Title: A phase II clinical study of SHR-1210 combined with apatinib mesylate for the treatment of extensive-stage small cell lung cancer failing first-line standard therapy (PASSION)

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A PHASE II CLINICAL STUDY OF SHR-1210 COMBINED WITH APATINIB MESYLATE FOR THE TREATMENT OF EXTENSIVE-STAGE SMALL CELL LUNG CANCER FAILING FIRST-LINE STANDARD THERAPY

(PASSION)

(RANDOMIZED, OPEN-LABEL, MULTI-CENTER)

STATISTICAL ANALYSIS PLAN

(SAP)

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ABBREVIATIONS

Abbreviations	Full Name
ADA	Anti-drug antibody
ADAS	ADA set
AE	Adverse event
BOR	Best overall response
CI	Confidence interval
CR	Complete response
DCR	Disease control rate
DoR	Duration of response
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report form
ED-SCLC	Extensive-stage disease small cell lung cancer
FAS	Full analysis set
FT3	Free triiodothyronine
FT4	Free thyroxine 4
irAE	Immuno-related adverse event
LD-SCLC	Limited-stage disease small cell lung cancer
MedDRA	Medical Dictionary for Regulatory Activities
NAb	Neutralizing antibody
NE	Not evaluable
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PBMCs	Peripheral blood mononuclear cells
PD	Progressive disease
PD-1	Programmed death-1
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PPS	Per-protocol set
PR	Partial response
PT	Preferred term
Q2W	Every 2 weeks
QD	Once daily

Abbreviations	**Full Name**
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SCLC	Small cell lung cancer
SD	Stable disease
SS	Safety set
T3	Triiodothyronine
T4	Thyroxine
TMB	Tumor mutant burden
TMKS	Tumor biomarker set
TSH	Thyroid-stimulating hormone
TTR	Time to response
VALG	Veterans Administration Lung Study Group
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

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1 REVISION

Not applicable.

2 INTRODUCTION

Lung cancer is the most common malignancy in China. The main types include non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). SCLC accounts for 10-15% of new lung cancers. As a highly aggressive neuroendocrine tumor, SCLC is significantly different from NSCLC clinically and pathologically, characterized by rapid growth, proneness to drug resistance, and early metastasis. Almost all patients with SCLC have a history of heavy tobacco use [9,10]. Traditionally, SCLC is classified into limited-stage disease (LD-SCLC, where tumor tissue surrounds a radiotherapy field) and extensive-stage disease (ED-SCLC, where tumor tissue exceeds the boundary of a radiotherapy field). Peripheral blood mononuclear cells (PBMCs) of patients with SCLC showed that those with a long survival have a high ratio of effector T cells to regulatory T cells [30]. Anti-PD-1 agents play a therapeutic role by blocking the binding of PD-L1 on tumor cells and PD-1 of T cells, blocking its inhibition on T cells. Compared with traditional cytotoxic chemotherapy, PD-1-targeted therapy has higher specificity, lower toxicity, and applicability to a variety of tumor types. Apatinib is a small-molecular targeted drug and exerts anti-angiogenesis effect to treat malignant tumors by inhibiting VEGFR. Hengrui conducted phase I/II clinical studies of the recombinant humanized anti-PD-1 monoclonal antibody injection (SHR-1210) in several tumor types of tumors, and preliminarily validated the safety, tolerability, and efficacy of SHR-1210 monotherapy in the treatment of advanced solid tumors. Considering the role of immune-related therapies in SCLC, as well as the role of immune checkpoint inhibitors combined with VEGF and VEGFR-2 inhibitors in patients with gastric cancer and renal cancer, the benefits from SHR-1210 combined with apatinib in the second-line treatment of SCLC are reasonable and worth looking forward to. Only topotecan (intravenously or orally administered) has been approved for the treatment of ED-SCLC after failure of first-line standard therapy by the FDA. No immunotherapy is commercially available currently. Preclinical data suggested that it has similar pharmacodynamics and anti-tumor effects to those of nivolumab and pembrolizumab. The studies on the PD-1/PD-L1-based combination therapy that have been published and ongoing abroad suggested that patients may benefit and the safety is controllable.

