial response (PR)/CR must be confirmed 4 weeks ± 7 days later. If disease progression is observed for the first time according to RECIST v1.1, radiological examination should be performed 4 ~ 6 weeks later for confirmation (except for rapid progression and significant clinical progression).

The allowable window period for imaging examination is ±7 days. Unscheduled imaging examinations can be performed when disease progression is suspected (e.g., worsening of symptoms).

[Thyroid Function Test] The test will be performed on Day 1 ± 7 days of Cycle 2, and performed subsequently once on Day 1 ± 7 days of each following cycle;

[Blood Pressure Monitoring] During the treatment period, blood pressure monitoring will be performed by the patients themselves and recorded in the patient's diary card. In the first two cycles, blood pressure should be measured at least three times per week. If blood pressure is abnormal, daily monitoring is required; if blood pressure is normal, blood pressure should be measured at least twice per week after the first two cycles. Additionally, at each follow-up visit, the investigator or study nurse will measure the patient's blood pressure.

**6.3. End of treatment / withdrawal**

If a patient experiences an event that meets the criteria in "4.3.1 Discontinuation Criteria", the patient's treatment will be terminated. At the end of the study treatment or withdrawal from the study, if the patient has not been examined within 14 days prior to the end of the study, the following tests should be conducted:

[Hematology] [Blood Chemistry] [Urinalysis] [Stool Routine] [Coagulation Function] [Pregnancy Test] [Thyroid Function Test] [Myocardial Zymogram] [Vital Signs]

[Physical Examination] [ECOG Score] [Electrocardiogram] [Blood Pressure Monitoring] [Adverse Events] [Concomitant Medications] [Recovery of Apatinib]

If no imaging examination has been performed within 4 weeks prior to the end of treatment, an imaging examination should be conducted at the end of the study treatment or upon withdrawal from the study for efficacy evaluation. For patients with non-imaging evidence of progression (intolerable, other circumstances), tumor assessments should be performed every 3 months until disease progression, death, or initiation of other anti-tumor treatments.

**6.4. Follow-up**

Thirty (30) days after the termination/completion of treatment (30 days ± 3 days after the last administration of the investigational drug)

[Vital Signs] [Physical Examination] [ECOG Score] [Hematology] [Urinalysis] [Blood Chemistry] [Adverse Events] [Concomitant Medications]

SAEs and irAEs will be followed up within 90 days after the last administration of SHR-1210. If the patient initiates a new anti-tumor treatment, follow-up should be performed until the initiation of the anti-tumor treatment if it starts within 30 days after the last administration, follow-up should be performed until at least 30 days after the last administration; if it starts after 30 days, follow-up should be performed until the initiation of the anti-tumor treatment).

[Survival Follow-up] After the termination of the study treatment, the survival status and subsequent anti-tumor treatment information can be collected every month through clinical follow-up or telephone follow-up until death.

**7. Evaluation**

**7.1. Efficacy evaluation**

**7.1.1. Efficacy endpoints**

The primary efficacy endpoint of this study is the ORR assessed based on RECIST 1.1 criteria.

ORR: It refers to the proportion of subjects who complete at least one efficacy evaluation after treatment and have a best overall response (BOR) of CR or PR according to RECIST 1.1 criteria. If first CR or PR is achieved, the response should be confirmed no less than 4 weeks ± 7 days after the first evaluation.

BOR refers to the best response recorded during the period from the date of initiation of treatment to the date of recorded objective progression according to RECIST 1.1 criteria or the date of initiation of new anti-tumor treatment (whichever occurs first).

For subjects who have not shown documented progression and have not initiated new anti-tumor therapy, the BOR will be determined based on all efficacy assessment results.

For subjects who continue to receive SHR-1210 after progression, the BOR should be determined based on the efficacy evaluation results recorded up to the initial occurrence of progression as defined by RECIST 1.1.

Secondary efficacy endpoints included:

- The ORR assessed by the investigator based on RECIST 1.1 criteria;
- PFS: It is defined as the time from the date of the first administration of the investigational drug to the date of the first documented tumor progression (assessed according to RECIST 1.1 criteria, regardless of whether the treatment is continued) or the date of death due to any cause (whichever occurs first).

In determining PFS, clinical deterioration occurring in the absence of definitive evidence of disease progression (according to RECIST 1.1) is not considered as disease progression. For subjects who have not previously reported progression before death, the death date will be considered as the date of disease progression. Subjects

with neither disease progression nor death will be censored on the date of their last evaluable tumor assessment. Subjects with no tumor assessments during the study and no death will be censored on the date of first treatment. Subjects who discontinue the study due to reasons other than disease progression (without subsequent radiological examination) will be censored at the time of study discontinuation. Subjects who have not previously reported disease progression but initiate subsequent anti-tumor therapy will be censored on the date of the last evaluable tumor assessment before starting subsequent anti-tumor therapy or at the time of initiating subsequent anti-tumor therapy. When subjects are not censored at the time of study discontinuation or the time of initiating subsequent anti-tumor therapy, the prescheduled sensitivity statistical analysis will only further confirm PFS based on the time of radiologically confirmed progression event. The occurrence of new tumors is not considered a disease progression event and is not used for data censoring.

- TTR: It is defined as the time from the date of first administration to the date of the first recorded tumor response (assessed according to RECIST 1.1 criteria).
- DoR: It is defined as the time from the date of first recorded tumor response (assessed according to RECIST 1.1 criteria) to the date of first recorded tumor objective progression (assessed according to RECIST 1.1 criteria) or the date of death due to any cause. Subjects with neither disease progression nor death will be censored on the date of their last tumor assessment. Subjects who start receiving any subsequent anti-tumor treatment (excluding treatment for non-target bone lesions or palliative radiotherapy during the study treatment) and have not previously reported progression will be censored at the time of their last tumor assessment prior to starting subsequent anti-tumor treatment, or on the day of starting subsequent anti-tumor therapy.

