

Title: A Phase II Clinical Study of Anti-PD-1 Antibody SHR-1210 Combined with Apatinib Mesylate in the Treatment of Advanced Non-Small Cell Lung Cancer

Clinical trial registration number: NCT03083041

Version Date: 10 Dec., 2018

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A PHASE II CLINICAL STUDY OF ANTI-PD-1 ANTIBODY SHR-1210 COMBINED WITH APATINIB MESYLATE IN THE TREATMENT OF ADVANCED NON-SMALL CELL LUNG CANCER STUDY PROTOCOL

Protocol No.:	SHR-1210-APTN-II-202-NSCLC
Version No.:	5.0
Version Date:	10 Dec., 2018
Study Director:	████████████████████
Leading Center of Clinical Study:	██
Sponsor:	Jiangsu Hengrui Pharmaceuticals Co., Ltd.

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Protocol Signature Page

Signature of Principal Investigator

I will carefully execute the duties as an investigator in accordance with the Chinese GCP, and personally participate in or directly lead this clinical study. We have read and confirmed this protocol (protocol no.: SHR-1210-APTN-II-202-NSCLC, version no.: 5.0, version date: 10 Dec., 2018). I agree to fulfill my duties in accordance with applicable Chinese laws, the Declaration of Helsinki, the Chinese GCP, and this study protocol. In addition, I confirm that any measures is subject to approval by the Ethics Committee before implementation, unless they must be taken to protect the safety, rights and interests of subjects.

Leading Site of Clinical Study:



Principal Investigator (print)

Principal Investigator (signature)

Signature Date
(DD/MM/YYYY)

Protocol Signature Page

Signature of Investigator

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Study Center:



Principal Investigator (print)

Principal Investigator (signature)

Signature Date
(DD/MM/YYYY)

Protocol Signature Page

Sponsor's Signature

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Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

		
Medical Director (print)	Medical Director (signature)	Signature Date (DD/MM/YYYY)

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PROTOCOL SYNOPSIS

Study Title	A Phase II Clinical Study of Anti-PD-1 Antibody SHR-1210 Combined with Apatinib Mesylate in the Treatment of Advanced Non-Small Cell Lung Cancer
Protocol Number	SHR-1210-APTN-II-202-NSCLC
Version No.	5.0
Version Date	10 Dec., 2018
Sponsor	Jiangsu Hengrui Pharmaceuticals Co., Ltd.
Study Population	Patients with advanced non-small cell lung cancer (NSCLC)
Study Objectives	<p>Primary objective of Stage I study:</p> <p>To evaluate the tolerability and safety of anti-PD-1 antibody SHR-1210 plus apatinib mesylate in patients with advanced NSCLC</p> <p>Secondary objectives of Stage I study:</p> <ol style="list-style-type: none"> To evaluate the pharmacokinetics of anti-PD-1 antibody SHR-1210 plus apatinib mesylate in patients with advanced NSCLC To preliminarily evaluate the efficacy of anti-PD-1 antibody SHR-1210 plus apatinib mesylate in patients with advanced NSCLC <p>Objectives of Stage II study:</p> <p>To observe and evaluate the efficacy and safety of anti-PD-1 antibody SHR-1210 plus apatinib mesylate in patients with advanced non-small cell lung cancer</p>
Endpoints	<p>Primary endpoints:</p> <p>Stage I:</p> <p>Incidence and severity of adverse events (AEs) and serious adverse events (SAEs)</p> <p>Stage II:</p> <p>Objective response rate (ORR)</p> <p>Secondary endpoints:</p> <p>Stage I:</p> <ol style="list-style-type: none"> Plasma concentrations of SHR-1210 and apatinib Pharmacokinetic parameters of SHR-1210 and apatinib, including $t_{1/2}$, C_{max}, AUC, etc. Tumor objective response rate (ORR) <p>Stage II:</p> <p>Incidence and severity of adverse events (AEs) and serious adverse events (SAEs)</p> <p>Stages I and II:</p> <ol style="list-style-type: none"> Clinical benefit rate (CBR): Proportion of subjects with CR, PR, or SD \geq 6 months during the study Duration of response (DoR) Time to response Progression free survival (PFS) based on RECIST 1.1

	<p>5. 12-month survival</p> <p>6. Overall survival (OS)</p> <p>7. Exploratory analysis of the relationship between biomarkers and efficacy</p>
Sample Size	<p>Stage I: 40-60 subjects</p> <p>Stage II: about 174 subjects</p>
Study Design	<p>Study design of Stage I:</p> <p>A multi-arm, multi-center, open-label clinical study</p> <p>Inclusion criteria: Patients with advanced NSCLC who have failed standard treatment.</p> <p>Three dose groups, i.e., 250 mg apatinib, oral, q.d. + 200 mg SHR-1210, IV, q2W, 375 mg apatinib, oral, q.d. + 200 mg SHR-1210, IV, q2W, and 500 mg apatinib, oral, q.d. + 200 mg SHR-1210, IV, q2W are set up to explore the tolerability of the combination therapy.</p> <p>Ten to twelve subjects will be enrolled in each dose group (to make sure that at least 10 subjects will complete the tolerability evaluation), and the first cycle (28 days) of continuous treatment will be used as the observation period for tolerability. A dose will be considered tolerable if the proportion of subjects with clinically significant toxicities is < 0.33.</p> <p>After completing the tolerability observation period, subjects will continue the treatment until occurrence of any event that meets the criteria for discontinuation.</p> <p>After completing the tolerability observation period, the study will enter Stage II for further observation of efficacy and safety.</p> <p>After the completion of the observation period for tolerability, 10 to 12 subjects will be enrolled in each dose group for an expanded pharmacokinetic study. In cycle 1 of the expanded PK study, one dose of SHR-1210 will be administered on D1 followed by PK blood sampling. Then, apatinib will be started on D22 after the completion of PK blood sampling, while another PK blood sampling will be carried out on D28. Starting from D1 in cycle 2, SHR-1210 will be administered once every 14 days, while apatinib will be administered orally every day. PK blood sampling will be carried out on D1 of cycle 2 after the administration of SHR-1210 and on D28 after the administration of apatinib. After the blood sampling is completed, the subjects will continue to receive the study treatment until an event meeting the criteria of study termination occurs.</p> <p>Design of Stage II:</p> <p>A single-arm/double-arm, multicenter, open-label clinical study</p> <p>According to the tolerable doses for combination therapy determined in Stage I, apatinib 250 mg, q.d. oral + SHR-1210 200 mg, IV, q2W are selected, and patients with advanced non-small cell lung cancer who failed first-line chemotherapy or patients with non-squamous non-small cell lung cancer with a high tumor mutation burden (TMB) confirmed by the central laboratory are planned to be enrolled. According to the molecular and pathological classifications, the subjects are divided into:</p> <p>Cohort 1. Non-squamous, non-small cell lung cancer with wild-type EGFR and ALK;</p> <p>Cohort 2. Non-small cell lung cancer with EGFR mutation or ALK fusion gene rearrangement. The subjects harboring sensitive EGFR mutations and ALK fusion gene rearrangement must have failed the treatment of at least one EGFR inhibitor or ALK inhibitor;</p> <p>Cohort 3. Non-central squamous cell lung cancer;</p> <p>Cohort 4. Non-squamous and non-small cell lung cancer with wild-type EGFR and ALK and with $\text{bTMB} \geq 1.54 \text{ muts/Mb}$ or $\text{tTMB} > 10 \text{ muts/Mb}$ confirmed by central laboratory.</p>

	The enrolled subjects are treated until the occurrence of any event that meets the criteria for discontinuation, so as to further evaluate the efficacy and safety of SHR-1210 in combination with apatinib in patients with advanced NSCLC.
Administration Regimen	SHR-1210 will be administered via intravenous infusion (without prophylactics) with a fixed dose of 200 mg given in 30 min (not less than 20 min, no more than 60 min), once every 2 weeks. Each cycle contains 4 weeks (the subjects for the expanded PK study receive one dose in Cycle 1 of the study) and the longest period of drug use is 2 years; Apatinib will be orally administered after meals, once a day through the study (the subjects for the expanded PK study will receive the drug orally under fasting conditions on D28 of Cycle 1 and D28 of Cycle 2).
Clinically Significant Toxicity	<p>Definition of clinically significant toxicity:</p> <ol style="list-style-type: none"> 1. Grade 4 hematological toxicity or Grade ≥ 3 thrombocytopenia with hemorrhage, Grade ≥ 3 neutropenia with fever and infection; 2. Grade ≥ 3 non-hematological toxicity (except for abnormal laboratory test parameters), hypertension, rash, diarrhea, nausea, and vomiting that cannot be controlled after symptomatic treatment; 3. Grade ≥ 3 abnormal laboratory test parameters that lead to medical intervention, hospitalization, or lasting for ≥ 7 days; 4. SHR-1210 interruption for > 14 days due to relevant toxicity (delayed administration in Cycle 1 or Cycle 2); 5. Apatinib interruption for > 7 days due to relevant toxicity. <p>Definition of subjects with incomplete tolerance evaluation:</p> <p>During the observation period of tolerability, the dose of SHR-1210 is $< 90\%$ of the prescribed dose due to non-clinically significant toxicity (such as injection reactions).</p>
Blood Sampling for PK Study	<p>In the expanded PK study, one dose of SHR-1210 will be administered on D1 of Cycle 1 (28D) via intravenous infusion. PK blood sampling will be performed within 0.5 h pre-administration, and at 5 min (± 5 min), 2 h (± 10 min) and 6 h (± 10 min) on D1, D2 (24 h, ± 1 h), D3 (48 h, ± 1 h), D8 (168 h, ± 1 h), D15 (336 h, ± 1 h) and D22 (504 h, ± 1 h) post-administration, with 3 mL of blood collected at each time point. After the completion of PK blood sampling on D22, the administration of apatinib mesylate tablets will be started on the same day and continued once a day. PK blood sampling will be performed within 0.5 h pre-administration on D28 and at 0.5 h (± 5 min), 1 h (± 5 min), 2 h (± 5 min), 3 h (± 5 min), 5 h (± 10 min), 8 h (± 10 min), 12 h (± 10 min), and 24 h (± 1 h) post-administration, with 3 mL of blood collected at each time point.</p> <p>On D1 of Cycle 2, PK blood sampling will be performed within 0.5 h before the administration of SHR-1210, and at 5 min (± 5 min), 2h (± 10 min) and 6 h (± 10 min) on D1, D2 (24 h, ± 1 h), D3 (48 h, ± 1 h), D8 (168 h, ± 1 h), and D15 (336 h, ± 1 h) post-administration, with 3 mL of blood collected at each time point. On D28 of Cycle 2, PK blood sampling will be performed within 0.5 h before the administration of apatinib, and at 0.5 h (± 5 min), 1 h (± 5 min), 2 h (± 5 min), 3 h (± 5 min), 5 h (± 10 min), 8 h (± 10 min), 12 h (± 10 min), and 24 h (± 1 h) post-administration, with 3 mL of blood collected at each time point.</p> <p>There will be a total of 35 blood sampling points.</p>
Inclusion Criteria	<ol style="list-style-type: none"> 1. Male and female patients aged 18-70 years old; 2. Pathologically confirmed advanced (Phase IIIB and IV) non-small cell lung cancer with at least one measurable lesion that meets the RECIST v1.1 criteria and has not been treated locally; 3. Able to provide previous tumor samples or agree to cooperate with biopsy (Stage II);

4. Stage I: Patients who have undergone the second-line and above chemotherapy (at least one of the previous chemotherapy regimens is a platinum-based chemotherapy doublet regimen) but failed the treatment or showed recurrence. The patients harboring EGFR mutations and ALK gene abnormalities must have failed the treatment with an EGFR inhibitor or ALK inhibitor.

Stage II: Patients who have undergone only one previous platinum-based doublet chemotherapy but failed the treatment or showed recurrence, or patients in the stage of palliative treatment who have received no systemic treatment (only for cohort 4).

- a. The replacement of platinum drugs due to drug toxicity will be considered as one treatment regimen;
- b. Postoperative adjuvant chemotherapy will not be counted as one previous chemotherapy regimen if the time from the end of treatment to recurrence is > 6 months.

According to the type of driver gene mutations and pathological classification, the subjects will be divided into the following four cohorts:

Cohort 1. Patients with confirmed absence of mutations in EGFR 18-21 exons and ALK fusion genes (the histochemistry result of ALK D5F3 antibody is negative);

Cohort 2. Patients with confirmed presence of mutations in EGFR 18-21 exons or ALK fusion genes (the histochemistry result of ALK D5F3 antibody is positive). Carriers of sensitive EGFR mutations must have received at least one targeted treatment with EGFR tyrosine kinase inhibitors (EGFR-TKI) and failed the treatment. Carriers of positive ALK fusion genes must have failed the treatment of at least one targeted treatment with ALK tyrosine kinase inhibitor (ALK-TKI) (treatment failure: progressive disease or intolerable toxicity during the treatment);

Cohort 3. Imaging confirmed non-central squamous cell lung cancer or adenosquamous carcinoma primarily consisted of squamous cell carcinoma (pathologically confirmed).

Cohort 4. Non-squamous and non-small cell lung cancer with wild-type EGFR and ALK and with bTMB ≥ 1.54 muts/Mb or tTMB > 10 muts/Mb confirmed by central laboratory, and patients in the stage of a palliative treatment who have received no systemic treatment.

5. ECOG PS: 0-1;
6. Life expectancy ≥ 12 weeks;
7. Major organ functions must meet the following rules (not including any use of blood components and cell growth factors within 14 days before the first dose):
 - Absolute neutrophil count $\geq 1.5 \times 10^9/L$;
 - Platelets $\geq 100 \times 10^9/L$;
 - Hemoglobin ≥ 9 g/dL;
 - Serum albumin ≥ 3 g/dL;
 - Thyroid stimulating hormone (TSH) \leq ULN (In the case of abnormalities, FT3 and FT4 levels should also be measured. If FT3 and FT4 levels are normal, the subject can be enrolled);
 - Bilirubin \leq ULN;
 - ALT and AST $\leq 1.5 \times$ ULN;

	<ul style="list-style-type: none"> • $AKP \leq 2.5 \times ULN$; • Serum creatinine $\leq 1.5 \times ULN$ or creatinine clearance ≥ 60 mL/min (using the standard Cockcroft-Gault formula, as shown in Appendix 3); <p>8. Female patients of a childbearing age who are not surgically sterilized should adopt a medically approved contraceptive measure (such as an intra-uterine contraceptive device, contraceptive pills or condoms) during the study treatment period and within 3 months after the end of the study treatment; female patients of a childbearing age who are not surgically sterilized must have a negative serum or urine HCG test result within 72 h prior to study enrollment, and must not be in the lactation period; male patients should be surgically sterilized or agree to use an appropriate contraceptive measure during the study period and within 3 months after the last dose of the study drug;</p> <p>9. Patients must participate voluntarily, sign the informed consent form, have good compliance, and cooperate with follow-up visits.</p>
Exclusion Criteria	<p>1. Patients with any active autoimmune diseases or a history of autoimmune diseases (including but not limited to the following: autoimmune hepatitis, interstitial pneumonitis, uveitis, enteritis, hepatitis, hypophysitis, vasculitis, nephritis, hyperthyroidism, hypothyroidism; adults with vitiligo or completely relieved childhood asthma can be enrolled if they do not require any intervention; patients with asthma requiring medical intervention with bronchodilators cannot be enrolled);</p> <p>2. Patients who are currently using immunosuppressive agents, or systemic or absorbable local hormonal therapies for immunosuppression purposes (> 10 mg/day prednisone or equivalent) and still use the above drugs within 2 weeks prior to enrollment;</p> <p>3. Patients who have experienced severe allergic reactions to other monoclonal antibodies;</p> <p>4. Patients with untreated metastases to central nervous system. Patients who have received the treatment of metastases to brains or meninges (radiotherapy or surgery) may be enrolled if they are clinically stable (MRI) for at least 1 month and have stopped systemic hormonal therapy (> 10 mg/day prednisone or an equivalent dose of other therapeutic hormones) for more than 2 weeks;</p> <p>5. Imaging (CT or MRI) results show that the tumor has invaded the large blood vessels or has an unclear boundary with the blood vessels;</p> <p>6. Imaging (CT or MRI) results show significant cavitation or necrosis of lung tumors; Patients with marginal adenocarcinoma with cavity may be considered for enrollment after discussion with the principal investigator.</p> <p>7. Patients with hypertension which cannot be well controlled by antihypertensives (systolic pressure ≥ 140 mmHg or diastolic pressure ≥ 90 mmHg);</p> <p>8. Patients with clinical symptoms or diseases of the heart that are not well controlled, such as (1) $> NYHA$ Class II cardiac failure; (2) unstable angina; (3) myocardial infarct within past 1 year; (4) clinically significant supraventricular or ventricular arrhythmia requiring treatment or intervention;</p> <p>9. Patients with abnormal coagulation functions (PT > 16 s, APTT > 43 s, TT > 21 s, Fbg < 2 g/L) and hemorrhagic diathesis or those who are currently treated by a thrombolytic or anticoagulant therapy;</p>

10. Patients with urinalysis results indicating that the urine protein is $\geq ++$ and the quantitative test of urine protein confirms that the 24-hour urine protein is > 1.0 g;
11. Patients who have previously received radiotherapy, chemotherapy or surgery that is less than 4 weeks before the study after the end of such treatments (last dose), or patients whose last dose of oral targeted drugs is less than 5 drug half-lives; Patients with adverse events caused by the previous treatment (except for alopecia) that have not returned to CTCAE Grade ≤ 1 ;
12. Patients with clinically symptomatic ascites or pleural effusion requiring therapeutic paracentesis or drainage;
13. Patients with obvious hemoptysis or a daily amount of hemoptysis of half a teaspoon (2.5 mL) or more within 2 months before randomization;
14. Patients with clinically significant hemorrhage symptoms or a clear hemorrhagic diathesis within 3 months prior to randomization, such as hemorrhage of digestive tract, stomach ulcer with hemorrhage, baseline fecal occult blood $++$ or above, or vasculitis;
15. Had events of arterial/venous thrombosis within 6 months prior to randomization, such as cerebrovascular accidents (including transient ischemic attacks, cerebral hemorrhage, brain infarction), deep vein thrombosis, and pulmonary embolism;
16. Known hereditary or acquired hemorrhage and thrombophilia (such as hemophilia, coagulopathy, thrombocytopenia, hypersplenism, etc.);
17. Patients with active infection or unexplained fever of > 38.5 °C during screening or prior to the first dose;
18. Patients with previous or current objective evidence of pulmonary fibrosis, interstitial pneumonia, pneumoconiosis, radiation pneumonitis, drug-induced pneumonitis, and severe lung function impairment;
19. Patients with congenital or acquired immunodeficiency, such as patients with HIV infection, or active hepatitis (hepatitis B: detection value of HBV DNA $> \text{ULN}$; for hepatitis C: HCV viral titre or RNA detection value $> \text{ULN}$);
20. Those who have used study drugs of other clinical trials within 4 weeks before the first dose of this study;
21. Patients with previous or concurrent malignancies at other sites (except for cured skin basal cell carcinoma and cervical carcinoma in situ);
22. Patients who may receive other systemic anti-tumor treatments during the study;
23. Patients with bone metastasis who have received a palliative radiotherapy in an area of $> 5\%$ of bone marrow area within 4 weeks prior to the participation in this study;
24. Patients who have previously received other anti-PD-1 antibody therapies or other immunotherapies targeting PD-1/PD-L1, or have previously received apatinib treatments;
25. Patients who have received live vaccines within less than 4 weeks before the first dose or may receive live vaccines during the study;
26. Patients who may have other factors leading to the discontinuation of the study as judged by the investigator, such as other serious diseases (including mental illness) requiring concomitant treatment, serious laboratory test abnormalities, or accompanied by family or social factors that can affect the safety of the subject or the collection of data and samples.

Discontinuation Criteria for Subjects	<p>A Subject must withdraw from/discontinue the treatment when any of the following conditions occurs:</p> <ol style="list-style-type: none"> 1. The subject withdraws informed consent and requests to withdraw from the study; 2. Imaging examinations show progressive disease; Upon the first discovery of progressive disease by imaging examinations, it must be confirmed after 4 weeks (except for rapid progression and significant clinical progression); If a subject shows local progression (1 to 4 lesions show progress) but the clinical symptoms are stable, the treatment can be continued according to the judgment of the investigator until imaging examinations show progressive disease again. Definition of clinically stable: a. no clinically significant symptoms or changes in laboratory tests; b. no changes in the performance status score (deterioration); and c. non-tumor rapid progression and tumor progression not involving major organs/sites (e.g., spinal cord compression). 3. Treated by SHR-1210 for 2 years (no progressive disease as shown by imaging); 4. Subjects with intolerable toxicity; 5. Subjects with poor compliance; 6. Subjects lost to follow-ups or show positive blood HCG results; 7. Other reasons for which the investigator considers withdrawal as necessary.
Criteria for Study Termination	<p>The termination criteria of this study include but are not limited to the following:</p> <ol style="list-style-type: none"> 1. Discovery of unexpected, important, or unacceptable risks to the subjects; 2. Major errors in the protocol found during the implementation of the study; 3. Ineffective study drug/treatment, or meaninglessness to continue the study; 4. The sponsor decides to terminate the study due to reasons such as serious delay in the enrollment of subjects or frequent protocol deviations.
Safety Endpoints	<p>The severity of AEs will be determined according to the CTCAE V4.0.3 criteria. The adverse event record form should be filled out correctly during the study, including the onset time, severity, duration, actions taken, and outcomes of the adverse events.</p>
Efficacy Evaluation	<p>The enrolled subjects shall undergo 1 imaging evaluation every 2 cycles (8 weeks). After 6 months from the first dose, clinical tumor imaging evaluation will be performed once every 12 weeks \pm 7 days as appropriate. Tumor efficacy will be evaluated based on RECIST 1.1 criteria, and the first evaluation of PR/CR subjects must be confirmed 4 weeks later.</p>
Determination of Sample Size	<p>The sample size in Stage I is primarily based on clinical considerations, and the number of subjects actually enrolled in each dose group is determined by the number of subjects who show clinically significant toxicity during the observation period for tolerability. During the expansion stage of PK study, 10-12 subjects are required for each group. The sample size in Stage I is 40-60 subjects.</p> <p>Stage II: For cohort 1. Assuming that the ORR of the combination therapy is 30% with a bilateral alpha of 0.05, enrollment of 62 subjects will have a 80% power to ensure that the ORR of the combination therapy has a lower 95% CI limit of $> 15\%$. If the dropout rate is 20%, 78 subjects should be enrolled.</p> <p>For cohorts 2 and 3, assume that the ORR point estimate of each cohort is 30% and the width of the 90% confidence interval is 0.3, 38 subjects are required for each group when a 20% dropout rate is considered.</p>

	<p>For cohort 4, assume that the ORR point estimate is 50% and the width of the 90% confidence interval is 0.4, 20 subjects are required to be enrolled.</p> <p>In Stage II, the four cohorts require to enroll a total of 174 subjects.</p>
Statistical Methods	<p>Study results will mainly be analyzed using descriptive statistics. Numerical data will be summarized in means, standard deviations, medians, maximums, and minimums. Categorical data will be summarized in frequencies (proportions), percentages, and confidence intervals.</p> <p>All statistical analyses will be performed using SAS version 9.2 or later.</p> <p>Safety analysis:</p> <p>Descriptive statistical analysis will be primarily used to analyze the adverse events, serious adverse events and adverse reactions in each dose group (the adverse reactions are defined as adverse events that are "definitely related, probably related, and indeterminable" to the study drug). Laboratory test results will describe the conditions that are normal before the study but become abnormal after treatment.</p> <p>Efficacy analysis:</p> <p>The point estimates of efficacy endpoints such as objective response rate (ORR) and clinical benefit rate (CBR) are provided with 95% confidence intervals representing the entire population. For survival, the median duration of progression-free survival, the 12-month survival rate, the median duration of survival, and their 95% confidence intervals representing the entire population will be estimated using the Kaplan-Meier method. In addition, survival plots will be plotted. Descriptive analysis will be performed for other secondary efficacy endpoints.</p> <p>PK analysis:</p> <p>The PK parameters C_{max}, T_{max}, AUC, and $t_{1/2}$ will be statistically described (n, mean, standard deviation, median, minimum, and maximum) by dose groups and planned blood sampling time points. A mean and/or median-time plot of serum concentration will be plotted. Statistical description will be given for the mean, standard deviation, median, minimum and maximum values, geometric mean and standard deviation, and %CV and 95% CI of natural log-transformed parameters (if applicable) by dose groups. Box and whisker plots will be drawn for primary parameters. The serum concentration-time plots will be drawn for each subject along with a list of serum concentrations and parameter data.</p> <p>Other analyses:</p> <p>SHR-1210-related solid tumor markers, such as expression levels of PD-L1 in tumor tissue samples, will also be analyzed using descriptive statistics.</p>
End of Study	<p>Stage I:</p> <p>The Stage I of this study will end at 3 months after the last dose of the last subject in the tolerability observation period if subjects in the PK expansion stage complete the specified PK blood sampling;</p> <p>Stage II:</p> <p>At 6 months after the first dose of the last subject in Stage II, the primary and secondary endpoints will be statistically analyzed.</p> <p>All subjects will be followed up until 12 to 24 months after the last dose of the last subject, and supplemental analysis of the primary and secondary endpoints will be performed thereafter.</p> <p>After the end of the study, if the subjects may continue to benefit from the study drug, the medication may be continued until a criterion for discontinuation is met. The occurrence of SAEs will be collected and recorded during the treatment and after the last dose according to the protocol.</p>
Study Period	Expected to be from Mar. 2017 to Sep. 2019