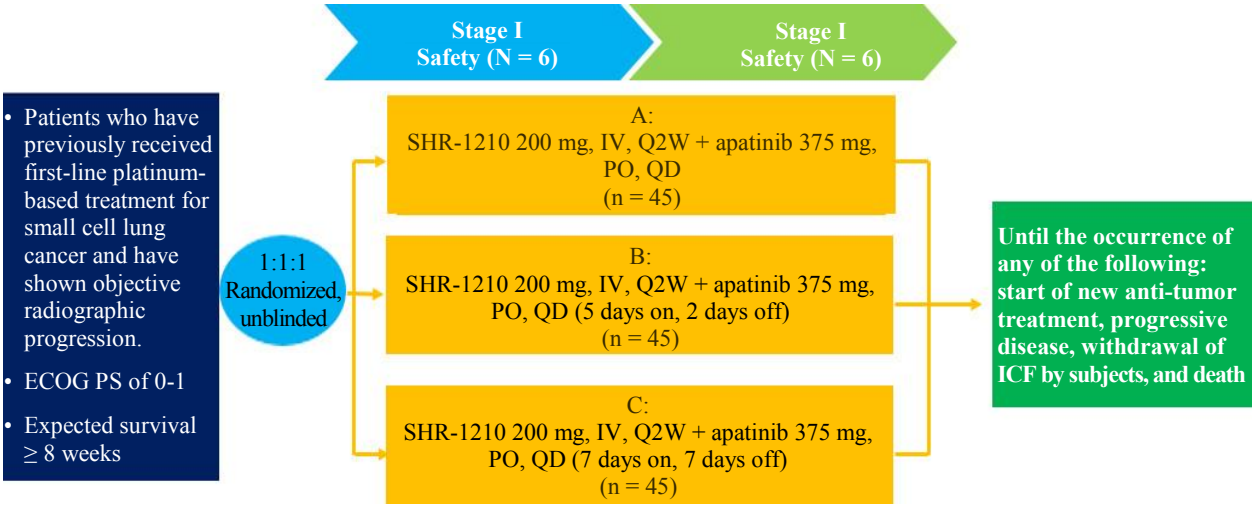
2.1 Study Design

This is a randomized, open-label, multi-center phase II clinical study. Eligible subjects after screening will be randomized into the following 3 groups in a 1:1:1 ratio, with 4 weeks as 1 treatment cycle. Refer to Figure 1 for the study design. Refer to Figure 2 for the study procedures.

The study consists of two stages. In Stage I, subjects will be randomized into 3 different dose groups, with 6 subjects in each group. It is planned that after the last subject in Stage I completes Cycle 1 treatment (28 days), the leading center's principal investigator and the sponsor will jointly perform a safety assessment of subjects enrolled in Stage I, decide the treatment group of Stage II, and choose one group of method of administration and a tolerated dose of apatinib for Stage II treatment.

A total of 39 subjects will be enrolled in Stage II. The primary analysis will be performed when the last subject has been treated for 180 days.

For any treatment group entering Stage II, if the safety is acceptable and the efficacy meets the corresponding statistical criteria, it indicates potential needs of further development.



Note: Subjects with PD for the first time must be confirmed; for medication after the first PD, refer to Section 6.1.2 of the protocol; for imaging confirmation and subsequent evaluations of the first PD, refer to Section 8.1.2 of the protocol

Figure 1. Design of the phase II study of SHR-1210 combined with apatinib

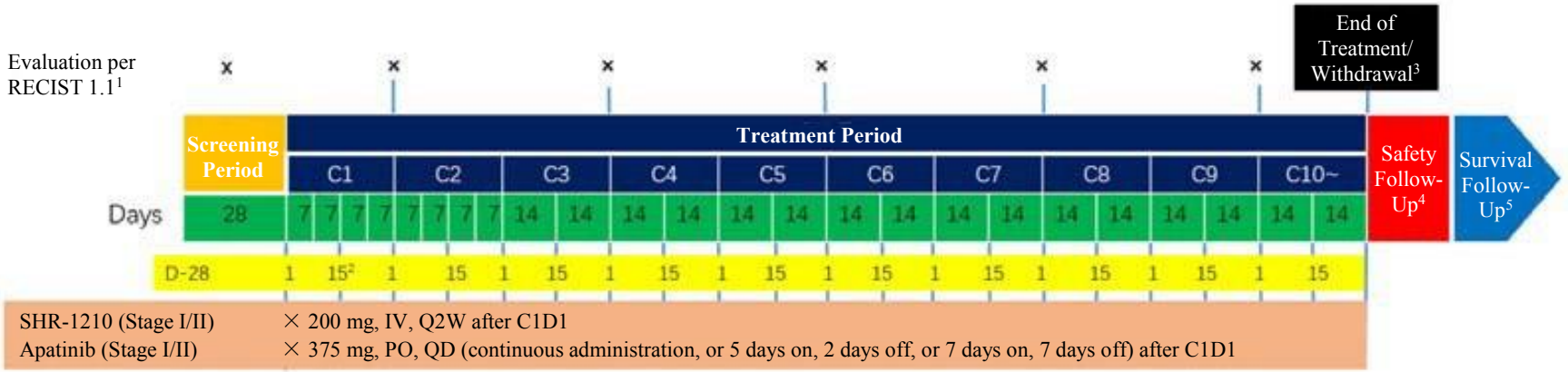


Figure 2. Study procedures of SHR-1210 combined with apatinib

2.2 Study Objectives

2.2.1 Primary objectives

- To evaluate the safety and efficacy of SHR-1210 combined with apatinib in the treatment of ED-SCLC after failure of the first-line standard therapy

2.2.2 Secondary objective

- To evaluate the immunogenicity

2.2.3 Exploratory objective

- To evaluate the correlation between biomarkers (including but not limited to PD-L1 and TMB) and efficacy

2.3 Sample Size

In this study, based on historical study data and study results of drugs of the same class and combined with clinical needs, a single-stage assessment method will be adopted to explore the efficacy of SHR-1210 combined with apatinib on ORR in ED-SCLC after failure of the first-line standard therapy.

