

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

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

**Statistical Analysis Plan
(SAP)**

Written by: [REDACTED]

Company: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

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Functional Role	Reviewer
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

ABBREVIATIONS

Term	Definition
AE	Adverse event
BOR	Best overall response
CBR	Clinical benefit rate
CR	Complete response
CTS	Change in tumor size
DOR	Duration of response
ECG	Electrocardiogram
ES	Evaluable analysis set
FAS	Full analysis set
LAB	Laboratory tests
NE	Not evaluable
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
12-OS%	12-month overall survival rate (12-month OS%)
PD	Progressive disease
PD-1	Programmed cell death protein 1
PE	Physical examination
PFS	Progression-free survival
PPS	Per-protocol set
PR	Partial response
PT	Preferred term
RECIST	Response evaluation criteria in solid tumors
SAS	Statistical analysis system
SD	Stable disease
SOC	System organ class
SS	Safety set
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TTR	Time to response
VS	Vital signs

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1. REVISION

NA.

2. INTRODUCTION

This statistical analysis plan is formulated to provide specific statistical analysis and reporting methods or strategies for a phase II clinical study to investigate and evaluate the tolerability, safety and efficacy of anti-PD-1 antibody SHR-1210 combined with apatinib mesylate in patients with advanced non-small cell cancer. This statistical analysis plan is drafted based on the final version of the study protocol (version no.: 5.0, version date: 10 Dec., 2018).

The final draft of this plan will be completed before database locking and will be signed by various functional departments for confirmation.

2.1. Study Design

Study design of Stage I:

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

Patients with advanced NSCLC who have failed standard treatment will be enrolled.

Three dose groups, i.e., apatinib 250 mg, oral, q.d. + SHR-1210 200 mg, IV, q2W, apatinib 375 mg, oral, q.d. + SHR-1210 200 mg, IV, q2W, and apatinib 500 mg, oral, q.d. + SHR-1210 200 mg, IV, q2W, are set to explore the tolerability of the combination therapy.

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 .

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

After completing the tolerability observation period, the study will enter Stage II for further observation of efficacy and safety.

After completing the tolerability observation period, 10 to 12 subjects will be enrolled in each dose group for an expanded pharmacokinetic (PK) 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 of 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, subjects will continue the treatment until occurrence of any event that meets the criteria for discontinuation.

Design of Stage II:

A single-arm/double-arm, multi-center, open-label clinical study

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 NSCLC who have 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 will be enrolled. 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.

2.2. Study Objectives

Primary objective at Stage I:

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

Secondary objectives at Stage I:

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

Primary objectives at Stage II:

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

2.3. 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 objective response rate (ORR) of the combination therapy is 30% with a two-sided 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, assuming that the point estimate of ORR in each cohort is 30% and the width of the 90% confidence interval is 0.3, 38 subjects are required for each cohort when a 20% dropout rate is considered.

For cohort 4, assuming that the point estimate of ORR 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.

3. STATISTICAL HYPOTHESES

No formal statistical hypothesis, no statistical inferences.

4. STUDY ENDPOINTS

4.1. Efficacy Endpoints

4.1.1. Objective response rate (ORR)

ORR (according to RECIST v1.1) refers to the percentage of subjects with complete response or partial response (CR or PR), and subjects with first assessment as CR/PR should be reexamined 4 weeks later.

The ORR will be assessed based on the documented efficacy evaluation from the date of first dose to the date of disease progression (PD) or the start of new anti-tumor treatment, whichever occurs first. For subjects without PD or initiation of new anti-tumor treatment, ORR results will be assessed based on all efficacy evaluations.

4.1.2. Best overall response (BOR)

The best overall response (BOR) will be calculated based on the documented best assessment from the date of first dose to the date of PD or the start of new anti-tumor treatment, whichever occurs first; or to the date of last efficacy evaluation if no PD occurs and no new anti-tumor treatment is initiated. BOR is classified as: CR, PR, SD, PD, and NE. If the tumor is assessed as

PD at a visit, the date of the PD should be recorded as the date of imaging assessment of the target lesion, the date of imaging assessment of the non-target lesion, or the date of discovery of the new lesion, whichever is earlier.

- Confirmed CR: Response evaluation of CR that has been reconfirmed as CR in a response evaluation 4 weeks later.
- Confirmed PR: Response evaluation of PR that has been reconfirmed as CR/PR in a response evaluation 4 weeks later, with no confirmed CR.
- SD: At least one SD (or better, such as CR, PR), with an interval not less than 6 weeks (i.e. ≥ 42 days) between the imaging date and the date of first dose, with no confirmed CR or PR.
- PD: Disease progression without confirmed CR, confirmed PR, or SD.
- NE: All other conditions.

See Appendix 1 for details.

4.1.3. Clinical benefit response (CBR)

Clinical benefit is defined as the percentage of subjects with a BOR of CR, PR, or SD ≥ 24 weeks according to RECIST v1.1.

4.1.4. Duration of response (DOR)

Duration of response is defined as the time from the first documentation of CR or PR to the date of first documentation of PD or death.