Schedule of Activities

Item	Screening Period			Treatment Period (28 days/cycle)			Post-Treatment		Survival follow-up
	Within 3 weeks before administration	Within 1 week before administration	Cycle 1		Cycles 2-26		End of treatment/ withdrawal (+ 3 d)	End of treatment visit (± 3 d)	Every 2 months (±3 d)
			Day 1	Day 15	Day 1	Day 15			
				(± 3 d)	(± 3 d)	(± 3 d)			
Baseline Data									
Signing of Informed Consent	×								
Demographics	×								
Tumor History/	×								
Other Medical History ^[1]									
Concomitant Medication ^[2]	×	×	×						
Laboratory tests									
Hematology ^[3]		×		×	×	×	×	×	
Urinalysis ^[4]		×		×	×	×	×	×	
Routine Stool Test ^[5]		×		×	×		×		
Blood biochemistry ^[6]		×		×	×	×	×	×	
Coagulation Function Test ^[7]		×		×	×		×		
T3, FT3, FT4, and TSH ^[8]	×				×		×		
Pituitary Adrenal Axis Test ^[9]	×								
Myocardial Zymogram ^[10]		×					×		
HBV, HCV, and HIV Tests ^[11]	×								

Item	Screening Period			Treatment Period (28 days/cycle)			Post-Treatment		Survival follow-up
	Within 3 weeks before administration	Within 1 week before administration	Cycle 1		Cycles 2-26		End of treatment/ withdrawal (+ 3 d)	End of treatment visit (± 3 d)	Every 2 months (±3 d)
			Day 1	Day 15	Day 1	Day 15			
				(± 3 d)	(± 3 d)	(± 3 d)			
Pregnancy Test ^[12]		×					×		
Detection of EGFR Mutations and ALK Fusion Genes ^[13]	×								
Clinical Evaluation and Examination									
AEs ^[14]	From informed consent to 30 days after the last dose								
Vital Signs ^[15]		×	×	×	×	×	×	×	
Physical Examination and Weight Measurement ^[16]		×	×	×	×	×	×	×	
ECOG PS		×			×		×	×	
ECG ^[17]		×		×	×	×	×		
Echocardiography ^[18]		×					×		
Blood Pressure Monitoring ^[19]	×	×		×	×	×	×		
Pulmonary Function Test ^[20]	×								
STUDY DRUGS									
Administration of SHR-1210 ^[21]			×	×	×	×			
Administration of Apatinib ^[22]			Oral administration once a day after meal						
Dispensation/Return of Apatinib ^[23]			×		×		×		

Item	Screening Period			Treatment Period (28 days/cycle)			Post-Treatment		Survival follow-up
	Within 3 weeks before administration	Within 1 week before administration	Cycle 1		Cycles 2-26		End of treatment/ withdrawal (+ 3 d)	End of treatment visit (± 3 d)	Every 2 months (±3 d)
			Day 1	Day 15	Day 1	Day 15			
				(± 3 d)	(± 3 d)	(± 3 d)			
Imaging Evaluation									
Imaging Examination ^[24]	×		Once every 2 cycles in the first 6 cycles, followed by once every 3 cycles				×		
Follow-Up after End of Treatment									
Time to Progression ^[25]							Imaging evaluation will be carried out once every 3 months (± 7 d) until progressive disease or the initiation of other cancer treatments (subjects with non-imaging PD)		
Time of Death ^[26]									×
Blood Sampling and Tumor Tissue Sampling/Sample Collection									
PK Blood Sampling ^[27]			×	×	×	×			
Sampling/Sample Collection and Detection of Biomarkers ^[28]	×								

Note:

- [1] History of tumor/other diseases: reports of pathological findings, detection of EGFR mutations, and detection of ALK fusion gene; history of tumor surgery, chemotherapy, radiotherapy, and other disease treatments; history of tumor other than non-small cell lung cancer.
- [2] Concomitant medications and treatments received within 30 days prior to the first dose and during the study period should be recorded. Once the study treatment is interrupted, only the concomitant medication and treatment used to solve new or unresolved treatment-related AEs will be recorded
- [3] Hematology: Hemoglobin, red blood cell count, white blood cell count, neutrophil count, lymphocyte count, and platelet count will be measured within 7 days before enrollment, on Day 15 of Cycle 1, Day 1 and Day 15 of subsequent cycles, upon completion of the study, and 30 days after the end of treatment.
- [4] Urinalysis: Urine protein, urine glucose, and urine occult blood (urine red blood cells and white blood cells). If two consecutive semi-quantitative protein tests show urine protein 2-3+, then a quantitative 24-h urine protein test is required. If semi-quantitative protein test shows urine protein > 3+, then a quantitative 24-h urine protein test shall be performed. The tests will be carried out within 7 days before the enrollment, on Day 15 of Cycle 1, Day 1 and Day 15 of subsequent cycles, upon completion of the study, and 30 days after the end of treatment.

- [5] Routine stool test: Occult blood; re-examination is required for fecal occult blood+; if fecal occult blood is confirmed, then a gastroscopy shall be performed. The test will be performed within 7 days before enrollment, on Day 15 of Cycle 1 and Day 1 of subsequent cycles, and upon completion of the study.
- [6] Blood biochemistry: bilirubin total, bilirubin conjugated, ALT, AST, AKP, γ -GT, protein total, albumin, urea or urea nitrogen, creatinine, uric acid, fasting blood glucose, TG, cholesterol, potassium, sodium, chlorine, calcium, phosphorus, blood lipase (only during the screening period and in the case of subsequent abdominal pain, abdominal distension and other symptoms of suspected pancreatitis), blood amylase (only during the screening period and subsequent abdominal pain, abdominal distension, and other symptoms of suspected pancreatitis). It will be carried out within 7 days before enrollment, on Day 15 of Cycle 1, Day 1 and Day 15 of subsequent cycles, upon completion of the study, and 30 days after the end of treatment.
- [7] Coagulation function: INR, APTT, PT, TT, FIB. The test will be performed within 7 days before enrollment, on Day 15 of Cycle 1 and Day 1 of subsequent cycles, and upon completion of the study.
- [8] Thyroid function test: including serum FT3, FT4 and TSH. The test will be performed 21 days before administration, on Day 1 of Cycle 2, and then once every 3 cycles.
- [9] Examination of the pituitary adrenal axis: including the test of ACTH, cortisol, and sex hormones, which will be performed during the screening period.
- [10] Myocardial zymogram: Performed once within 7 days before enrollment, then only at the onset of symptoms of precordial pain and palpitations and abnormal electrocardiograms, and at the end of treatment/upon withdrawal.
- [11] Hepatitis B, hepatitis C, and HIV tests: hepatitis B panel [If the test results are abnormal, viral replication (HBV DNA) test should be performed]; hepatitis C virus antibody (anti-HCV) test (If the test results are abnormal, virus titer should be tested); HIV antibody test.
- [12] Pregnancy test: The urine pregnancy test will be performed 72 h before the first dose for females of a childbearing age. If the result of the urine pregnancy test is positive, a serum pregnancy test shall be performed. If necessary, re-tests can be performed for confirmation.
- [13] If the subjects have previously been tested for EGFR mutations and ALK fusion gene, retests are not required; otherwise, the study site will perform relevant tests. If the subjects are positive for EGFR mutations, the test of ALK fusion gene will no longer be performed.
- [14] Adverse events: Adverse events will be collected from the time when the subjects sign the informed consent form. AEs unrelated to the study drugs will be collected to 30 days after the last dose. Treatment-related AEs will be collected until 90 days after the last dose of SHR-1210 or 30 days after the last dose of targeted anti-angiogenic therapy (whichever is longer). See the AE/SAE collection time limit in Section 8.3 for details.
- [15] Vital sign examination: Body temperature, respiration, pulse, blood pressure. The examination will be performed within 7 days before enrollment, on Day 1 and Day 15 of Cycle 1, Day 1 and Day 15 of subsequent cycles, upon completion of the study, and 30 days after treatment.
- [16] Physical examination and weight measurement: Examination of major body systems (head and face, skin system, lymph nodes, eyes, ears, nose, throat, oral cavity, respiratory system, cardiovascular system, abdomen, urogenital system, musculoskeletal system, nervous system and mental state) will be performed within 7 days before enrollment, on D1 and D15 of Cycle 1, D1 and D15 of subsequent cycles, upon completion of the study, and 30 days after the end of treatment. Body weight measurement will be started on D1 of Cycle 1 and performed on D1 of subsequent cycles, upon completion of the study, and 30 days after the end of treatment.
- [17] 12-Lead ECG: Performed within 7 days before enrollment, on Day 15 of Cycle 1, Day 1 and Day 15 of subsequent cycles, and upon completion of the study. Abnormalities in ECG must be confirmed twice via additional ECG tests.
- [18] Echocardiography: Performed within 7 days prior to the enrollment and upon completion of the study, and when clinically significant abnormalities are found during the study.

- [19] Blood pressure monitoring: The blood pressure measurement of subjects will be performed by the investigator during the screening period; during each blood pressure measurement, smoking and coffee are prohibited for 30 min before the measurement, and subjects should at least rest for 10 min, and the sitting position will be taken during the measurement by placing the elbow at the same level as the heart. Each blood pressure measurement will be taken on the same side of the body; during the study, the blood pressure monitoring will be performed by the subjects themselves and recorded in their diary card. Blood pressure will be measured at least 3 times a week in the first 2 cycles. If the blood pressure is abnormal, the measurement will be carried out every day; If the blood pressure is normal, the blood pressure measurement will be carried out twice a week after 2 cycles; In addition, the blood pressure will be measured by the investigator during each follow-up. During each blood pressure measurement, smoking and coffee are prohibited for 30 min before the measurement, and subjects should at least rest for 10 min, and the sitting position will be taken during the measurement by placing the elbow at the same level as the heart. Each blood pressure measurement will be taken on the same side of the body.
- [20] Pulmonary function test: Maximum vital capacity, the forced expiratory flow at 25-75% of forced vital capacity (FEF25-75), the peak expiratory flow rate (PEF), the maximum expiratory volume per second, diffusing capacity of the lungs for carbon monoxide (DLCO) and oxygen saturation. The test will be carried out during the screening period and then according to the judgment of the investigator in subsequent cycles.
- [21] SHR-1210 administration: SHR-1210 will be administered via intravenous injection (no prophylactics) with a fixed dose of 200 mg given in 30 min (no less than 20 min and no more than 60 min), once every 2 weeks. Each cycle contains 4 weeks (the subjects for the expanded PK study receive one dose on D1 of Cycle 1) and the longest period of drug use is 2 years. After 6 cycles of SHR-1210 administration, the treatment can be discontinued if the imaging evaluation confirms a CR.
- [22] Apatinib will be taken orally after meals, once a day, and continued throughout the study (the subjects for the expanded PK study receive the drug starting on Day 22 of Cycle 1. The administration on Day 28 of Cycle 1 and Day 28 of Cycle 2 will be given orally under fasting conditions).
- [23] Return and dispensation of apatinib. Apatinib will be dispensed on Day 1 of Cycle 1 (dispensed to subjects in the drug expansion study from Day 22 of Cycle 1). From Day 1 of Cycle 2, the return and dispensation of apatinib will be performed on Day 1 of each cycle. The remaining drugs will be returned first to verify the dose actually taken before new study drugs are dispensed.
- [24] Imaging examination: Including CT or MRI of the chest, abdomen, and brain. The baseline tumor assessment during the screening period can be extended to up to 3 weeks before treatment. Qualified CT/MRI scan results obtained before signing the informed consent can be used for tumor assessment during the screening period. Bone scan should be performed upon clinically suspected bone metastasis. Absence of cerebral hemorrhage should be confirmed within 21 days before randomization for subjects with stable brain metastases.
- During the treatment period, imaging examinations should be performed under the same conditions as those at baseline (layer thickness of the scan, use of contrast agent, etc.), and the lesions found at baseline should be checked every 2 cycles in the first 6 cycles of the treatment (bone scan shall be performed in the case of suspected bone progression or for CR confirmation). After 6 cycles, imaging examinations can be performed every 3 weeks as appropriate and can be performed upon the discovery of suspected new lesions. Initial assessment of PR/CR must be confirmed after 4 weeks; initial assessment of PD must be confirmed after 4 to 6 weeks (except for significant changes in the subjects' symptoms or rapid tumor progression).
- The window period for imaging examination schedule is ± 7 days. Unscheduled imaging examinations can be performed when progressive disease is suspected (such as worsening of symptoms).
- [25] A tumor assessment is required at the end of treatment for subjects who discontinue study treatment for reasons other than radiographic PD, if not performed within 4 weeks prior to study completion. Also, treatment efficacy will be followed up once every 3 months after study completion, until documentation of confirmed PD or start of a new anti-tumor treatment.

- [26] Survival follow-up: After the study treatment is discontinued, the survival status and subsequent anti-tumor treatment can be collected through clinical or telephone follow-ups every 2 months until death.
- [27] PK blood sampling: In the stage of expanded PK study, PK blood sampling will be performed within 0.5 h before the administration of SHR-1210, and post-dose at 5 min (\pm 3 min), 2 h (\pm 10 min), 6 h (\pm 10 min), 24 h (\pm 0.5 h), 48 h (\pm 1 h), 168 h (\pm 1 h), 336 h (\pm 1 h), and 504 h (\pm 1 h) on D1, with 3 mL of blood collected at each time point. After the completion of PK blood sampling on D22, the administration of apatinib mesylate tablets will be started on the same day and continued at a administration frequency of once a day. PK blood sampling will be performed within 0.5 h pre-dose on D28 and post-dose at 0.5 h (\pm 3 min), 1 h (\pm 5 min), 2 h (\pm 5 min), 3 h (\pm 5 min), 5 h (\pm 10 min), 8 h (\pm 10 min), 12 h (\pm 10 min), and 24 h (\pm 1 h), with 3 mL of blood collected at each time point.
- On D1 of Cycle 2, PK blood sampling will be performed within 0.5 h before the administration of SHR-1210, and at 5 min (\pm 3 min), 2 h (\pm 10 min), 6 h (\pm 10 min), 24 h (\pm 0.5 h), 48 h (\pm 1 h), 168 h (\pm 1 h), and 336 h (\pm 1 h) after the administration of SHR-1210, with 3 mL of blood collected at each time point. On D28 of Cycle 2, PK blood sampling will be performed within 0.5 h before the administration of apatinib, and at 0.5 h (\pm 5 min), 1 h (\pm 5 min), 2 h (\pm 5 min), 3 h (\pm 5 min), 5 h (\pm 10 min), 8 h (\pm 10 min), 12 h (\pm 10 min), and 24 h (\pm 1 h) after the administration of apatinib, with 3 mL of blood collected at each time point.
- [28] A total of 14 mL of blood sample will be collected from each subject at baseline and divided into 1 tube of 10 mL and 1 tube of 4 mL. The collected blood samples will be transported to the central laboratory at room temperature according to the requirements specified in the central laboratory manual (no additional processing by the study center is required). Subjects with CR/PR during the study period shall undergo an additional biomarker blood sampling upon the onset of CR/PR and PD, respectively, with 10 mL in 1 tube, and the collection and transport requirements are the same as those in the baseline period; archived paraffin-embedded tumor tissue samples or fresh biopsy specimens will be collected. At least 10 slices are required, including 3-5 slices of 3-4 μ m thickness for PD-L1 detection, and 5-8 slices of 5-8 μ m thickness (paraffin blocks may be directly collected without mounting onto slides), otherwise fresh biopsy specimens are required for detection of biomarkers such as tumor mutation burden (TMB).
- For cohort 4, the test results of tumor mutation burden (TMB) in the peripheral blood and/or tumor tissues will be verified before the subjects take the first dose of the study drug, so the TMB test for cohort 4 must be completed before the first dose. However, the delay in the screening period caused by TMB testing is allowed, but other tests (including imaging examinations) must be completed within 21 days prior to the first dose.
- See the laboratory manual for biomarker blood sampling and tumor tissue sampling/sample collection and disposal.

List of Abbreviations

Abbreviations and Terms	Full Name
ADA	Anti-drug antibody
ADRs	Adverse drug reactions
AE	Adverse event
AKP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under curve
BP	Blood pressure
BUN	Blood urea nitrogen
B-scan	-
Ca	Calcium
CFDA	China Food and Drug Administration (now NMPA)
Cl	Chlorine
Cr	Creatinine
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DBIL	Direct bilirubin
DCR	Disease control rate
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data collection
FAS	Full analysis set
FIB	Fibrinogen
FDA	Food and Drug Administration
FT3	Free triiodothyronine
FT4	Free thyroxine
GCP	Good Clinical Practice
Glu	Glucose

Abbreviations and Terms	Full Name
Hb	Hemoglobin
IBIL	Indirect bilirubin
ieAE	Immune-related adverse event
INR	International normalized ratio
IRB	Institutional review board
ITT	Intention to treat
K	Potassium
LLN	Lower limit of normal
LVEF	Left ventricular ejection fraction
mPFS	Median progression-free survival
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
Na	Sodium
NCCN	National Comprehensive Cancer Network
NCI-CTC	National Cancer Institute Common Terminology Criteria
ORR	Objective response rate
OS	Overall survival
P	Phosphorus
PD	Progressive disease
PD-1/PD-L1	Programmed death 1/programmed death ligand 1
PFS	Progression-free survival
PK	Pharmacokinetics
PLT	Platelet
PPS	Per-protocol set
PR	Partial response
PT	Prothrombin time
QoL	Quality of life
RBC	Red blood cell
RO	Receptor occupancy
RECIST	Response evaluation criteria in solid tumors
SAE	Serious adverse event
SAS	Statistical analysis software
SD	Stable disease
SOP	Standard operating procedure
SS	Safety analysis set
TB	Total bilirubin

Abbreviations and Terms	Full Name
TC	Total cholesterol
TCM	Traditional Chinese medicine
TG	Triglyceride
TP	Plasma total protein
TSH	Thyroid-stimulating hormone
TT	Thrombin time
UA	Blood uric acid
UICC	Union for International Cancer Control
ULN	Upper limit of normal
WBC	White blood cell
γ -GT	γ -Glutamyltransferase

1 BACKGROUND

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

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

A number of multinational pharmaceutical companies are currently developing monoclonal antibodies against programmed cell death protein-1 (PD-1, CD279). By blocking the binding between PD-L1/PD-1, these monoclonal antibodies maximize a patient's own immune response against the tumor, thereby achieving the purpose of killing tumor cells. BMS and Merck's PD-1 monoclonal antibodies are currently the most advanced anti-PD-1 antibody drugs.

In Jul. 2014, Nivolumab was approved by the Japanese Ministry of Health and Welfare for the treatment of advanced melanoma. It was approved by the FDA for the treatment of melanoma in Dec. 2014, approved by the FDA for the treatment of non-small cell lung cancer in Mar. 2015, and approved by the FDA for the treatment of renal cell carcinoma in Nov. 2015. In 2016, indications of Nivolumab were added by its approval for use in the treatment of classical Hodgkin's lymphoma.

In Sep. 2014, Pembrolizumab was approved by the FDA for the treatment of advanced melanoma. In Oct. 2015, Pembrolizumab was approved by the FDA for the treatment of non-small cell lung cancer.

PD-1/PD-L1 inhibitors, including nivolumab, Atezolizumab, and Avelumab, will play a leading role in the combination treatment regimens of cancer patients. These drugs will break through the current treatment regimens and become the backbone of the combination therapy. This idea has been confirmed in melanoma patients. In a double-blind clinical study of CheckMate-069, the combination therapy of nivolumab and a CTLA-4 inhibitor ipilimumab reduced the mortality by 60% (HR: 0.40; 95%CI: 0.22-0.71; $P < .002$) compared with the use of ipilimumab alone. For melanoma patients harboring wild-type BRAF, the ORR of the combination therapy was 60%, while the ORR of ipilimumab alone was 11%. Therefore, FDA accelerated the approval of nivolumab in combination with ipilimumab (Yervoy) as a treatment for patients with unresectable or metastatic melanoma who harbor wild-type BRAF V600. According to the reports in the 2016 Annual Meeting of the American Gastroenterological Association and the annual meeting of the American Society of Clinical Oncology, in the Checkmate-032 study for Nivolumab, 59 patients with advanced esophageal cancer and gastric cancer were assigned to the Nivolumab group, and the overall response rate was 14%. The response rate of PD-L1 positive ($> 1\%$) patients was 27%, including a case of complete response, and the 1-year survival rate was 36%.

Anti-angiogenic drugs include mAb targeting the vascular endothelial growth factor (VEGF), such as bevacizumab, and multi-targeted TKIs that have been used in the early clinical studies of the combination therapy of anti-PD-1/PD-L1 mAb. In metastatic RCC, a phase I study was carried out using the combination therapy of Nivolumab + Sunitinib ($n = 33$), and Nivolumab + Pazopanib ($n = 20$). Grade 3/4 TEAEs were reported in 73% ($n = 24/33$) patients receiving Nivolumab plus Sunitinib and 60% ($n = 12/20$) patients receiving Nivolumab plus Pazopanib. These resulted in treatment discontinuation in 24% ($n = 8/33$) of patients receiving sunitinib and 20% ($n = 4/20$) of patients receiving pazopanib. In addition to anti-angiogenic effects, blockage of VEGF has been reported to exert immunomodulatory effects such as promoting the activity of effector T-cells, reducing MDSCs, T-regulatory cells, and inhibitory cytokines in the tumor microenvironment. The combination of bevacizumab and atezolizumab was studied in the metastatic clear-cell RCC and metastatic CRC, and the known AEs of bevacizumab were not aggravated. This combination is being studied in a phase II study of RCC (NCT01984242).

Although this type of therapy has not obtained some data and there are many studies in progress, it is not to be overlooked that a large proportion of patients still do not respond to the therapy and will increase some adverse reactions. From the current point of view, the combination therapy will be one of the inevitable trends in the future development of immunomodulatory therapy of tumors. How to carry out the combination therapy is a problem to be solved by the medical community. Alternative combination therapies include targeted therapies, immunosuppressive/stimulating molecules, vaccines, chemotherapy, and radiation therapy.

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

Some key factors should be considered in the clinical development of combination therapies, such as optimizing administration regimens, minimizing treatment-related toxicity, selecting appropriate endpoints to assess the efficacy, and so on.

This clinical study involves recombinant humanized anti-PD-1 monoclonal antibody injection (SHR-1210 for injection), a new class 1 therapeutic biological product that has not been marketed in China or abroad. Drugs of same class are marketed abroad. Preclinical studies have shown that recombinant humanized anti-PD-1 monoclonal antibody injection developed by Hengrui has comparable in vivo efficacy and safety compared with those of drugs of same class abroad, and may have a better potential in anti-tumor clinical applications. Since 2015, Hengrui has carried out the phase I clinical studies of SHR-1210 in several types of tumors in Australia and China, and has initially validated the safety, tolerability and efficacy of SHR-1210 monotherapy in the treatment of advanced solid tumors.

This study also involves a product with the trade name of apatinib® and generic name of apatinib mesylate tablets (English name: Apatinib Mesylate), a small molecule tyrosine kinase inhibitor. The National Medical Products Administration has approved the use of apatinib in the treatment of advanced gastric cancer on 17 Nov., 2014. Apatinib has also shown efficacy in a phase II clinical study of advanced non-small cell lung cancer (NSCLC) by significantly prolonging the progression-free survival (PFS) of patients.

1.1 Product Name and Physicochemical Properties

[Generic Name] Recombinant Humanized Anti-PD-1 Monoclonal Antibody for Injection (SHR-1210)

[English Name] SHR-1210 for Injection

[Molecular Weight] About 143 KD

[Dosage Form] Lyophilized Powder for Injection

[Strength] 200 mg/vial

[Generic Name] Apatinib Mesylate Tablets

[English Name] Apatinib Mesylate Tablets

[Molecular Weight] About 493.58 KD

[Dosage Form] Tablet

[Strength] 250 mg/tablet; 375mg/tablet

1.2 Pharmacology and Mechanism of Action

Programmed Death-1 (PD-1) is a protein receptor located on the surface of T cells and is involved in the process of cell apoptosis. PD-1 belongs to the CD28 family and is mainly expressed on activated T cells, B cells and myeloid cells. PD-1 has two ligands, PD-L1 and PD-L2. PD-L1 is mainly expressed on T cells, B cells, macrophages and dendritic cells, and its expression is up-regulated on activated cells. In contrary, the expression of PD-L2 is mainly restricted to antigen presenting cells, such as activated macrophages and dendritic cells.

Humanized anti-PD-1 monoclonal antibody can specifically bind to PD-1 and block the interaction between PD-1 and its ligands, allowing T cells to recover tumor-targeting immune responses.

Apatinib is a potent and selective inhibitor of vascular endothelial growth factor receptor-2 (VEGFR-2). The activity assay showed that its inhibitory effect against VEGFR-2 is stronger than that of drugs of same class (sorafenib, sunitinib, pazopanib, etc.); its selectivity for VEGFR-2 is ≥ 30 times stronger than that of other targets (VEGFR-1/PDGFR, SRC, etc.). Apatinib can effectively inhibit the *in vitro* lumen formation of Human Umbilical Vein Endothelial Cells (HUVEC) and the formation of arterial ring capillaries in rats, and has a strong inhibitory effect against neovascularization.

1.3 Pharmacodynamics

Studies on the binding affinity of SHR-1210 antibody to human, monkey and rat antigens showed that the affinities of SHR-1210 to human and monkey PD1 antigens were quite close at 6.9 nM and 4.1 nM, respectively, but no binding was detected with rat PD-1 antigens. The binding affinity of SHR-1210 to human PD-1 antigen was 3.0 nM, which was similar to those of the control antibodies nivolumab and pembrolizumab.