Assume that in this study, it is expected that the ORR in each treatment group of SHR-1210 + apatinib combination therapy is ≥ 30% (alternative hypothesis), and assume that there is no need to continue the study if the ORR is ≤ 15% (null hypothesis), at the significance level of 0.1 and a power of 80%, 40 subjects should be enrolled. If ≥ 9 (22.5%) of the 40 subjects have response, it can be considered that the ORR in this treatment group is 15% and the investigational drug is worthy of continued development.

With a dropout rate of 10% taken into account, each treatment group should enroll about 45 subjects, for a total of 135 subjects.

3 STATISTICAL HYPOTHESIS

This study does not involve any statistical hypotheses and inference.

A single-stage assessment method will be adopted to explore the efficacy of SHR-1210 combined with apatinib on ORR in ED-SCLC after failure of the first-line standard therapy. The potential need for further development is indicated when the predefined number of responses (objective response) of a treatment group is reached (see Section 2.3 for details).

4 STUDY ENDPOINTS

4.1 Primary Endpoints

1. Incidence rate of adverse events (AEs) evaluated per CTCAE 4.03, especially the incidence rate of AEs meeting any of the following:

    1) Hematologic toxicity:

        - Grade 4, or
        - Grade ≥ 3 thrombocytopenia with hemorrhage, or
        - Grade ≥ 4 neutropenia with pyrexia and infection

    2) Grade ≥ 3 non-hematologic toxicity (except for laboratory abnormalities), hypertension, rash, diarrhea, nausea, and vomiting that cannot be controlled after symptomatic treatment

    3) Grade ≥ 3 laboratory abnormalities that lead to medical interventions or hospitalization, or last for ≥ 7 days

    4) Any Grade 5 AEs

2. Objective response rate (ORR): defined as the proportion of enrolled subjects with a best overall response (BOR) of CR or PR as per RECIST 1.1. Response confirmation should be conducted for CR and PR.

    Best overall response (BOR) is defined as the best response from the start of medication until progressive disease (PD) or the start of a new anti-tumor treatment. New anti-tumor therapy is defined as concomitant anti-tumor therapy that occurs after the start of medication. BOR in this study will be based on the confirmed efficacy, with reference to the RECIST 1.1 as the confirmation criteria (Appendix 1).

    - Confirmed PR: The response evaluated as CR should be reconfirmed as CR at a later time point (at least 4 weeks later).
    - Confirmed PR:
        - The response is evaluated as CR, but it is reconfirmed as PR (CR is not reached) at a later time point (at least 4 weeks later).
        - The response is evaluated as PR, but it is reconfirmed as CR/PR at a later time point (at least 4 weeks later).

- Confirmed SD:
  - The response is evaluated as CR/PR (at least 4 weeks from baseline evaluation), but it is reconfirmed as CR/PR not reached.
  - The response is evaluated as SD at least once within the shortest time interval (not less than 4 weeks) after the start of the study.

4.2 Secondary Endpoints

- Incidence of AEs and serious adverse events (SAEs) as per CTCAE V4.03, as well as laboratory measurements, ECG, vital signs, and other safety parameters
- Overall survival (OS): defined as the time from the first dose to the death of the subject of any cause.
- 6- and 12-month OS rates
- Progress-free survival (PFS): the time from the date of first dose to the first documented objective tumor progress as per RECIST 1.1 or death of any cause, whichever occurs first.
- Time to response (TTR): defined as the period of time from the date of first dose to the first documented tumor response (CR or PR). CR and PR must be evaluated per the RECIST 1.1 and confirmed for efficacy.
- Duration of response (DoR): the date from the first documented tumor response (CR or PR) to the first documented objective tumor progress (PD) or the date of death of any cause. Response defined by CR and PR must be assessed per the RECIST 1.1 and confirmed for efficacy. The start date of response duration is the first observed response, instead of the confirmed response.
- Disease control rate (DCR): defined as the proportion of enrolled subjects who are evaluated as CR, PR, or SD (for at least 4 weeks) per the RECIST 1.1. Response confirmation should be conducted for CR and PR.
- Immunogenicity evaluation: Positive rates of ADA and NAb

4.3 Exploratory Endpoint

- Tumor biomarkers (including but not limited to expression levels of PD-L1 and TMB in tumor samples)

5 STATISTICAL ANALYSIS

5.1 General Considerations

5.1.1 Analysis sets

The analysis sets in this study included:

Full analysis set (FAS): an analysis set determined based on the intent-to-treat principle. This analysis set includes all enrolled subjects who have received at least one dose of the study drug. Based on the FAS, the subjects will be analyzed according to their scheduled doses.

Per-protocol set (PPS): a subset of the FAS. Subjects with major protocol violations that have a major effect on the study results will be excluded from this set. The list of subjects included into or excluded from the PPS should be reviewed and determined by the sponsor and the investigator before the database is locked.

Safety set (SS): all subjects who have received at least one dose of the study drug and underwent post-administration safety evaluation. Analyses based on the safety set will be carried out according to the actual treatment received by the subjects.

ADA set (ADAS): All enrolled subjects who have received at least one dose of the study drug and have baseline and at least one post-baseline ADA evaluation data.

Tumor biomarkers set (TMKS): all enrolled subjects who have received at least one dose of the study drug and have tumor biopsy samples (including peripheral blood) make up the PD-L1 or TMB set.