- 6-month survival rate: It is defined as the proportion of patients with a survival duration of ≥ 6 months from the date of initial treatment;
- 9-month survival rate: It is defined as the proportion of patients with a survival duration of ≥ 9 months from the date of initial treatment;
- 12-month survival rate: It is defined as the proportion of patients with a survival duration of ≥ 12 months from the date of initial treatment;
- OS: It is defined as the time from the date of first drug administration to the date of death due to any cause. For subjects who are still alive at the last follow-up, their OS data will be censored at the last follow-up. For subjects who are lost to follow-up, their OS data will be censored at the last confirmed survival time before being lost to follow-up. The censored OS is defined as the time from the date of first drug administration to the date of data censoring.

**7.1.2. Efficacy evaluation criteria**

The primary and secondary efficacy endpoints of SHR-1210 in combination with apatinib mesylate in the treatment of advanced mucosal malignant melanoma will be evaluated according to RECIST v1.1.

The lesions identified at baseline should be examined every 2 cycles during the first 12 treatment cycles (bone scans should be performed when there is suspicion of bone progression or when confirming a CR), and every 3 cycles thereafter. This schedule is not affected by interruptions or delays in treatment. If new lesions are suspected, timely examinations can be performed. The first PR or CR must be confirmed 4 weeks ± 7 days later. If disease progression is observed according to RECIST 1.1, imaging examinations should be performed 4 ~ 6 weeks later for confirmation (except for rapid progression and significant clinical progression).

Survival records and assessment: After the treatment withdrawal, the subjects will be

followed up once a month for survival status via telephone, until death, loss to follow-up, withdrawal of informed consent, or termination of the study. The evaluation of tumor response will involve all known or suspected sites of lesions.

Radiological imaging examinations include CT scans or MRI scans of the chest, abdomen, or pelvis; brain CT or MRI scan is used for subjects with known or suspected brain metastases; bone scan is used for subjects with known or suspected bone metastases (see section 7.1 for details on imaging examinations).

If the overall health condition of a subject deteriorates, requiring discontinuation of the medication, but there is no objective evidence of disease progression at this time, it should be reported as symptomatic worsening.

If no imaging examination has been performed within 4 weeks before the end of treatment, an imaging examination should be conducted at the end of the study treatment or upon withdrawal from the study for efficacy evaluation. For patients with non-imaging evidence of progression (intolerable, other circumstances), tumor assessments should be performed every 3 months until disease progression, death, or initiation of other anti-tumor treatments.

### 7.2. Safety evaluation

#### 7.2.1. Adverse events

The incidence and severity of AEs and SAEs will be assessed according to the National Cancer Institute (NCI) - Common Terminology Criteria for Adverse Events (CTCAE) V4.03 criteria.

Dose interruption rate and dose discontinuation rate due to AEs will be calculated.

#### 7.2.2. Laboratory safety evaluation

All laboratory abnormalities with clinical significance or meeting the definitions of AE/SAE should be recorded in the CRF:

In the report, investigators should use clinical terms as much as possible instead of laboratory terms (such as anemia, rather than low hemoglobin value).

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

Vital signs and physical examinations and body weight measurement will be performed according to the study schedule.

During the screening period, a comprehensive physical examination must be conducted, and all examination results must be recorded in the CRF.

During the study, a comprehensive physical examination must be conducted, and only abnormal findings should be recorded in the CRF. If there is no change compared with the screening period, there is no need to repeat the recording.

### 7.3. Biomarkers evaluation

This study will investigate the relationship between the expression level of PD-L1 in tumor tissue and/or peripheral blood samples collected at baseline, the proportion of positive cells, and/or other biomarkers, such as baseline TMB, and the therapeutic efficacy.

## 8. Adverse Events Reporting

### 8.1. Adverse events (AEs)

#### 8.1.1. Definition of AEs

AEs refer to untoward medical events that occur in clinical subjects after receiving a drug, but do not necessarily have a causal relationship with the treatment. In this study, AEs will be collected from the time the subject signs the ICF until at least 30 days after the last administration of the drug. It is required to follow up and collect SAEs and irAEs within 90 days after the last administration of SHR-1210. If the patient starts a new anti-tumor treatment, follow-up will be performed until the initiation of the anti-tumor treatment (if it starts within 30 days after the last administration,

follow-up will be performed until at least 30 days after the last administration of SHR-1210; if it starts after 30 days, follow-up will be performed until the initiation of the anti-tumor treatment). AEs can be any unfavorable and unexpected symptoms, signs, laboratory abnormalities, or diseases, including the following situations:

1) Worsening of pre-existing (prior to entering the clinical study) medical conditions/diseases (including aggravation of symptoms, signs, and laboratory abnormalities);

2) Newly occurring AEs: Any newly occurring adverse medical conditions (including symptoms, signs, newly diagnosed diseases);

3) Abnormal laboratory test values or results with clinical significance that are not caused by concomitant diseases.

Investigators should document any AEs experienced by the subjects in detail, including: description of the AEs and all related symptoms, onset time, severity, cause, relationship to the study drug, duration, measures taken, final results and outcome.

### 8.1.2. Criteria for AE severity

Refer to the NCI-CTCAE 4.03 version for the grading criteria of drug-related AEs. If an AE not listed in the NCI-CTCAE 4.03 version table occurs, refer to the following criteria:

**Table 2 Criteria for AE Severity**

| Grade | Clinical Description of Severity |
|---|---|
| 1 | Mild; asymptomatic or minor clinical symptoms; only clinical or laboratory abnormalities; no treatment required. |
| 2 | Moderate; requiring minor, local, or non-invasive treatment; limitations in age-appropriate instrumental activities of daily living (ADL); instrumental ADL refer to cooking, shopping, making phone calls, and counting money, |

| | |
|---|---|
| | etc. |
| 3 | Severe or medically serious symptoms but not immediately life-threatening; leading to hospitalization or prolongation of hospitalization; disability; limitations in self-care ADL. Self-care ADL refer to bathing, dressing, undressing, feeding self, using the toilet, taking medications, etc., and not being bedridden. |
| 4 | Life-threatening; urgent treatment indicated |
| 5 | Leading to death |

#### 8.1.3. Assessment of the relationship between AEs and study drugs

The possible causality between the AE and the study drug should be assessed using a five-level classification system: "Definitely related," "Possibly related," "Doubtfully related," "Not related," and "Unable to determine". The AEs with the causalities of "Definitely related," "Possibly related," and "Unable to determine" are all considered as adverse drug reactions. When calculating the incidence of AEs, the total number of subjects involved in the three categories will be used as the numerator, and the total number of subjects for safety evaluation will be used as the denominator.