Experimental results from inhibition of PD-1/PD-L1 binding by SHR-1210 showed that the *in vitro* binding inhibition activity of SHR-1210 was comparable to those of nivolumab and pembrolizumab. The IC₅₀ of inhibition activities of SHR-1210, nivolumab and pembrolizumab were 0.70 nM/0.79 nM and 0.79 nM/0.77 nM, respectively.

Apatinib can effectively inhibit VEGFR2 (KDR) at very low concentrations and can also inhibit VEGFR2 (Flt 1), PDGFR, and c-Kit at higher concentrations. Apatinib is also highly selective. See the table below for details. The effect of apatinib on VEGFR2 is 13.7-fold higher than PTK787; apatinib also inhibits VEGFR2-mediated downstream signaling. Apatinib also inhibits the growth of KDR/NIH3T3 cell lines with high-expression of VEGF, inhibits VEGF-induced proliferation, migration and lumen formation of HUVEC cells, and inhibits the germination of microvessels on rat arterial rings. Apatinib has remarkable anti-tumor effects on a variety of human tumors such as colon cancer, lung cancer, and gastric cancer xenografts in nude mice. And it exerts obvious synergistic effects on traditional cytotoxic drugs such as oxaliplatin, 5-Fu, docetaxel, and doxorubicin.

1.4 Toxicology Studies

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

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

Apatinib primarily caused slight changes in body weight, food intake, liver function, and bone in rats. After 4 weeks of drug discontinuation, all other changes were recovered except that the bone changes were partially recovered. 15 mg/(kg·d): The safe dose in male and female rats. 50 mg/(kg·d): The toxicity dose of male and female rats, and female rats are more sensitive. The 3 months oral application of 30 mg/(kg·d) of apatinib capsules in Beagle dogs showed no significant toxicity.

1.5 Pharmacokinetic Study

1.5.1 PK of SHR-1210 after administration

For SHR-1210 PK parameters after a single intravenous infusion in cynomolgus monkeys, see Table 1.

Table 1-1. Pharmacokinetic parameters obtained after a single intravenous infusion of different doses of SHR-1210 in cynomolgus monkeys

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

1.5.2 Pharmacokinetic data of apatinib

1.5.2.1 Pharmacokinetic studies in healthy population

Previous studies have found that after a single oral administration of apatinib mesylate in healthy subjects under fasting conditions, the parent form drug was absorbed fast in the body and time to reach the maximum plasma concentration was about 1.7-2.3 h. Its elimination is slow and its half-life was 7.9-9.4 h. The time to reach the maximum plasma concentration of three hydroxylated metabolites (cis-3-hydroxy apatinib M1-1, trans-3-hydroxy apatinib M1-2, and apatinib-25-N-oxide M1-6) and the hydroxylated and glucuronic acid conjugate (the glucuronic acid conjugate of M1-1 is M9-2) were quite late (about 2.7-5.8 h), and their elimination half-lives were about 9-18 h. In the 250 mg and 500 mg dose groups, the plasma exposure of parent form drug and its four metabolites was directly proportional to the dose, but there was no further increase in the plasma exposure of parent form drug and its metabolites in the 750 mg dose group. The primary pharmacokinetic parameters of apatinib and its metabolites showed no significant gender differences in healthy subjects.

1.5.2.2 Pharmacokinetic studies in patients with advanced solid tumors

The single oral doses used in this study included: 500, 750, and 850 mg/person. The low dose group enrolled 7 male and 5 female tumor subjects. The medium dose group enrolled 6 males and 3 females. The high dose group enrolled 6 males and 6 females. In this study, the drug was administered 0.5 h after meals. Blood and urine samples were collected at multiple time points within 48 h. The results showed that M1 was a major metabolite produced by apatinib in humans. The AUCM1/AUC of apatinib was 1.15-5.06, the Cum.AeM1/Cum.Ae excretion of apatinib in 48 h via urine was 24.5-353. The $t_{1/2}$ of apatinib and M1 was 8.93 ± 0.81 h and 12.5 ± 1.666 h, respectively. At the same dose, subjects showed greater individual differences in their exposure levels of apatinib and M1 (AUC and C_{max}), and only the high dose group showed statistically significant gender differences ($p < 0.05$), with the AUC and C_{max} in females 1.96 times and 3.57 times higher than those in males, respectively. The levels of apatinib and M1 exposure in male and female subjects were not dose-proportional but were positively correlated to oral doses.

1.5.2.3 Food-effect studies

The food-effect study mainly compared the differences in absorption of a single oral dose of apatinib given at 1 h before meals and 0.5 h after meals. The concentrations of M1 were also examined. Blood and urine samples were collected at multiple time points within 48 h. The results showed that there was no significant difference in the T_{max} and C_{max} of apatinib in the blood of male and female subjects with respect to the order of eating and drug administration ($P > 0.05$). In addition, the AUC, $t_{1/2}$ and Cum.Ae of apatinib, and relevant pharmacokinetic parameters of M1 were not affected by the order of eating and drug administration ($P > 0.05$).

1.6 Results of Tolerability in the Clinical Studies

Based on the modified Fibonacci method, the initially designed doses of apatinib were 250 mg, 500 mg, 750 mg, 850 mg, and 1000 mg. According to the study design, the Grade 4 hematological toxicity and/or Grade ≥ 3 non-hematological toxicity occurring in the first course of treatment (28 days) were determined as DLT. A total of 19 patients were evaluable for tolerability, with 6 patients in the 850 mg dose group and 3 patients each in remaining dose groups.

The DLT of apatinib appeared in the 1000 mg dose group, which was characterized by Grade 3 hypertension and Grade 3 hand-and-foot syndrome. Among the 3 patients, 2 patients had Grade 3 hypertensive toxicity and 1 patient had Grade 3 hand-and-foot syndrome. The toxicity could be controlled by delaying the dose and resuming treatment at a reduced dose after the toxicity was alleviated. In the additional 850 mg dose group, none of the 6 patients showed DLT. For further safety considerations, the observation time of the 850 mg group was extended to two cycles and DLT was still not present, thus 850 mg was identified as the maximum tolerated dose.

In the first course of apatinib treatment, the primary manifestations of toxicity were: Hypertension (10/16), hand-and-foot syndrome (7/16), bone marrow suppression (7/16), oral ulcers (5/16), esophagitis (2/16), chest and back pain (2/16), hoarse voice (2/16), asthenia (2/16), diarrhea (1/16), and proteinuria (1/16).

In the 750 mg and lower dose groups, hematological toxicities were all Grade 1-3, including leukopenia and thrombocytopenia, while other non-hematological toxicities were all Grade 1-2, which could recover to normal after symptomatic treatment.

1.7 Progress in Stage I Clinical Studies

1.7.1 Progress in the clinical studies of SHR-1210

The phase I clinical study of SHR-1210 was launched in Australia in 2015. Since it was issued with the approval for the clinical study of national class I new drug (certificate no. 2016L01455) in February 2016, it had been tested in phase I clinical studies at Cancer Hospital Chinese Academy of Medical Sciences, Sun Yat-sen University Cancer Center, and Beijing Cancer Hospital against multiple types of solid tumors (primarily nasopharyngeal carcinoma, non-small cell lung cancer, triple negative breast cancer, melanoma, and various GI cancers). The study focused on human safety and tolerability of SHR-1210, and examined the pharmacokinetic characteristics and preliminary efficacy of SHR-1210 in humans. The study adopted a classic 3+3 dose escalation method to investigate the safety and tolerability of SHR-1210 in humans. A dose expansion group was set up to investigate the preliminary efficacy and safety of SHR-1210. Preliminary results indicated that SHR-1210 was safe and tolerable with a certain preliminary efficacy in a variety of solid tumors, including non-small cell lung cancer.

Up to now (data as of 31 Oct., 2016), 111 subjects with solid tumor have been enrolled in China and abroad, including 87 subjects enrolled in China. Tolerability observation showed that different doses of SHR-1210 (1 mg/kg, 3 mg/kg, 10 mg/kg and fixed doses of 60 mg, 200 mg, and 600 mg) were well tolerated in human, and no DLT was observed in any of the dose groups during the observation period, i.e., the maximum tolerated dose (MTD) is greater than 10 mg/kg or the fixed dose of 600 mg.

In terms of safety, the overall incidence of adverse events (AEs) in domestic studies was 77% (67/87), which were primarily skin reactions, fever, hypothyroidism, transaminase increased, and gastrointestinal reactions. The AEs were mostly related to the mechanism of drug action, and were mostly mild to moderate. After symptomatic treatment or interruption of SHR-1210, the AEs were resolved or disappeared.

The investigator determines that the incidence of SHR-1210-related AEs was 59.8% (52/87), and the most were mild to moderate as shown in the table below:

Treatment-related AEs in three phase I clinical studies of SHR-1210 in China (data as of 31 Oct., 2016)

System Organ Class/Preferred Term		Total (N = 67) 67 (77.0%)	
Number of Subjects with at Least One Event			
Investigations	22 (25.3%)	Skin and Subcutaneous Tissue Disorders	36 (41.4%)
Alanine Aminotransferase Increased	7 (8.0%)	Hemangioma of skin	32 (36.8%)
Aspartate Aminotransferase Increased	7 (8.0%)	Rash	7 (8.0%)
White Blood Cell Count Decreased	3 (3.4%)	Pruritus	6 (6.9%)
Blood Bilirubin Increased	3 (3.4%)	Rash Maculo-Papular	3 (3.4%)
Electrocardiogram QT prolonged	2 (2.3%)	Flushed skin	1 (1.1%)
Elevated CR-MB	2 (2.3%)	Palmar-plantar erythrodysesthesia syndrome	1 (1.1%)
Troponin increased	1 (1.1%)	Urticaria	1 (1.1%)
White Blood Cell Count Increased	1 (1.1%)		
Neutrophil count decreased	1 (1.1%)	General Disorders and Administration Site Conditions	18 (20.7%)
Blood Thyroid Stimulating Hormone Increased	1 (1.1%)	Pyrexia	9 (10.3%)
Blood prolactin increased	1 (1.1%)	Asthenia	5 (5.7%)
Blood myoglobin increased	1 (1.1%)	Fatigue	4 (4.6%)
Blood creatine phosphokinase increased	1 (1.1%)	Chills	1 (1.1%)
Blood Creatinine Increased	1 (1.1%)		
Hypokalaemia	1 (1.1%)	Endocrine Disorders	9 (10.3%)
		Hypothyroidism	8 (9.2%)
		Hyperthyroidism	1 (1.1%)
		Gastrointestinal Disorders	7 (8.0%)
		Nausea	2 (2.3%)
		Diarrhea	2 (2.3%)
		Abdominal Distension	1 (1.1%)
		Mouth Ulceration	1 (1.1%)
		Vomiting	1 (1.1%)
		Constipation	1 (1.1%)
		Blood and Lymphatic System Disorders	4 (4.6%)
		Anemia	4 (4.6%)
		Nervous System Disorders	3 (3.4%)
		Insomnia	1 (1.1%)
		Headache	1 (1.1%)
		Dizziness	1 (1.1%)
		Hepatobiliary Disorders	2 (2.3%)
		Hepatic function abnormal	2 (2.3%)

System Organ Class/Preferred Term	Total (N = 67) 67 (77.0%)	
Number of Subjects with at Least One Event		
	Metabolism and Nutrition Disorders	7 (8.0%)
	Decreased Appetite	3 (3.4%)
	Hypertriglyceridaemia	2 (2.3%)
	Oedema Peripheral	1 (1.1%)
	Hyperglycaemia	1 (1.1%)
	Infections and Infestations	1 (1.1%)
	Conjunctivitis	1 (1.1%)
	Immune System Disorders	1 (1.1%)
	Anaphylaxis	1 (1.1%)

The incidence of Grade 3 or greater AEs was 10.3%, and the incidence of Grade 3 or greater treatment-related AEs was 2.3%. Grade 3 or greater AEs are shown in the table below:

Grade 3 or greater AEs in three phase I clinical studies of SHR-1210 in China (data as of 31 Oct., 2016)

System Organ Class/Preferred Term		Total (N = 67)	
Number of Subjects with at Least One Event		67 (77.0%)	
Highlighted are treatment-related AEs as judged by the investigator			
Investigations	5 (5.7%)	Gastrointestinal Disorders	2 (2.3%)
Hypochloraemia	2 (2.3%)	Abdominal Pain	1 (1.1%)
		Upper Gastrointestinal Haemorrhage	1 (1.1%)
Hyponatraemia	2 (2.3%)		
Aspartate Aminotransferase Increased	2 (2.3%)		
Blood Bilirubin Increased	1 (1.1%)	Metabolism and Nutrition Disorders	1 (1.1%)
Hypophosphatemia	1 (1.1%)	Hypercalcaemia	1 (1.1%)
Alanine Aminotransferase Increased	1 (1.1%)		
Elevated CR-MB	1 (1.1%)	Hepatobiliary Disorders	1 (1.1%)
		Hepatic function abnormal	1 (1.1%)
General Disorders and Administration Site Conditions			
Site Conditions	3 (3.4%)		
Pyrexia	1 (1.1%)	Musculoskeletal and Connective Tissue Disorders	1 (1.1%)
Progressive disease	1 (1.1%)	Back pain	1 (1.1%)
Death	1 (1.1%)	Lumbago	1 (1.1%)
Blood and Lymphatic System Disorders			
Anemia	2 (2.3%)	Endocrine Disorders	1 (1.1%)
		Hypothyroidism	1 (1.1%)

Preliminary safety data indicated that the overall safety of the SHR-1210 was acceptable.

The assay of PD1 receptor binding rate showed that a single dose of 1 mg/kg of SHR-1210 could achieve > 80% PD1 receptor occupancy, and the receptor binding effect of SHR-1210 was continuous. This indicates that the clinical dose of SHR-1210 is able to achieve a sustained and high binding rate to PD1, so as to play a role in overcoming tumor immune escape.

The pharmacokinetic study of SHR-1210 in patients with advanced solid tumors showed that the in vivo exposure (AUC) and C_{max} of SHR-1210 increased proportionally with the increasing dose of the drug, and no pharmacokinetic saturation was observed. The elimination half-life ($t_{1/2}$) of SHR-1210 in human is about 3.5 d (1-3 mg/kg), and the $t_{1/2}$ of a fixed dose of 200 mg is 5.83 ± 0.91 d, supporting q2w (14 d/dose) administration.

In terms of efficacy, as of 15 Nov., 2016, clinical studies in China showed a preliminary efficacy of SHR-1210 against solid tumors that have failed multiple standard treatments. The overall objective response rate (ORR) was 20.8% (10/48); the disease control rate (DCR) was 41.7% (20/48). Among them, the objective response rate (ORR) of SHR-1210 in non-small cell lung cancer was 9.1% (1/11), and the disease control rate (DCR) was 45.5% (5/11). The efficacy of SHR-1210 was also similar to the efficacy data reported by drugs of the same class, and SHR-1210 had a longer duration of tumor response/benefit. Subjects with objective tumor response or stability had a longer duration of response/benefit (this was an observed trend due to ongoing studies and lack of exact data support).

The phase I clinical studies of SHR-1210 in patients with advanced solid tumors have shown that SHR-1210 has excellent safety and tolerability; PK, PD characteristics and worth exploring preliminary efficacy.

1.7.2 Progress in the clinical studies of apatinib

1.7.2.1 Stage I tolerability study of apatinib

According to the modified Fibonacci method, the designed doses of apatinib were 250 mg, 500 mg, 750 mg, 850 mg, and 1000 mg. According to the study design, the Grade 4 hematological toxicity and/or Grade ≥ 3 non-hematological toxicity occurring in the first course of treatment (28 days) were determined as dose limiting toxicity (DLT). A total of 18 subjects were evaluable for tolerability, with 3 subjects in each dose group (6 subjects in the 850 mg dose group). DLT appeared in the 1000 mg dose group and was featured as Grade 3 hypertension (2/3) and Grade 3 hand and foot skin reactions (1/3). In the additional 850 mg dose group, none of the 6 patients showed DLT. Therefore, the 850 mg dose was identified as the maximum tolerated dose (MTD).

The primary AEs in Cycle 1 of the tolerability test included: hand and foot skin reaction, hypertension, leukopenia, oral mucositis, fever, thrombocytopenia, asthenia, bilirubin increased, headache, abdominal pain, nausea, and transaminases increased. The most AEs were mild to moderate. Treatment-related adverse reactions primarily included hand and foot skin reactions, leukopenia, hypertension, fever, bilirubin increased, oesophagitis, dermal toxicity, thrombocytopenia, nausea, asthenia, headache, transaminases increased, oral mucositis, upper abdominal discomfort, tongue pain, hoarseness, stomach discomfort, chest tightness and cough, proteinuria, and sinus bradycardia. In groups of 850 mg and lower doses, hematological toxicities were Grade 1-3, while other non-hematological toxicities were all Grade 1-2, which could recover to normal after symptomatic treatment.

1.7.2.2 Phase I clinical pharmacodynamic (PD) observation of apatinib

From May 2007 to Dec. 2008, a phase I clinical study of apatinib was conducted at Fudan University Shanghai Cancer Center, including 3 studies, i.e., a tolerability study, a pharmacokinetic study, and a phase I supplement clinical study. A total of 81 subjects with advanced solid tumors were enrolled. Nine of the subjects were not evaluated, and another 3 subjects were only administered with a low dose of 250 mg/day. A total of 69 subjects received apatinib treatment at doses of 500-1000 mg/day (only 3 subjects received 1000 mg/day), and a total of 56 patients were evaluated. Of the 69 subjects included in the statistics, 16 subjects were given 500 mg, 37 subjects were given 750 mg, 13 subjects were given 850 mg, and 3 subjects were given 1000 mg.

Table 1. Efficacy of apatinib in the treatment of different solid tumors

	Gastric Cancer	Colorectal Cancer	Lung Cancer	Breast Cancer	Nasopharyngeal Carcinoma	Renal Cancer	Esophageal Cancer	Hepatic Cancer	Small Intestinal Stromal Tumor	Neurilemmoma Malignant of Left Iliac Fossa
Not Evaluable	1	7	1	1	1	0	1	1	0	0
CR	0	0	0	0	0	0	0	0	0	0
PR	2	2	0	0	0	1	0	0	1	0
SD	5	15	3	4	1	0	4	1	0	0
PD	1	7	1	2	0	0	0	0	0	1
Death Without Evaluation	3	1	0	0	0	0	0	0	0	0
Objective Response Rate	18.1%	8%	0	0	0	100%	0	0	100%	0
Disease control rate	63.6%	68%	75%	66.7%	100%	100%	100%	100%	100%	0
Total	12	32	5	7	2	1	5	2	1	1

The results showed that, objective response rate: 1 subject each of renal cancer and small intestinal stromal tumor both had efficacy of PR; 11 and 25 evaluable patients were included for the gastric cancer and colorectal cancer respectively, and higher response rates of 18.1% and 8%, respectively, were achieved. Disease control rate: 1 evaluable subject each for nasopharyngeal carcinoma, hepatic cancer, and GIST, respectively, and their efficacy was all SD; the disease control rates of evaluable patients of esophageal cancer, lung cancer, and breast cancer were 100%, 75% and 66.7%, respectively. However, the efficacy is still difficult to determine due to the small number of subjects.

1.7.2.3 Stage I clinical pharmacokinetic studies of apatinib

A single oral dose study of apatinib was performed at doses of 500, 750, and 850 mg, and all drug administration was performed 0.5 h after meals. Blood and urine samples were collected at multiple time points within 48 h post-administration. The results showed that M1 was a major metabolite produced by apatinib in humans. The AUCM1/AUC of apatinib was 1.15-5.06, and the Cum.AeM1/Cum.Ae excretion of apatinib in 48 h via urine was 24.5-353. The $t_{1/2}$ of apatinib and M1 was 8.93 ± 0.81 h and 12.5 ± 1.666 h, respectively. At the same dose, subjects showed greater individual differences in their exposure levels of apatinib and M1 (AUC and C_{\max}), and only the high dose group showed statistically significant gender differences ($p < 0.05$), with the AUC and C_{\max} in females 1.96 times and 3.57 times higher than those in males, respectively. The levels of apatinib and M1 exposure in male and female subjects were not dose-proportional but were positively correlated to oral doses.

The multiple-dose study focused on investigating the accumulation of M1 in the body and observing the concentration change of apatinib ($t_{1/2}$: 9.24 ± 1.40 h) during the study. The drug was administered once a day for 4 weeks, and blood and urine samples at multiple time points within 24 h post-administration were collected on Day 1, 14, and 28 after the start of the study. The results of the study showed that M1 and apatinib did not significantly accumulate in the subjects based on the comparison of the values obtained on Day 1 and Day 14 after the start of the study ($P > 0.05$). However, the M1 exposure level in male subjects significantly increased on Day 28 compared with that on Day 1 ($P < 0.05$). There was no significant accumulation of apatinib and M1 based on the cumulative levels of urinary and renal excretion ($P > 0.05$).

Food impact experiment: The results showed that there was no significant difference in the T_{\max} and C_{\max} of apatinib in the blood of male and female subjects with respect to the order of eating and drug administration ($P > 0.05$). In addition, the AUC, $t_{1/2}$ and Cum.Ae of apatinib, and relevant pharmacokinetic parameters of M1 were not affected by the order of eating and drug administration ($P > 0.05$).

1.7.2.4 Phase II clinical study results of apatinib in the treatment of advanced non-squamous and non-small cell lung cancer

The phase II clinical study of apatinib in the treatment of advanced non-squamous non-small cell lung cancer enrolled a total of 138 subjects, with 92 subjects in the treatment group and 46 subjects in the placebo group. A total of 136 subjects completed the study (2 patients obtained random numbers but withdrew from the study without using the drug), including 68 males and 68 females. Among these 136 subjects, 45 subjects were in the placebo group and 91 subjects were in the treatment group. There were 4 dropouts in the study and the drop-out rate was 2.94%; 2 subjects were rejected and the rejection rate was 1.47%.

The analysis of primary efficacy endpoints showed that in the FAS analysis set, the patients' mPFS in the treatment group was significantly higher than that in the placebo group (4.7 months vs. 1.9 months), and the difference was statistically significant ($P < 0.0001$). The hazard ratio between the treatment group and the placebo group was 0.278, and its 95% CI was 0.170-0.455 ($P < 0.0001$). In terms of secondary efficacy endpoints, in the FAS analysis set, the apatinib group showed a good efficacy by improving the objective response rate and clinical benefit rate of the patients compared with the placebo group. The objective response rate was 16.67% in the treatment group and 0% in the placebo group. The difference between the two groups was statistically significant at $P = 0.0158$. The objective response rate of the treatment group was higher than that of the placebo group. The disease control rate was 68.89% in the treatment group and 24.44% in the placebo group. The difference between the two groups was statistically significant at $P < 0.0001$. The disease control rate of the treatment group was higher than that of the placebo group.

The primary adverse reactions were hypertension, proteinuria, thrombocytopenia, leukopenia, hand-and-foot syndrome, and bilirubin increased. Most of adverse reactions were mild to moderate, and relieved after symptomatic treatment. Apatinib showed a good safety profile.

Combining the characteristics of two types of drugs, SHR-1210 can achieve sustained effective disease response/control in clinical applications by acting as an immunotherapy; it is proven that apatinib has significant efficacy in non-small cell lung cancer - it significantly prolongs PFS with a high tumor response rate. The combination therapy of SHR-1210 and apatinib may improve the short-term objective response rate of tumors while maintaining the sustained efficacy of immunotherapy. In addition, previous animal experiments have shown that the combination therapy of SHR-1210 and apatinib can show synergy in their anti-tumor efficacy (data to be published). In this study, a fixed dose of 200 mg SHR-1210 is selected (studies on drugs of same class has confirmed that in the sensitive population, the high dose group had a better efficacy than the low dose group); a 500 mg dose of apatinib (q.d.) will be administered in combination

(the preliminary results of the study indicated that at a dose of 750 mg apatinib, the rates of toxicity-induced dose interruption and reduction were high). At the same time, considering the continuity of the efficacy of SHR-1210, the combination therapy will be administered for a long time. In order to ensure the tolerability of long-term drug administration, another dose of 250 mg of apatinib (q.d.) and a fixed dose of 200 mg of SHR-1210 were chosen for the combination therapy. A two-stage design will be used, with safety and tolerability observations carried out in Stage I, and efficacy and long-term safety observations carried out in Stage II. The objective is to evaluate the safety and efficacy of the combination therapy of SHR-1210 and apatinib in the treatment of advanced non-small cell lung cancer.

This study will investigate the combination therapy of a small molecule drug apatinib mesylate targeting the VEGFR signaling pathway and anti-PD-1 antibody SHR-1210 in the treatment of advanced non-small cell lung cancer, to meet the urgent needs for new options of clinical treatment. The combination therapy has a good basis of study and relatively controllable risk, and some patients are expected to benefit from this treatment regimen and help to promote the optimization of the regimen.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

Primary objective of Stage I study:

To evaluate the tolerability and safety of anti-PD-1 antibody SHR-1210 plus apatinib mesylate in patients with advanced NSCLC

Secondary objectives of Stage I study:

- 1) To evaluate the pharmacokinetics of anti-PD-1 antibody SHR-1210 plus apatinib mesylate in patients with advanced NSCLC
- 2) To preliminarily evaluate the efficacy of anti-PD-1 antibody SHR-1210 plus apatinib mesylate in patients with advanced NSCLC

Objectives of Stage II study:

To observe and evaluate the efficacy and safety of anti-PD-1 antibody SHR-1210 plus apatinib mesylate in patients with advanced non-small cell lung cancer

2.2 Endpoints

Primary endpoints:

Stage I:

Incidence and severity of adverse events (AEs) and serious adverse events (SAEs)

Stage II:

Tumor objective response rate (ORR)

Secondary endpoints:

Stage I:

Plasma concentrations of SHR-1210 and apatinib

Pharmacokinetic parameters of SHR-1210 and apatinib, including $t_{1/2}$; C_{max} ; AUC, etc.