Table X. Analysis sets and corresponding endpoints

Endpoint	Analysis Sets				
	FAS	**PPS**	**SS**	**ADAS**	**TMKS**
Safety Endpoints			X		
ORR	X	X			
OS and 6/12-month OS rates	X				
PFS	X				
TTR	X				
DoR	X				
DCR	X				
Immunogenicity Evaluation				X	
Tumor Biomarkers					X

5.1.2 General analysis

Unless otherwise specified, standard descriptive statistics will be summarized by different type of variables:

- Continuous variables will be summarized by mean, standard deviation, median, maximum, and minimum. The decimal places for the minimum and maximum should be consistent with those on the eCRF. There should be 1 additional decimal place for the mean and median compared to the raw data, and 2 additional decimal places for standard deviation, with up to 4 decimal places.
- Categorical variables will be summarized by frequency and percentage, with 1 decimal place for percentages;
- For time-to-event data, the Kaplan-Meier method will be used to estimate the survival function and median time to event onset, and the survival curves will be plotted.

If not otherwise specified, the baseline is generally defined as the last pre-administration observation before the first dose (including the day of administration). The last non-missing measurement value will be decided by the date of measurement. If there are multiple measurements on the same day, then:

- If both scheduled and unscheduled visits are present, the value obtained from the scheduled visit will be considered as the last non-missing measured value.
- If there are multiple scheduled visits, the value obtained from the visit with the largest visit number will be considered as the last non-missing measured value.
- If there is no scheduled visit but are multiple unscheduled visits, the value obtained from the visit with the largest number of unscheduled visit will be considered as the last non-missing measured value.

The date of first dose in this study is defined as the date of first dose of apatinib or the date of first dose of SHR-1210, whichever is earlier.

5.1.3 Derived variables

Not applicable.

5.1.4 Covariates and subgroups

Subgroup analysis of the primary endpoint ORR will be based on the FAS:

- Sensitive recurrence: progress in ≥ 90 days from the last chemotherapy
- Drug-resistant recurrence: progress during chemotherapy or within 90 days from the last chemotherapy

The time between progress and the last chemotherapy is calculated as follows: date of the most recent progress/relapse − date of the last chemotherapy. Sensitive recurrence is determined if the time between progress and the last chemotherapy is ≥ 90 days; otherwise, drug-resistant recurrence is determined.

5.1.5 Analysis window

The study days is defined as the days from the first dose of study drugs to the safety/efficacy evaluation. The day of first dose of study drugs (SHR-1210 or apatinib, whichever is used first) is used as the start date of the study (Day 1).

The study date is calculated as follows:

Study days = evaluation date – start date of study + 1, in the case of evaluation after the first dose of study drugs

Or

Study date = evaluation date – start date of study, in the case of evaluation before the first dose of study drugs.

Data obtained from post-baseline visits will be summarized by protocol visits of SHR-1210 shown in eCRF. There is no need to consider whether the visit window specified by the protocol has been exceeded.

5.1.6 Missing data

5.1.6.1 Medical history

For disease-related records before the first dose of study drugs:

- If the day is missing, the day will be imputed with the 1st of the month;
- If the month and day are missing, the day will be imputed with 1 Jan.;
- If the date is completely missing, the day will not be imputed.

5.1.6.2 Adverse Event

- If the day of the onset date is missing, and the year and month are the same as those of the first dose, the day will be imputed with the date of first dose; otherwise, it is imputed with the 1st of the month;
- If the month and day of the onset date are missing, and the year is the same as those of the first dose, the day will be imputed with the date of first dose; otherwise, it is imputed with 1 Jan. of the year;

- If the onset date is completely missing, the day will be imputed with the date of first dose;
- If the day of the end date is missing, the day will be imputed with the last day of the month or the date of death (if applicable), whichever is earlier;
- If the year or month of the end date is missing, the day will not be imputed.

5.1.6.3 Concomitant medications

The dates of concomitant medications are imputed in the same way as AEs.

5.1.6.4 Last survival date

If the investigator is not informed of subject's death by the cutoff date of analysis, the latest complete date of the following data will be used as the last survival date:

- The dates of the subject's all assessments
- The start and end dates of new anti-tumor treatment after the discontinuation of study treatment
- The start and end dates of AEs
- The date of the last known survival status of the subject on the survival follow-up page
- The start and end dates of study treatment
- The date of withdrawal of informed consent form
- The date on the study discontinuation page (if the reason for discontinuation is "lost to follow up", the date of lost to follow up will not be calculated)

Only the date of actual examinations can be used to derive the last survival date. The dates of examinations and evaluations carried out after the cutoff date will not be used to derive the last survival date.

5.1.6.5 Death date

- If the day of the death date is missing, the day will be imputed with the last day of the month or the last survival date + 1, whichever is later;
- If the month and day of the death date are missing, the day will be imputed with 1 Jan. of the year or the last survival date + 1, whichever is later;
- If the death date is completely missing, the day will be imputed with the last survival date + 1.

5.1.6.6 New anti-tumor treatment

If the start date of a new anti-tumor treatment is not completely missing, it will be imputed according to the following rules and used to derive the end date of the study treatment. The date of PD mentioned below is date of the first documented PD.