The censoring rules are as follows:

- If there is no radiographic PD or death before the start of any new anti-tumor treatment, censoring will be based on the date of the last effective efficacy evaluation prior to the new anti-tumor treatment.
- If the subject does not have radiographic PD or die before the end of study or dropout, and has not received new anti-tumor treatment before the end of study or dropout, censoring will be based on the date of the last effective efficacy evaluation.
- For death or PD occurring after two or more missed planned visits, censoring will be performed based on the date of the last effective efficacy evaluation prior to death or PD.

4.1.5. Time to response (TTR)

Time to response is defined as the time from the date of first dose to the first documentation of CR or PR (whichever occurs first). Tumor response is based on confirmed response. The date of response is the date of first observation, not the date of confirmation.

4.1.6. Progression-free survival (PFS)

Progression-free survival (PFS): defined as the period of time from the date of first dose to the date of the first documented tumor progression (as per RECIST v1.1, regardless of whether treatment is continued) or death of any cause (whichever occurs first).

Censoring rules:

- If there is no baseline tumor measurement or there is baseline tumor evaluation but with missing tumor evaluation after baseline, censoring will be based on the date of first dose.
- If there is no radiographic PD or death before the start of any new anti-tumor treatment, censoring will be based on the date of the last effective efficacy evaluation prior to the new anti-tumor treatment.
- If the subject does not have radiographic PD or die before the end of study or dropout, and has not received new anti-tumor treatment before the end of study or dropout, censoring will be based on the date of the last effective efficacy evaluation.
- For death or PD occurring after two or more missed planned visits, censoring will be performed based on the date of the last effective efficacy evaluation prior to death or PD.

4.1.7. 12-month overall survival rate (12-OS%)

The 12-month overall survival rate refers to the probability of being alive at Month 12 from the first dose of study treatment, and is assessed by Kaplan-Meier method.

4.1.8. Overall survival (OS)

Overall survival (OS): defined as the time from the date of first dose to death due to any cause.

Censoring rules are as follows:

- If there is no death or dropout by the end of study, the censoring date will be the last date when the survival status (alive) is obtained.

4.1.9. Change in tumor size (CTS)

The difference in tumor size from baseline as a percentage of baseline tumor size will be calculated based on the maximum decrease in tumor size or the minimum increase in tumor size after baseline.

Tumor size is defined as the sum of the longest diameters of target lesions assessed as per RECIST v1.1.

4.2. Safety Endpoints

The following safety data will be collected and summarized following the study protocol:

- Adverse events
- Laboratory test data
- Vital signs data
- ECOG PS
- ECG
- Physical examinations
- Other safety endpoints

4.2.1. Adverse events

Treatment-emergent adverse events (TEAEs) are defined as adverse events that occur on or after the day of the first study treatment.

4.2.2. Laboratory test

Laboratory data including hematology, urinalysis, stool routine, blood biochemistry, coagulation function, and thyroid function (T3, FT3, FT4, TSH) will be collected at the visit time points specified in the protocol.

4.2.3. Vital signs

Vital signs including body temperature, pulse, respiration, diastolic blood pressure, and systolic blood pressure will be collected at the protocol-preset time points.

4.2.4. 12-Lead ECG

Heart rate, PR, QT, QTc, and QRS data will be collected at the protocol-preset time points.

4.2.5. Physical examination

Physical examinations include general condition, head and face, skin system, lymph nodes, eyes, ears, nose and throat, oral cavity, respiratory system, cardiovascular system, abdomen, reproductive-urinary system, musculoskeletal system, nervous system, and mental state. These data will be collected at protocol-specified visit/time points.

4.2.6. Other safety endpoints

Echocardiography, etc.

5. STATISTICAL ANALYSIS

All efficacy and safety analyses will be based on the following populations/groups:

- **Driver gene negative population:** Subjects who are negative or not tested for EGFR and also negative or not tested for ALK fusion gene are classified into negative population. Including:
 - (1) Apatinib 250 mg + SHR1210 200 mg (Stage I): subjects who are negative or not tested for EGFR and also negative or not tested for ALK fusion gene;
 - (2) Cohort 1;
 - (3) Cohort 3;

Apatinib 250 mg + SHR1210 200 mg are used in both Cohorts 1 and 3 in Stage II.

- **Driver gene positive population:** Subjects who are positive for EGFR or ALK fusion gene are classified into positive population. Including:
 - Subjects who use apatinib 250 mg + SHR1210 200 mg and are positive for EGFR or ALK fusion gene in Stage I;
 - Cohort 2: Apatinib 250 mg + SHR1210 200 mg are used in Cohort 2.
- **Cohort 4:** Apatinib 250 mg + SHR1210 200 mg are used in Cohort 4.
- **Apatinib 375 mg + SHR1210 200 mg:** Only subjects who receive apatinib 375 mg + SHR1210 200 mg in Stage I are included.

5.1. General Considerations

5.1.1. Analysis sets

Full analysis set (FAS)

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

Evaluable analysis 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 response evaluation. If there is a new anti-tumor treatment, there should be a post-baseline tumor imaging response evaluation no later than the start date of the new anti-tumor treatment.