### 8.2. Serious adverse events (SAEs)

#### 8.2.1. Definition of SAEs

SAEs refer to medical events that occur during the clinical study, leading to hospitalization or prolongation of hospital stay, disability, impairment of work capacity, life-threatening condition, death, or congenital malformations, including the following unexpected medical events:

- Events leading to death;
- Life-threatening events (defined as a situation where the subject is at immediate risk of death when the event occurs);

- Events requiring hospitalization or prolongation of hospitalization;
- Events that can lead to permanent or significant disability/incapacity/impairment of work;
- Congenital anomaly or birth defect;
- Other significant medical events (refer to events that are not immediately life-threatening, leading to death or hospitalization, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed in the definition above). Examples of these events include, but are not limited to, the following: allergic bronchospasm requiring intensified treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, potential drug-induced liver injury, suspected transmission of pathogens (such as pathogenic or non-pathogenic pathogens) through the study drug, pregnancy, drug overdose, secondary tumors, and so on.

#### 8.2.2. Hospitalization

In clinical studies, AEs leading to hospitalization or prolongation of hospitalization should be considered as SAEs. Hospitalization does not include the stay in rehabilitation institutions, nursing homes, routine emergency rooms, or for day surgery (such as outpatient/day/ambulatory surgeries). Any hospitalization or prolongation of hospitalization unrelated to the worsening of AEs is not considered as an SAE. For example:

- Hospitalization due to a pre-existing disease without a new AE or exacerbation of the pre-existing disease (such as hospitalization to check for laboratory abnormalities that occurred prior to the study and are still present);

- Hospitalization for administrative reasons (e.g., annual routine physical examination);
- On-study hospitalization as specified in the protocol (e.g., protocol-specified procedures);
- Elective hospitalization unrelated to the worsening of AEs (e.g., elective surgery);
- Pre-scheduled treatment or surgery which should be documented in the study protocol and/or the subject's baseline data;
- Hospitalization for blood product use only.

Any invasive procedures (such as surgery) and non-invasive procedures for diagnosis or treatment should not be reported as an AE. However, if the medical condition leading to the procedure meets the definition of an AE, it should be reported as an AE. For example, acute appendicitis occurring during the AE reporting period should be reported as an AE, while the appendectomy performed as a result should be documented as the treatment of the AE.

#### 8.2.3. Disease progression

Disease progression is defined as the worsening of the patient's condition caused by the investigational drug targeting the primary tumor, including radiographic progression and the progression of clinical symptoms and signs. The emergence of new metastatic lesions relative to the primary tumor, or the progression of existing metastatic lesions, are considered as disease progression. It will be not reported as an SAE for the events that are life-threatening due to the symptoms and signs of disease progression, requiring hospitalization or prolongation of hospitalization, or lead to permanent or serious disability/incapacity/impairment of work capacity, congenital anomaly, or birth defect. It will be reported as an SAE for deaths caused by symptoms

and signs of disease progression.

#### 8.2.4. Other anti-tumor therapies

SAEs will be recorded from the signing of the ICF until 90 days after the last dose of the investigational drug. If the subject starts a new anti-tumor treatment, follow-up will be conducted until the initiation of the anti-tumor treatment (if it starts within 30 days after the last administration, follow-up will be conducted until at least 30 days after the last administration of SHR-1210; if it starts after 30 days, follow-up will be conducted until the initiation of the anti-tumor treatment). If death occurs within the SAE reporting period after the end of the study treatment, it must be reported regardless of whether the patient has received other treatments.

#### 8.2.5. Follow-up of AEs / SAEs

All AEs/SAEs should be followed up until disappearance, alleviation to baseline level or ≤ grade 1, reaching a stable state, or obtaining a reasonable explanation (such as lost to follow-up, death).

The investigator should inquire about any AEs or SAEs that occurred since the last visit at each visit, and provide follow-up information promptly according to the sponsor's query requirements.

### 8.3. Infusion reactions

Investigators need to closely monitor the possible infusion-related and/or allergic reactions, especially acute immune-mediated adverse reactions (including cytokine storms), throughout the study.

In general, prophylaxis is not required before the infusion of SHR-1210. Based on the published literature, allergic reactions/events are most likely to occur within 24 hours of infusion. If this occurs, the infusion should be slowed down or interrupted according to the situation, clinical supportive treatment should be provided, and

prophylactic medication should be administered before future treatments. Possible allergic reactions may manifest as fever, cold intolerance, chills, headache, rash, pruritus, joint pain, hypotension/hypertension, or bronchospasm. All grade 3 or 4 infusion reactions should be reported according to the SAE reporting procedures.

## 9. Recommendations for Management of Adverse Events

### 9.1. Immune-related adverse events (irAEs)

irAEs are clinically significant side effects that are consistent with the immunological mechanism of the drug. Further serological, immunological, and pathological (biopsy) data are required to support their diagnosis. At the same time, other potential causes, such as tumor, infection, metabolism, and toxin, must be ruled out.

**Principles for handling irAEs (see Appendix IV for details):**

The management of immune-related adverse reactions should be carried out according to the medical practices and guidelines of the study site. The following are treatment recommendations for immune-related adverse reactions for reference.

Patients treated with hormones should be given calcium and vitamin D3 supplementation, acid suppression, and gastric mucosal protection therapy.

