Title: A Single-Arm, Open-Label, Phase II Clinical Trial Evaluating Anti-PD-1 Antibody SHR-1210 in Combination with Apatinib Mesylate in Treatment of Advanced Hepatocellular Carcinoma
Clinical trial registration number: NCT03463876
Version Date: 10 Apr., 2021

A SINGLE-ARM, OPEN-LABEL, PHASE II CLINICAL STUDY EVALUATING ANTI-PD-1 ANTIBODY SHR-1210 IN COMBINATION WITH APATINIB MESYLATE IN TREATMENT OF ADVANCED HEPATOCELLULAR CARCINOMA

STATISTICAL ANALYSIS PLAN
(SAP)

Author: [redacted]

Company: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Version: 2.0/Final Draft

Date: 10 Apr., 2021

This statistical analysis plan has been reviewed by the following personnel before being approved and effective.

Functional Role	Reviewer
Medical Science	[redacted]
Statistics	[redacted]

ABBREVIATIONS

Term	Definition
ADR	Adverse drug reaction
BOR	Best overall response
CR	Complete response
DCR	Disease control rate
DOR	Duration of response
ECG	Electrocardiogram
ES	Evaluable analysis set
FAS	Full analysis set
IRC	Independent review committee
LE	Investigator evaluation
NE	Not evaluable
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-L1	Programmed death ligand 1
PFS	Progression-free survival
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
TTF	Time to treatment failure
TTP	Time to progression
TTR	Time to response

TABLE OF CONTENTS

ABBREVIATIONS **2**
1. REVISION **6**
2. INTRODUCTION **6**
2.1. Study Design 6
2.2. Study Objectives 7
2.2.1. Primary objectives 7
2.2.2. Secondary objectives 7
2.2.3. Exploratory objectives 7
2.3. Sample Size 8
3. STATISTICAL HYPOTHESIS AND DECISION RULE **8**
4. STUDY ENDPOINTS **9**
4.1. Efficacy Endpoints 9
4.1.1. Primary efficacy endpoints 9
4.1.2. Secondary efficacy endpoints 9
4.2. Safety Endpoints 12
4.2.1. Adverse events 12
4.2.2. Laboratory test 12
4.2.3. Vital signs 13
4.2.4. Electrocardiogram (ECG) 13
4.2.5. Physical examination 13
4.2.6. Other safety endpoints 13
4.3. Exploratory Endpoints 13
4.3.1. Pharmacokinetics and pharmacodynamics 13
4.3.2. Immunogenicity 13
4.3.3. Quality of life index 13
4.3.4. Biomarker 13
4.3.5. Other exploratory endpoints 13
5. STATISTICAL ANALYSIS **14**
5.1. General Considerations 14
5.1.1. Analysis sets 14

5.1.2. General rule and analysis 14
5.1.3. Derived variables 16
5.1.4. Covariates and subgroups 16
5.1.5. Analysis window 16
5.1.6. Missing data 16
5.2. Study Subjects 19
5.2.1. Disposition of subjects 20
5.2.2. Demographics 20
5.2.3. Tumor diagnosis 21
5.2.4. Medical history 21
5.2.5. Tumor treatment history 21
5.2.6. Prior therapy and concomitant medication 22
5.2.7. Protocol deviations 22
5.3. Treatment Compliance 22
5.4. Efficacy Analysis 22
5.4.1. Primary efficacy analysis 23
5.4.2. Secondary efficacy analysis 23
5.4.3. Exploratory analyses 26
5.4.4. Subgroup analysis 26
5.4.5. Other analyses 26
5.5. Safety Analysis 27
5.5.1. Extent of exposure 27
5.5.2. Adverse events 29
5.5.3. Laboratory evaluations 31
5.5.4. Vital signs 32
5.5.5. Electrocardiogram 32
5.5.6. ECOG PS 32
5.5.7. Physical examination 33
5.5.8. Other safety measures 33
5.6. Exploratory Analyses 33
5.6.1. Immunogenicity 33
5.6.2. Quality of life index 33

5.6.3. Other exploratory analysis 33
5.7. Pharmacokinetics and Pharmacodynamics 33
6. INTERIM ANALYSIS 33
7. REFERENCES 33
8. APPENDICES 34

List of Tables

Table 1. Derived variables of SHR-1210 and Apatinib 28

1. REVISION

This version is drafted based on the study protocol (version no.: 3.0, version date: 29 May, 2019).