Tumor objective response rate (ORR)

Stage II:

Incidence and severity of adverse events (AEs) and serious adverse events (SAEs)

Stages I and II:

Clinical benefit rate (CBR): Proportion of subjects with CR, PR, or SD ≥ 6 months during the study

Duration of response (DoR)

Time to response

Progression free survival (PFS) based on RECIST 1.1

12-month survival

Overall survival (OS)

Exploratory analysis of the relationship between biomarkers and efficacy

3 STUDY DESIGN

3.1 Overview of Study Design

Study design of Stage I:

A multi-arm, multi-center, open-label clinical study.

Inclusion criteria: Patients with advanced NSCLC who have failed standard treatment.

Three dose groups, i.e., 250 mg apatinib, oral, q.d. + 200 mg SHR-1210, IV, q2W, 375 mg apatinib, oral, q.d. + 200 mg SHR-1210, IV, q2W, and 500 mg apatinib, oral, q.d. + 200 mg SHR-1210, IV, q2W are set up. Ten to twelve subjects will be enrolled in each dose group (to make sure that at least 10 subjects will complete the tolerability evaluation), and the first cycle (28 days) of continuous treatment will be used as the observation period for tolerability. A dose will be considered tolerable if the proportion of subjects with clinically significant toxicity is < 0.33 .

Tolerability observation will be performed sequentially from the low dose group to the high dose group, and the tolerability observation of a latter dose group can only be carried out after the previous dose group is confirmed to be tolerable.

The first 3 subjects in each dose group will be enrolled on a case-by-case basis with an interval of not less than 14 days, and subsequent subjects can be enrolled at the same time.

After completing the tolerability observation period, subjects will continue the treatment until occurrence of any event that meets the criteria for discontinuation.

After the completion of the tolerability observation in Stage I, the study will enter Stage II for further observation of efficacy and safety.

In addition, after a certain dose group completes the tolerability observation in Stage I and is confirmed as tolerable, 10 to 12 subjects will be enrolled into this dose group for an expanded pharmacokinetic study. In cycle 1 of the expanded PK study, one dose of SHR-1210 will be administered on D1 followed by PK blood sampling. Then, apatinib will be started on D22 after the completion of PK blood sampling, while another PK blood sampling will be carried out on D28. Starting from D1 in cycle 2, SHR-1210 will be administered once every 14 days, while apatinib will be administered orally every day. PK blood sampling will be carried out on D1 of cycle 2 after the administration of SHR-1210 and on D28 after the administration of apatinib. After the blood sampling is completed, the subjects will continue to receive the study treatment until an event meeting the criteria of study termination occurs.

Design of Stage II Study:

A single-arm/double-arm, multicenter, open-label clinical study.

According to the results of tolerability observation in Stage I and upon the discussion between the sponsor and the principal investigators, 250 mg of apatinib, q.d. oral + 200 mg of SHR-1210, IV, q2W are selected for the Stage II study.

Patients of advanced NSCLC who have failed first-line chemotherapy or patients of non-squamous and non-small cell lung cancer with a high tumor mutation burden (TMB) confirmed by the central laboratory will be enrolled in the Stage II study. According to the molecular and pathological classifications, the subjects are divided into:

Cohort 1. Non-squamous, non-small cell lung cancer with wild-type EGFR and ALK;

Cohort 2. Non-small cell lung cancer with EGFR mutation or ALK fusion gene rearrangement. The subjects harboring sensitive EGFR mutations and ALK fusion gene rearrangement must have failed the treatment of at least one EGFR inhibitor or ALK inhibitor;

Cohort 3. Non-central squamous cell lung cancer;

Cohort 4. Non-squamous and non-small cell lung cancer with wild-type EGFR and ALK and with bTMB ≥ 1.54 muts/Mb or tTMB > 10 muts/Mb confirmed by central laboratory.

The enrolled subjects are treated until the occurrence of any event that meets the criteria for discontinuation, so as to further evaluate the efficacy and safety of SHR-1210 in combination with apatinib in patients with advanced NSCLC.

3.1.1 Definition of clinically significant toxicity

1. Grade 4 hematological toxicity or Grade ≥ 3 thrombocytopenia with hemorrhage, Grade ≥ 3 neutropenia with fever and infection;
2. Grade ≥ 3 non-hematological toxicity (except for abnormal laboratory test parameters), hypertension, rash, diarrhea, nausea, and vomiting that cannot be controlled after symptomatic treatment;
3. Grade ≥ 3 abnormal laboratory test parameters that lead to medical intervention, hospitalization, or lasting for ≥ 7 days;
4. SHR-1210 interruption for > 14 days due to relevant toxicity (delayed administration in Cycle 1 or Cycle 2);
5. Apatinib interruption for > 7 days due to relevant toxicity.

3.1.2 Definition of subjects with incomplete tolerance evaluation:

During the observation period of tolerability, the dose of SHR-1210 is < 90% of the prescribed dose due to non-clinically significant toxicity (such as injection reactions).

Subjects who do not complete the tolerability evaluation will not be included in the overall number of subjects undergoing tolerability evaluations, and each dose group is required to have ≥ 10 subjects for the tolerability observation.

Exemption: If ≥ 7 subjects in a dose group do not develop clinically significant toxicity during the tolerability observation period, the dose group is considered to be tolerable and no new subjects will be enrolled into this dose group.

3.1.3 Follow-up treatment of subjects with clinically significant toxicity

In the observation period of tolerability, the subjects with clinically significant toxicity may receive subsequent combination therapy of SHR-1210 and apatinib based on the investigator's judgment after they have recovered from toxicity: interrupt, reduce (for subjects using 500 mg/d or 375 mg/d apatinib) or discontinue apatinib administration according to the dose modification principles, or discontinue the treatment. Subjects will also be followed up and their data will be collected according to the study procedure.

3.2 Pharmacokinetic Study

3.2.1 Study procedure and arrangement of blood sampling points

After the completion of the tolerability observation, 10 to 12 subjects will be enrolled in each dose group for an expanded pharmacokinetic study. In the expanded pharmacokinetic study, one dose of SHR-1210 will be administered on D1 of Cycle 1 (28 d) via intravenous infusion. Pharmacokinetic blood sampling will be performed within 0.5 h pre-dose, and at 5 min (± 5 min), 2 h (± 10 min) and 6 h (± 10 min) after the administration of SHR-1210 on D1, and on D2 (24 h, ± 1 h), D3 (48 h, ± 1 h), D8 (168 h, ± 1 h), D15 (336 h, ± 1 h) and D22 (504 h, ± 1 h), with 3 mL of blood collected at each time point. After the completion of pharmacokinetic blood sampling on D22, the administration of apatinib mesylate tablets (250 mg/tablet·1 tablet, 375 mg/tablet·1 tablet or 250 mg/tablet·2 tablets) will be started on the same day and continues at a administration frequency of once a day. Pharmacokinetic blood sampling will be performed within 0.5 h pre-dose on D28 and at 0.5 h (± 5 min), 1 h (± 5 min), 2 h (± 5 min), 3 h (± 5 min), 5 h (± 10 min), 8 h (± 10 min), 12 h (± 10 min), and 24 h (± 1 h) after the administration, with 3 mL of blood collected at each time point.

On D1 of Cycle 2, PK blood sampling will be performed within 0.5 h before the administration of SHR-1210, and at 5 min (± 5 min), 2 h (± 10 min) and 6 h (± 10 min) on D1, D2 (24 h, ± 1 h), D3 (48 h, ± 1 h), D8 (168 h, ± 1 h), and D15 (336 h, ± 1 h) post-administration, with 3 mL of blood collected at each time point. On D28 of Cycle 2, PK blood sampling will be performed within 0.5 h before the administration of apatinib, and at 0.5 h (± 5 min), 1 h (± 5 min), 2 h (± 5 min), 3 h (± 5 min), 5 h (± 10 min), 8 h (± 10 min), 12 h (± 10 min), and 24 h (± 1 h) post-administration, with 3 mL of blood collected at each time point.

There will be a total of 35 blood sampling points. After the blood sampling is completed, the subjects will continue to receive the study treatment until an event meeting the criteria of study termination occurs.

If a subject interrupts the administration of apatinib during the period of pharmacokinetic blood sampling due to adverse events and if the interruption of apatinib occurs during C1D22-D28, the subject will not be subject to pharmacokinetic blood sampling in the future and will be deemed as not completing the pharmacokinetic study; if the interruption of apatinib occurs during C2D23-C2D28, the pharmacokinetic blood sampling will not be carried out on C2D28. Then, after the administration of apatinib is resumed and continued for 7 days, the administration of apatinib and the blood sampling will be carried out on D7 according to the administration method of apatinib (administration under fasting) and the time points of blood sampling specified for C2D28.

If the administration of SHR-1210 can not be carried out normally during C2D1-C2D28 due to adverse events, the pharmacokinetic blood sampling will not be performed starting from C2D1 and the subject will be deemed as not completing the pharmacokinetic study.

The administration of SHR-1210 should be performed at the scheduled time on C2D1 of the pharmacokinetic study, and no time window for delayed administration is set. The delayed administration of SHR-1210 on C2D15 is allowed as long as the time of administration does not exceed the planned time by more than 3 days.

Substitution of subjects is required for those who have not completed the pharmacokinetic study to ensure that 10 to 12 subjects can complete the pharmacokinetic study.

Subjects who have not completed pharmacokinetic blood sampling may continue to receive the study drug according to the investigator's judgment until an event meeting the criteria for treatment discontinuation occurs.

3.2.2 Blood sample processing and testing

Blood sampling will be carried out before and after the administration of SHR-1210 on D1-D22 of Cycle 1 and D1-D15 of Cycle 2, with 3 mL of whole blood collected into a coagulation tube at each blood sampling time point, and the coagulation tube should be inverted several times to mix the blood sample evenly. After placing the blood sample at room temperature for 30 min, it should be centrifuged at 4 °C and 1500 g (centrifugal force) for 10 min; then, the supernatant will be aliquoted into 2 tubes (about 500 µL per tube).

Blood sampling will be carried out before and after the administration of apatinib on D28 of Cycle 1 and D28 of Cycle 2, with 3 mL of whole blood collected into an anti-coagulation tube at each blood sampling time point, and the anti-coagulation tube should be inverted several times to mix the blood sample with the anticoagulant in the tube. Blood samples will be centrifuged within 30 min after blood sampling at 4 °C and 1500 g (centrifugal force) for 10 min; the supernatant will be aliquoted into 2 tubes (at least 500 µL per tube).

After being well-marked, the separated plasma/serum samples are temporarily kept in a freezer at -20 °C or below, or at -60 °C for a longer period prior to future testing.

Each sample will be assigned with a unique sample number. The actual date and time of blood sampling as well as the exact time of drug administration should be recorded on the PK blood sampling page of the eCRF. The problems encountered during blood sampling should be noted in the eCRF.

3.3 Collection of Biomarker Samples

For all enrolled subjects, their blood samples will be collected at baseline. For subjects showing CR/PR during the study, their blood samples will be collected during the first evaluation of CR/PR and the first evaluation of PD, with 10 mL of blood samples collected each time (14 mL of blood will be collected at baseline and divided into two tubes, with 10 mL in one tube and 4 mL in the other tube). These blood samples will be sent to the central laboratory for blood-based detection of tumor mutation burden (TMB), while the detection of circulating tumor cells (CTC) and the detection of PD-L1 based on circulating tumor cells (CTC) will also be performed in the baseline period. See the central laboratory manual for blood sampling, disposal, and transportation.

For subjects participating in the Stage II of the study, their tumor tissue samples will be collected at baseline. Among these tumor tissue samples, 3-5 slices of 3-4 µm thick paraffin tissue sections will be sent to the central laboratory for the detection of levels of PD-L1 and tumor-associated macrophages (TAM) in tumor tissues; 5-8 slices of 5-8 µm thick tumor biopsy samples or paraffin tissue sections collected before the first dose will also be sent to the central laboratory

for the detection of TMB level in tumor tissues. The biopsy samples can be directly sent to the central laboratory through cold chain transportation. Paraffin blocks can be directly sent to the central laboratory without mounting onto slides. See the central laboratory manual for tissue sampling and transportation.

In order to avoid the impact of previous treatment on tumor mutation burden, the tumor tissue samples should be collected from biopsy or surgical resection carried out at a time point closest to the first dose for the detection of TMB levels.

4 RANDOMIZATION AND BLINDING

4.1 Randomization

Subjects will not be randomized in the tolerability observation period of Stage I. The tolerability observation will be carried out first for the dose group of 250 mg apatinib, oral, q.d. + 200 mg SHR-1210, IV, q2W. After it is confirmed that the dose group of 250 mg apatinib, oral, q.d. + 200 mg SHR-1210, IV, q2W is safe and tolerable, the tolerability observation for the dose groups of 375 mg and 500 mg apatinib, oral, q.d. + 200 mg SHR-1210, IV, q2W will be carried out in sequence.

After completing the tolerability observation of a group, 10 to 12 additional subjects will be enrolled in each group for an expanded pharmacokinetic (PK) study.

If two doses are selected for the Stage II, the subjects enrolled in Stage II will be randomized in a 1:1 ratio using the randomization system provided by Jiangsu Hengrui Pharmaceuticals Co., Ltd. into two groups for observation.

4.2 Blinding

This study is an open-label study and does not involve blinding.

5 SUBJECT SELECTION AND WITHDRAWAL/DISCONTINUATION

5.1 Inclusion Criteria

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

1. Male and female patients aged 18-70 years old;
2. Pathologically confirmed advanced (Phase IIIB and IV) non-small cell lung cancer with at least one measurable lesion that meets the RECIST v1.1 criteria and has not been treated locally;
3. Able to provide previous tumor samples or agree to cooperate with biopsy (Stage II);

4. Stage I: Patients who have undergone the second-line and above chemotherapy (at least one of the previous chemotherapy regimens is a platinum-based chemotherapy doublet regimen) but failed the treatment or showed recurrence. The patients harboring EGFR mutations and ALK gene abnormalities must have failed the treatment with an EGFR inhibitor or ALK inhibitor.

Stage II: Patients who have undergone only one previous platinum-based doublet chemotherapy but failed the treatment or showed recurrence, or patients in the stage of palliative treatment who have received no systemic treatment (only for cohort 4).

- a. The replacement of platinum drugs due to drug toxicity will be considered as one treatment regimen;
- b. Postoperative adjuvant chemotherapy will not be counted as one previous chemotherapy regimen if the time from the end of treatment to recurrence is > 6 months.

According to the type of driver gene mutations and pathological classification, the subjects will be divided into the following four cohorts:

Cohort 1. Patients with confirmed absence of mutations in EGFR 18-21 exons and ALK fusion genes (the histochemistry result of ALK D5F3 antibody is negative);

Cohort 2. Patients with confirmed presence of mutations in EGFR 18-21 exons or ALK fusion genes (the histochemistry result of ALK D5F3 antibody is positive). Carriers of sensitive EGFR mutations must have received at least one targeted treatment with EGFR tyrosine kinase inhibitors (EGFR-TKI) and failed the treatment. Carriers of positive ALK fusion genes must have failed the treatment of at least one targeted treatment with ALK tyrosine kinase inhibitor (ALK-TKI) (treatment failure: progressive disease or intolerable toxicity during the treatment);

Cohort 3. Imaging confirmed non-central squamous cell lung cancer or adenosquamous carcinoma primarily consisted of squamous cell carcinoma (pathologically confirmed).

Cohort 4. Non-squamous and non-small cell lung cancer with wild-type EGFR and ALK and with bTMB ≥ 1.54 muts/Mb or tTMB > 10 muts/Mb confirmed by central laboratory, and patients in the stage of a palliative treatment who have received no systemic treatment.

5. ECOG PS: 0-1;
6. Life expectancy ≥ 12 weeks;

7. Major organ functions must meet the following rules (not including the use of blood components or cell growth factors during screening):
 - Absolute neutrophil count $\geq 1.5 \times 10^9/L$;
 - Platelets $\geq 100 \times 10^9/L$;
 - Hemoglobin ≥ 9 g/dL;
 - Serum albumin ≥ 3 g/dL;
 - Thyroid stimulating hormone (TSH) \leq ULN (In the case of abnormalities, FT3 and FT4 levels should also be measured. If FT3 and FT4 levels are normal, the patient can be enrolled);
 - Total bilirubin \leq ULN;
 - ALT and AST $\leq 1.5 \times$ ULN;
 - AKP $\leq 2.5 \times$ ULN;
 - Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance ≥ 60 mL/min (using the standard Cockcroft-Gault formula, as shown in Appendix 3);
8. Female patients of a childbearing age who are not surgically sterilized should adopt a medically approved contraceptive measure (such as an intra-uterine contraceptive device, contraceptive pills or condoms) during the study treatment period and within 3 months after the end of the study treatment; female patients of a childbearing age who are not surgically sterilized must have a negative serum or urine HCG test result within 72 h prior to study enrollment, and must not be in the lactation period; male patients should be surgically sterilized or agree to use an appropriate contraceptive measure during the study period and within 3 months after the last dose of the study drug;
9. Patients must participate voluntarily, sign the informed consent form, have good compliance, and cooperate with follow-up visits.

5.2 Exclusion Criteria

Patients meeting any of the following are ineligible to participate in this study:

1. Patients with any active autoimmune diseases or a history of autoimmune diseases (including but not limited to the following: autoimmune hepatitis, interstitial pneumonitis, uveitis, enteritis, hepatitis, hypophysitis, vasculitis, nephritis, hyperthyroidism, hypothyroidism; adults with vitiligo or completely relieved childhood asthma can be enrolled if they do not require any intervention; patients with asthma requiring medical intervention with bronchodilators cannot be enrolled);

2. Patients who are currently using immunosuppressive agents, or systemic or absorbable local hormonal therapies for immunosuppression purposes (> 10 mg/day prednisone or equivalent) and still use the above drugs within 2 weeks prior to enrollment;
3. Patients who have experienced severe allergic reactions to other monoclonal antibodies;
4. Patients with untreated metastases to central nervous system. Patients who have received treatment for brain or meningeal metastasis can be included if they are clinically stable (MRI) for at least 1 month and have stopped systemic hormonal therapy (> 10 mg/day prednisone or equivalent) for more than 2 weeks;
5. Imaging (CT or MRI) results show that the tumor has invaded the large blood vessels or has an unclear boundary with the blood vessels;
6. Imaging (CT or MRI) results show significant cavitation or necrosis of lung tumors;
Patients with marginal adenocarcinoma with cavity may be enrolled after discussion with the leading site.
7. Patients with hypertension which cannot be well controlled by antihypertensives (systolic pressure ≥ 140 mmHg or diastolic pressure ≥ 90 mmHg);
8. Patients with clinical symptoms or diseases of the heart that are not well controlled, such as (1) $>$ NYHA Class II cardiac failure; (2) unstable angina; (3) myocardial infarct within past 1 year; (4) clinically significant supraventricular or ventricular arrhythmia requiring treatment or intervention;
9. Patients with abnormal coagulation functions (PT > 16 s, APTT > 43 s, TT > 21 s, Fbg < 2 g/L) and hemorrhagic diathesis or those who are currently treated by a thrombolytic or anticoagulant therapy;
10. Patients with urinalysis results indicating that the urine protein is $\geq ++$ and the quantitative test of urine protein confirms that the 24-hour urine protein is > 1.0 g;
11. Patients who have previously received radiotherapy, chemotherapy or surgery that is less than 4 weeks before the study after the end of such treatments (last dose), or patients whose last dose of oral targeted drugs is less than 5 drug half-lives; Patients with adverse events caused by the previous treatment (except for alopecia) that have not returned to CTCAE Grade ≤ 1 ;
12. Patients with clinically symptomatic ascites or pleural effusion requiring therapeutic paracentesis or drainage;

13. Patients with obvious hemoptysis or a daily amount of hemoptysis of half a teaspoon (2.5 mL) or more within 2 months before randomization;
14. Patients with clinically significant hemorrhage symptoms or a clear hemorrhagic diathesis within 3 months prior to randomization, such as hemorrhage of digestive tract, stomach ulcer with hemorrhage, baseline fecal occult blood ++ or above, or vasculitis;
15. Had events of arterial/venous thrombosis within 6 months prior to randomization, such as cerebrovascular accidents (including transient ischemic attacks, cerebral hemorrhage, and brain infarction), deep vein thrombosis, and pulmonary embolism;
16. Known hereditary or acquired hemorrhage and thrombophilia (such as hemophilia, coagulopathy, thrombocytopenia, hypersplenism, etc.);
17. Patients with active infection or unexplained fever of $> 38.5^{\circ}\text{C}$ during screening or prior to the first dose;
18. Patients with previous or current objective evidence of pulmonary fibrosis, interstitial pneumonia, pneumoconiosis, radiation pneumonitis, drug-induced pneumonitis, and severe lung function impairment;
19. Subjects with congenital or acquired immunodeficiency (such as HIV infection), or active hepatitis (hepatitis B: HBsAg positive and HBV DNA $>$ upper limit of normal; hepatitis C: HCV antibody positive and HCV virus titer $>$ upper limit of normal);
20. Those who have used study drugs of other clinical trials within 4 weeks before the first dose of this study;
21. Patients with previous or concurrent malignancies at other sites (except for cured skin basal cell carcinoma and cervical carcinoma in situ);
22. Patients who may receive other systemic anti-tumor treatments during the study;
23. Patients with bone metastasis who have received a palliative radiotherapy in an area of $> 5\%$ of bone marrow area within 4 weeks prior to the participation in this study;
24. Patients who have previously received other anti-PD-1 antibody treatments or other immunotherapies targeting PD-1/PD-L1;
25. Patients who have received live vaccines within less than 4 weeks before the first dose or may receive live vaccines during the study;

26. Patients who may have other factors leading to the discontinuation of the study as judged by the investigator, such as other serious diseases (including mental illness) requiring concomitant treatment, serious laboratory test abnormalities, or accompanied by family or social factors that can affect the safety of the subject or the collection of data and samples.

5.3 Subject's Withdrawal

5.3.1 Criteria for withdrawal/treatment discontinuation

1. The subject withdraws informed consent and requests to withdraw from the study;
2. Imaging examinations show progressive disease;

Upon the first discovery of progressive disease by imaging examinations, it must be confirmed after 4 weeks (except for rapid progression and significant clinical progression);

If a subject shows local progression (1 to 4 lesions show progress) but the clinical symptoms are stable, the treatment can be continued according to the judgment of the investigator until imaging examinations show progressive disease again.

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

3. Treated by SHR-1210 for 2 years (no progressive disease as shown by imaging);
4. Subjects with intolerable toxicity;
5. Subjects with poor compliance;
6. Subjects lost to follow-ups or show positive blood HCG results;
7. Other reasons for which the investigator considers withdrawal as necessary.

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

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

5.3.2 Handling of withdrawn subjects

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

5.4 End of Study

Stage I:

The Stage I of this study will end at 3 months after the last dose of the last subject in the tolerability observation period if subjects in the PK expansion stage complete the specified PK blood sampling;

Stage II:

At 6 months after the first dose of the last subject in Stage II, the primary and secondary endpoints will be statistically analyzed.

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

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

5.5 Termination Criteria

1. Discovery of unexpected, important, or unacceptable risks to the subjects;
2. Major errors in the protocol found during the implementation of the study;
3. Ineffective study drug/treatment, or meaninglessness to continue the study;
4. Extreme difficulties in completing the study due to reasons such as severe delays in subject recruitment or frequent protocol deviations.

6 STUDY DRUGS

6.1 Overview of Study Drugs

6.1.1 Drug information

- **SHR-1210:**

Name: SHR-1210 for injection

Manufacturer: Shanghai Hengrui Pharmaceutical Co., Ltd./Suzhou Suncadia Biopharmaceuticals Co., Ltd.

Dosage Form: Lyophilized powder for injection

Route of Administration: Intravenous injection

Strength: 200 mg/20 mL vial.

Storage and stability: Placed in a 2-8 °C medical refrigerator during storage and the shelf life is tentatively set to 2 years. Do not freeze.

- **Apatinib:**

Name: Apatinib Mesylate Tablets (Apatinib)

Manufacturer: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Dosage Form: Tablets

Route of Administration: Oral

Strength: 250 mg/tablet; 375 mg/tablet

Storage and Stability: Away from light, sealed, stored at below 25 °C. Valid for 2 years.

6.1.2 Drug packaging and labeling

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

SHR-1210 drug label (for illustration only and the actual label shall prevail), the drug number is increased incrementally from 0001.

Small Box Label			Vial Label		
SHR-1210 for Injection	Clinical Study Approval No.: 2016L01455	Strength: 200 mg/vial	SHR-1210 for Injection	Clinical Study Approval No.: 2016L01455	Strength: 200 mg/vial
For Clinical Study Use Only			For Clinical Study Use Only		
Study Name: A Phase II Clinical Study of Anti-PD-1 Antibody SHR-1210 Combined with Apatinib Mesylate in the Treatment of Advanced Non-Small Cell Lung Cancer Study No.: SHR-1210-APTN-II-202-NSCLC Dosage Form: Lyophilized powder Study Center: Shanghai Pulmonary Hospital, Tongji University Usage: 200 mg, Q2W, IVGTT. Note: Prepare as per study protocol. Drug No. _____ Quantity: 1 vial/box Storage Method: Store at 2-8 °C away from light Batch No.: _____ Expiry Date: DD/MM/20YY Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.			Study Name: A Phase II Clinical Study of Anti-PD-1 Antibody SHR-1210 Combined with Apatinib Mesylate in the Treatment of Advanced Non-Small Cell Lung Cancer Study No.: SHR-1210-APTN-II-202-NSCLC Dosage Form: Lyophilized powder Study Center: Shanghai Pulmonary Hospital, Tongji University Usage: 200 mg, Q2W, IVGTT. Note: Prepare as per study protocol. Drug No. _____ Preparation Date: ____/____/____ Storage Method: Store at 2-8 °C away from light Batch No.: _____ Expiry Date: DD/MM/20YY Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.		