Per-protocol set (PPS)

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

Safety set (SS)

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

DLT analysis set

Subjects enrolled in Stage I who have developed DLT during the tolerability observation period (four weeks) or have completed the tolerability observation period. Subjects with SHR-1210 dose < 90% of the prescribed dose due to non-clinically significant toxicity (such as injection reaction) during the tolerability observation period are not included in the DLT analysis set.

Table 1. Analysis sets and corresponding endpoints

Endpoint	Analysis Sets				
	FAS	ES	PPS	SS	DLT Analysis Set
BOR (%)	X	X	X		
ORR (%)	X	X	X		
CBR (%)	X	X	X		
TTR (months)	X				
PFS (months)	X				
DoR (months)	X				
12-Month Overall Survival Rate (%)	X				
OS (months)	X				
Safety (AE, LAB, VS, ECG, and PE)				X	
DLT Events					X

5.1.2. General rule and analysis

Baseline

Unless otherwise stated, the "baseline" in this study is defined as the last non-missing measurement value obtained prior to the first dose of study drug, including 1) visits during screening period before the first dose of study drug; 2) measurements taken on the day of and prior to the first dose (do not serve as baseline value if time is not distinguishable). In the event of repeated measurements on the same day which cannot be distinguished by time, the mean value of a continuous variable will serve as baseline value, or the lower-severity grade of a categorical variable will serve as baseline value.

Study days

The day of the first dose is used as the start date of the study (Day 1).

- If the evaluation date (adverse event, laboratory tests, etc.) is on or after the study medication, the study days shall be calculated as follows: Study days = evaluation/event date – start date of study + 1.
- If the evaluation date (baseline characteristics, medical history, etc.) is before the study medication, the study days shall be a negative figure and shall be calculated as follows:
Study days = evaluation/event date – start date of study;

General analysis

Unless otherwise specified, the following descriptive statistics will be summarized by the type of variables:

- The continuous variables will be summarized using mean, standard deviation, median, maximum, minimum, and quartile.
- The categorical variables will be summarized using frequency and percentage;
- For time-to-event data, Kaplan-Meier method will be used to estimate the survival function and median time to event onset, and a survival curve will be plotted.

Number of decimal places

Unless otherwise specified, number of decimal places in the analysis report will be determined as per the following rules:

- The decimal places of the minimum and maximum will remain the same as those of the raw data to be acquired. Mean and median should have one more decimal place than those of the raw data, and the standard deviation should have 2 more decimal places than that of the raw data. However, there can only be at most 4 decimal places.
- The percentage will be rounded to 1 decimal place. If the frequency is 0, the percentage is not displayed.
- The *P* value will retain four decimal places. If the *P* value is < 0.0001, it will be expressed as "< 0.0001". If the *P* value is > 0.9999, it will be reported as "> 0.9999".
- The 95% CI, if being a decimal, will retain at least 2 decimal places, up to 4 decimal places. Details are as follows: The 95% confidence interval will have one more decimal place than that of the raw data. If the raw data have no decimal place, the 95% confidence interval will retain 2 decimal places; if the raw data have 4 or more decimal places, the 95% confidence interval will retain at most 4 decimal places.
- Time to event (months) will be rounded to one decimal place.

Analysis software

All statistical analyses will be conducted using SAS® 9.4.

5.1.3. Derived variables

Table 2. Derived variables of apatinib

Variable	Apatinib
Protocol-Specified Method of Administration	Administered once daily in 4-week cycles. Subjects who receive apatinib 375 mg + SHR1210 200 mg in Stage I: 375 mg per dose; others: 250 mg per dose
Duration of Drug Exposure (months)	$(\text{Date of last dose} - \text{date of first dose} + 1) / 30.4375$
Planned Duration of Treatment (months)	$(\text{Date of last dose} - \text{date of first dose} + 1) / 30.4375$
Actual Cumulative Dose of All Cycles (mg)	Summarize the actual dose in all cycles (mg): $[\text{duration of drug exposure (months)} \times 30.4375 \text{ (days/month)} - (\text{end date of dose modification} - \text{start date of dose modification} + 1) \text{ (days)}] \times \text{first dose} + (\text{end date of dose modification} - \text{start date of dose modification} + 1) \text{ (days)} \times \text{dose after modification (mg/day)} - (\text{end date of dose interruption} - \text{start date of drug interruption} + 1) \text{ (days)} \times \text{interrupted dose (mg/day)}$
Planned Dose Intensity (mg/day)	Subjects who receive apatinib 375 mg + SHR1210 200 mg in Stage I: 375 (mg/day); others: 250 (mg/day)
Actual Dose Intensity (mg/day)	$\text{Actual cumulative dose of all cycles (mg)} / [\text{planned duration of treatment (days)}]$
Relative Dose Intensity (%)	$100 \times [\text{actual dose intensity (mg/day)}] / [\text{planned dose intensity (mg/day)}]$