Content	Before	After	Reason for Revision
Cover	1. The version number is 1.0 2. The version date is 31 Mar., 2020	1. The version number is 2.0 2. The version date is 10 Apr., 2021	Version upgrade
8. APPENDICES		Appendices 2-5 were revised	MedDRA has been upgraded to v24.0, based on which the preferred terms of adverse events in Appendices 2-5 were updated

2. INTRODUCTION

This statistical analysis plan is developed for a phase II study on the efficacy of PD-1 antibody SHR-1210 in combination with apatinib mesylate in patients with advanced hepatocellular carcinoma, which will provide specific statistical analysis and reporting methods or strategies. This statistical analysis plan is drafted based on the final version of the study protocol (version no.: 3.0, version date: 29 May, 2019).

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

The study is a single-arm, open-label, and national multicenter phase II clinical trial intended to observe and evaluate the efficacy and safety of anti-PD-1 antibody SHR-1210 in combination with apatinib mesylate in patients with advanced hepatocellular carcinoma.

The study focuses on patients with advanced hepatocellular carcinoma who cannot be cured by radical treatment, and these patients have a history of systemic first-line treatment failure or are unwilling or financially unable to afford the systemic first-line treatment.

In this study, objective response rate (ORR) will be used as the primary efficacy endpoint. About 136 subjects are planned to be enrolled, among whom at least 80 (later increase to 120) subjects must have a history of systemic first-line treatment failure, and about 56 patients must have not received the systemic first-line treatment.

After being fully informed and signing informed consents, eligible subjects will receive apatinib 250 mg p.o., q.d. + SHR-1210 200 mg I.V., q2W, in treatment cycles, 4 weeks each cycle. Treatment will continue until the criteria for treatment discontinuation (as specified in the

protocol) are met. After discontinuation, subjects will continue safety follow-ups and survival follow-ups. Subjects who discontinue the treatment due to reasons other than progressive disease (PD)/death will also be followed for tumor progression after discontinuation.

After subjects are enrolled in the study, safety follow-up will be conducted before medication of SHR-1210 on D1 and D15 of each treatment cycle. After treatment begins, response will be assessed by imaging examination once every 2 weeks for the first 12 cycles, and once every 3 weeks afterwards until the end of treatment, withdrawal of informed consent, or death.

This study will also explore the anti-HBV efficacy of the combination therapy as well as biomarkers for predicting response. Subjects who have abnormal HBV test results at baseline will undergo regular HBV titer and HBsAg tests during the study. Subjects who provide informed consent for biomarker sample collection will have their blood and tumor specimens collected at baseline and during the study, including possibly a baseline biopsy. Some results of the exploratory biomarker study will be reported separately and not included in this clinical study report. The results from the exploratory biomarker study may be combined and analyzed with biomarker data from other studies of the investigational drug to formulate a hypothesis which will be further validated in future studies.

2.2. Study Objectives

2.2.1. Primary objectives

- To evaluate the ORR of SHR-1210 in combination with apatinib mesylate in patients with advanced hepatocellular carcinoma.

2.2.2. Secondary objectives

- To observe and evaluate the progression-free survival (PFS), duration of response (DOR), time to response (TTR), time to progression (TTP), disease control rate (DCR), overall survival (OS), as well as 6/9/12/15/18-month survival rates of SHR-1210 in combination with apatinib mesylate in patients with advanced hepatocellular carcinoma.
- To evaluate the safety of SHR-1210 in combination with apatinib mesylate in patients with advanced hepatocellular carcinoma.