Big Box Label		
SHR-1210 for injection	Clinical study approval No.: 2016L01455	Strength: 200 mg/vial
For Clinical Study Use Only		
Study Name: A Phase II Clinical Study of Anti-PD-1 Antibody SHR-1210 Combined with Apatinib Mesylate in the Treatment of Advanced Non-Small Cell Lung Cancer Study No.: SHR-1210-APTN-II-202-NSCLC Dosage Form: Lyophilized powder, 200 mg/vial Study Center: Shanghai Pulmonary Hospital, Tongji University Usage: 200 mg, Q2W, IVGTT. Note: Prepare as per study protocol. Quantity: 20 vials per box Storage Method: Store at 2-8 °C away from light Batch No.: _____ Expiry Date: DD/MM/20YY Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd. Manufacturer: Shanghai Hengrui Pharmaceutical Co., Ltd.		

Packaging specifications and quantity of apatinib:

The label content includes:

Label name: Drugs to be used in the phase II clinical study of anti-PD-1 antibody SHR-1210 combined with apatinib mesylate in the treatment of advanced non-small cell lung cancer

Strength: 250mg/tablet or 375 mg/tablet

Indication: For the treatment of advanced non-small cell lung cancer

Usage: 1 tablet per day (250 mg/d and 375 mg/d dose groups); 2 tablets per day (500 mg/d dose group), once a day taken orally after meal

Drug number, storage conditions, batch number, expiration date, study site (Jiangsu Hengrui Pharmaceuticals Co., Ltd.)

Precautions: For clinical use only; please return the remaining drug to the physician

The drug is packaged in aluminum-plastic blister packs with 10 tablets per pack, and each small box contains 3 or 6 packs.

6.2 Preparation of SHR-1210

SHR-1210 is a lyophilized powder for injection, which needs to be formulated before intravenous drip (see the pharmacy manual of SHR-1210 for details).

Since this product does not contain preservatives, please perform aseptic operations when formulating the drug preparation.

- Each vial of lyophilized powder is quantitatively reconstituted in 5 mL of distilled water for injection. During the operation, the distilled water is slowly added into the vial along the vial wall. Please do not directly drop the distilled water onto the surface of the lyophilized powder (the post-reconstitution concentration is 40 mg/mL)
- Do not vigorously shake the vial during reconstitution. Instead, reconstitute the powder in a gentle way with slow vortex. After reconstitution, allow the vial to stand for 6 min to allow the foam to disappear.
- Visually observe the solution after reconstitution to see whether there are particles and discoloration. After reconstitution, the liquid should be colorless or slightly yellowish. There may be a small number of light-gray small particles falling into the vial due to the puncture of vial stopper by the needle. However, these particles will be filtered by the 0.2 μ M filter attached to the infusion set and hence will not affect the subsequent use of the drug solution. If there are other particles other than the ones mentioned above, please do not continue to use this vial of drug.
- Draw a corresponding volume of the reconstituted solution from the vial and dilute it in 100 mL of 5% glucose for injection or 0.9% sodium chloride for injection. Avoid generating a large number of air bubbles during the dilution process. After dilution, slowly invert the infusion bag several times to mix well. Maintain the final concentration at between 0.5 mg/mL and 10 mg/mL.
- Within 2 h after the dilution is completed, use an infusion set equipped with an in-line filter (0.2 μ M) to finish the injection via intravenous drip. After the drug injection is completed, use about 20 mL of 5% glucose for injection to flush the remaining drug in the infusion line into the body. Do not use this infusion line to administer other drugs. Each infusion takes 30 min (not less than 20 min, no more than 60 min) (including the final rinse stage).

6.3 Administration Regimen

SHR-1210 will be administered via intravenous drip (without prophylaxis) with a fixed dose of 200 mg within 30 min (not less than 20 min, no more than 60 min), once every 2 weeks. Each cycle contains 4 weeks (the subjects for the expanded PK study will receive one dose on D1 of Cycle 1 of the study) and the longest period of drug use is 2 years.

Apatinib will be orally administered after meals (the subjects for the expanded PK study will receive the drug orally under fasting on Day 28 of Cycle 1 and Day 28 of Cycle 2), once a day, and one tablet (250 mg/tablet or 375mg/tablet) or 2 tablets (250 mg/tablet, 500 mg dose group) each time. The drug administration will be continued through the study.

Subjects enrolled for the study in the tolerability observation stage and subjects enrolled for the Stage II of the study will be given SHR-1210 on D1 and D15 of each cycle from the beginning of treatment; apatinib will be given via oral administration once daily.

Subjects enrolled for the expanded PK study will be given SHR-1210 on D1 in Cycle 1 and on D1 and D15 in each cycle starting from Cycle 2. These subjects will also be given daily oral administration of apatinib continuously starting from D22 in Cycle 1.

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

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

6.4 Dose Modification

The study treatment may be modified according to the toxic side effects appeared. The options for treatment modification include: interruption, dose reduction, change in method of administration, and discontinuation;

In this study, only interruptions for up to 12 weeks are permitted for SHR-1210 treatment; A SHR-1210 dose delayed by more than 3 days shall be skipped, and the administration may be resumed at 200 mg at the next scheduled time point.

Dose modifications caused by apatinib-related toxicity include: dose interruption, dose reduction (500 mg/d or 375 mg/d dose groups), change in method of administration (first modification: 5 days of drug administration followed by 2 days of dose interruption; re-modification: 1 day of drug administration followed by 1 day of dose interruption), and discontinuation. Further adjustments will not be allowed after the dose or method of administration of apatinib is modified during the study period, unless such adjustments are agreed upon by the investigator and the sponsor after discussion.

In the event of an apatinib-related adverse reaction, the dose should be interrupted first. After the toxicity has returned to an acceptable level, the following options may be selected as appropriate: resume administration using the original dose, reduce the dose, modify the method of administration or discontinue the drug. Subjects may continue SHR-1210 as monotherapy if apatinib treatment is discontinued.

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

Rules for Dose Modifications

Treatment-Related Toxicity		Grade	Whether to Interrupt Treatment		Criteria for Resuming	Dose Modification Method	Criteria for Discontinuation
			SHR-1210	Apatinib			
Toxicity related to SHR-1210 and apatinib	Hematologic toxicity (except for decreased lymphocyte count)	Grade 1-2	No	No	—	—	—
		Grade 3	No	Yes	Until the toxicity returns to Grade ≤ 2	Resume at original dose	Two episodes of Grade 4 hematological toxicity
		Grade 4	Yes	Yes	Until the toxicity returns to Grade ≤ 2	Dose reduction or modification of method of administration	
	Non-hematologic toxicity	Grade 1	No	No	—	—	—
		Grade 2 (last for ≥ 7 d)	Yes	Yes	Until the toxicity returns to Grade ≤ 1	Resume at original dose	SHR-1210 interruption for more than 12 weeks
		Grade 3	Yes	Yes	Until the toxicity returns to Grade ≤ 1	Dose reduction or modification of method of administration	
Toxicity related to SHR-1210	Reactive capillary endothelial proliferation	Grade 3	Yes	No	Until the toxicity returns to Grade ≤ 2	Resume at original dose	SHR-1210 interruption for more than 12 weeks

Treatment-Related Toxicity		Grade	Whether to Interrupt Treatment		Criteria for Resuming	Dose Modification Method	Criteria for Discontinuation
			SHR-1210	Apatinib			
Apatinib-Related Toxicities	Hypertension	Grade 3 (after corrective treatment)	No	Yes	Wait until blood pressure returns to within 140/90 mmHg	Dose reduction or modification of method of administration	Subjects with persistent Grade 3 hypertension after the best corrective treatment and the modification of method of administration of apatinib
	Proteinuria (without significant increase in blood creatinine)	Grade 3 (24 h urine protein quantification)	No	Yes	Until the toxicity returns to Grade ≤ 2	Dose reduction or modification of method of administration	Subjects with persistent Grade 3 proteinuria after the best corrective treatment and the modification of method of administration of apatinib
	Hand-and-foot syndrome	Grade 3	No	Yes	Until the toxicity returns to Grade ≤ 1	Dose reduction or modification of method of administration	Subjects with persistent Grade 3 hand-and-foot syndrome after the best corrective treatment and the modification of method of administration of apatinib
	Headache	Grade 2 (last for ≥ 7 d) or Grade 3	No	Yes	Until the toxicity returns to Grade ≤ 1	Dose reduction or modification of method of administration	Apatinib interruption for more than 28 days

The investigator may consider interrupting the treatment for subjects who experience significant toxicity during the study, such as Grade 3 or greater treatment-related toxicity, or Grade 2 non-hematological toxicity lasting for 2 weeks and longer (except for asymptomatic Grade 2 hypertension), abnormal laboratory findings (except < 2 g/24 h proteinuria). After the toxicity resolves, the dose of apatinib should be reduced or the method of apatinib administration should be adjusted accordingly.

In the course of the study and based on the above regulations for dose modification, the investigator may modify the dose appropriately by comprehensively considering the treatment-related toxicity in the subjects (if a subject experiences multiple Grade 2 treatment-related toxicities and shows poor tolerance to the study drug, the dose of apatinib can be reduced or the administration of apatinib can be maintained at the original dose by given intermittently with observation after treatment delay and recovery from toxicity).

During the study, if a subject has fever ($> 38^{\circ}\text{C}$) and needs to use medications for corrective treatment; in the case of obvious wheezing, polypnea, symptoms of suffocation or rash, the administration of SHR-1210 should be skipped for the current or next scheduled time of SHR-1210 administration before the symptoms are recovered. After the symptoms are relieved and become stable for more than 7 days, the subjects can be given SHR-1210 according to the subsequent administration schedule. For subjects with fever and wheezing, the possibility of pneumonitis should be ruled out by imaging examinations before drug administration if necessary.

In the case of hypertensive crisis, cerebral hemorrhage, Grade ≥ 2 pulmonary hemorrhage, other Grade ≥ 3 hemorrhage, arterial thrombosis, Grade 4 venous thrombosis, leukoencephalopathy syndrome, or gastrointestinal perforation, apatinib should be discontinued, SHR-1210 should be interrupted and active symptomatic treatment should be given. The resumption of SHR-1210 treatment shall depend on the toxicity recovery.

During the study, in the case of Grade ≥ 3 immune-related pneumonitis, Grade ≥ 3 TBIL elevation (recurrent), Grade 4 ALT/AST elevation (recurrent), other Grade 4 immune-related toxicities (except for hypothyroidism), Grade 4 injection reactions, or the interruption of SHR-1210 administration for more than 12 weeks due to immune-related toxicity but the toxicity is still unable to return to Grade ≤ 1 or baseline levels (subjects with baseline abnormality), SHR-1210 should be permanently discontinued.

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

6.5 Drug Management, Dispensation and Return

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

The study drugs should be stored according to the drug storage conditions detailed in the drug information. The drug receipt forms must be signed by two people during drug dispensation. The form is in duplicate copies, of which one is for the study center and the other is for the sponsor. Remaining drugs and empty boxes will be retrieved at the end of the study and a retrieval form will also be signed by both parties. The dispensation and return of every drug should be immediately documented on designated forms.

The clinical research associate (CRA) is responsible for monitoring the supply, usage, and storage of the study drugs, and the management of remaining products.

6.6 Concomitant Medications

6.6.1 Medications that are prohibited during the study and medications that should be used with caution

Drugs that may have drug-drug interactions with apatinib:

In vitro studies have shown that apatinib is prominently metabolized by the liver P450 enzyme CYP3A4. Apatinib has a strong inhibitory effect on CYP3A4 and CYP2C9, and has a moderate inhibitory effect on CYP2C19. CYP3A4 inducers (dexamethasone, carbamazepine, rifampicin and phenobarbital) and inhibitors (ketoconazole, itraconazole, erythromycin and clarithromycin), CYP3A4 substrates (simvastatin, cyclosporine and pimozide), and other drugs metabolized via CYP3A4 (such as benzodiazepines, dihydropyridine, calcium ion antagonist and HMG-CoA reductase inhibitors) should be used with caution during the treatment. Omeprazole should be used with caution during the treatment (except when omeprazole must be used to treat serious adverse drug reactions).

The substrates of CYP2C9 and CYP2C19 should be used with caution, as shown in the table below.

P450 enzyme	Substrate
CYP2C9	Diclofenac, phenytoin, piroxicam, S-warfarin, and tolbutamide
CYP2C19	Diazepam, imipramine, lansoprazole, and S-mephenytoin

Drugs that prolong the QT interval of the heart

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

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

- Antifungal drugs: voriconazole, posaconazole
- Antimalarial drugs: mefloquine, chloroquine
- Antihistamines: terfenadine, astemizole, hydroxyzine
- Gastrointestinal drugs: antiemetics: ondansetron, granisetron, dolasetron, droperidol (0.625 to 1.25 mg may be a safe dose), hydroxyzine; prokinetics: cisapride, domperidone, metoclopramide
- Antidepressants: amitriptyline, imipramine, clomipramine, dosulepin, and doxepin

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

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

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

During the treatment period, anti-tumor drugs and adjuvant drugs related to tumor treatment, such as anti-tumor traditional Chinese medicine (see Appendix I for a detailed list), immunological agents, etc., should be discontinued.

6.6.2 Drugs and treatments that may be used as appropriate during the study:

In Stage I, for subjects enrolled in the tolerability observation study, except that the subjects experiencing hypertension, rash, diarrhea, nausea and vomiting can be given symptomatic treatments, all other adverse reactions with no clinically significant toxicity occurring during the tolerability observation period (Cycle 1 of drug administration) will not be treated in principle, so as to observe the possible adverse effects and their extent/reversibility of the study drugs. However, in the event of a clinically significant toxicity as specified in the protocol, the treatment should be interrupted and a proactive approach should be used to manage the event. Used medications should be recorded on the eCRF. For subjects experiencing clinically significant toxicity, the treatment can be resumed at the original dose (when the original dose is the lowest dose) or the nearest lower level after the toxicity returns to Grade ≤ 1 after management.

In other cases, the subjects should be given an optimal supportive care during the treatment. Comorbidities and various adverse reactions, especially immune-related adverse reactions, should be actively treated.

Subjects can receive bisphosphonate for the treatment of bone metastases. If systemic or local analgesia is not effective in controlling painful lesions of bone metastases, a small area of palliative radiotherapy (the area of the radiotherapy must be $< 5\%$ of the bone marrow region, and the percent bone marrow content in human skeleton is shown in the figure of **Appendix VI**) is allowed.

Palliative treatment for lesions outside the lungs and liver is allowed during the study (when the treatment of the subjects is needed to improve symptoms upon the onset of PD), including the treatments for pleural effusion, ascites, pericardial effusion, and radiotherapy for brain lesions. During such treatment, the study drugs should be interrupted until the end of the recovery period of palliative treatment.

All concomitant treatments and medications used within 30 days prior to the first dose and during the study should be documented in the eCRF in strict accordance with the GCP regulations. Subjects will be closely monitored if adverse reactions occur, and active symptomatic treatment will be given if necessary. The drugs used will be documented and described in the CRFs. Once the study treatment is interrupted, only the concomitant medication and treatment used to solve new or unresolved treatment-related AEs will be recorded.

7 STUDY PROCEDURES

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

7.1 Screening Period (D-21 to D-1)

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

[Signing of ICF] A written ICF must be signed by the subject before any procedures of the clinical study are carried out.

[Demographics] gender, date of birth, ethnicity, height, weight, smoking history.

[Tumor history] including pathological diagnosis and clinical diagnosis:

- (1) Tumor diagnosis: the date of initial diagnosis of the tumor, histological classification, site of primary tumor and metastatic lesions, pathological staging, and clinical staging;
- (2) History of surgery: the surgical history of primary lesions and the surgical history of metastatic lesions;
- (3) History of chemotherapy (including new/adjuvant chemotherapy): the history of systemic chemotherapy, the history of targeted drug therapy, and the history of local chemotherapy;
- (4) History of radiotherapy: date, dose, and site (systemic/local);
- (5) Results of gene mutation detection (if applicable): whether there are gene mutations, sites of mutation, and detection date;
- (6) The date of PD or disease recurrence after the last systemic treatment.

[Concomitant disease] Concomitant disease and related treatment history (such as diabetes, hypertension and other chronic diseases), history of tumors other than non-small cell lung cancer.

[Concomitant medication] Concomitant medications and treatments received within 30 days prior to the first dose and during the study period should be recorded. Once the study treatment is interrupted, only the concomitant medication and treatment used to solve new or unresolved treatment-related AEs will be recorded;

[Thyroid function] Including serum FT3, FT4, and TSH;

[Examination of the pituitary adrenal axis] Including ACTH and cortisol.

[Hepatitis B, hepatitis C, and HIV examinations] hepatitis B panel (If the test results are abnormal, viral replication [HBV DNA] test should be performed); hepatitis C virus antibody (anti-HCV) test (If the test results are abnormal, virus titer should be tested); HIV antibody test.

[Detection of EGFR mutations and ALK fusion gene] If the subjects have previously been tested for EGFR mutations and the ALK fusion gene, they do not need to be tested again. If the subjects have not been tested previously, the study site will carry out relevant tests. If the subjects are positive for EGFR mutations, the test of ALK fusion gene will no longer be performed.

[Adverse events] Adverse events will be recorded from the time when the subjects sign the informed consent form. AEs unrelated to the study drugs will be recorded to 30 days after the last dose. Treatment-related AEs will be collected until 90 days after the last dose of SHR-1210 or 30 days after the last dose of targeted anti-angiogenic therapy (whichever is longer). See the AE/SAE collection time limit in Section 8.3 for details.

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

[Pulmonary function test] Maximum vital capacity, the forced expiratory flow at 25-75% of forced vital capacity (FEF25-75), the peak expiratory flow (PEF), maximum expiratory volume per second, diffusing capacity of the lungs for carbon monoxide (DLCO) and oxygen saturation. Carried out during the screening period and then according to the judgment of the investigator in subsequent cycles;

[Imaging examination] Including CT or MRI of the chest, abdomen, and brain. The baseline tumor assessment during the screening period can be extended to up to 3 weeks before treatment. Qualified CT/MRI scan results obtained before signing the informed consent can be used for tumor assessment during the screening period. Bone scan should be performed upon clinically suspected bone metastasis. Absence of cerebral hemorrhage should be confirmed within 21 days before randomization for subjects with stable brain metastases;

[Biomarker sampling/sample collection and detection] Archived paraffin-embedded tumor samples or fresh biopsy specimens will be collected to make ≥ 10 slices, of which 3-5 slices of 3-4 μm tumor sections (mounted slides) will be collected for the histochemistry detection of biomarkers such as PD-L1, and 5-8 slices of 5-8 μm paraffin sections (paraffin rolls can be directly collected without being mounted on the slides) or fresh biopsy specimens will be collected for the detection of biomarkers such as tumor mutation burden (TMB). Refer to the laboratory manual for details on tumor tissue sampling/sample collection and disposal methods.

For cohort 4, the test results of tumor mutation burden (TMB) in the peripheral blood and/or tumor tissues will be verified before the subjects take the first dose of the study drug, so the TMB test for cohort 4 must be completed before the first dose. However, the delay in the screening period caused by TMB testing is allowed, but other tests (including imaging examinations) must be completed within 21 days prior to the first dose.

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

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

[Urinalysis] Urine protein (Note: if urine protein $\geq 2+$, 24-h urine protein quantification test shall be performed), urinary red blood cells, urinary white blood cells, and urine glucose;

[Routine stool test] Occult blood; re-examination is required for fecal occult blood+; if fecal occult blood is confirmed, then a gastroscopy shall be performed. Performed within 7 days before enrollment, on Day 15 of Cycle 1 and Day 1 of subsequent cycles, and upon completion of the study;

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

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

[Myocardial zymography]

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

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

[Physical examinations] General conditions, head and face, skin, lymph nodes, eyes (sclera, pupil), ear, nose, throat, respiratory system, cardiovascular system, abdomen (including liver and spleen), reproductive-urinary system, musculoskeletal system, nervous system, and mental status;

[ECOG PS] See Appendix II;

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

[Echocardiography]

[Blood sampling for tumor markers] In the baseline period (before drug administration), 14 mL of blood samples will be collected and divided into two tubes, with 10 mL in one tube and 4 mL in the other tube. See the laboratory manual for methods of blood sampling and disposal.

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

7.2 Treatment Period

- Stage I study (except for subjects participating in the expanded PK study) and Stage II study
D1 of Cycle 1 [Vital signs] [Physical examinations and weight measurement] [Intravenous drip of SHR-1210] [Dispensation of apatinib] [Administration of apatinib]

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

Apatinib is administered continuously from D1 of Cycle 1, and its dose can be interrupted or modified according to the occurrence of adverse events.

D1 of subsequent cycles [Hematology] [Blood biochemistry] [Urinalysis] [Routine stool test] [Coagulation function] [Vital signs] [Physical examinations and weight measurement] [ECOG PS] [ECG] [Intravenous drip of SHR-1210] [Adverse events] [Concomitant medication] [Return/dispensation of apatinib]

D15 of Cycle 1: [Hematology] [Blood biochemistry] [Urinalysis] [Routine stool test] [Coagulation function] [Vital signs] [Physical examinations] [ECG] [Intravenous drip of SHR-1210] [Adverse events] [Concomitant medication]

D15 of subsequent cycles: [Hematology] [Blood biochemistry] [Urinalysis] [Coagulation function] [Vital signs] [Physical examinations] [ECG] [Intravenous drip of SHR-1210] [Adverse events] [Concomitant medication]

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

- Subjects participating in the expanded PK study

D1 of Cycle 1: [Vital signs] [Physical examinations and weight measurement] [Intravenous drip of SHR-1210] [PK blood sampling]

D15 of Cycle 1: [PK blood sampling] [Hematology] [Blood biochemistry] [Urinalysis] [Routine stool test] [Coagulation function] [Vital signs] [Physical examinations] [ECG] [Adverse events] [Concomitant medication]

After the blood sampling on D22 of Cycle 1 is completed, continuous oral administration of apatinib will be started at a frequency of once a day.

PK blood sampling will be carried out on D28 of Cycle 1 after the administration of apatinib.

D1 of Cycle 2: [Hematology] [Blood biochemistry] [Urinalysis] [Routine stool test] [Coagulation function] [Vital signs] [Physical examinations and weight measurement] [ECOG PS] [ECG] [Adverse events] [Concomitant medication] [Return/dispensation of apatinib] [Intravenous drip of SHR-1210] [PK blood sampling]

D15 of Cycle 2 and subsequent cycles: [Hematology] [Blood biochemistry] [Urinalysis] [Coagulation function] [Vital signs] [Physical examinations] [ECG] [Intravenous drip of SHR-1210] [Adverse events] [Concomitant medication]

PK blood sampling will be carried out on D28 of Cycle 2 after the administration of apatinib.

See the flow chart and "3.3.2 Blood Sample Processing and Testing" for the time points, volume, and processing of blood sampling.

D1 of subsequent cycles [Hematology] [Blood biochemistry] [Urinalysis] [Routine stool test] [Coagulation function] [Vital signs] [Physical examinations and weight measurement] [ECOG PS] [ECG] [Intravenous drip of SHR-1210] [Adverse events] [Concomitant medication] [Return/dispensation of apatinib]

[Imaging evaluation] During the treatment period, imaging examinations should be performed under the same conditions as those at baseline (layer thickness of the scan, use of contrast agent, etc.), and the lesions found at baseline should be checked every 2 cycles in the first 6 cycles of the treatment (bone scan shall be performed in the case of suspected bone progression or for CR confirmation). After 6 cycles, imaging examinations can be performed every 3 weeks as appropriate and can be performed upon the discovery of suspected new lesions. Initial assessment of PR/CR must be confirmed after 4 weeks; initial assessment of PD must be confirmed after 4 to 6 weeks (except for significant changes in the subjects' symptoms or rapid tumor progression).

[Thyroid function test] Performed on Day 1 of Cycle 2 and then once every 3 cycles.

[Biomarker collection] For subjects showing CR/PR during the study, an additional collection of 1 tube of 10 mL blood sample for biomarker detection should be performed upon the onset of CR/PR and PD, respectively. The collection requirements are the same as those in the baseline period.

7.3 End of Treatment/Withdrawal

Subjects shall discontinue study treatment upon the occurrence of an event that meets the "5.3.1 Criteria for subject withdrawal/treatment discontinuation". At the end of the study treatment or upon withdrawal from the study, if a subject has not undergone examinations within 14 days prior to the end of the study, the subject should undergo the following examinations:

[Hematology] [Blood biochemistry] [Urinalysis] [Routine stool test] [Coagulation function] [Pregnancy test] [Thyroid function test] [Myocardial zymogram] [Vital signs] [Physical examinations and weight measurement] [ECOG PS] [ECG] [Echocardiogram] [Blood pressure monitoring] [Adverse events] [Concomitant medication] [Return of apatinib]

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

7.4 Follow-up Period

30 days after discontinuation/end of treatment

[Vital signs] [Physical examinations and weight measurement] [ECOG PS] [Hematology] [Urinalysis] [Blood biochemistry] [Adverse events] [Concomitant medication]

Adverse events will be recorded from the time when the subjects sign the informed consent form. AEs unrelated to the study drugs will be recorded to 30 days after the last dose.