Table 3. Derived variables of SHR-1210

Variable	SHR-1210
Protocol-Specified Method of Administration	Administered once every 14 days, 200 mg each time, in 4-week cycles
Duration of Drug Exposure (months)	$(\text{Date of last dose} - \text{date of first dose} + 14) / 30.4375$
Planned Duration of Treatment (months)	$(\text{Date of last dose} - \text{date of first dose} + 14) / 30.4375$
Actual Cumulative Doses of All Cycles (doses)	Total number of SHR-1210 doses actually received by the subject
Planned Dose Frequency Intensity (doses/2 weeks)	1
Actual Dose Frequency Intensity (times/2 weeks)	$(\text{Actual cumulative doses of all cycles} / [\text{planned duration of treatment (months)} \times 30.4375 / 7 \text{ (weeks/month)} / 2])$
Relative Dose Frequency Intensity (%)	$100 \times [\text{actual dose frequency intensity (doses/2 weeks)}] / [\text{planned dose frequency intensity (doses/2 weeks)}]$

5.1.4. Covariates and subgroups

Baseline characteristics may affect the efficacy, and the efficacy will be analyzed according to subgroup classification. Baseline characteristics include: gender (male/female); age (≥ 65 years or < 65 years); ECOG performance status (0/1); smoking history (yes/no); number of metastasis sites (≤ 2 or > 2); clinical stage (IIIb/IV); brain metastases (yes/no); liver metastases (yes/no); history of tumor surgery (yes/no); history of radiotherapy (yes/no); PD-L1 expression on tumor cells (TC) in tumor tissue ($\geq 1\%$ / $< 1\%$); KRAS mutation (positive/negative), etc.

5.1.5. Missing data

5.1.5.1. Medical history

For the missing dates of medical history (including the dates of first pathological diagnosis, progression/recurrence, and response prior to the first dose of the study drug), the rules for imputing are as follows:

- If the day is missing, it will be imputed with 1 of that month.
- If both month and day are missing and the year is prior to the year of the first administration, the date will be imputed with 1 Jan.
- If both month and day are missing and the year is the same as that of the first administration, the date will be imputed with 1 Jan.
- If the date is completely missing, it will not be imputed.

5.1.5.2. Adverse events

If the date related to an AE is missing, the rules for imputing are as follows:

- If the start date of an AE is completely missing, the date will be imputed with the date of the first administration.
- If only the day of the start date of the AE is missing with the same year and month as those of the first administration, the day will be imputed with that of the date of the first administration.
- If both the month and day of the start date of the AE are missing with the same year as that of the first administration, the month and day will be imputed with those of the date of the first administration.
- In other cases, if the month or day of the start date of the AE is missing, it will be imputed with 1.

- If only the day of the end date of the AE is missing, the date will be imputed with the last day of the month (before the date of death). If the last day of the month is later than the date of death, it will be imputed with the date of death.
- In other cases, if the end date of the AE is missing, the date will not be imputed.

5.1.5.3. Drug exposure

The date of the first dose will not be imputed. If the date of the last dose is unknown or partially missing, it will be imputed according to the following rules:

- If the date of the last dose is completely or partially missing while the date of death or CRF page for treatment discontinuation is present, the date of the last dose will be imputed as follows:
 - = 31-12-YYYY (if the year YYYY is known, and if YYYY < min (year) [date of treatment discontinuation, date of death])
 - = The last day of the month (if both the year and month are not missing, and if YYYY < min (year) [date of treatment discontinuation, date of death])
 - = The last day of the month (if both the year and month are not missing, and if YYYY = min (year) [date of treatment discontinuation, date of death], and MM < min (month) [date of treatment discontinuation, date of death])
 - = min (date of treatment discontinuation, date of death), other cases.

5.1.5.4. Rules for imputing last survival date and start date of new anti-tumor treatment

5.1.5.4.1. Last survival date

If the investigator is not informed of subject death, the latest date of the following data will be taken as the last survival date:

- All dates of examinations and evaluations of the subjects (tumor response evaluation, blood tests (laboratory, PK), vital signs, physical examination, ECOG PS, pregnancy test, urinalysis, stool routine test, etc.)
- The start and end dates of concomitant medications/concomitant non-drug treatments
- 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
- Date of withdrawal of informed consent form
- Date of enrollment
- 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)

5.1.5.4.2. Date of death

If the date of death is completely or partially missing, the last survival date will be used to impute the date of death:

- If the date of death is completely missing, the last survival date + 1 day will be used as the date of death.
- If the day is missing or if both month and day are missing, the date of death = max (last survival date + 1, the date imputed below).
 - Day is missing: 01-MM-YYYY
 - Month and day are missing: 01-01-YYYY

5.1.5.4.3. Start date of new anti-tumor treatment

If the start date of a new anti-tumor treatment is missing, it will be imputed according to the following rules after the end date of study treatment is imputed.