2.2.3. Exploratory objectives

- To explore the anti-HBV effect of SHR-1210 in combination with apatinib mesylate.
- To explore biomarkers for predicting response.

2.3. Sample Size

This is a single-arm study with its primary efficacy endpoint being ORR. This study includes patients who have systemic first-line treatment failure and patients who have not received systemic first-line treatment. The sample sizes of patients in the two groups are respectively estimated based on the following assumptions.

Patients with systemic first-line treatment failure

Assuming that the standard treatment efficacy is no greater than 10%, that the efficacy of SHR-1210 in combination with apatinib mesylate is 25%, and that alpha = 0.05 (two-sided), 64 patients enrolled are able to achieve a power of at least 90%. If the dropout rate is 20%, 80 patients need to be enrolled.

In the late period of the trial, the number of patients who have systemic first-line treatment failure will be increased to 120 to observe the efficacy and safety of the investigational drug in more such patients.

Patients who have not received systemic first-line treatment

Assuming that the standard treatment efficacy is no greater than 15%, that the efficacy of SHR-1210 in combination with apatinib mesylate is 30%, and that alpha = 0.05 (two-sided), the enrollment of 56 patients can ensure that the half width of 95% confidence interval (CI) of overall ORR be no more than 12%.

3. STATISTICAL HYPOTHESIS AND DECISION RULE

Statistical hypothesis for patients with systemic first-line treatment failure is as follows:

Null hypothesis: ORR = 10%

Alternative hypothesis: ORR ≠ 10%

If the lower limit of 95% CI of ORR is greater than 10%, PD-1 antibody SHR-1210 in combination with apatinib can be considered effective in the treatment of advanced hepatocellular carcinoma with systemic first-line treatment failure.

The decision rule for patients who have not experienced systemic first-line treatment failure is as follows:

If the lower limit of 95% CI of ORR is greater than 15%, it suggests that PD-1 antibody SHR-1210 in combination with apatinib is effective in the treatment of advanced hepatocellular carcinoma without systemic first-line treatment failure.

4. STUDY ENDPOINTS

4.1. Efficacy Endpoints

Investigator evaluation is based on RECIST v1.1, and the independent review committee (IRC) is based on RECIST v1.1 and mRECIST to evaluate the following efficacy endpoints: ORR, DCR, TTR, TTP, DOR, and PFS; other efficacy endpoints include OS, 6/9/12/15/18-month survival rates, and TTF. In addition, new anti-cancer treatments mentioned in all efficacy endpoints do not include traditional Chinese medicine anti-cancer treatment with a duration of treatment of 14 days or less.

4.1.1. Primary efficacy endpoints

The primary efficacy endpoint in this study is objective response rate (ORR) assessed by IRC based on RECIST v1.1.

ORR: It refers to the proportion of all subjects whose best overall response (BOR) is assessed as complete response (CR) or partial response (PR) as per RECIST v1.1.

BOR refers to the best overall response assessed by IRC and recorded from the date of first administration to the date of first progression objectively recorded in accordance with RECIST v1.1 or to the date of initiation of new anti-cancer treatment (whichever occurs first). Subjects with first assessment as CR/PR should be reexamined 4 weeks later for confirmation. For subjects who have no recorded progression or initiation of new anti-cancer treatment, the BOR will be determined based on all efficacy assessment results.

4.1.2. Secondary efficacy endpoints

4.1.2.1. Objective response rate (ORR)

Secondary efficacy endpoints of ORR include the objective response rates assessed by the investigators based on RECIST v1.1 and by IRC based on mRECIST. Secondary efficacy endpoints of BOR include the best overall response assessed by the investigators based on RECIST v1.1 and by IRC based on mRECIST.

4.1.2.2. Disease control rate (DCR)

Disease control rate (DCR): It is defined as the proportion of all subjects receiving study treatment, whose BOR is assessed as CR, PR, and SD (SD occurs at least 6 weeks after first administration) by IRC or investigators as per RECIST v1.1 (or mRECIST).