Treatment-related AEs will be collected until 90 days after the last dose of SHR-1210 or 30 days after the last dose of targeted anti-angiogenic therapy (whichever is longer). See the AE/SAE collection time limit in Section 8.3 for details.

[Survival follow-up] After the study treatment is discontinued, the survival status and subsequent anti-tumor treatment can be collected through clinical or telephone follow-ups every 2 months until death.

Schedule of Activities

Item	Screening Period			Treatment Period (28 days/cycle)			Post-Treatment		Survival Follow-up
	Within 3 weeks before administration	Within 1 week before administration	Cycle 1		Cycles 2-26		End of Treatment/ Withdrawal (+ 3 d)	End of treatment visit (± 3 d)	Every 2 months (±3)
			Day 1	Day 15 (± 3 d)	Day 1 (± 3 d)	Day 15 (± 3 d)			
Baseline Data									
Signing of Informed Consent	×								
Demographics	×								
Tumor History/ Other Medical History ^[1]	×								
Concomitant Medication ^[2]		×	×	×					
Laboratory Tests									
Hematology ^[3]		×		×	×	×	×	×	
Urinalysis ^[4]		×		×	×	×	×	×	
Routine Stool Test ^[5]		×		×	×		×		
Blood biochemistry ^[6]		×		×	×	×	×	×	
Coagulation Function Test ^[7]		×		×	×		×		
T3, FT3, FT4, and TSH ^[8]	×				×		×		
Pituitary Adrenal Axis Test ^[9]	×								

Item	Screening Period			Treatment Period (28 days/cycle)			Post-Treatment		Survival Follow-up
	Within 3 weeks before administration	Within 1 week before administration	Cycle 1		Cycles 2-26		End of Treatment/ Withdrawal (+ 3 d)	End of treatment visit (± 3 d)	Every 2 months (±3)
			Day 1	Day 15 (± 3 d)	Day 1 (± 3 d)	Day 15 (± 3 d)			
Myocardial Zymogram ^[10]		×					×		
HBV, HCV, and HIV Tests ^[11]	×								
Pregnancy Test ^[12]		×					×		
Detection of EGFR Mutations and ALK Fusion Genes ^[13]	×								
Clinical Evaluation and Examination									
Adverse Events ^[14]	From informed consent to 30 days after the last dose								
Vital Signs ^[15]		×	×	×	×	×	×	×	
Physical Examination and Weight Measurement ^[16]		×	×	×	×	×	×	×	
ECOG PS		×			×		×	×	
ECG ^[17]		×		×	×	×	×		
Echocardiography ^[18]		×					×		
Blood Pressure Monitoring ^[19]				×	×	×	×		
Pulmonary Function Test ^[20]	×								

Item	Screening Period			Treatment Period (28 days/cycle)			Post-Treatment		Survival Follow-up
	Within 3 weeks before administration	Within 1 week before administration	Cycle 1		Cycles 2-26		End of Treatment/ Withdrawal (+ 3 d)	End of treatment visit (± 3 d)	Every 2 months (±3)
			Day 1	Day 15 (± 3 d)	Day 1 (± 3 d)	Day 15 (± 3 d)			
STUDY DRUGS									
Administration of SHR-1210 ^[21]			×	×	×	×			
Administration of Apatinib ^[22]			Oral administration once a day after meal						
Dispensation/Return of Apatinib ^[23]		×	×	×	×	×	×		
Imaging Evaluation									
Imaging Examination ^[24]	×		Once every 2 cycles in the first 6 cycles, followed by once every 3 cycles				×		
Follow-Up After End of Treatment									
Time to Progression ^[25]							Imaging evaluation will be carried out once every 3 months (± 7 d) until progressive disease or the initiation of other cancer treatments (subjects with non-imaging PD)		
Time of Death ^[26]									×
Blood Sampling and Tumor Tissue Sampling/Sample Collection									
PK Blood Sampling ^[27]			×	×	×	×			
Collection and Detection of Biomarkers ^[28]	×								

Note:

- [1] History of tumor/other diseases: reports of pathological findings, detection of EGFR mutations, and detection of ALK fusion gene; history of tumor surgery, chemotherapy, radiotherapy, and other disease treatments; history of tumor other than non-small cell lung cancer.
- [2] Record the concomitant medication and concomitant treatment given within 30 days prior to randomization and during the study period. Once the study treatment is interrupted, only the concomitant medication and treatment used to solve new or unresolved treatment-related AEs will be recorded.
- [3] Hematology: Hemoglobin, red blood cell count, white blood cell count, neutrophil count, lymphocyte count, and platelet count will be measured within 7 days before enrollment, on Day 15 of Cycle 1, Day 1 and Day 15 of subsequent cycles, upon completion of the study, and 30 days after the end of treatment.
- [4] Urinalysis: Urine protein, urine glucose, and urine occult blood (urine red blood cells and white blood cells). If two consecutive semi-quantitative protein tests show urine protein 2-3+, then a quantitative 24-h urine protein test is required. If semi-quantitative protein test shows urine protein > 3+, then a quantitative 24-h urine protein test shall be performed. The tests will be carried out within 7 days before the enrollment, on Day 15 of Cycle 1, Day 1 and Day 15 of subsequent cycles, upon completion of the study, and 30 days after the end of treatment.
- [5] Routine stool test: Occult blood; re-examination is required for fecal occult blood+; if fecal occult blood is confirmed, then a gastroscopy shall be performed. The test will be performed within 7 days before enrollment, on Day 15 of Cycle 1 and Day 1 of subsequent cycles, and upon completion of the study.
- [6] Blood biochemistry: bilirubin total, bilirubin conjugated, ALT, AST, AKP, γ -GT, protein total, albumin, urea or urea nitrogen, creatinine, uric acid, fasting blood glucose, TG, cholesterol, potassium, sodium, chlorine, calcium, phosphorus, blood lipase (only during the screening period and in the case of subsequent abdominal pain, abdominal distension and other symptoms of suspected pancreatitis), blood amylase (only during the screening period and subsequent abdominal pain, abdominal distension, and other symptoms of suspected pancreatitis). It will be carried out within 7 days before enrollment, on Day 15 of Cycle 1, Day 1 and Day 15 of subsequent cycles, upon completion of the study, and 30 days after the end of treatment.
- [7] Coagulation function: INR, APTT, PT, TT, FIB. The test will be performed within 7 days before enrollment, on Day 15 of Cycle 1 and Day 1 of subsequent cycles, and upon completion of the study.
- [8] Thyroid function test: including serum FT3, FT4 and TSH. The test will be performed 21 days before administration, on Day 1 of Cycle 2, and then once every 3 cycles.
- [9] Examination of the pituitary adrenal axis: including the tests of ACTH, cortisol, and sex hormones; carried out during the screening period.
- [10] Myocardial zymogram: Perform once within 7 days before enrollment and retest only upon the onset of symptoms of precordial pain and palpitations, and abnormal electrocardiograms hereafter; perform upon completion of the study.

- [11] Hepatitis B, hepatitis C, and HIV tests: hepatitis B panel [If the test results are abnormal, viral replication (HBV DNA) test should be performed]; hepatitis C virus antibody (anti-HCV) test (If the test results are abnormal, virus titer should be tested); HIV antibody test.
- [12] Pregnancy test: The urine pregnancy test will be performed 72 h before the first dose for females of a childbearing age. If the result of the urine pregnancy test is positive, a serum pregnancy test shall be performed. If necessary, re-tests can be performed for confirmation.
- [13] If the subjects have previously been tested for EGFR mutations and ALK fusion gene, retests are not required; otherwise, the study site will perform relevant tests. If the subjects are positive for EGFR mutations, the test of ALK fusion gene will no longer be performed.
- [14] Adverse events: Adverse events will be collected from the time when the subjects sign the informed consent form. AEs unrelated to the study drugs will be collected to 30 days after the last dose. Treatment-related AEs will be collected until 90 days after the last dose of SHR-1210 or 30 days after the last dose of targeted anti-angiogenic therapy (whichever is longer). See the AE/SAE collection time limit in Section 8.3 for details.
- [15] Vital sign examination: Body temperature, respiration, pulse, blood pressure. The examination will be performed within 7 days before enrollment, on Day 1 and Day 15 of Cycle 1, Day 1 and Day 15 of subsequent cycles, upon completion of the study, and 30 days after treatment.
- [16] Physical examination and weight measurement: Examination of major body systems (head and face, skin system, lymph nodes, eyes, ears, nose, throat, oral cavity, respiratory system, cardiovascular system, abdomen, urogenital system, musculoskeletal system, nervous system and mental state) will be performed within 7 days before enrollment, on D1 and D15 of Cycle 1, D1 and D15 of subsequent cycles, upon completion of the study, and 30 days after the end of treatment. Body weight measurement will be started on D1 of Cycle 2 and carried out on D1 of subsequent cycles, upon completion of the study, and 30 days after the end of treatment.
- [17] 12-Lead ECG: Performed within 7 days before enrollment, on Day 15 of Cycle 1, Day 1 and Day 15 of subsequent cycles, and upon completion of the study. Abnormalities in ECG must be confirmed twice via additional ECG tests.
- [18] Echocardiography: Performed within 7 days prior to the enrollment and upon completion of the study, and when clinically significant abnormalities are found during the study.
- [19] Blood pressure monitoring: The blood pressure monitoring will be performed by the subjects themselves and recorded in their diary card. Blood pressure will be measured at least 3 times a week in the first 2 cycles. If the blood pressure is abnormal, the measurement will be carried out every day; If the blood pressure is normal, the blood pressure measurement will be carried out twice a week after 2 cycles; In addition, the blood pressure will be measured by the investigator during each follow-up. During each blood pressure measurement, smoking and coffee are prohibited for 30 min before the measurement, and subjects should at least rest for 10 min, and the sitting position will be taken during the measurement by placing the elbow at the same level as the heart. Each blood pressure measurement will be taken on the same side of the body.

- [20] Pulmonary function test: Maximum vital capacity, the forced expiratory flow at 25-75% of forced vital capacity (FEF25-75), the peak expiratory flow rate (PEF), the maximum expiratory volume per second, diffusing capacity of the lungs for carbon monoxide (DLCO) and oxygen saturation. The test will be carried out during the screening period and then according to the judgment of the investigator in subsequent cycles.
- [21] SHR-1210 administration: SHR-1210 will be administered via intravenous injection (no prophylactics) with a fixed dose of 200 mg given in 30 min (no less than 20 min and no more than 60 min), once every 2 weeks. Each cycle contains 4 weeks (the subjects for the expanded PK study receive one dose on D1 of Cycle 1) and the longest period of drug use is 2 years. After 6 cycles of SHR-1210 administration, the treatment can be discontinued if the imaging evaluation confirms a CR.
- [22] Apatinib will be taken orally after meals, once a day, and continued throughout the study (the subjects for the expanded PK study receive the drug starting on Day 22 of Cycle 1. The administration on Day 28 of Cycle 1 and Day 28 of Cycle 2 will be given orally under fasting conditions).
- [23] Return and dispensation of apatinib. Apatinib will be dispensed on Day 1 of Cycle 1 (dispensed to subjects in the drug expansion study from Day 22 of Cycle 1). From Day 1 of Cycle 2, the return and dispensation of apatinib will be performed on Day 1 of each cycle. The remaining drugs will be returned first to verify the dose actually taken before new study drugs are dispensed.
- [24] Imaging test: including CT or MRI of the chest, abdomen, and brain. The baseline tumor assessment during the screening period can be extended to up to 3 weeks before treatment. Qualified CT/MRI scan results obtained before signing the informed consent can be used for tumor assessment during the screening period. Bone scan should be performed upon clinically suspected bone metastasis. Absence of cerebral hemorrhage should be confirmed within 21 days before randomization for subjects with stable brain metastases.
- During the treatment period, imaging examinations should be performed under the same conditions as those at baseline (layer thickness of the scan, use of contrast agent, etc.), and the lesions found at baseline should be checked every 2 cycles in the first 6 cycles of the treatment (bone scan shall be performed in the case of suspected bone progression or for CR confirmation). After 6 cycles, imaging examinations can be performed every 3 weeks as appropriate and can be performed upon the discovery of suspected new lesions. Initial assessment of PR/CR must be confirmed after 4 weeks; initial assessment of PD must be confirmed after 4 to 6 weeks (except for significant changes in the subjects' symptoms or rapid tumor progression).
- The window period for imaging examination schedule is ± 7 days. Unscheduled imaging examinations can be performed when progressive disease is suspected (such as worsening of symptoms).
- [25] A tumor assessment is required at the end of treatment for subjects who discontinue study treatment for reasons other than radiographic PD, if not performed within 4 weeks prior to study completion. Also, treatment efficacy will be followed up once every 3 months after study completion, until documentation of confirmed PD or start of a new anti-tumor treatment.
- [26] Survival follow-up: After the study treatment is discontinued, the survival status and subsequent anti-tumor treatment can be collected through clinical or telephone follow-ups every 2 months until death.

- [27] PK blood sampling: In the stage of expanded PK study, PK blood sampling will be performed within 0.5 h before the administration of SHR-1210, and post-dose at 5 min (± 3 min), 2 h (± 10 min), 6 h (± 10 min), 24 h (± 0.5 h), 48 h (± 1 h), 168 h (± 1 h), 336 h (± 1 h), and 504 h (± 1 h) on D1, with 3 mL of blood collected at each time point. After the completion of PK blood sampling on D22, the administration of apatinib mesylate tablets will be started on the same day and continued at administration frequency of once a day. PK blood sampling will be performed within 0.5 h pre-dose on D28 and post-dose at 0.5 h (± 3 min), 1 h (± 5 min), 2 h (± 5 min), 3 h (± 5 min), 5 h (± 10 min), 8 h (± 10 min), 12 h (± 10 min), and 24 h (± 1 h), with 3 mL of blood collected at each time point.

On D1 of Cycle 2, PK blood sampling will be performed within 0.5 h before the administration of SHR-1210, and at 5 min (± 3 min), 2 h (± 10 min), 6 h (± 10 min), 24 h (± 0.5 h), 48 h (± 1 h), 168 h (± 1 h), and 336 h (± 1 h) after the administration of SHR-1210, with 3 mL of blood collected at each time point. On D28 of Cycle 2, PK blood sampling will be performed within 0.5 h before the administration of apatinib, and at 0.5 h (± 5 min), 1 h (± 5 min), 2 h (± 5 min), 3 h (± 5 min), 5 h (± 10 min), 8 h (± 10 min), 12 h (± 10 min), and 24 h (± 1 h) after the administration of apatinib, with 3 mL of blood collected at each time point.

- [28] A total of 14 mL of blood sample will be collected from each subject at baseline and divided into 1 tube of 10 mL and 1 tube of 4 mL. The collected blood samples will be transported to the central laboratory at room temperature according to the requirements specified in the central laboratory manual (no additional processing by the study center is required). Subjects with CR/PR during the study period must be subject to an additional biomarker blood sampling upon the onset of CR/PR and PD, respectively, with 10 mL in 1 tube, and the collection and transport requirements are the same as those in the baseline period; archived paraffin-embedded tumor tissue samples or fresh biopsy specimens will be collected. At least 10 slices are required, including 3-5 slices of 3-4 μm thickness for PD-L1 detection, and 5-8 slices of 5-8 μm thickness (paraffin blocks may be directly collected without mounting onto slides), otherwise fresh biopsy specimens are required for detection of biomarkers such as tumor mutation burden (TMB).

For cohort 4, the test results of tumor mutation burden (TMB) in the peripheral blood and/or tumor tissues will be verified before the subjects take the first dose of the study drug, so the TMB test for cohort 4 must be completed before the first dose. However, the delay in the screening period caused by TMB testing is allowed, but other tests (including imaging examinations) must be completed within 21 days prior to the first dose.

See the laboratory manual for biomarker blood sampling and tumor tissue sampling/sample collection and disposal.

8 SAFETY EVALUATION

8.1 Adverse Events (AEs)

8.1.1 Definition of adverse event

An adverse event (AE) refers to any untoward medical occurrence in a study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. For the specific period of AE collection in this study, please refer to Section 8.3. AEs include the following:

- 1) Worsening of pre-existing (prior to entering clinical study) medical conditions/diseases (including worsening symptoms, signs, or laboratory abnormalities);
- 2) Any new AEs: Any new adverse medical conditions (including symptoms, signs, and newly diagnosed diseases);
- 3) Clinically significant abnormal laboratory findings.

The investigator should record any AEs that have occurred in detail, including the description of the AEs and all relevant symptoms, time of occurrence, severity, causality with the study drugs, duration, measures taken, and final results and outcomes.

8.1.2 Criteria for severity assessment of adverse events

The severity of AEs will be determined using NCI-CTCAE v4.03. The following criteria can be used as references if an unlisted AE occurs:

Grade 1: mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; treatment not indicated.

Grade 2: moderate; minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (e.g., cooking, shopping, using the telephone, counting money, etc.);

Grade 3: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living. Self-care ADL: Refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Grade 4: life-threatening consequences; urgent intervention indicated.

Grade 5: death related to AE.

8.1.3 Criteria for the causality between AEs and investigational drug

AEs include all unexpected clinical manifestations. All the AEs occurring after the signing of the ICF must be reported in the form of a clinical report according to AE reporting, regardless of whether the AEs are related to the investigational drug, whether the subject is administered with the investigational drug, and whether the subject has been administered with drugs. During the treatment, any discomfort or abnormal changes in objective laboratory tests should be recorded truthfully. The severity, duration, measures taken and outcome of the AE should be indicated. The clinical physician should comprehensively assess the causality between the AE and the study drugs by considering the timing between the administration of study drug and the occurrence of AE, characteristics and toxicology of the study drug, concomitant medications, underlying diseases, medical history, family history, etc. The causality assessment will be provided using the following five categories "definitely related, possibly related, unlikely related, definitely unrelated, and indeterminable".

Related: The AE has a reasonable correlation with the study drug and can be attributed to the study drug from the medical (pharmacological or clinical) point of view.

Unrelated: The AE has no reasonable correlation with the study drug and cannot be attributed to the study drug from the medical (pharmacological or clinical) point of view, and/or there are other reasonable reasons to explain the AE, such as underlying diseases, complications, and concomitant medications.

8.2 Serious Adverse Events (SAEs)

8.2.1 Definition of serious adverse event

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

- Events resulting in death;
- Life-threatening events (defined as when the subject is at immediate risk of death at the time of the event);
- Events resulting in hospitalization or prolonged hospitalization;
- Events resulting in permanent or serious disability/incapacity/impairment of work ability;
- Congenital anomalies or birth defects;
- Other important medical events (defined as events that may jeopardize the subject or require interventions to prevent any of the above).

8.2.2 Progressive disease and death

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

Death of a subject during the study, regardless of whether a new anti-tumor treatment is administrated, must be reported as an SAE. Deaths caused by symptoms and signs of PD as determined by the investigator shall be recorded in the eCRF and reported as SAEs. The term "death" shall not be used as an AE or SAE, but an outcome of an event. Events that result in death shall be recorded as AEs or SAEs. If the cause of death is unknown and cannot be determined at the time of reporting, the AE or SAE term "death of unknown cause" shall be used for documentation.

8.2.3 Hepatic enzyme abnormalities

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

Baseline Period	Normal (AST/ALT and TBIL)	Abnormal (AST/ALT/TBIL)
Treatment period	ALT or AST $\geq 3 \times \text{ULN}$ with TBIL $\geq 2 \times \text{ULN}$ and ALP $\leq 2 \times \text{ULN}$ and no hemolysis	AST or ALT $\geq 2 \times \text{baseline level}$, and $\geq 3 \times \text{ULN}$ or AST or ALT $\geq 8 \times \text{ULN}$ with <u>increase</u> in TBIL by $\geq 1 \times \text{ULN}$ or TBIL level $\geq 3 \times \text{ULN}$

8.2.4 Other anti-tumor treatments

If the subjects start other anti-tumor treatments, please refer to Section 8.3 for the period of AEs/SAEs reporting. If a death occurs after the end of the study treatment but within the reporting period of serious adverse events, it must be reported promptly regardless of whether the subject received other treatments.

8.2.5 Hospitalization

AEs that result in hospitalization (even if for less than 24 h) or prolonged hospitalization during the clinical study should be considered as SAEs.

Hospitalization does not include the following:

- Hospitalization at a rehabilitation institution
- Hospitalization at a sanatorium
- General emergency admission (less than 24 h)
- Day surgery (e.g., outpatient/same-day/ambulatory surgery)
- For social reasons (medical insurance reimbursement, etc.)

Hospitalization or prolonged hospitalization unrelated to the worsening of an AE is not a SAE.

For example:

- Hospitalization due to the pre-existing disease without new AEs and aggravation of the pre-existing disease (e.g., hospitalization to examine laboratory abnormalities that have persisted before the study until now);
- Hospitalization for management reasons (e.g., annual physical examination);
- Hospitalization during the study as specified in the study protocol (e.g., as required by the protocol);
- Elective hospitalization unrelated to the exacerbation of an AE (e.g., elective cosmetic surgery);
- Scheduled treatment or surgery that should be documented throughout the entire study protocol and/or in the subjects' individual baseline information;
- Hospitalization merely for use of blood products.

Diagnostic or therapeutic invasive (e.g., surgery) or non-invasive procedures should not be reported as AEs. However, the disease condition leading to such procedures should be reported if it meets the definition of an AE. For example, acute appendicitis during the AE reporting period should be reported as an AE, and the resulting appendectomy should be recorded as the treatment of the AE.

8.2.6 Reporting of serious adverse events

In the event of an SAE, whether it is an initial or follow-up report, the investigator must complete the "Serious Adverse Event Report Form" immediately with signature and date, and notify the sponsor within 24 h of awareness. Relevant authorities must be informed of such an SAE in a timely manner according to regulatory requirements.

The symptoms, severity, causality with the study drug, time of onset, time of treatment, measures taken, time and method of follow-up, and outcomes should be documented in detail in the SAE report. If the investigator believes that an SAE is not related to the study drug but potentially related to the study conditions (such as the discontinuation of past treatment, or comorbidities during the study), the causality should be explained in the description section of the SAE report form. If the severity of an ongoing SAE or its relationship to the study drug changes, a follow-up report should be submitted immediately. If an error is found in a previously reported SAE, such SAE may be revised, revoked, or downgraded in follow-up reports and reported in accordance with the SAE reporting procedure.

Email the SAE reports to: hengrui_drug_safety@hrglobe.cn

8.3 Collection and Follow-Up of AEs/SAEs

The collection of AEs/SAEs should start from the time when the subjects sign the informed consent form and end 90 days after the last dose of SHR-1210 or 30 days after the last dose of anti-angiogenic targeted therapy (whichever is longer). SAEs occurring after this period that are suspected to be related to the study drug should be collected. See [Table 8-1](#) below for specific requirements. Any AE/SAE should be followed-up until the event resolves, returns to the baseline level or \leq Grade 1, reaches a steady state, or is reasonably explained (e.g., lost to follow-up, death). The investigator should try to obtain the best outcome and clear causality with the study drug.

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

Table 8-1. Collection period of AEs/SAEs

Classification	Collection/Recording Requirements
AEs Unrelated to the Study Drug	Up to 30 days after the last dose
Treatment-Related AEs ^a	Up to 90 days after the last dose of SHR-1210 or 30 days after the last dose of apatinib (whichever is longer)
SAEs Unrelated to the Study Drug ^a	<ul style="list-style-type: none"> Fatal SAEs: up to 90 days after the last dose of SHR-1210 or 30 days after the last dose of apatinib (whichever is longer) Non-fatal SAEs: up to 30 days after the last dose
Treatment-Related SAEs ^b	No time limit

^a Non-serious AEs

^b Including fatal and non-fatal SAEs.

8.4 Pregnancy

If a female subject becomes pregnant, she must withdraw from the study. The investigator must report to the sponsor within 24 h of being notified of the pregnancy and fill out the "Pregnancy Report/Follow-up Form for Hengrui Clinical Studies". If the partner of a male subject becomes pregnant, the subject may continue the clinical study. The investigator must report to Hengrui within 24 h of being notified of the pregnancy and fill out the "Pregnancy Report/Follow-up Form for Hengrui's Clinical Studies". The investigator should follow up the pregnancy until 1 month after delivery, and report the results to Hengrui.

A negative pregnancy outcome (stillbirth, spontaneous abortion, or congenital malformation) is considered an SAE and should be reported according to the time requirements for SAEs.

If the subject also meets the criteria for an SAE, an SAE report form should be filled out and the SAE should be reported according to the requirements for SAEs as well.

8.5 Adverse Events of Special Interest

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

- Grade ≥ 3 infusion reaction
- Grade ≥ 2 diarrhea/colitis, uveitis, interstitial pneumonitis
- Other Grade ≥ 3 immune-related AEs

- Any possible events of hepatic enzyme abnormalities (see 8.2.3, lacking other related causes of the abnormalities at the same time, e.g., PD, acute viral hepatitis, cholestasis, concomitant medication, concurrent liver disease, etc.)
- Grade 4 amylase or lipase increased

8.6 Infusion Reactions

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

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

8.7 Immune-Related Adverse Events (irAEs)

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

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

● Immune-related pneumonitis

In the clinical study of SHR-1210, the monitoring of signs and symptoms of immune-related pneumonia, such as cough and chest discomfort, in the subjects will be strengthened. Examinations will be carried out via imaging tests (e.g., X-ray), and a high-dose hormone therapy will be given to subjects with a Grade 2 or greater event. Subjects with a Grade 2 event can interrupt SHR-1210 and be treated, but subjects with a Grade 3 or 4 event should permanently discontinue SHR-1210.