- If the end date of the new anti-tumor treatment is partially missing or not missing, it 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 while the year is not missing, 31 Dec. will be 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 start date of a new anti-tumor treatment is completely missing or only the year is not missing, it will be derived and imputed according to the following rules:
 - The date of the new anti-tumor treatment is completely missing
The imputed start date = min [max (PD date + 1, date of last dose + 1), end date of the new anti-tumor treatment]
 - Only the year (YYYY) of the start date of the new anti-tumor treatment is not missing

- 1) If $YYYY < \min(\text{year}) [\max(\text{PD date} + 1, \text{date of last dose} + 1), \text{end date of new anti-tumor treatment}]$, the date will be imputed as 31-12-YYYY.
 - 2) In other cases, if $YYYY = \min(\text{year}) [\max(\text{PD date} + 1, \text{date of last dose} + 1), \text{end date of new anti-tumor treatment}]$, the date imputed = $\min [\max(\text{PD date} + 1, \text{date of last dose} + 1), \text{end date of new anti-tumor treatment}]$.
 - 3) In other cases, if $YYYY > \min(\text{year}) [\max(\text{PD date} + 1, \text{date of last dose} + 1), \text{end date of new anti-tumor treatment}]$, the date imputed = 01-01-YYYY.
- The year (YYYY) and month (MM) of the start date of new anti-tumor treatment are not missing
 - If $YYYY = \min(\text{year}) [\max(\text{PD date} + 1, \text{date of last dose} + 1), \text{end date of new anti-tumor treatment}]$, and if $MM < \min(\text{month}) [\max(\text{PD date} + 1, \text{date of last dose} + 1), \text{end date of new anti-tumor treatment}]$, the date will be imputed with the last day of MM.
 - In other cases, if $YYYY = \min(\text{year}) [\max(\text{PD date} + 1, \text{date of last dose} + 1), \text{end date of new anti-tumor treatment}]$, and $MM = \min(\text{month}) [\max(\text{PD date} + 1, \text{date of last dose} + 1), \text{end date of new anti-tumor treatment}]$, then the date imputed = $\min [\max(\text{PD date} + 1, \text{date of last dose} + 1), \text{end date of new anti-tumor treatment}]$.
 - In other cases, if $YYYY = \min(\text{year}) [\max(\text{PD date} + 1, \text{date of last dose} + 1), \text{end date of new anti-tumor treatment}]$, and $MM > \min(\text{month}) [\max(\text{PD date} + 1, \text{date of last dose} + 1), \text{end date of new anti-tumor treatment}]$, then the date imputed = 01-MM-YYYY.
 - In other cases, if $YYYY < \min(\text{year}) [\max(\text{PD date} + 1, \text{date of last dose} + 1), \text{end date of new anti-tumor treatment}]$, the day imputed will be the last day of MM.
 - In other cases, if $YYYY > \min(\text{year}) [\max(\text{PD date} + 1, \text{date of last dose} + 1), \text{end date of new anti-tumor treatment}]$, then the date imputed = 01-MM-YYYY.

5.2. Study Subjects

5.2.1. Disposition of subjects

The number of screened subjects, number of enrolled subjects, number and percentage of treated subjects, number and percentage of subjects in analysis sets (including full analysis set, evaluable analysis set, per-protocol set, safety set, and DLT analysis set), number of subjects who discontinue the study/treatment, and number and percentage of corresponding subjects to the reasons for discontinuation will be summarized.

5.2.2. Demographics

The age, gender, ethnicity, height, weight, body mass index BMI (kg/m²), vital capacity, maximal mid-expiratory flow, peak expiratory flow, forced expiratory volume in 1 second, diffusing capacity for carbon monoxide, oxygen saturation, ECOG PS, smoking history (yes, no), and cigarettes used will be summarized by group using descriptive statistics.

The BMI calculation formula is: $\text{BMI (kg/m}^2\text{)} = \text{baseline weight (kg)} / \text{baseline body height (m}^2\text{)}$.

5.2.3. Tumor diagnosis

The following tumor indicators will be summarized by group using descriptive statistics: histological classification, presence of metastases, number of organs involved in metastasis (≤ 2 , > 2), pathological grade, clinical stage, EGFR, ALK fusion gene, course of disease (years), etc. A detailed listing of subjects for tumor diagnosis will be provided.

The course of disease (years) is defined as the period from the date of initial pathological diagnosis to the date before the first dose. The calculation formula is: $(\text{date of first dose} - \text{date of initial pathological diagnosis} + 1) / 365.25$.

5.2.4. Medical history

A detailed listing of medical history will be provided.

5.2.5. Tumor treatment history

Tumor treatment history mainly includes history of tumor surgery, chemotherapy, targeted therapy, radiotherapy, and other tumor treatments.

For tumor treatment history, the following descriptive statistics are provided:

- Number and percentage of subjects who have previously received any of the above tumor treatments;
- Number and percentage of subjects who have previously received tumor surgery, and number and percentage of subjects by surgery nature;
- Number and percentage of subjects who have received chemotherapy, and number and percentage of subjects by treatment mode;
- Number and percentage of subjects who have received targeted therapy, and number and percentage of subjects by treatment mode and regimens;
- Number and percentage of subjects who have received radiotherapy;
- Number and percentage of subjects who have received other tumor treatments, and number and percentage of subjects by treatment type.

In addition, a detailed listing of subjects will be provided.

5.2.6. Prior therapy and concomitant medication

All prior medications, concomitant medications, and concomitant non-drug treatments will be listed. The information of anti-tumor treatments (including chemotherapy, targeted therapy, radiotherapy, surgery, and others) used after withdrawal due to PD will be summarized and listed. Subsequent anti-tumor treatment refers to other anti-tumor treatment after the last dose.