- If the end date of the new anti-tumor treatment is partially missing or not missing, the end date of the new anti-tumor treatment will be used to derive the start date of the new anti-tumor treatment
  - If the month and day of the end date of the new anti-tumor treatment are missing but the year is not missing, 31 Dec. is used as the end date of the new anti-tumor treatment.
  - If only the day of the end date of the new anti-tumor treatment is missing, the last day of the month will be used as the end date of the new anti-tumor treatment.
- If the month (MM) or day (DD) of the start date of new anti-tumor treatment are missing or the date of the start date of new anti-tumor treatment is completely missing, the rules for deriving and imputing the date are as follows:
  - If the start date of a new anti-tumor treatment is completely missing, the imputed start date = min [max (PD date + 1, date of the last dose + 1), end date of the new anti-tumor treatment]
  - Only the year (YYYY) of the start date of new anti-tumor treatment is not missing
    1) If YYYY < min (year) [max (PD date + 1, date of last dose + 1), end date of new anti-tumor treatment], the date is imputed as 31 Dec., YYYY.
    2) If YYYY = min (year) [max (PD date + 1, date of the last dose + 1), end date of new anti-tumor treatment], the imputed date = min [max (PD date + 1, date of the last dose +1), end date of new anti-tumor treatment].
    3) If YYYY > min (year) [max (PD date + 1, date of the last dose + 1), end date of new anti-tumor treatment], then the imputed date = 1 Jan. YYYY.
- The year (YYYY) and month (MM) of the start date of new anti-tumor treatment are not missing
  - If YYYY = min (year) [max (PD date + 1, date of the last dose + 1), end date of new anti-tumor treatment], and if MM < min (month) [max (PD date + 1, date of the last dose + 1), end date of new anti-tumor treatment], the date will be imputed with the last day of MM.

- If YYYY = min (year) [max (PD date + 1, date of the last dose + 1), end date of new anti-tumor treatment], and MM = min (month) [max (PD date +1, date of the last dose +1), end date of new anti-tumor treatment], the date imputed = min [max (PD date + 1, date of the last dose + 1), end date of new anti-tumor treatment].
- If YYYY = min (year) [max (PD date + 1, date of the last dose + 1), end date of new anti-tumor treatment], and if at the same time MM > min (month) [max (PD date +1, date of the last dose +1), the end date of new anti-tumor treatment], then the imputed date = 1 MM, YYYY.
- If YYYY < min (year) [max (PD date + 1, date of the last dose + 1), end date of new anti-tumor treatment], then the day of the imputed date is the last day of MM.
- If YYYY > min (year) [max (PD date + 1, date of the last dose + 1), end date of new anti-tumor treatment], then the imputed date = 1 MM, YYYY.

All imputed dates must be before the date of withdrawal of informed consent form, lost to follow-up, and death.

Missing data of laboratory evaluations are not imputed.

The rules for imputation of missing data for the remaining study endpoints will be detailed in the specific sections of analyses.

5.2 Study Subjects

5.2.1 Disposition of subjects

All enrolled subjects will be divided by stage and dose group using frequency and percentage. In addition, in the disposition of subjects, the frequency and percentage of the following information will be summarized by dose group:

- Number of screened subjects and reasons for screening failure;
- Number of enrolled subjects;
- Number of subjects with study termination/treatment discontinuation;
- Reasons for study termination/treatment discontinuation;

Reasons for screening failure, subject enrollment, treatment discontinuation and reasons, and study discontinuation and reasons will be listed.

A listing will be provided on whether the enrolled subjects are included in the FAS, PPS, SS, ADAS, and TMKS. The listing will include rejected analysis sets and reasons for rejection at least.

5.2.2 Demographics and baseline characteristics

5.2.2.1 Demographics

The subjects' age, gender, ethnicity, height, weight, and body mass index will be summarized using descriptive statistics. Quantitative variables such as age, height, weight, and body mass index will be summarized using descriptive statistics such as number of evaluable subjects, mean and standard deviation, median, minimum and maximum. Categorical variables such as gender and ethnicity will be summarized using descriptive statistics, including number of evaluable subjects per category and corresponding percentage in total population.

5.2.2.2 Other baseline characteristics

The subjects' allergy, smoking, and alcohol history will be summarized and listed using descriptive statistics.

The diagnosis of small cell lung cancer in the subjects, including the VALG stage of the initial diagnosis, presence of metastases, course of disease, and time to the most recent progress/recurrence will be summarized using descriptive statistics. The course of disease (month) is defined as the time from the date of first pathological diagnosis to the date before the first dose, calculated as: (date of the first dose − date of the first pathological diagnosis) / 30.4375. The time to the most recent progress/recurrence (month) is defined as the time from the most recent progress/recurrence to the date before the first dose, calculated as: (date of the first dose − date of the most recent progress/recurrence) / 30.4375. The date of the first diagnosis, location of the primary tumor, location of the metastasis, diagnostic method, the VALG stage of the first diagnosis, date of the most recent progress/recurrence, course of the disease, and time to the most recent recurrence/progress will be listed.