- **Immune-related pneumonia**

In the clinical studies of SHR-1210, the monitoring of signs and symptoms of immune-related pneumonia will be strengthened in patients, such as cough and chest discomfort. Chest CT scans will be performed for examination, and high-dose hormonal therapy will be given to patients with ≥ grade 2 immune-related pneumonia. Treatment with SHR-1210 may be suspended for patients with grade 2 immune-related pneumonia, while patients experiencing grade 3 or 4 will permanently discontinue SHR-1210. A consultation with a pulmonologist is recommended. Please refer to the following suggestions for specific procedures:

Grade 2 pneumonia: 1 mg/kg/day of methylprednisolone is administered intravenously or orally at an equivalent dose. Closely monitor CT changes and, once the event recovers to grade 1, 0.5 mg/kg/day of prednisone is administered orally for 2 weeks. Subsequently, reduce the prednisone dose by 5 mg per week until discontinuation.

Grade 3 pneumonia: 2 ~ 4 mg/kg/day methylprednisolone is administered intravenously or orally at an equivalent dose. Closely monitor CT changes, once the event recovers to grade 1, reduce the dose by 50% every 3 days and administer 0.5 mg/kg/day of prednisone orally for 2 weeks, then reduce the prednisone dose by 5 mg per week until discontinuation.

If there is no improvement or worsening within 3 ~ 5 days of hormonal therapy, the investigator may communicate with the sponsor to consider the combined use of immunosuppressive agents for treatment.

- **Immune-related hepatitis**

In the clinical studies of SHR-1210, the monitoring of signs and symptoms of immune-related hepatitis will be strengthened in patients, such as liver discomfort and abnormal transaminases increased. High-dose hormonal therapy will be given to patients with ≥ grade 2 immune-related hepatitis. Please refer to the following suggestions for specific procedures:

Grade 2 hepatitis: 0.5 ~ 1 mg/kg/day of methylprednisolone is administered intravenously or orally at an equivalent dose. Closely monitor changes in liver function indicators, once the event recovers to grade 1, gradually reduce the hormone dose over a period of no less than one month.

Grade 3 hepatitis: 1 ~ 2 mg/kg/day of methylprednisolone is administered intravenously or orally at an equivalent dose. Closely monitor changes in liver

function indicators, once the event recovers to grade 1, gradually reduce the hormone dose over a period of no less than one month.

If there is no improvement or worsening within 3 ~ 5 days of hormonal therapy, the investigator may communicate with the sponsor to consider the combined use of immunosuppressive agents for treatment.

- **Immune-related enteritis**

In the clinical studies of SHR-1210, the monitoring of signs and symptoms of immune-related enteritis will be strengthened in patients, such as abdominal pain, diarrhea, and hematochezia. High-dose hormonal therapy will be given to patients with ≥ grade 2 immune-related enteritis. Patients with grade 2 or 3 immune-related enteritis may temporarily discontinue SHR-1210 and receive treatment, while those with grade 4 will permanently discontinue SHR-1210.

- **Immune-related thyroid dysfunction**

Abnormal thyroid function can occur at any time during the study; therefore, in the studies of SHR-1210, patients' thyroid function will be regularly monitored and special attention will be paid to the clinical symptoms of abnormal thyroid function. Patients with immune-related hyperthyroidism will be treated with high-dose cortisone/prednisone. Hormone replacement therapy will be used for treatment of hypothyroidism, but glucocorticoids are not applicable.

In the clinical studies of SHR-1210, the monitoring of signs and symptoms of immune-related thyroid dysfunction will be strengthened in patients. High-dose hormonal therapy will be given to patients with ≥ grade 3 immune-related thyroid dysfunction, and those with grade 4 immune-related thyroid dysfunction will permanently discontinue SHR-1210.

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

In the clinical studies of SHR-1210, the monitoring of signs and symptoms of immune-related nephritis will be strengthened in patients. For patients with ≥ grade 2 immune-related nephritis, high-dose hormonal therapy will be given. Patients with grade 2 immune-related nephritis may temporarily discontinue SHR-1210 and receive treatment, while patients with grade 3 or 4 immune-related nephritis will permanently discontinue SHR-1210.

- **Immune-related hypophysitis**

In the clinical studies of SHR-1210, the monitoring of signs and symptoms of immune-related hypophysitis will be strengthened in patients. For patients with ≥ grade 2 immune-related hypophysitis, high-dose hormonal therapy will be given. Treatment with SHR-1210 may be suspended for patients with grade 2 and 3 immune-related hypophysitis, while patients with grade 4 immune-related hypophysitis will permanently discontinue SHR-1210.

- **Other immune-related adverse reactions**

In principle, based on the severity of adverse reactions, the primary action is to suspend SHR-1210. When the severity of the adverse event recovers to ≤ grade 1, the re-administration of SHR-1210 can be considered. If a severe grade 3 or life-threatening grade 4 adverse reaction occurs, SHR-1210 will be permanently discontinued

**9.2. Handling and reporting of serious adverse events (SAEs)**

1) When a SAE is considered, the principal investigator or other responsible physicians should be notified by the attending physician. If the patient's condition is severe, the project leader should be informed while simultaneously providing emergency treatment. If necessary, discontinue the investigational drug immediately.

2) If a SAE is judged, based on the clinical manifestations, appropriate treatment or rescue measures should be taken immediately according to the standards of tumor specialty clinical rescue treatment. If the severe toxicity is caused by drug overdose, the investigator will decide to take rescue measures such as accelerating drug excretion to maintain the stability of patient's vital signs as far as possible. If necessary, ECG monitoring should be performed, and consultations and assistance from relevant departments can be requested if needed.

3) When an out-of-hospital subject is judged to have a SAE and is unable to visit the clinic, it is recommended that the subject returns to the hospital or seeks medical attention at a local hospital promptly, while immediately notifying the project leader to obtain further advice. If the subject seeks medical attention at a local hospital, establish contact with the attending physician to understand the specific situation and provide treatment recommendations. If necessary, go to the local hospital for treatment or transfer back to the study site for treatment.