5.2.7. Protocol deviations

Before database lock, all subject data on the CRF will be categorized according to the company's protocol deviation classification rules (critical, major, minor). All critical and major protocol deviations will be summarized and described by group and type, and a listing (including subject ID, protocol deviation reasons) will be provided for analysis.

5.3. Efficacy Analysis

The efficacy analysis will be performed based on the investigator's assessments. BOR, ORR, and CBR will be analyzed based on the FAS, PPS, and ES. DOR, TTR, 12-OS%, and OS will be analyzed based on the FAS. See [Table 1](#) for details. Efficacy should be presented by cohort/group.

5.3.1. Best overall response (BOR)

See Section 4.1.2 for BOR.

BOR (CR, PR, SD, PD, and NE) will be summarized by frequency and percentage.

5.3.2. Objective response rate (ORR)

ORR is defined in Section 4.1.1.

ORR and its two-sided 95% CI will be calculated, the CI will be estimated using the Clopper-Pearson method, and a swimmer plot will be drawn.

5.3.3. Clinical benefit rate (CBR)

CBR is defined in Section 4.1.3.

CBR and its two-sided 95% CI will be calculated, and the CI will be estimated using the Clopper-Pearson method.

5.3.4. Duration of response (DoR)

DoR is defined in Section 4.1.4.

The Kaplan-Meier method will be used to analyze the median survival of DoR of each population/cohort, its 95% CI will be calculated using the Brookmeyer-Crowley method, and the DoR curve will be plotted. The Kaplan-Meier method will be used to analyze the 6-, 9-, and 12-month overall survival rates, and the corresponding two-sided 95% CIs will be calculated (using the log(-log) transformation by normal approximation with back transformation).

5.3.5. Time to response (TTR)

TTR is defined in Section 4.1.5.

TTR (months) will be described by population/cohort using mean, standard deviation, median, maximum, and minimum.

5.3.6. Progression-free survival (PFS)

PFS is defined in Section 4.1.6.

According to population/cohort, the Kaplan-Meier method will be used to analyze the median PFS, the corresponding 95% CI will be calculated using the Brookmeyer-Crowley method, and the PFS plot will be drawn. The proportion of subjects with PFS greater than or equal to 6/9/12 months will also be analyzed. The Kaplan-Meier method will be used to analyze the 6-, 9-, and 12-month PFS rates, and the corresponding two-sided 95% CIs will be calculated (using the log(-log) transformation by normal approximation with back transformation).

The K-M curve of PFS of apatinib 250 mg + SHR1210 200 mg (Stage I) vs. apatinib 375 mg + SHR1210 200 mg will be plotted.

5.3.7. 12-month overall survival rate (12-OS%)

12-OS% is defined in Section 4.1.7.

The Kaplan-Meier method will be used to analyze the 12-OS% of each population/cohort, and the corresponding two-sided 95% CI will be calculated (using the log(-log) transformation by normal approximation with back transformation).

5.3.8. Overall survival (OS)

OS is defined in Section 4.1.8.

The Kaplan-Meier method will be used to analyze the median overall survival of each population/cohort, its 95% CI will be calculated using the Brookmeyer-Crowley method, and the survival curve will be plotted. The proportion of subjects with OS greater than or equal to 12/18/24 months will also be analyzed. The Kaplan-Meier method will be used to analyze 12-, 18-, and 24-month overall survival rates and the corresponding two-sided 95% CIs will be calculated (using the log(-log) transformation by normal approximation with back transformation).

The K-M curve of OS of apatinib 250 mg + SHR1210 200 mg (Stage I) vs. apatinib 375 mg + SHR1210 200 mg will be plotted.

5.3.9. Change in tumor size (CTS)

CTS is defined in Section 4.1.9. The waterfall plot of the maximum change in tumor size will be plotted.

5.3.10. Exploratory analyses

Based on the FAS, the 4 groups including driver gene negative population, driver gene negative population (non-squamous cell carcinoma), driver gene positive population, and cohort 4 will be analyzed (in terms of ORR, PFS, and OS) using SHR-1210-related tumor biomarkers, such as PD-L1 expression levels on tumor cells (TC) in tumor tissues ($\text{PD-L1} \geq 1\%$ or $< 1\%$), TAM (TAM expression \geq median or $<$ median), tumor mutation burden in plasma ($\text{bTMB} \geq 1.54$ muts or < 1.54 muts), tumor mutation burden in tissues ($\text{tTMB} \geq$ median or $<$ median), and proportion of positive PD-L1 expression on circulating tumor cells (CTC) ($\text{PD-L1} \geq 1\%$ or $< 1\%$), including calculation of ORR and its 95% CI, median PFS and OS and their 95% CIs.

Driver gene negative population (non-squamous cell carcinoma) refers to 1) Apatinib 250 mg + SHR1210 200 mg (Stage I): subjects who are negative or not tested for EGFR and also negative or not tested for ALK fusion gene; 2) Cohort 1: non-squamous, non-small cell lung cancer with wild-type EGFR and ALK.