5.2.3 Prior illnesses

Medical history will be coded by system organ class (SOC) and preferred term (PT) in the Chinese version of the ICH Medical Dictionary for Regulatory Activities (MedDRA) 21.0.

The prior illness of the subjects will be statistically summarized correspondingly by treatment group.

All prior illness will be listed.

5.2.4 Prior treatment and concomitant medication

5.2.4.1 History of anti-tumor treatment

History of anti-tumor treatment mainly includes systemic anti-tumor treatment, radiotherapy, and surgery, which correspond to history of anti-tumor treatment, radiotherapy history, and surgical history, respectively.

Anti-tumor treatments are descriptively summarized by the following categories, and the numbers and percentages of subjects undergoing corresponding anti-tumor treatment are calculated:

- Classification and indication of systemic treatment
- Number of systemic regimens (using different chemotherapy drugs) received in the past
- Indication of radiotherapy
- Type of surgery and classification of tumor surgery

The duration between the end date of the last anti-tumor treatment and the time (months) of the first dose will be summarized, calculated as: (date of the first dose − end date of the last anti-tumor treatment) / 30.4375.

All treatment histories (including anti-tumor treatment and non-anti-tumor treatment) are listed in detail.

5.2.4.2 Prior/concomitant medication

A list of prior medications and concomitant medications will be provided.

5.2.5 New anti-tumor treatment

The number and percentage of subjects who have received new anti-tumor treatment after withdrawal will be summarized by dose group, and a detailed listing will be provided.

5.2.6 Protocol deviations

Before database locking, data of all subjects on the eCRF will be checked for important protocol deviations. All potential important protocol deviations will be reviewed and evaluated by the investigator and the sponsor.

All important protocol deviations will be summarized and described by type and tabulated for analysis.

Definitions of important protocol deviations:

- Serious violation of the inclusion/exclusion criteria;
- Incorrect treatment by study drugs (not treated using the drug or dose as per randomization);
- Other protocol deviations jointly recognized by the investigator and the sponsor.

5.3 Extent of Exposure and Treatment Compliance

Based on the SS, the use of study drugs will be summarized using descriptive statistics by drug and dose group. The use of all study drugs will be listed in detail.

5.3.1 SHR-1210

Compliance (%) = (actual number of doses / scheduled number of doses) ×100%

Scheduled number of doses = scheduled duration of administration / 14 (days).

The frequency and reasons of SHR-1210 treatment interruption and permanent discontinuation will be summarized.

5.3.2 Apatinib

Actual dose (tablets): The sum of the documented actual doses of a subject during the treatment period, calculated as the actual number of days of administration ×1 tablet/day. The actual number of days of administration is subject to the records of apatinib administration. The number of consecutive dosing days for each period is calculated as: end date − start date + 1.

Scheduled dose (tablets): number of treatment cycles during the treatment period ×scheduled number of days of administration ×1 tablet/day. O ne treatment cycle contains 28 days.

Apatinib Treatment Cycle	Scheduled Number of Days of Administration in Each Treatment Cycle
QD	28
QD (5 days on, 2 days off)	20
QD (7 days on, 7 days off)	14

Subject compliance (%) = (actual dose / scheduled dose) × 100%.

The frequency and reasons of apatinib dose reduction, treatment interruption, and permanent discontinuation will be summarized.

5.4 Efficacy Analysis

5.4.1 Primary efficacy analysis

Based on the FAS, the number and percentage of subjects of BOR, ORR, and DCR are calculated by dose group, and 95% CIs are estimated using the Clopper-Pearson method.

The above analyses will be repeatedly conducted based on the PPS.

Handling of missing data: When calculating CR, missing data will be considered as cases not achieving CR, while the handling of PR, SD, and PD is the same as that of CR.

5.4.2 Secondary efficacy analysis

5.4.2.1 OS

The analysis of OS will be based mainly on the FAS.

The Kaplan-Meier product-limit approach will be used to calculate the median survival, its 95% CI will be calculated using the Brookmeyer-Crowley method based on log-log transformation, and the survival curves will be plotted. Also, the 6- and 12-month OS rates will be calculated using the Kaplan-Meier product-limit approach and their 95% CIs will be calculated using the pointwise method based on log-log transformation.

OS (months) is calculated as: (OS event or censoring date − date of the first dose + 1) / 30.4375.

Missing data: This study will do everything possible to track subject survival until an OS event is observed. Inevitably, an OS event may not be observed for a subject before the end of the study, or a subject drops out before an OS event is observed, in this case, the time from the start date of randomization of this subject to the last observed survival date of the subject is taken as the subject's survival time, and this survival time is recorded as right censored data (the actual survival time is greater than the recorded time). If the date of death is incomplete, the day will be imputed with the earliest possible date.

5.4.2.2 PFS

The analysis of PFS will be based mainly on the FAS using the same method as that of OS.

PFS (months) is calculated as: (PFS event or censoring date − date of the first dose + 1) / 30.4375.

The baseline tumor evaluation is defined as the last tumor evaluation before the first dose.

The date of visit corresponding to the PD as shown in tumor evaluation will be based on the earlier date of the following:

- The date of imaging examination showing a new lesion (if PD is based on the occurrence of a new lesion), or
- The date of the last imaging examination of observed lesions (if progressive disease is based on the increased total observed lesions). If there is no PD (including PR, CR, SD, and NE), the date of tumor evaluation will be based on the latest date recorded in the visit (target lesion or non-target lesion).