4) The project leader must report any SAEs in writing within 24 hours to the following parties: the principal investigator, the ethics committee of study site, the sponsor, the SAE specialist at the GCP center, and then the GCP center office will report to the State Food and Drug Administration (SFDA) and the provincial food and drug administration. The content of reporting the serious adverse reaction can use the standard forms provided by the sponsor or the SFDA. The sponsor's reporting should ensure compliance with all reporting procedures required by laws and regulations.

5) The study doctor should maintain accurate records of AEs, which should include at least: description of the AE, onset time, the time of resolution, severity and frequency, whether treatment is required, and if so, the treatment provided.

6) In the original case report, the occurrence, development, and treatment of the SAE

should be recorded in as much detail as possible and documented in the CRF. The SAE should be followed up until it is properly resolved, the condition is stable, or the cause is clear. In addition, the principal investigator of the study at the GCP center, the ethics committee of the study site, the sponsor, the National Medical Products Administration, and other relevant parties should be provided with the final report (in written form if necessary for some departments).

**9.3. Infusion reactions**

Since SHR-1210 is a fully humanized monoclonal antibody, it is unlikely to cause infusion reactions, and no prophylactic medication is required before infusion. If an infusion reaction occurs, it should be managed according to the situation by slowing down or interrupting the infusion, providing clinical supportive care, and administering prophylactic medication before subsequent treatments. Acute infusion reactions (including cytokine release syndrome, vascular edema, anaphylactic shock, and allergic reactions, please refer to NCI CTCAE v4.03 criteria) usually occur at the time of infusion or shortly after drug infusion, with symptoms and signs typically disappearing within 24 hours after the infusion is completed. Symptoms and signs include:

Allergic reactions/hypersensitivity reactions (including drug-induced fever), cough, cold intolerance, chills/shivering, dizziness, headache, fatigue (asthenia, somnolence), rash/peeling, pruritus cutaneous/pruritus, joint pain, muscle pain, hypotension or hypertension, nausea, vomiting, sweating (diaphoresis), tachycardia, tumor pain, urticaria (rubella), dyspnea (shortness of breath) or bronchospasm. All grade 3 or 4 infusion reactions should be reported to the sponsor within 24 hours, and if they meet the criteria for SAEs, they should be reported as SAEs. The management of allergic reactions should be based on the medical practice and guidelines of the study site. The

following are treatment recommendations for infusion reactions, for reference.

**Table 5 Recommendations for Infusion Reactions Treatment**

| CTCAE Grade | Clinical Symptoms | Clinical Management | SHR-1210 Treatment |
|---|---|---|---|
| Grade 1 (mild) | Mild transient reaction; | Bedside observation, close monitoring until recovery. (Subsequently, it is recommended to administer prophylactic medication before infusion: at least 30 minutes prior to SHR-1210 administration, diphenhydramine 50 mg or equivalent, and/or acetaminophen 325 ~ 1000 mg) | Continue |
| Grade 2 (moderate) | Moderate reactions, therapy or infusion interruption indicated but respond promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, | Intravenous infusion of normal saline, diphenhydramine 50 mg IV or equivalent and/or acetaminophen 325 ~ 1000 mg; Bedside observation, close monitoring until recovery. According to clinical needs, corticosteroids or bronchodilators may be considered; The amount of study drug infused should be recorded in the original medical records; | Suspend treatment. When resuming administration after symptom disappearance, use 50% of the initial infusion rate. If no complications occur within 30 minutes, the |

| | | | |
|---|---|---|---|
| | narcotics, bronchodilators, intravenous infusion etc.) | Subsequently, it is recommended to administer prophylactic medication before infusion: at least 30 minutes prior to SHR-1210 administration, diphenhydramine 50 mg or equivalent, and/or acetaminophen 325 ~ 1000 mg. If necessary, hormone cortisol can be used (at a dose equivalent to a 25 mg of hydrocortisone). | infusion rate can be increased to 100% of the original rate. Closely monitor the patient. If symptoms reoccur after resolution, do not administer the current infusion of SHR-1210. |
| ≥ Grade 3 (severe) | Grade 3: severe reactions, which do not immediately respond to therapy and/or dose interruption; or the symptoms reoccur after resolution; sequelae requiring | Immediately discontinue infusion of SHR-1210;<br>Initiate intravenous infusion of normal saline.<br>• Bronchodilators: subcutaneous injection of 1:1000 epinephrine solution at a dose of 0.2 ~ 1 mg, or slow intravenous injection of 1:10000 epinephrine solution at a dose of 0.1 ~ 0.25 mg, and/or if necessary, intravenous injection of diphenhydramine 50 mg + methylprednisolone 100 mg or | Permanently discontinue. |

| | | | |
|---|---|---|---|
| | hospitalization.<br>Grade 4: Life-threatening | equivalent drug;<br>• Follow the study site's guidelines for treating allergic reactions; conduct bedside observation, close monitoring until recovery. | |

**9.4. Symptomatic management of apatinib-related adverse reactions**

1) Hand and foot syndrome (HFS)

HFS is characterized by palmar-plantar hypoaesthesia or erythema of extremities, which is a type of skin toxicity that becomes more apparent in areas subjected to pressure or force. This can occur in cancer patients receiving chemotherapy or molecular targeted therapy. The features of hand and foot skin reactions (HFSR) include numbness, dysesthesia, paresthesia, tingling sensation, painlessness or pain, skin swelling, erythema, desquamation, rhagades, indurated blisters, and severe pain.

HFS grading:

Grade 1: Numbness/dysesthesia /paresthesia of hands and/or feet, painless swelling or erythema, and/or discomfort not affecting normal activities.

Grade 2: Painful erythema and swelling of the hands and/or feet, and/or discomfort affecting the daily activities of patients.

Grade 3: Wet desquamation, ulcer, blisters, or severe pain of the hands and/or feet, and/or severe discomfort that prevents the patient from working or performing daily activities. Severe pain and loss of skin function are relatively rare.