- **Immune-related enteritis**

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

- **Immune-related hepatitis**

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

- **Immune-related thyroid dysfunction**

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

In the clinical study of SHR-1210, the monitoring of signs and symptoms of immune-related thyroid dysfunction in the subjects will be strengthened. A high-dose hormone therapy will be given to subjects with a Grade 3 or greater event, but subjects with a Grade 4 event should permanently discontinue SHR-1210.

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

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

● Immune-related hypophysitis

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

● Other immune-related adverse reactions

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

The treatment of immune-related adverse reactions should be based on the medical practice and guidelines of the study center. The treatment recommendations for irAEs are shown in Table 8-2 for reference.

Table 8-2. Treatment recommendations for irAEs related to SHR-1210 for injection

CTCAE Grade	Clinical Management*	SHR-1210 Treatment
Grade 1 (mild)	<ul style="list-style-type: none"> - Close observation, especially for diarrhea • Supportive care 	Continue
Grade 2 (moderate)	<ul style="list-style-type: none"> - Closely monitoring • Supportive care • Local application of steroids, such as for dermatitis/colitis, etc. <p>Symptoms persist for ≥ 7 days, start 1 mg/kg of prednisone or equivalent</p> <p>Symptoms are aggravated, give intravenous or oral administration of 1 mg/kg prednisone</p>	Interrupt, resume when recovers to Grade ≤ 1
Grade ≥ 3 (severe)*	-2 mg/kg of prednisone or equivalent	Permanent discontinuation

* The treatment may not be interrupted for Grade 3 local skin and endocrine disorders, because they can often heal (skin) or be treated using an alternative treatment (endocrine)

(Weber, Jeffrey S. MD, PhD, et al., "Toxicities of immunotherapy for the practitioner," J Clin Oncol, April 2015)

9 MANAGEMENT OF ADVERSE EVENTS

9.1 Immune-Related Adverse Events (irAEs)

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

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

The treatment of immune-related adverse reactions should be based on the medical practice and guidelines of the study center. The treatment recommendations for irAEs are as follows. The details are shown in Appendix IV for reference.

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

● **Immune-related pneumonitis**

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

For specific operations, refer to the followings:

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

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

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

● Immune-related hepatitis

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

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

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

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

● Immune-related enteritis

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

● Immune-related thyroid dysfunction

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

In the clinical study of SHR-1210, the monitoring of signs and symptoms of immune-related thyroid dysfunction in the subjects will be strengthened. A high-dose hormone therapy will be given to subjects with a Grade 3 or greater event, but subjects with a Grade 4 event should permanently discontinue SHR-1210.

● Immune-related nephritis and renal failure

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

● Immune-related hypophysitis

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

● Other immune-related adverse reactions

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

9.2 Infusion Reactions

As a fully humanized monoclonal antibody, SHR-1210 poses relatively lower risks of infusion reactions and prophylactic is therefore not required. Once an infusion reaction occurs, the infusion should be slowed or interrupted accordingly, and a supportive treatment should be given. Also, prophylactics should be given before further administrations. For acute infusion reactions (including cytokine release syndrome, angioedema, anaphylactic shock, allergic reactions, please refer to terms and criteria of NCI CTC AE v4.03), their relevant symptoms and signs usually occur during drug infusion or shortly after infusion, and usually disappear within 24 h after the infusion is completed. The signs and symptoms include: allergic reaction/hypersensitivity reaction (including drug-induced fever), coughing, chills, rigor, dizziness, headache, fatigue (weakness, somnolence), rash/peeling skin, pruritus/itching, arthralgia, myalgia, hypotension/hypertension, nausea, vomiting, diaphoresis, tachycardia, cancer pain, urticaria, dyspnea (shortness of breath), or bronchospasms. Any Grade 3 or 4 infusion reactions must be reported to the sponsor within 24 hours, and should be reported as SAEs if the criteria for SAE are met.

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

Table 9-1. Treatment recommendations for infusion reactions

CTCAE Grade	Clinical Symptoms	Clinical Management	SHR-1210 Treatment
Grade 1 (mild)	Mild and transient reactions;	Bedside observation and close monitoring until recovery. (Prophylactics are recommended for subsequent infusion: diphenhydramine 50 mg or equivalent, and/or acetaminophen 325-1000 mg, at least 30 minutes prior to SHR-1210 administration)	Continue
Grade 2 (moderate)	Moderate reactions requiring treatment or interruption; rapidly resolve after symptomatic treatment (such as antihistamines, non-steroidal antiphlogistics, anesthetics, bronchodilators, intravenous fluids, etc.)	Intravenous drip of normal saline, 50 mg of diphenhydramine IV or equivalent and/or 325-1000 mg of acetaminophen; Bedside observation and close monitoring until recovery. Corticosteroids or bronchodilators can be considered based on clinical needs; The amount of study drug infused should be recorded in the original medical record; Prophylactics are recommended for subsequent infusion: diphenhydramine 50 mg or equivalent, and/or acetaminophen 325-1000 mg, at least 30 minutes prior to SHR-1210 administration. Use corticosteroids (equivalent to 25 mg of hydrocortisone) when necessary.	Interrupt. Re-administer at 50% of the initial rate after symptoms resolve. If no reaction occurs within 30 min, restore the original infusion rate (100%). Closely monitor. If the symptoms recur, the administration of the current SHR-1210 dose will be discontinued.
Grade \geq 3 (severe)	Grade 3: Severe reactions with no rapid resolution after intervention and/or treatment interruption; symptom recurrence after resolution; sequelae requiring hospitalization. Grade 4: life-threatening	Immediately discontinue SHR-1210; Administer normal saline by intravenous infusion. <ul style="list-style-type: none"> Bronchodilators are recommended: 0.2-1 mg of subcutaneous 1:1000 adrenaline injection or slow intravenous injection of 1:10000 adrenaline solution 0.1-0.25 mg, and/or intravenous diphenhydramine 50 mg plus methylprednisolone 100 mg or equivalent if necessary; Based on the guidelines for anaphylaxis of the study center; Bedside observation and close monitoring until recovery.	Permanently discontinue.

9.3 Symptomatic Treatment for Apatinib-Related Adverse Reactions

1) Hand-and-foot syndrome (HFS)

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

HFS grading:

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

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

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

Symptomatic treatment and management of HFS:

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

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

2) Hypertension

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

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

If hypertension occurs or aggravates during the administration, 1) give or adjust the dose of antihypertensive drugs, and 2) adjust the study drug as per the study protocol.

Recommended antihypertensive drugs during study: 1) dihydropyridine calcium channel antagonists (such as nifedipine sustained release tablets); 2) angiotensin converting enzyme inhibitors (ACEIs); 3) angiotensin II receptor blockers (ARBs); 4) Beta blockers.

Diuretic antihypertensive drugs are not recommended. Antihypertensive drugs with an inhibitory effect on CYP3A4, such as nifedipine, diltiazem and verapamil, are prohibited during the administration period of the study drug. Subjects with hypertensive crisis should discontinue apatinib and withdraw from the study.

3) Hemorrhage

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

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

Note: The subjects diagnosed with cerebral hemorrhage, pulmonary hemorrhage of Grade 2 or greater, and hemorrhage of Grade 3 or greater should discontinue the study treatment, receive symptomatic treatment, and withdraw from the study. If hemorrhage and coagulation abnormalities (except for cerebral hemorrhage and pulmonary hemorrhage of Grade 2 or greater) occur, adjust the dose following the principles below:

4) Proteinuria

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

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

5) Thrombosis

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

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

6) Reversible posterior leukoencephalopathy syndrome

Reversible posterior leukoencephalopathy syndrome has not been reported in completed clinical studies of apatinib, but has been found in clinical application of newly marketed anti-angiogenic macromolecular antibodies and small molecule inhibitors.

The clinical manifestations are headache, altered consciousness/confusion, abnormal vision/blindness, and convulsion, often accompanied by hypertension. The causes of reversible posterior leukoencephalopathy syndrome are yet unidentified. Once the symptoms are suspected, the study drug should be discontinued immediately, and symptomatic treatment and strict blood pressure control should be given. The subject will withdraw from the study once the imaging diagnosis is confirmed.

7) Fatigue and weakness

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

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

Therefore, close attention should be paid when a patient show and report Grade 2 or greater fatigue and weakness. In the case of Grade 3 or greater fatigue and weakness, the patient should be admitted to the hospital immediately for detailed examinations to exclude possible reasons such as electrolyte disturbance, abnormal liver function, cardiac dysfunction (ECG, echocardiography), and abnormal hormone levels (adrenal hormones, thyroid hormones). A symptomatic treatment should be given and the dose should be interrupted or modified according to the principle of dose modification.

8) Abdominal pain

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

9) Interstitial pulmonary fibrosis

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

Note: Consult specialists when necessary.

10 EFFICACY EVALUATION

The objective response rate (ORR), duration of response (DoR), clinical benefit rate (CBR), time to response, progression-free survival (PFS), 12-month survival, and overall survival (OS) will be evaluated.

The tumor imaging assessment will be performed once every 2 cycles (8 weeks) based on RECIST v1.1 (Appendix V). For subjects with CR/PR for the first time, the results should be confirmed after 4 weeks. The tumor assessment will be carried out once every 3 cycles (12 weeks) 6 months after the first dose of the drug.

Imaging results (including MRI and CT) of all subjects should be confirmed by blinded independent imaging experts. Subjects with efficacy evaluation results of CR, PR, SD, and PD should first be reviewed by the Principal Investigator (PI) of each study site, with all imaging results of response evaluation saved and finally collectively and independently assessed and confirmed by imaging experts.

11 STUDY MANAGEMENT

11.1 Ethics and Informed Consent

This clinical study must comply with the "Declaration of Helsinki (1996)", NMPA's "Good Clinical Practice (GCP)" and relevant regulations. The study can only be initiated after obtaining the approval from the IRB/IEC. During the study, amendments to this study protocol must be reported to the IRB/IEC and be archived.

The clinical investigator must follow all applicable laws and regulations to protect the subjects. The informed consent form used in the informed consent process must be approved by the IRB/IEC and be readily available for inspection.

The clinical investigator must inform subjects that participation in the clinical study is voluntary and that they have the right to withdraw from the study without being discriminated or retaliated, and their medical treatment and right will not be affected, and they can continue to receive other therapies. All subjects should be informed that the participation of the study and their personal information will be kept confidential. Also, the subjects should be informed of the nature, objectives, expected potential benefits, and possible risks and inconvenience of the clinical study, other alternative treatment options, and rights and obligations of the subjects in accordance with the "Declaration of Helsinki". Subjects should be given sufficient time to consider whether to participate in the study and sign the informed consent form.

Before the implementation of any process required by the study protocol, the subjects must:

- Be informed of information relevant to the study and all content and terms in the informed consent form.
- Be given sufficient time to ask questions and consider whether to participate in the study.
- Be enrolled in the study voluntarily.
- Sign and date the informed consent form approved by the IRB/IEC.

In the case of major changes during the study, the protocol should be amended. Unless it is necessary to eliminate obvious direct harms to subjects, the investigator must not make any change to the study without the approval of the IRB/IEC and sponsor. Changes to the study protocol intended to eliminate obvious direct risks to subjects can be implemented immediately, but the changes must be recorded in protocol amendments, reported to the IRB/IEC, and submitted to relevant regulatory authorities within a required period. The process of protocol amendment must follow the same process of review and approval of the original protocol.

11.2 Protocol Amendments

The "Clinical Study Protocol" and "Clinical Study Case Report Form" are formulated by the PI, agreed upon by Hengrui, which is the study sponsor and study drug provider, and approved by the Ethics Committee of the hospital before implementation. During the clinical study, any changes to the study protocol must be discussed with Hengrui, and approved by the Ethics Committee.

11.3 Quality Assurance of Clinical Study

To ensure the quality of the study, the sponsor and PI will jointly discuss and formulate a clinical study plan before the formal study initiation. All the relevant study staff in the clinical study shall be trained for the study protocol and GCP.

The study drug in the clinical study shall be managed in accordance with the SOP, including receiving, storage, dispensing, and returning.

Hengrui may conduct monitoring and auditing on the request of the PI. The CRA shall follow the GCP and SOP, make visits to the study site for clinical monitoring on a regular basis or according to the actual conditions, supervise the implementation and progress of the clinical study, check and confirm that all data recorded are correct and intact and are consistent with source data, and ensure that the clinical study is implemented following the study protocol. The investigator should cooperate with the monitor actively.

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

11.4 Data Management

Data management is to ensure the reliability, integrity, and accuracy of the data, with an objective to obtain authentic data of high quality for statistical analysis.

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

11.4.1 Data collection

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

Hengrui is the sole owner of all original eCRFs. Aside from Hengrui or the representatives from regulatory authorities, no one is allowed to provide any data to a third party. The investigator is ultimately responsible for collection and report of all clinical and laboratory data recorded in eCRFs and other data collection forms (source records) to ensure the attributability, legibility, timeliness, primitiveness, accuracy, durability, integrity, and consistency of the data.

Signature of the investigator or authorized personnel must sign to confirm the authenticity of the data in eCRFs. Any data correction in source record or eCRF should be dated, signed, and given with necessary explanations. Source data cannot be covered.

Source records are usually graphs from a hospital or a physician, In this case, the data collected in the eCRF must be consistent with those in the graph. An eCRF can be used as a source record under certain circumstances. The study site is required to provide documents to clarify the data that should be recorded in eCRF and to use the eCRF as a source record.

11.4.2 Data management and quality control

To ensure authenticity and reliability and improve the quality of the clinical data, the CRA will monitor the integrity, consistency, and accuracy of the study data in the database, and guide the study site staff to add or correct the data whenever necessary. The CRA or data manager will send electronic query form to the PI or CRC for problematic data. The PI or CRC must respond and provide correction or explanation of the problematic data. Multiple queries may be raised when necessary until the problem is solved. The medical director and data manager should perform consistency comparison of SAEs periodically.

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

11.4.3 Data review and study site monitoring

Before the initiation of the study, a representative from Jiangsu Hengrui Pharmaceuticals Co., Ltd. will introduce study protocol and eCRF (Part 2) to the investigator and staff at the initial visit to the study site. During the study, the CRA will visit the study center on a regular basis to monitor the integrity of the subjects' records and accuracy of the eCRF, compliance with the study protocol and GCP, and progress of the enrollment, and to ensure that the storage, dispensing, and count of the study drug are performed according to the requirements. During these visits, the major research personnel are required to assist the work of CRA.

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

The investigator must ensure that all source documents are available for monitoring to verify their consistency with the eCRF. Jiangsu Hengrui Pharmaceuticals Co., Ltd. requires to completely monitor the signed informed consent forms, compliance with inclusion/exclusion criteria, SAEs records, and all data required for evaluation of primary endpoints and safety endpoints. Additional monitoring will be performed on consistency of source data and eCRF according to monitoring plan specified by the study. No information related to subjects' identity in the source document will be disclosed.

11.4.4 Record retention

To fulfill the review and/or audit requirement of regulatory authorities or Hengrui, the investigator/study site must agree to keep all relevant records, including all subjects' ID number (with sufficient information linked to the records, such as the CRF and medical record), all original informed consent forms, all copies of the CRF, safety reports, source records, detailed treatment records, and relevant communication documents (such as letters, minutes, and telephone reports). The investigator/study site should keep the records according to related specifications.

If the study record cannot be kept for any reasons, the investigator/study site should inform Hengrui in advance. Study documents should be kept by the study site for 5 years after completion of the clinical study. Hengrui will inform the investigator/study site if the documents are no longer required to be retained.

12 DATA MANAGEMENT AND INTELLECTUAL PROPERTY RIGHTS

12.1 Data Processing

After the completion of the study, data will be processed by the data statistics company authorized by the sponsor. Inconsistency in the documents will be discovered via data verification. Any inconsistency in the documents should be clarified by the investigator through CRA. Database will be locked after the data is verified. No access is allowed without authorization. Following database locking, the statistician will unblind the data after applying with the sponsor and PI and obtaining agreement from all the three parties. To ensure the safety of the data, irrelevant personnel cannot access or modify data. Data should be backed up. Any changes to the data should be approved with written agreements by the principal investigator, statistician, and data manager before it can be changed.

12.2 Publication of Study Results

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

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

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

13 STATISTICAL ANALYSIS

13.1 Determination of Sample Size

The sample size in Stage I is primarily based on clinical considerations, and the number of subjects actually enrolled in each dose group is determined by the number of subjects who show clinically significant toxicity during the observation period for tolerability. During the expansion stage of PK study, 10-12 subjects are required for each group. The sample size in Stage I is 40-60 subjects.

In Stage II, for cohort 1, assuming that the ORR of the combination therapy is 30% with a bilateral alpha of 0.05, enrollment of 62 subjects will have a 80% power to ensure that the ORR of the combination therapy has a lower 95% CI limit of > 15%. If the dropout rate is 20%, 78 subjects should be enrolled.

For cohorts 2 and 3, assume that the ORR point estimate of each cohort is 30% and the width of the 90% confidence interval is 0.3, 38 subjects are required for each group when a 20% dropout rate is considered.

For cohort 4, assume that the ORR point estimate is 50% and the width of the 90% confidence interval is 0.4, 20 subjects are required to be enrolled.

In Stage II, the four cohorts require to enroll a total of 174 subjects.

13.2 Statistical Hypotheses

The primary endpoint in Stage II is ORR.

Null hypothesis: $ORR = 15\%$

Alternative hypothesis: $ORR \neq 15\%$

13.3 Analysis Sets

Full analysis set (FAS)

All subjects who have received at least one dose of the study drug.

Evaluable set (ES)

ES is a subset of FAS, which is defined as the subjects who have received at least one dose of the study drug, and have at least one post-baseline imaging assessment for efficacy. **Per-protocol set**

All enrolled subjects who have received at least one dose of the study drug without major protocol deviation.

Safety analysis set

All enrolled subjects who have received at least one dose of the study drug and have safety record after administration. This analysis set is used for safety analysis.

Pharmacokinetic analysis set (PKS):

1) Concentration analysis set

PK concentration analysis set is defined as the subjects who have received the study drug and have at least one blood concentration observation per cycle.

2) Parameter analysis set

PK parameter analysis set is defined as the subjects who have received the study drug and have at least one primary PK parameter per cycle. Subjects who have not completed the PK study should be excluded.

13.4 Statistical Analysis Plan

Main part of the study is defined as 6 months after the last subject have received the first dose of the drug in Stage I and Stage II. Statistical analysis will be carried out after the completion of the main part, and the report will be submitted. At the end of study, which is 12-24 month after the first does of the last subject in Stage II, the secondary endpoints, including 12-month survival rate and overall survival, will be included in supplementary analysis.

13.4.1 General analysis

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

All statistical analyses will be performed using SAS version 9.2 or later.

13.4.2 Basic characteristics

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

13.4.3 Efficacy analysis

Endpoints such as the ORR and CBR will be analyzed using Clopper-Pearson method with 2-sided 95% CI. For survival, the median duration of progression-free survival, the 12-month survival rate, the median duration of survival, and their 95% confidence intervals representing the entire population will be estimated using the Kaplan-Meier method. In addition, survival plots will be plotted. Descriptive analysis will be performed for other secondary efficacy endpoints.

13.4.4 Safety evaluation

Descriptive statistical analysis will be primarily used to analyze the adverse events, serious adverse events and adverse reactions in each dose group (the adverse reactions are defined as adverse events that are "definitely related, probably related, and indeterminable" to the study drug). Laboratory test results will describe the conditions that are normal before the study but become abnormal after treatment. The mean, standard deviation, median, minimum, and maximum of vital signs (blood pressure, pulse, body temperature, and respiratory rate) before and after single-dose administration will be respectively calculated by dose group.

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

Laboratory parameters, ECG, the number and rate of laboratory parameters "changed from normal to abnormal" or "exacerbated", and abnormalities after the study and their clinical explanations will be tabulated.

13.4.5 PK analysis

The following PK parameters: C_{max} , T_{max} , AUC and $t_{1/2}$ will be summarized by dose group and planned blood sampling time points and analyzed using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). A mean and/or median-time plot of serum concentration will be plotted. Statistical description will be given for the mean, standard deviation, median, minimum and maximum values, geometric mean and standard deviation, and %CV and 95% CI of natural log-transformed parameters (if applicable) by dose groups. Box-plots will be drawn for primary parameters. The serum concentration-time plots will be drawn for each subject along with a list of serum concentrations and parameter data.

13.4.6 Other analyses

SHR-1210-related biomarkers of solid tumor, such as PD-L1 expression level and TMB level in tumor tissue samples, will also be analyzed using descriptive statistics.

14 EXPECTED STUDY SCHEDULE

The study is expected to be carried out from Mar. 2017 to Sep. 2019.

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Appendix I Prohibited Traditional Chinese Medicine (TCM)

Huatan Huisheng tablet

Brucea Javanica oil soft capsule

Mandarin melon berry syrup

Cantharidin

Cinobufotalin

Bufotoxin

Kang'ai injection

Kanglaite injection

Zhongjiefeng injection

Aidi injection

Awei Huapi ointment

Kangaiping pill

Fukang capsule

Xiaoaping

Pingxiao capsule

Pingxiao tablet

Shendan Sanjie capsule

Ankangxin capsule

Boshengaining

Zedoary turmeric oil and glucose injection

Kanglixin capsule

Cidan capsule

Appendix II Performance Status Criteria (ECOG)

(Eastern Cooperative Oncology Group)

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

Appendix III Calculation of Creatinine Clearance

Creatinine Clearance Calculation Using the Cockcroft-Gault Formula

Please choose the appropriate formula corresponding to the unit of serum creatinine test:

If the unit of serum concentration of creatinine is mg/dL

$$\text{Creatinine Clearance in Males (mL/min)} = \frac{(140 - \text{Age}) \times (\text{Weight})}{72 \times \text{Serum creatinine}}$$

$$\text{Creatinine Clearance in Females (mL/min)} = \frac{0.85 \times (140 - \text{Age}) \times (\text{Weight})}{72 \times \text{Serum creatinine}}$$

If the unit of serum concentration of creatinine is mol/L

$$\text{Creatinine Clearance in Males (mL/min)} = \frac{(140 - \text{Age}) \times (\text{Weight})}{0.81 \times \text{Serum creatinine}}$$

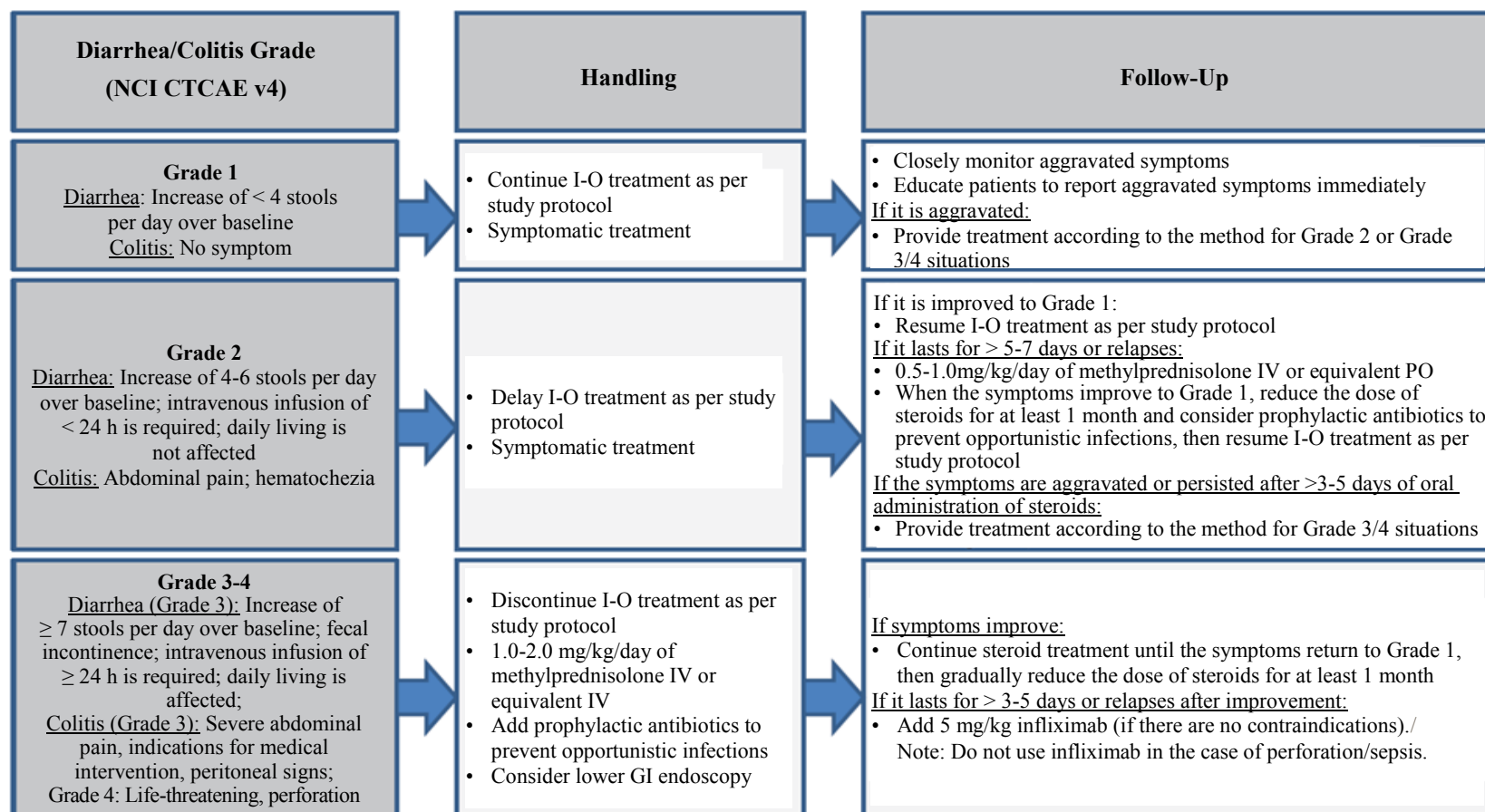
$$\text{Creatinine Clearance in Females (mL/min)} = \frac{0.85 \times (140 - \text{Age}) \times (\text{Weight})}{0.81 \times \text{Serum creatinine}}$$

Note: The unit of age is years old, and the unit of body weight is kilogram (kg).