4.1.2.3. Time to response (TTR)

Time to response (TTR): It is defined as the time from the date of first administration to the date of first recorded tumor response (assessed as per RECIST v1.1 or mRECIST) in subjects whose BOR is CR and PR.

4.1.2.4. Time to progression (TTP)

Time to progression (TTP): It is defined as the time from the date of first administration to the date of first occurrence of imaging PD (assessed by IRC or investigators as per RECIST v1.1 or mRECIST).

Censoring rules:

- If there is no baseline tumor measurement or there is baseline tumor measurement with absence of post-baseline tumor evaluation, censoring will be based on the date of first administration.
- If the subject does not have PD prior to the termination of the study/cut-off date for analyses or dropout and is not using a new anti-cancer drug prior to PD, censoring will be based on the date of the last valid efficacy evaluation.
- If a new anti-cancer treatment has been initiated before PD, censoring will be based on the date of the last valid efficacy evaluation prior to the new anti-cancer treatment.
- If death occurs before PD, censoring will be based on the date of the last valid efficacy evaluation prior to death.
- For PD after the absence of two or more planned visits (two visits are planned to be conducted at 26 weeks after 12 cycles of first administration and at 18 weeks prior to 12 cycles), censoring will be based on the date of the last valid efficacy evaluation prior to PD.
- For PD after the absence of two planned visits after first administration, censoring will be based on the date of first administration.

4.1.2.5. Duration of response (DOR)

Duration of response (DOR): It is defined as the time from the date of first recorded tumor response (RECIST v1.1 or mRECIST) to the date of first recorded tumor objective progression (RECIST v1.1 or mRECIST) or the date of death due to any cause, whichever occurs first, in subjects whose BOR is CR and PR.

Censoring rules:

- If there is no baseline tumor measurement or there is baseline tumor measurement with absence of post-baseline tumor evaluation, censoring will be based on the date of first administration.
- If the subject does not have PD or die prior to the termination of the study/cut-off date for analyses or dropout and is not using a new anti-cancer drug prior to PD or death, censoring will be based on the date of the last valid efficacy evaluation.
- If a new anti-cancer treatment has been initiated before PD or death, censoring will be based on the date of the last valid efficacy evaluation prior to the new anti-cancer treatment.
- For death or progression with the absence of two or more planned visits (two visits are planned to be conducted at 26 weeks after 12 cycles of first administration and at 18 weeks prior to 12 cycles), censoring will be based on the date of the last valid efficacy evaluation prior to death or progression.
- For death or PD with the absence of two planned visits after first administration, censoring will be based on the date of first administration.

4.1.2.6. Progression-free survival (PFS)

Progression-free survival (PFS): It is defined as the time from the date of first administration to the date of first recorded tumor progression (assessed as per RECIST v1.1 or mRECIST) or the date of death due to 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 administration.
- If the subject does not have PD or die prior to the termination of the study/cut-off date for analyses or dropout and is not using a new anti-cancer drug prior to PD or death, censoring will be based on the date of the last valid efficacy evaluation.
- If a new anti-cancer treatment has been initiated before PD or death, censoring will be based on the date of the last valid efficacy evaluation prior to the new anti-cancer treatment.

- For death or progression with the absence of two or more planned visits (two visits are planned to be conducted at 26 weeks after 12 cycles of first administration and at 18 weeks prior to 12 cycles), censoring will be based on the date of the last valid efficacy evaluation prior to death or progression.
- For death or PD with the absence of two planned visits after first administration, censoring will be based on the date of first administration.

4.1.2.7. Overall survival (OS)

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

Censoring rules are as follows:

- If the subject withdraws and is still alive, the censoring date is the last follow-up date when the survival status is obtained.
- If the subject is lost to follow up, the censoring date is the last follow-up date when the survival status is obtained prior to the lost of follow-up.

4.1.2.8. 6/9/12/15/18-month overall survival (6/9/12/15/18-month OS%)

It is defined as the 6/9/12/15/18-month overall survival (OS) after the date of first administration. The 6/9/12/15/18-month OS will be estimated by Kaplan-Meier method.