5.3.11. Subgroup analysis

Subgroup analysis will be performed on the 4 groups including driver gene negative population, driver gene negative population (non-squamous cell carcinoma), driver gene positive population, and cohort 4 based on the following variables, which include: gender (male/female); age (≥ 65 years or < 65 years); ECOG performance status (0/1); smoking history (yes/no); number of metastasis sites (≤ 2 or > 2); clinical stage (stage IIIb/IV); brain metastases (yes/no); liver metastases (yes/no); history of tumor surgery (yes/no); history of radiotherapy (yes/no); PD-L1 expression levels on tumor cells (TC) in tumor tissues ($\geq 1\%$ / $< 1\%$); KRAS mutation (positive/negative), etc., and a forest plot of ORR (the vertical axis of Cohort 4 is 30%, and the vertical axis of other analyzed populations is 15%) will be drawn. In addition, subgroup analysis will be performed on the driver gene negative population, driver gene negative population (non-squamous cell carcinoma), and driver gene positive population based on the number of prior treatment lines (first-line/ \geq second-line). Subgroup analysis will also be performed on the driver gene positive population based on the gene mutation type (exon 19/L858R/exon 20).

Driver gene negative population (non-squamous cell carcinoma) refers to 1) Apatinib 250 mg + SHR1210 200 mg (Stage I): subjects who are negative or not tested for EGFR and also negative or not tested for ALK fusion gene; 2) Cohort 1: non-squamous, non-small cell lung cancer with wild-type EGFR and ALK.

5.3.12. Other analyses

NA.

5.4. Safety Analysis

All safety analyses will be conducted based on the SS.

5.4.1. Extent of exposure

Extent of exposure is defined in Section 5.1.3. The specific definitions of the derived variables of apatinib and SHR1210 are shown in [Table 2](#) and [Table 3](#).

The actual cumulative dose of all cycles, duration of drug exposure, actual dose intensity, relative dose intensity, etc. of apatinib, and the actual cumulative doses of all cycles, duration of drug exposure, actual dose frequency intensity, and relative dose frequency intensity of SHR1210 will all be described using mean, standard deviation, maximum, minimum, and median. The use of study drugs SHR-1210 and apatinib in the treatment period will be summarized by descriptive statistics. For the relative dose frequency intensity of SHR-1210, the relative dose intensity values of apatinib are summarized in two categories: $<$ or $\geq 80\%$.

The dose interruption and dose modification of apatinib and the dose interruption of SHR1210 during the study will be summarized.

5.4.2. DLT evaluation

DLT analysis is based on DLT analysis set. Clinically significant toxicity events will be listed. Clinically significant toxicities will be summarized by dose group using frequency and percentage.

5.4.3. Adverse events

AEs will be classified by treatment stage (before and after study treatment).

All AEs will be coded using MedDRA V24.0 and graded using NCI-CTCAE v4.03. Subject will be counted only once, even if the subject experiences more than one event within the same system organ class (SOC) and/or preferred term (PT). For the same AE reported in one subject multiple times but varying in CTCAE grade, the highest grade will be counted.

AEs will be ordered by descending incidence of SOC, and by descending incidence of PT within each SOC. If the incidence of ≥ 2 PTs is equal, the AEs will be ordered alphabetically. If there is no AE under a SOC or PT, the analysis will not be conducted.

Only TEAEs will be summarized. All AEs will be listed. AEs with completely missing onset time will be treated as TEAEs.

For AEs occurring after the start of study treatment, treatment-related AEs include those whose causality with the study drug is related, possibly related, or unassessable; if the causality assessment is missing, then the AE will be deemed treatment-related for analysis. AEs with any missing CTCAE grade will be analyzed based on the highest grade.

In AE summary table, AEs after study drug treatment will be analyzed according to the population/cohort, and the frequency and proportion will be used for statistical description. Analyses of AEs include but are not limited to the following:

- Any TEAE
- Treatment-related TEAE
- Any treatment-emergent serious adverse event (TESAE)
- Treatment-related TESAE
- CTCAE Grade ≥ 3 TEAE
- CTCAE Grade ≥ 3 treatment-related TEAEs
- Any TEAE with an incidence of $\geq 5\%$
- Treatment-related TEAE with an incidence of $\geq 5\%$
- AEs leading to treatment discontinuation
- Treatment-related AEs leading to treatment discontinuation
- AEs leading to discontinuation of SHR-1210
- Treatment-related AEs leading to discontinuation of SHR-1210
- AEs leading to discontinuation of apatinib
- Treatment-related AEs leading to discontinuation of apatinib
- AEs leading to interruption of SHR-1210
- Treatment-related AEs leading to interruption of SHR-1210
- AEs leading to interruption of apatinib
- Treatment-related AEs leading to interruption of apatinib
- AEs leading to dose reduction of apatinib
- Treatment-related AEs leading to dose reduction of apatinib
- AEs leading to death
- Treatment-related AEs leading to death
- TEAEs of special interest (SIEs, see Appendix 2 for specific classification)
- Immune-related TEAEs (irAEs)

The incidence of an AE will be calculated based on the number of subjects experiencing the AE, instead of the number of AE episodes.