Appendix IV Management Principles for irAEs

1. Management Principles for Gastrointestinal AEs

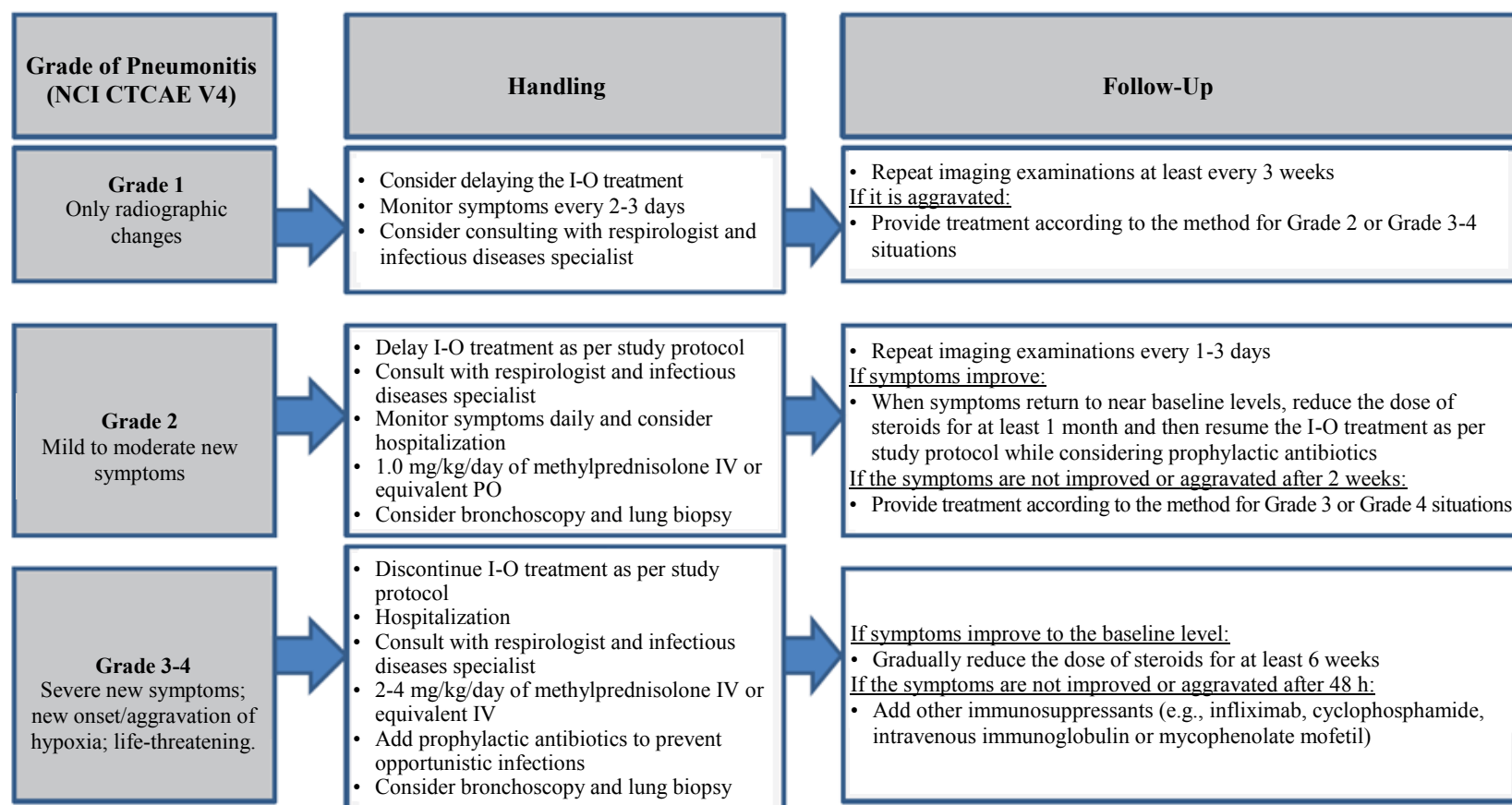
Non-inflammatory causes of disease should be excluded. Opioids/anesthetics may mask the symptoms of perforation. Do not use infliximab in the case of perforation/sepsis.



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

2. Management Principles for Pulmonary AEs

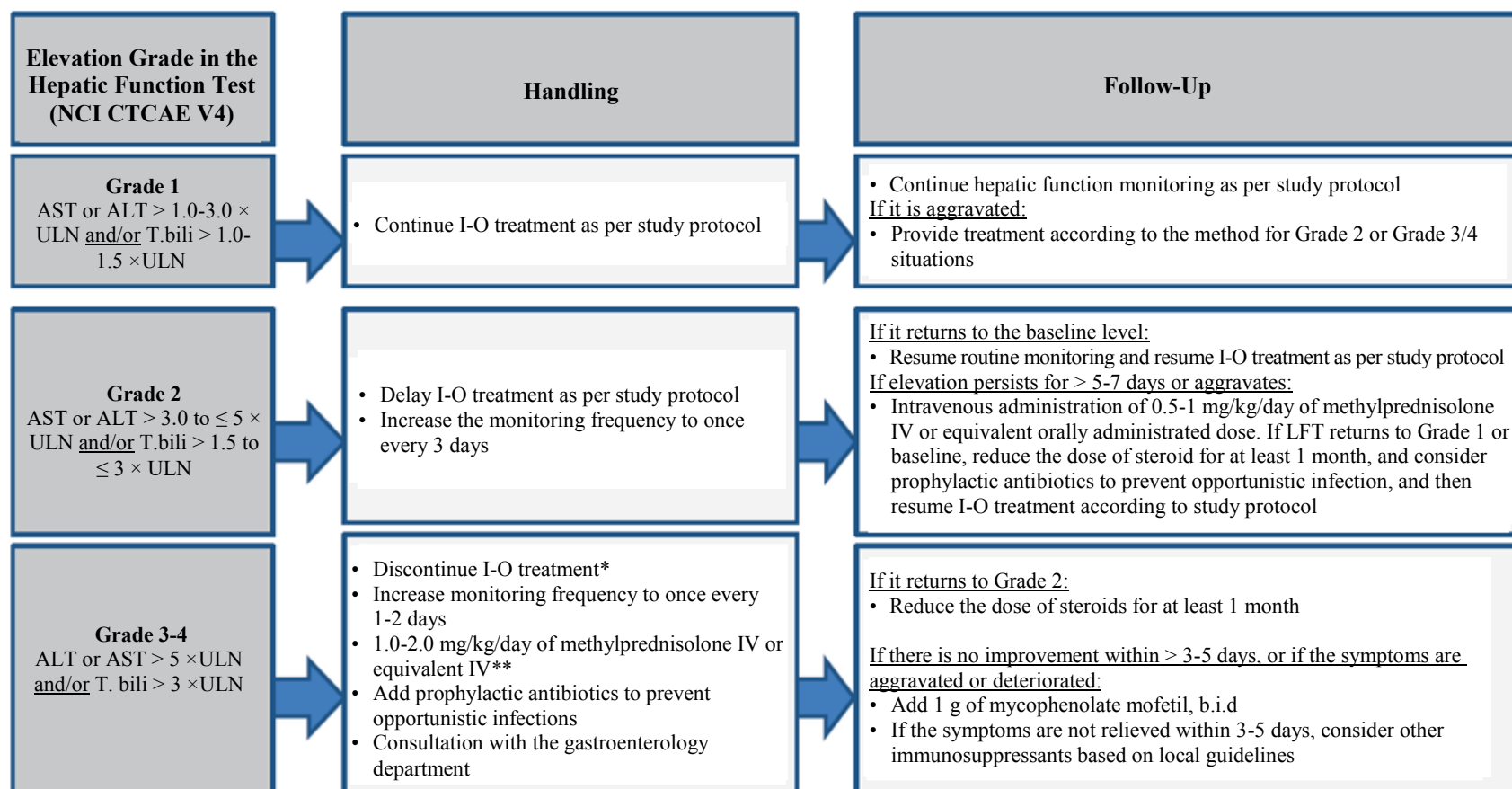
Non-inflammatory causes of disease should be excluded. If it is due to a non-inflammatory cause, a symptomatic treatment should be given while the I-O therapy should be continued. Imaging evaluation and consultations with the respiratory department should be performed.



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

3. Management Principles for Hepatic Adverse Events

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



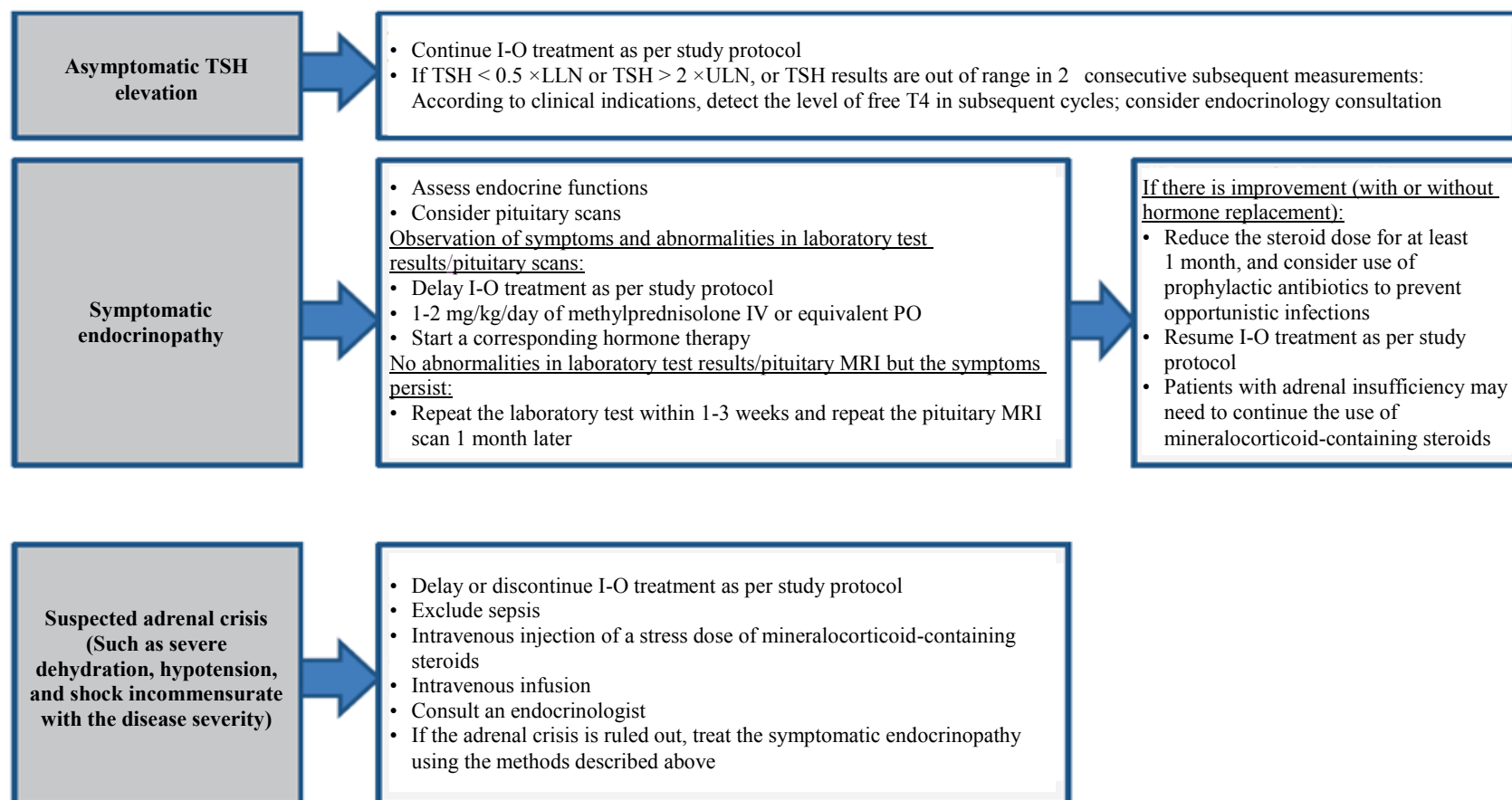
If subjects receiving intravenous injection of steroids show continuous clinical improvements, it is allowed, at the start of dose tapering or earlier, to switch to oral administration of corticosteroids (such as prednisone) at equivalent dose. When switching to oral corticosteroids with an equivalent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

* If AST/ALT $\leq 8 \times$ ULN and T. Bili $\leq 5 \times$ ULN, I-O treatment can be delayed rather than discontinued.

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

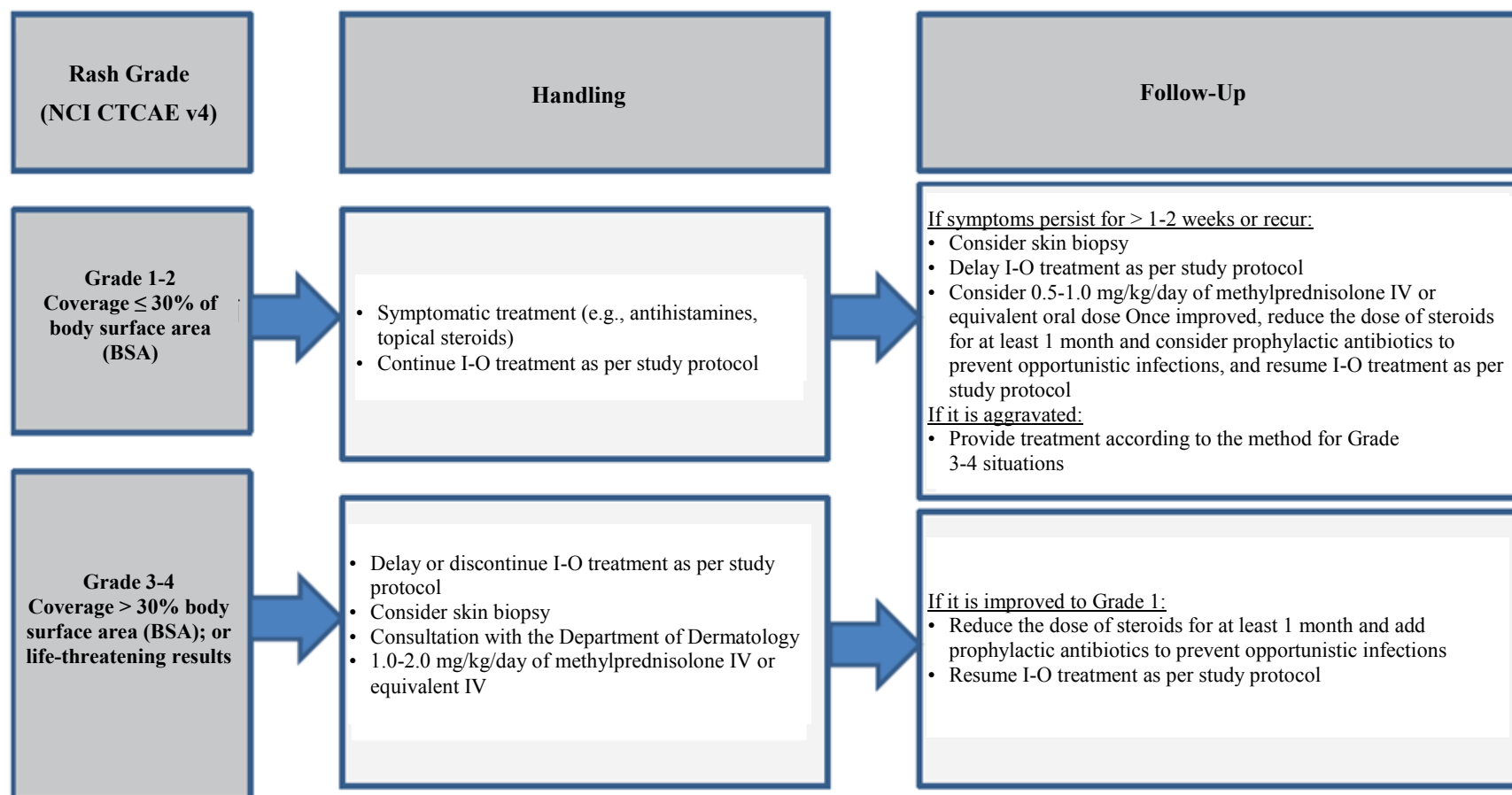
4. Management Principles for Endocrine Adverse Events

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



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

5. Management Principles for Skin Adverse Events



Once a patient given intravenous injections of steroids shows a sustained clinical improvement, the patient can switch to an equivalent dose of oral corticosteroids (e.g., prednisone) by the time or before the dose of steroid injections starts to be gradually reduced.

When switching to oral corticosteroids with an equivalent dose in the lungs and liver, it should be considered that the bioavailability of oral corticosteroids is relatively low.

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

Appendix V Response Evaluation Criteria in Solid Tumors

Response Evaluation Criteria in Solid Tumors Version 1.1 (Excerpt)

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

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

1 BACKGROUND

Omitted

2 PURPOSE

Omitted

3 MEASURABILITY OF TUMOR AT BASELINE

3.1 Definition

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

3.1.1 Measurable lesions

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

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

3.1.2 Non-measurable lesions

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodule with ≥ 10 mm to < 15 mm short axis) as well as truly non-measurable lesions.

Non-measurable lesions include: meningeal disease, ascites, pleural or pericardial effusion, inflammatory breast cancer, lymphangitis carcinomatosa of the skin or lung, abdominal masses unable to be diagnosed or followed by imaging techniques, and cystic lesions.

3.1.3 Special considerations regarding lesion measurability

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

Bone lesions:

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

Cystic lesions:

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

Lesions with prior local treatment:

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

3.2 Specifications by Methods of Measurements

3.2.1 Measurements of lesions

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

3.2.2 Method of Assessment

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

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

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

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

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

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

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

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

4 TUMOR RESPONSE ASSESSMENT

4.1 Assessment of Overall Tumor Burden and Measurable Disease

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

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

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

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

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

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

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

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

4.3 Response Criteria

4.3.1 Evaluation of target lesions

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

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

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

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

4.3.2 Special notes on the evaluation of target lesions

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

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

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

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

4.3.3 Evaluation of non-target lesions

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

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

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

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

4.3.4 Special notes on assessment of progression of non-target lesions

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

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

4.3.5 New Lesions

The appearance of new malignant lesions denotes PD; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of radiographically detected lesions; however, the finding of a new lesion should be unequivocal. For example, it should not be attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some new bone lesions that may be simply healing, or re-occurrence of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a new cystic lesion, which it is not.

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

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

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

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

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

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

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

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

4.4 Evaluation of Best Overall Response

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

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

4.4.1 Time point response

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

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

Target Lesion	Non-Target Lesion	New Lesion	Overall Response
CR	CR	Non	CR
CR	Non-CR/Non-PD	Non	PR
CR	Inevaluable	Non	PR
PR	Non-PD or not all evaluated	Non	PR
SD	Non-PD or not all evaluated	Non	SD
Not all evaluated	Non-PD	Non	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable

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

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

Non-Target Lesion	New Lesion	Overall Response
CR	Non	CR
Non-CR/Non-PD	Non	Non-CR/Non-PD ^a
Not all evaluated	Non	Inevaluable
Equivocal PD	Yes or No	PD
Any	Yes	PD

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

4.4.2 Missing assessments and unevaluable designation

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

4.4.3 Best overall response: all time points

The BOR is determined once all the data for the patient are known.

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

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

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

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

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

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

4.4.4 Special notes on response assessment

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

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

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

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

In some circumstances it may be difficult to distinguish residual lesions from normal tissues. When the evaluation of complete response depends upon this definition, it is recommended to perform a biopsy before evaluating the efficacy of complete remission of local lesions. FDG-PET may be used to confirm a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

4.5 Frequency of Tumor Re-Evaluation

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

After the treatment, the need for tumor re-evaluations depends on whether the study has as made the response rate or the time to an event (progression/death) an endpoint. If time to an event (e.g., TTP/DFS¹/PFS) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomized comparative studies in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6-8 weeks on treatment or every 3-4 months after treatment) and should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment group in the timing of disease assessment.

4.6 Confirmatory Measurement/Duration of Response

4.6.1 Confirmation

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

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

4.6.2 Duration of overall response

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

¹ Disease free survival

4.6.3 Duration of stable disease

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

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

4.7 PFS/TTP

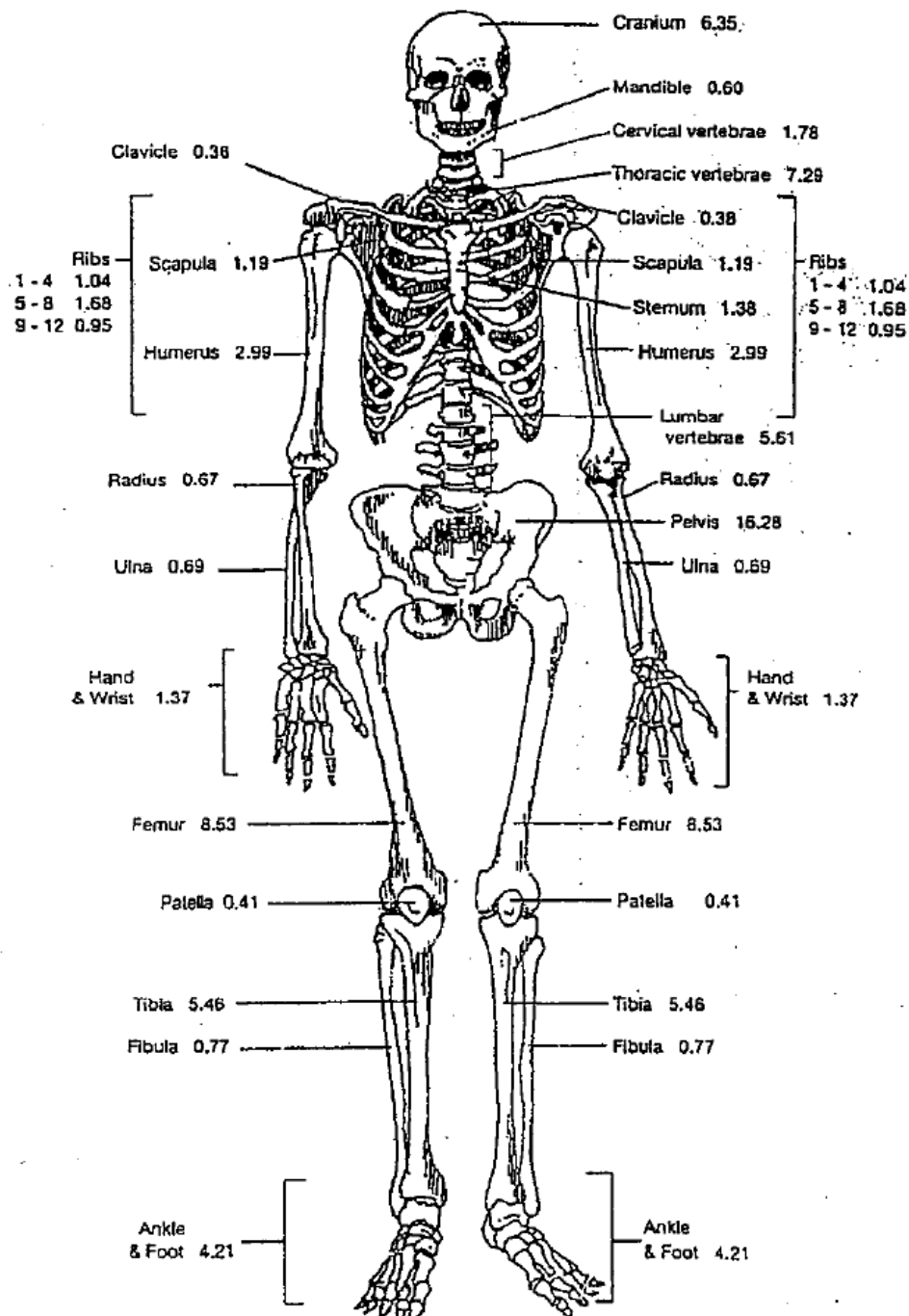
4.7.1 Phase II clinical studies

This guideline is focused primarily on the use of objective response as study endpoints for phase II trials. In some circumstances, response rate may not be the optimal method to assess the potential anti-tumor activity of new agents/regimens. In such cases, PFS/PPF at landmark time points might be considered appropriate alternatives to provide an initial signal of biologic effect of new agents. It is clear, however, that in an uncontrolled trial, these measures are subject to criticism since an apparently promising observation may be related to biological factors such as patient selection and not the impact of the intervention. Thus, phase II screening trials utilizing these endpoints are best designed with a randomized control. Exceptions may exist where the behavior patterns of certain cancers are so consistent (and usually consistently poor), that a non-randomized trial is justifiable. However, in these cases it will be essential to document with care the basis for estimating the expected PFS or PPF in the absence of an active control.²

² Proportion of progress-free

Appendix VI Percent Bone Marrow Content in Human Skeleton

Percent Bone Marrow in the Adult Skeleton



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