Symptomatic treatment and management of HFS:

It is recommended to implement some necessary symptomatic supportive treatments, including: enhancing skin care, maintaining skin cleanliness, and avoiding secondary

infections; avoiding pressure or friction; using moisturizers or lubricants, topically applying emulsions or lubricants containing urea and corticosteroids; when necessary, topically using antifungal or antibiotic treatments.

Note: If ≥ grade 3 HFS occurs consecutively for 3 times and shows a worsening trend, the study drug will be discontinued and the patient will be withdrawn from the clinical study.

2) Hypertension

For patient enrollment, the inclusion and exclusion criteria regarding blood pressure requirements should be followed strictly. Hypertensive patients can achieve blood pressure control before taking the investigational drug by adjusting the dose of antihypertensive medication or adding a new antihypertensive drug. Blood pressure must be controlled within 140/90 mmHg before randomization (the mean of 2 blood pressure measurements, with a 24-hour or longer interval). Monitoring and management of such hypertension: During the first 2 cycles of targeted drug therapy, blood pressure should be monitored at least 3 times per week.

Since anti-VEGF/VEGFR targeted therapy drugs cause a decrease in NO synthesis, ultimately activating the renin-angiotensin-aldosterone system and leading to hypertension, it is preferable to use angiotensin-converting enzyme (ACE) inhibitors (such as captopril, enalapril, benazepril, and cilazapril) for antihypertensive treatment. For patients who are allergic or intolerant to ACE inhibitors, angiotensin II receptor blockers (ARBs, such as losartan, valsartan, irbesartan, and telmisartan) can be used. In addition to lowering blood pressure, ARBs also have benefits in alleviating proteinuria. ACE inhibitors can be used in patients with chronic kidney disease, proteinuria, and metabolic syndrome; dihydropyridine calcium channel blockers are suitable for elderly patients.

If patients experience hypertension or worsening of hypertension during the treatment, the following actions should be taken: 1) Perform dose modifications of the study drugs according to the protocol requirements; 2) Initiate antihypertensive medication or adjust the dose of antihypertensive medication.

In the study, it is recommended to use the following antihypertensive medications: 1) ACE inhibitors; 2) ARBs; 3) Dihydropyridine calcium channel blockers; 4) β-adrenergic receptor blockers.

It is not recommended to use diuretic antihypertensive drugs, and the use of nifedipine, diltiazem, and verapamil, which have CYP3A4 inhibitory effects, is prohibited during the treatment with the study drugs. For patients with hypertensive crisis, the use of apatinib should be discontinued.

3) Hemorrhage

Haemorrhage of digestive tract, including fecal occult blood (++) or above, hematemesis, or bloody stools, should be actively managed with symptomatic treatment. Patients with upper gastrointestinal haemorrhage should be fasted and given therapies such as acid suppression, gastric mucosal protection, and hemostatic agents (such as tranexamic acid and reptilase). If necessary, octreotide can be used. For patients with lower gastrointestinal haemorrhage, hemostasis, blood transfusion, and supportive care should be provided. For patients with uncontrolled bleeding, surgical assistance is required immediately.

Patients with coughing blood or hemoptysis should be given hemostasis, blood transfusion, and supportive treatment; if bleeding cannot be controlled, surgical assistance is required.

Note: In cases of confirmed hemorrhage brain, ≥ grade 2 pulmonary hemorrhage, or ≥ grade 3 hemorrhage, the drug must be discontinued immediately, symptomatic

treatment should be provided, and the use of apatinib should be terminated, with the administration of SHR-1210 suspended. After the symptoms have alleviated or disappeared, the use of SHR-1210 will be continued as appropriate.

4) Proteinuria

Throughout the treatment period, closely monitor proteinuria in all patients, and strengthen monitoring for those with a history of hypertension. For patients with proteinuria of ++ to +++ for 2 consecutive times, a 24-hour urine protein measurement is required. For patients with proteinuria of ++++ and above, a 24-hour urine protein measurement is also required.

Note: If nephrotic syndrome occurs, the medication will be permanently discontinued, and the subject will withdraw from this clinical study.

5) Thrombus

In the event of any arterial thrombosis (such as cerebral ischemia, stroke, angina, myocardial infarction), the medication should be stopped immediately, and the subject should withdraw from the study. If symptomatic venous thrombosis (grade 4) occurs, the medication should be stopped, and the subject should withdraw from the study. Thrombosis symptoms should be treated immediately with symptomatic treatment, surgery, or anticoagulants.

6) Fatigue and weakness

Fatigue and weakness are common tumor-related clinical symptoms, and electrolyte disturbance, abnormal liver function, and abnormal cardiac function may lead to fatigue and weakness. In addition, fatigue and weakness are common clinical adverse reactions of angiogenesis-targeting drugs such as sunitinib, pazopanib, and sorafenib. Clinical studies have shown that angiogenesis-targeting drugs may increase the incidence of fatigue and weakness by causing hypothyroidism.

In previously completed clinical studies of apatinib, the incidence of fatigue and weakness in patients in the apatinib treatment group was higher than that in the control group. However, the specific mechanism underlying the increased incidence of fatigue and weakness induced by apatinib is not yet clear.

Therefore, when patients experience or report ≥ grade 2 fatigue and weakness, it should be paid more attention to. If ≥ grade 3 fatigue and weakness occur, patients should be admitted to the hospital immediately for examination. Potential causes, such as electrolyte disturbance, abnormal liver function, abnormal cardiac function (electrocardiogram, echocardiography), and abnormal hormone levels (adrenal hormones, thyroid hormones), should be considered and ruled out one by one. Symptomatic treatment should be provided, and according to the dose adjustment principles, the dose interruption or adjustment should be performed on the investigational drug accordingly.

7) Abdominal pain

Abdominal pain is not uncommon in apatinib treatment, often as a symptom associated with the tumor. Moreover, gastrointestinal perforation occasionally occurs in clinical studies of apatinib and other types of anti-angiogenic drugs. For patients experiencing abdominal pain, investigators should be vigilant for the possibility of gastrointestinal perforation. Once gastrointestinal perforation is identified, the medication must be stopped immediately, the patient should withdraw from the study, and active symptomatic treatment should be initiated.