4.1.2.9. Time to treatment failure (TTF)

Time to treatment failure (TTF): It is defined as the time from the date of first administration to the date of treatment termination or death.

Censoring rules are as follows:

- If the treatment is unterminated, the censoring date will be the date of the last survival.

4.2. Safety Endpoints

4.2.1. Adverse events

Treatment-emergent adverse events (TEAEs) are defined as any adverse events (AEs) that are new or worse than those at baseline (before treatment) after initiation of the study drugs.

4.2.2. Laboratory test

The laboratory test data of hematology, blood biochemistry, urinalysis, routine stool test, coagulation function test, thyroid function test, pituitary adrenal axis examination, viral examination, alpha fetoprotein, and pregnancy test will be collected at protocol-specified visit time points.

4.2.3. Vital signs

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

4.2.4. Electrocardiogram (ECG)

The data of heart rate, PR, QT, QTc, and QRS will be collected at protocol-preset time points.

4.2.5. Physical examination

Physical examination includes general condition, head and face, skin, lymph nodes, eyes, ears, nose, throat, mouth, respiratory system, cardiovascular system, abdomen (including liver and spleen), reproductive-urinary system, musculoskeletal system, nervous system, mental condition, and others. These data will be collected at protocol-specified visit/time points.

4.2.6. Other safety endpoints

Ultrasound cardiogram, ECOG PS, and other examinations.

4.3. Exploratory Endpoints

4.3.1. Pharmacokinetics and pharmacodynamics

Not applicable.

4.3.2. Immunogenicity

Not applicable.

4.3.3. Quality of life index

Not applicable.

4.3.4. Biomarker

To explore the relationship between baseline alpha fetoprotein level and efficacy.

To explore the relationship between PD-L1 expression level in tumor tissue and efficacy.

4.3.5. Other exploratory endpoints

To explore the HBsAg loss during the trial.

5. STATISTICAL ANALYSIS

5.1. General Considerations

5.1.1. Analysis sets

5.1.1.1. Full analysis set (FAS)

The analysis set is based on the intention-to-treat principle. All enrolled subjects who have at least one medication record are included in this analysis set. The full analysis set is the primary analysis set for the efficacy analysis of this study.

5.1.1.2. Safety analysis set (SS)

All enrolled subjects who have received the study drugs at least once are included in the safety analysis set. This dataset is used for safety analysis.

5.1.1.3. Evaluable analysis set (ES)

All enrolled subjects who have received at least one study dose and at least one effective post-baseline imaging evaluation are included in this analysis set.

5.1.1.4. PD-L1 analysis set (PD-L1)

All enrolled subjects who have at least one medication record and have tumor biopsy samples for PD-L1 expression level detection are included in this analysis set.

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 use of the study drugs, including the measurements taken on the day of and prior to the first dose.

Study day

The date of first administration is defined as the starting date of the study (Day 1) and the starting date of the study as the basis. The study days corresponding to the examination or event are calculated according to the following formula:

- If the examination/event date is prior to the starting date of the study, the study days = the examination date - the starting date of the study;
- If the examination/event date is on or after the starting date of the study, the study days = the examination date - the starting date of the study + 1.

General analysis

Unless otherwise specified, the following descriptive statistical summary will be given according to variable type:

- The continuous variables are summarized by using mean, standard deviation, median, maximum, minimum, and quartile.
- The categorical variables are summarized by frequency and percentage.
- The time-to-event data: Kaplan-Meier method is used to estimate the survival function and the median time to event occurrence, and the survival curve is drawn.

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 raw data to be acquired; there should be one additional decimal place for the mean and median, and 2 additional decimal places for standard deviation, up to 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".
- If there is a decimal in 95% CI, at least 2 decimal places and at most 4 will be retained. Details are as follows: The 95% CI has one more decimal place than that of the raw data. If the raw data have no decimal place, the 95% CI will retain 2 decimal places; if the raw data have 4 or more decimal places, the 95% CI will retain at most 4 decimal places.
- For time to event occurrence (month), one decimal place will be retained.