The censoring rules for PFS events are as follows:

For subjects experiencing PD or death:

- If a subject has begun a new anti-tumor treatment (excluding radiotherapy) before the PFS event, the date will be censored based on the date of the last tumor evaluation before the start of new anti-tumor treatment or the date of the first dose (whichever is later).
- Progressive disease or death after two or more scheduled tumor evaluations that are missing will be censored based on the date of the last tumor response evaluation before PD or death or the date of first dose (whichever is later). The missing of two or more scheduled tumor evaluations is defined as a situation where the interval between the event and the most recent tumor evaluation (including baseline) is longer than 126 days.

For subjects experiencing no PD or death:

- If there is no baseline tumor evaluation or post-baseline tumor evaluation (missing tumor evaluation or tumor evaluation as NE/NA at the corresponding visit), censoring will be based on the date of the first dose.
- If a subject has not experienced a PFS event on the end date of study/analysis or before dropout, the censoring will be carried out using the date of the last tumor response evaluation.

If the date of death is incomplete, the day will be imputed with the earliest possible date.

If the start date of the new anti-tumor treatment is incomplete, it will be imputed with the earliest possible date.

5.4.2.3 TTR

The analysis of TTR will be based mainly on the FAS. Only subjects with confirmed tumor response (CR or PR) are descriptively summarized by treatment group.

TTR (months) is calculated as: (date of the first documented CR or PR − date of the first dose +1) / 30.4375.

5.4.2.4 DoR

DoR will only be analyzed for subjects with confirmed tumor response (CR or PR) after treatment. The censoring rules for DoR are the same as those for PFS, and the end date of response must be consistent with the date of progressive disease or death of the PFS. For DoR, the Kaplan-Meier product-limit approach will be used to calculate the median survival by treatment group, the corresponding 95% confidence interval (CI) will be calculated using the Brookmeyer-Crowley method based on log-log transformation, and the survival curves will be plotted.

DoR (months) is calculated as: (date of PFS event − date of the first documented CR or PR + 1) / 30.4375.

5.4.2.5 Immunogenicity evaluation

Immunogenicity analysis will be based on the ADAS.

The ADA will be statistically analyzed using descriptive statistics in the form of listing based on the confirmatory results of immunogenicity.

The numbers and percentages of subjects who are non-treatment emergent ADA positive, treatment-enhanced ADA positive, treatment-induced ADA positive, ADA positive, and ADA negative will be summarized.

In treatment-induced ADA positive subjects, the time when first tested positive, as well as the number and percentage of transiently positive, persistently positive, and other positive subjects after baseline will be summarized.

Also, the number and percentage of neutralizing antibody (Nab) positive and negative subjects will be summarized.

The classification of immunogenicity is as follows:

(1) Non-treatment emergent ADA positive includes two situations: (a) positive at baseline and negative after baseline; (b) positive at baseline and positive after baseline, with a titer < 4 × that of the baseline ADA positive sample.

(2) Treatment-enhanced ADA positive: positive at baseline and positive after baseline, with a titer ≥ 4 × that of the baseline ADA positive sample; treatment-induced ADA positive: negative at baseline and positive after baseline; ADA positive: including treatment-enhanced ADA positive as well as treatment-induced ADA positive. Situations other than ADA positive are regarded as ADA negative.

(3) Transiently positive refers to negative at baseline and with ADA positive for only once that is not persistent after baseline to the time before the last test.

Persistently positive consists of two categories: (a) negative at baseline but with at least 2 post-baseline samples, with the interval between the first and last positive samples more than 16 weeks; (b) negative at baseline but with last post-baseline sample tested positive, or with the last post-baseline sample negative and the penultimate post-baseline sample tested positive.

"Other" refers to negative at baseline, with at least two ADA-positive samples but not persistently positive and with negative last sample.

(4) Nab positive: negative at baseline and positive after baseline; Nab negative: negative after baseline; all other circumstances are classified as indeterminable.

5.4.3 Exploratory analyses

PD-L1 expression will be analyzed using descriptive statistics based on the TMKS.

5.4.4 Subgroup analysis

Based on the FAS, the following subgroup analyses will be performed on the primary efficacy endpoint ORR, as well as the secondary endpoints OS, PFS, and 6/12-month OS rates:

- Sensitive recurrence: progress in ≥ 90 days from the last chemotherapy
- Drug-resistant recurrence: progress during chemotherapy or within 90 days from the last chemotherapy

5.5 Safety Analysis

Unless otherwise specified, the safety statistical analysis will be summarized and tabulated by the treatment group. All safety analyses will be conducted based on the SS. Normal and abnormal parameters for safety evaluation will be summarized based on scheduled and unscheduled visits. Single unscheduled examinations will only be listed.

5.5.1 Adverse events

Adverse events (AEs) will be analyzed based on the treatment-emergent adverse events (TEAEs):

1) All AEs that occur from the first study dose to 90 days after the last dose;
2) An AE that starts before the first study dose but worsens after administration.