8) Pulmonary interstitial fibrosis

Clinical physicians should have a thorough understanding of the patient's disease condition and be familiar with drugs that may cause pulmonary toxicity. the patient's clinical symptoms and changes in chest X-ray or CT scans should be closely

monitored. Once the patient experiences unexplained symptoms such as cough, chest tightness, breathlessness, difficulty breathing, and hemoptysis, it is crucial to promptly identify the cause and discontinue the medication as soon as other causes (such as infection and heart failure) are ruled out.

Bronchoalveolar lavage examination and surgical lung biopsy are important methods for diagnosing interstitial lung disease. Currently, there is no satisfactory treatment for pulmonary fibrosis. It is recommended to refer to the guidelines for the diagnosis and treatment of idiopathic pulmonary (interstitial) fibrosis issued by the Respiratory Diseases Branch of the Chinese Medical Association, correct hypoxemia, and drugs such as glucocorticoids should be used in a timely manner.

Note: Consult with a specialist if necessary to assist in diagnosis and treatment.

## 10. Data Analysis / Statistical Methods

Screening-failed subjects (those who signs the ICF but do not receive any treatment) will not be included in any analysis. However, these subjects will be reported separately in the form of a list.

### 10.1. Sample size

This study is a single-arm study, with the primary efficacy endpoint being ORR. It is planned to enroll 30 patients.

### 10.2. Statistical analysis plan

The detailed methods for summarization and statistical analysis of the data collected in this study will be included in the Statistical Analysis Plan (SAP), which will be finalized and filed by the sponsor. Any changes to this study protocol, if deemed by the sponsor or principal investigator to have a significant impact on the SAP, the SAP will be revised to maintain consistency with the study protocol. The SAP may revise relevant content in this protocol, but if the revision involves major and/or key factors

such as the definition of endpoints or their analyses, the revision should also be reflected in the amended version of the protocol.

### 10.3. Analysis populations

Full Analysis Set: includes all patients who are enrolled and receive at least one dose of study drug, and have at least one efficacy evaluation.

Safety Analysis Set: all enrolled patients who have received at least one dose of study drug and have safety records after drug administration. This dataset is used for safety analysis in the study.

### 10.5. Statistical methods

#### 10.5.1. Basic methods

The main results of this study will be presented using descriptive statistical methods. The mean, standard deviation, median, maximum, and minimum values will be listed for measurement data, while the frequency (proportion), rate, and CI will be listed for counting data and ranking data. All statistical analyses will be programmed and calculated using SAS 9.4 or above.

#### 10.5.2. Baseline characteristics

The mean, standard deviation, median, maximum, and minimum values will be calculated for measurement data such as age, height, and weight. The frequency and percentage will be listed for qualitative data such as gender and ECOG score.

#### 10.5.3. Analysis of efficacy endpoints

The point estimates will be performed for efficacy endpoints such as ORR and DCR, and their 95% CIs will be provided. The interval estimates will be performed using the Clopper-Pearson method.

PFS, DOR, OS, 6-month, 9-month and 12-month survival rates will be estimated using the Kaplan-Meier method, and 95% CIs will be calculated. TTR will be

described using mean, standard deviation, median, maximum, and minimum values.

### 10.5.4. Safety analysis

The descriptive statistical analysis will be used for analyzing AEs, SAEs with ≥ CTCAE grade 3, and adverse reactions (adverse reactions are defined as AEs with the causality to the study drug as "definitely related/possibly related/not evaluable"), adverse reactions with ≥ CTCAE grade 3, AEs leading to dose modifications occurring in population in each dose group. The worst clinical grade will be described for the laboratory test results at baseline and post-baseline.

Additionally, the summary analysis of AEs mentioned above is also applicable for each category of immune-related AEs, including immune-related pneumonia, immune-related enteritis, immune-related thyroid dysfunction, immune-related nephritis and renal failure, immune-related hypophysitis, and other immune-related adverse reactions.

### 10.5.5. Exploratory analyses

For the SHR-1210-related tumor markers, such as PD-L1 in tumor tissues and TMB in tumors and plasma, descriptive statistics will be used for analysis.

## 11. Ethics of Clinical Studies

The clinical study will follow the relevant regulations of the World Medical Association's Declaration of Helsinki and other related provisions. The clinical study will be conducted only after the study protocol has been approved by the Ethics Committee. Before each subject is enrolled in the study, the investigator has the responsibility to provide the subject or his/her representative with a complete and comprehensive introduction of the objectives, procedures, and potential risks of the study, and to sign a written ICF. Subjects should be informed that they have the right to withdraw from the study at any time, and the ICF should be retained as a clinical

study file for future reference. The privacy and data confidentiality of the subjects will be protected throughout the study.

**12. Clinical Study Schedule**

Estimated first subject enrollment: January 2019

Estimated last subject enrollment: July 2021

Estimated end of study: January 2022

**13. References**

**1.** Fecher LA, Cummings SD, Keefe MJ, et al. Toward a molecular classification of melanoma. J Clin Oncol 2007；25(12)：1606-1620.

**2.** Chin L. The genetics of malignant melanoma： lessons from mouse and man. Nat Rev Cancer 2003(8)；3：559-570.

**3.** De Snoo FA, Hayward NK. Cutaneous melanoma susceptibility and progression genes.Cancer Lett 2005；230(2)：153-186.

**4.** Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2009(Vintage 2009 Populations), National Cancer Institute. Bethesda, MD, http ://seer.cancer.gov/csr/1975_2009_pops09/, based on November 2011 SEER data submission, posted to the SEER web site, April 2012.

**5.** Siegel R, Naishadham D, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014；64(1)：9-29.

**6.** Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide： IARC CancerBase No. 11 [Internet]. Lyon, France： International Agency for Research on Cancer；

2013. Available from： http：//globocan.iarc.fr, accessed on 2/10/2014.

**7.** Chi Z, Li S, Sheng X, et al. Clinical presentation, histology, and prognoses of malignant melanoma in ethnic Chinese： A study of 522 consecutive cases. BMC Cancer 2011；11：85.