SIEs include:

- Grade ≥ 3 infusion reaction
- Grade ≥ 2 diarrhea/colitis, uveitis, and interstitial pneumonia
- Other Grade ≥ 3 irAEs
- Grade 4 amylase or lipase increased
- Reactive capillary endothelial proliferation
- Hepatic enzyme abnormal

Time to the first onset of event (days) = Date of first onset of event – Date of first dose + 1;

All AEs will be listed. Treatment-related AEs, SAEs, irAEs, and AEs leading to treatment discontinuation, interruption, or dose reduction will be listed separately.

In addition, AEs will be summarized by group (apatinib 250 mg + SHR1210 200 mg, apatinib 375 mg + SHR1210 200 mg) using descriptive statistics, including but not limited to the following:

- Any TEAE
- Treatment-related TEAE
- Any treatment-emergent serious adverse event (TESAE)
- Treatment-related TESAE
- CTCAE Grade ≥ 3 TEAE
- CTCAE Grade ≥ 3 treatment-related AEs
- Special interest events (SIEs)
- Immune-related adverse events (irAEs)
- Treatment-related AEs leading to treatment discontinuation
- Treatment-related AEs leading to discontinuation of SHR-1210
- Treatment-related AEs leading to discontinuation of apatinib
- Treatment-related AEs leading to interruption of SHR-1210
- Treatment-related AEs leading to interruption of apatinib
- Treatment-related AEs leading to dose reduction of apatinib

5.4.4. Laboratory evaluations

The shift table will be used to summarize the baseline and post-baseline laboratory test results by worst clinical significance (normal, abnormal without clinical significance, abnormal with clinical significance), including hematology, blood biochemistry, coagulation function, stool routine, urinalysis, and thyroid function tests (T3, FT3, FT4, TSH). The post-baseline measurements of each subject are summarized according to the worst severity grades. Severity, in descending order: Abnormal with clinical significance, abnormal without clinical significance, normal, and not examined.

Based on the SS, the median values of alanine aminotransferase, aspartate aminotransferase, total bilirubin, γ -glutamyl transferase, and alkaline phosphatase from subjects with clinically significant abnormalities in alanine aminotransferase or aspartate aminotransferase tests post baseline will be plotted by visits.

All laboratory test results will be listed.

5.4.5. Vital signs

Vital signs will be summarized by visit using descriptive statistics for each population/cohort.

All vital signs will be listed.

5.4.6. 12-Lead ECG

Mean values of 12-lead ECG results will be taken at each visit. Examination items of ECG include: HR (beats/min), PR interval (ms), QT interval (ms), QTc (ms), and QRS (ms).

The baseline and worst grade post baseline or clinical significance will be summarized by shift table. Clinical significance includes normal, abnormal without clinical significance, and abnormal with clinical significance.

Measurements of each ECG variable at each time point will be analyzed using descriptive statistics.

ECG parameters measured at the study site will be summarized as follows:

- Maximum PR interval ≥ 300 ms
- Maximum QT interval ≥ 500 ms
- Maximum QTc interval (ms) (450-<480, 480-<500, ≥ 500)
- Maximum QTc interval ≥ 480 ms or increase > 60 ms from baseline

Related data will also be reported in listing.

5.4.7. ECOG PS

The baseline and highest ECOG PS post baseline for each population/cohort will be summarized using a shift table.

All ECOG PS will be reported in the form of listing.

5.4.8. Physical examination

Data of physical examination will be listed.

5.4.9. Other safety measures

Echocardiography results will be listed.

5.5. Pharmacokinetic Analysis

See independent PK analysis report.

5.6. Other Analyses

NA.

6. INTERIM ANALYSIS

NA.

7. REFERENCES

NA.

8. APPENDIX

Appendix 1: 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 = not 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.

Appendix 2: List of Preferred Terms for Special Interest Events

Special Interest Event	Classification	AE Preferred Term (coded as per v24.0)
Grade 4 amylase or lipase increased	Amylase increased	Amylase increased
Grade 4 amylase or lipase increased	Lipase increased	Lipase increased
Reactive capillary endothelial proliferation		Reactive capillary endothelial proliferation
Grade ≥ 3 infusion reaction		Infusion related reaction
Grade ≥ 2 diarrhea/colitis	Colitis	Colitis ulcerative
Grade ≥ 2 diarrhea/colitis	Colitis	Enterocolitis
Grade ≥ 2 diarrhea/colitis	Colitis	Colitis
Grade ≥ 2 diarrhea/colitis	Diarrhea	Frequent bowel movements
Grade ≥ 2 diarrhea/colitis	Diarrhea	Diarrhoea
Grade ≥ 2 uveitis		Uveitis
Grade ≥ 2 uveitis		Eye pain
Grade ≥ 2 interstitial pneumonia		Interstitial lung disease

Special Interest Event	Classification	AE Preferred Term (coded as per v24.0)
Hepatic enzyme abnormal		Hepatic enzyme abnormal
Other Grade ≥ 3 irAEs	Immune-mediated lung disease	Immune-mediated lung disease
Other Grade ≥ 3 irAEs	Pneumonia	Pneumonitis
Other Grade ≥ 3 irAEs	Immune-related hepatitis	Immune-mediated hepatitis
Other Grade ≥ 3 irAEs	Hepatic function abnormal	Hepatic function abnormal