Treatment-related AEs are defined as TEAEs with a causality of definitely related, possibly related, or indeterminable. If the relationship between an AE and the study drug is missing, the AE will be considered as a treatment-related AE.

All AEs will be coded with MedDRA 21.0. and graded by NCI-CTCAE v4.03. For the same SOC and/or PT, multiple cases of the same events that occur in one subject will be counted only once. For the same AE reported in one subject multiple times but varying in CTCAE grade, the AE of the greatest grade will be enumerated.

The incidence of AEs will be sorted from high to low based on their corresponding SOC in the SHR-1210 200 mg, IV, Q2W + apatinib 375 mg (or apatinib 250 mg), PO, QD group. The incidence of AEs in each SOC will be sorted from high to low based on their PT. If the incidences of ≥ 2 PTs are equal, the AEs will be sorted alphabetically. If there is no AE under a SOC or PT, then analysis is not conducted.

The number of TEAE cases as well as the number of subjects based on the SS will be summarized in a table by dose group. The summary table should at least include the number of subjects with at least one TEAE/SAE/, TEAEs leading to treatment discontinuation, TEAEs leading to dose interruption or dose reduction, SAEs, SAEs leading to death, TEAEs of special interest, immune-related TEAEs (irAEs), and CTCAE grading. For all categories included in the summary table, CTCAE Grade ≥ 3 TEAEs and treatment-related AEs with an incidence of ≥ 5% will be summarized by SOC and PT, respectively. Laboratory abnormalities with an incidence of ≥ 10% will be summarized. TEAEs leading to treatment discontinuation, TEAEs leading to dose interruption or dose reduction, and all treatment-related AEs will be analyzed respectively for SHR-1210 and apatinib. An immune-related AE is determined in the case of an indeterminable immune-related AE.

In particular, the incidences and outcomes of AEs assessed per the CTCAE 4.03 below are separately analyzed:

- Hematologic toxicity
  - Grade 4, or
  - Grade ≥ 3 thrombocytopenia with hemorrhage, or
  - Grade ≥ 4 neutropenia with pyrexia and infection
- Grade ≥ 3 non-hematologic toxicity (except for laboratory abnormalities), hypertension, rash, diarrhea, nausea and vomiting that cannot be controlled after symptomatic treatment
- Grade ≥ 3 laboratory abnormalities that lead to medical interventions or hospitalization, or last for ≥ 7 days
- Any Grade 5 TEAE

The following protocol-specified AEs of special interest will be summarized by SOC and PT:

- Grade ≥ 3 infusion reaction
- Other Grade ≥ 3 immune-related adverse events (irAEs)

For reactive capillary endothelial proliferation, the collected patient information will also be listed.

Important TEAEs will be summarized by SOC and PT. Important TEAEs are defined as:

- Any TEAE leading to interruption or permanent discontinuation of SHR-1210 or apatinib
- Any TEAE leading to dose reduction of SHR-1210
- Any targeted treatment with concomitant medication, i.e., TEAE with corrective treatment

All AEs (including non-TEAEs) are listed.

5.5.2 Laboratory evaluations

A baseline laboratory evaluation is defined as the last evaluations prior to the first dose (screening period).

The worst grade (abnormality grade sorted from high to low: abnormality with clinical significance > abnormality without clinical significance > normal) of results of such laboratory evaluations as hematology, clinical chemistry, myocardial zymography, coagulation function, routine stool, urinalysis, thyroid function tests (T3, T4, FT3, FT4, and TSH) at baseline and post-baseline of each dose group will be summarized using a shift table.

All laboratory evaluations will be listed by subject ID and indicated for clinical significance if any.

5.5.3 Vital signs

Vital sign measurements at each scheduled visit point (including baseline) will be summarized and listed using descriptive statistics. Changes in vital signs from baseline at each visit point after baseline will be summarized and listed using descriptive statistics.

Baseline is defined as the last measurement before the first dose.

5.5.4 Electrocardiogram

Normal/abnormal ECG changes from baseline at each visit point after baseline will be summarized using a shift table. ECG results will be listed.

5.5.5 Physical examination

Physical examinations are only listed for reporting.

5.5.6 ECOG PS

The ECOG PS of each dose group will be analyzed using descriptive statistics. The worst ECOG PS at baseline and post-baseline will be summarized using a shift table.

All ECOG PS will be listed.

5.5.7 Other safety analyses

Pituitary-adrenal axis test, echocardiography, pulmonary function examination, arterial blood gas analysis, virology, blood pregnancy test, and tumor tissue sample collection are listed in detail.

6 INTERIM ANALYSIS

It is planned that after the 18th subject in Stage I completes Cycle 1 treatment (28 days), a safety analysis will be conducted. The leading center's principal investigator and the sponsor will jointly perform a safety assessment of subjects enrolled in Stage I and decide the treatment groups of Stage II.

This analysis only provides a listing of subjects' AEs and laboratory evaluations and does not involve the analysis of the efficacy endpoints.

7 REFERENCES

8 APPENDICES

8.1 Appendix 1. Best Overall Response with CR and PR to Be Confirmed

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

Note: CR is complete response, PR is partial response, SD is stable disease, PD is progressive disease, and NE is non-evaluable. 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 has 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.