**8.** McLaughlin CC, Wu XC, Jemal A, et al. Incidence of noncutaneous melanomas in the U.S.Cancer 2005；103(5)：1000-1007.

**9.** Eggermont AM, Gore M. Randomized adjuvant therapy trials in melanoma：surgical and systemic. Semin Oncol 2007；34：509-15.

**10.** Garbe C, Eigentler TK, Keilholz U, Hauschild A, Kirkwood JM. Systematic review of medical treatment in melanoma： current status and future prospects. Oncologist 2011；16：5-24.

**11.** Kirkwood JM, Strawderman MH, Ernstoff MS, Smith TJ, Borden EC, Blum RH. Interferon alfa-2b adjuvant therapy of high-risk resected cutaneous melanoma： the Eastern Cooperative Oncology Group Trial EST 1684. J Clin Oncol 1996；14：7-17.

**12.** Kirkwood JM, Ibrahim JG, Sondak VK, Richards J, Flaherty LE, Ernstoff MS, et al. High- and low-dose interferon alfa-2b in high-risk melanoma：first analysis of intergroup trial E1690/S9111/C9190. J Clin Oncol 2000 ;18 :2444-58.

**13.** Kirkwood JM, Ibrahim JG, Sosman JA, Sondak VK, Agarwala SS, Ernstoff MS, et al. High-dose interferon alfa-2b significantly prolongs relapse-free and overall survival compared with the GM2-KLH/QS-21 vaccine in patients with resected stage IIB-III melanoma： results of intergroup trial E1694/S9512/C509801. J Clin Oncol 2001；19：2370-80.

**14.** Chang AE, Karnell LH, Menck HR. The National Cancer Data Base report on cutaneous and noncutaneous melanoma : a summary of 84, 836 cases from the past decade. The American College of Surgeons Commission on Cancer and the American Cancer Society.Cancer 1998 ; 83 : 1664-78.

**15.** An JS, Wu LY, Li N, Li B, Yu GZ, Liu LY. [Clinical analysis of 42 cases of primary malignant melanoma in female genital tract]. Zhonghua Fu Chan Ke Za Zhi 2007 ; 42 : 320-4.

**16.** Li ZY, Cai JQ, Cui XZ, Shao YF, Jin YB. [Outcome of malignant melanoma in gastrointestinal tract : clinical analysis of 70 cases]. Zhonghua Wai Ke Za Zhi 2008 ; 46 : 574-6.

**17.** Yang X, Ren GX, Zhang CP, Zhou GY, Hu YJ, Yang WJ, et al. Neck dissection and post-operative chemotherapy with dimethyl triazeno imidazole carboxamide and cisplatin protocol are useful for oral mucosal melanoma. BMC Cancer 2010 ; 10 : 623.

**18.** Yi JH, Yi SY, Lee HR, Lee SI, Lim do H, Kim JH, et al. Dacarbazinebased chemotherapy as first-line treatment in noncutaneous metastatic melanoma : multicenter, retrospective analysis in Asia. Melanoma Res 2011 ; 21 : 223-7.

**19.** Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annu Rev Immunol 2005 ; 23 : 515-48.

**20.** Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2- domaincontaining tyrosine phosphatase 2 to phosphotyrosine. Proc

Natl Acad Sci USA 2001；98：13866-71.

**21.** Thompson RH, Dong H, Lohse CM, Leibovich BC, Blute ML, Cheville JC, et al. PD-1 is expressed by tumor-infiltrating immune cells and is associated with poor outcome for patients with renal cell carcinoma. Clin Cancer Res 2007；13：1757-61.

**22.** Gao Q, Wang XY, Qiu SJ, Yamato I, Sho M, Nakajima Y, et al. Overexpression of PDL1 significantly associates with tumor aggressiveness and postoperative recurrence in human hepatocellular carcinoma. Clin Cancer Res 2009；15：971-9

**23.** Hamanishi J, Mandai M, Iwasaki M, Okazaki T, Tanaka Y, Yamaguchi K, et al.Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. Proc Natl Acad Sci USA 2007；104：3360-5

**24.** Mu CY, Huang JA, Chen Y, Chen C, Zhang XG. High expression of PD-L1 in lung cancer may contribute to poor prognosis and tumor cells immune escape through suppressing tumor infiltrating dendritic cells maturation. Med Oncol. 2011；28：682-8.

**25.** Liotta F, Gacci M, Frosali F, uerci V, Vittori G, Lapini A, et al. Frequency of regulatory T cells in peripheral blood and in tumour-infiltrating lymphocytes correlates with poor prognosis in renal cell carcinoma. BJU Intern 2010；107：1500-6.

**26.** Sznol M, Powderly JD, Smith DC, Brahmer JR, Drake CG, McDermott DF, et al. Safety and anti-tumor activity of biweekly MDX-1106 (anti-PD-1,

BMS-936558/ONO-4538) in patients with advanced refractory malignancies. Proc Am Soc Clin Oncol. 2010；28：abstr. 2506.

**27.** Topalian S，Sznol M，McDermott D，Kluger H，Carvajal R，Sharfman W. Safety，Activity，and Immune Correlates of Anti-PD-1 Antibody in Cancer. N Engl J Med. 2012；(366)：2443-2454.

**28.** Omid Hamid. "Preliminary Clinical Efficacy and Safety of MK-3475 (Anti-PD-1 Monoclonal Antibody) in Patients with Advanced Melanoma." Society of Melanoma Research. Los Angeles. 11 November 2012. Conference Presentation.

**29.** Hamid O，Robert C，Daud A，Hodi FS，Hwu WJ，Kefford R，et al. Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma. New Eng J Med. 2013；369：134-144.

**30.** Topalian S，et al. Survival，Durable Tumor Remission，and Long-Term Safety in Patients With Advanced Melanoma Receiving Nivolumab. J Clin Oncol. 2014；32