Analysis software

All statistical analyses will be performed on the statistical analysis software SAS® v9.4.

Results of laboratory tests

The results of laboratory tests are generally continuous numerical variables or character variables. If continuous numerical variables recorded in eCRF contain special characters (such as < xx and > xx), the following rules will be applied:

(1) When < xx or ≤ xx appears, half value of xx will be taken for analysis.

(2) When > xx or ≥ xx appears, the value of xx will be taken for analysis.

5.1.3. Derived variables

Refer to Section 5.5.1 "Extent of exposure" for the derived variables related to study drug exposure information, and for other derived variables, refer to the corresponding definition of derived rules in each section for details.

5.1.4. Covariates and subgroups

Subgroup variables involved in the statistical analysis of this trial:

Age, gender, baseline ECOG PS, extrahepatic metastasis, vascular invasion, BCLC stage, body weight, HBV infection, baseline alpha fetoprotein level, etc. See Section 5.4.4 "Subgroup analysis" for details.

5.1.5. Analysis window

For analysis that needs to be summarized according to the visits (visits after baseline, see Section 5.1.2 for the definition of baseline), it will be summarized based on the protocol visits filled in eCRF without considering whether the examination has exceeded the protocol-specified visit time window.

When safety analysis is conducted according to the visit, statistical analysis will be performed based on the planned protocol visit time points, that is, there is no need to present the unplanned protocol time points.

5.1.6. Missing data

If the missing date and month needs to be imputed, they will be imputed in accordance with the Hengrui imputation rules for date-type data. The following imputation rules apply only to the missing data for AE occurrence date, first tumor pathology diagnosis date, system treatment history starting date, new anti-cancer treatment starting date, and death date. Other missing dates such as those for laboratory test, electrocardiogram examination, and vital signs will not be imputed.

5.1.6.1. Adverse events

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

- If the starting 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 starting 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 starting 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 starting date of the AE is missing, it will be imputed with 1.
- If only the day of the ending 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, the date will be imputed with the date of death.
- In other cases, if the ending date of the AE is missing, the date will not be imputed.

5.1.6.2. Medical history

If the date of past medical history (that is before first administration of the study drugs including first tumor pathological diagnosis date and others) is missing, the rules for imputing the date are as follows:

- If the day is missing, the day will be imputed with 1 of the 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.

5.1.6.3. Starting date of systemic treatment history

If the starting date of systemic treatment history is missing, the rules for imputing the date are as follows:

- If the day is missing, the day will be imputed with 1 of the 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.

5.1.6.4. Starting date of new anti-cancer treatment

If the starting date of new anti-cancer treatment is incomplete, the rules for imputing the date are as follows:

- If the ending date of new anti-cancer treatment is partially missing or not missing, the ending date will be used to derive the starting date of new anti-cancer treatment:
  - If only month and day of the ending date of new anti-cancer treatment are missing but the year is not missing, the month and day will be imputed with 31 Dec. as the ending date of new anti-cancer treatment.
  - If only day of the ending date of new anti-cancer treatment is missing but the year and month are not missing, the day will be imputed with the last day of the month as the ending date of new anti-cancer treatment.
- If the starting date of new anti-cancer treatment is completely or partially missing, the rules for deriving and imputing the date are as follows:
  - The starting date of new anti-cancer treatment is completely missing

The starting date imputed = min [max (first PD date + 1, the date of last administration + 1), the ending date of new anti-cancer treatment]

- Only the year (YYYY) of the starting date of new anti-cancer treatment is not missing

1) If YYYY < min (year) [max (first PD date + 1, the date of last administration + 1), the ending date of new anti-cancer treatment], the starting date will be imputed with 31 Dec., YYYY;
2) If YYYY = min (year) [max (first PD date + 1, the date of last administration + 1), the ending date of new anti-cancer treatment], the starting date will be imputed with min [max (first PD date + 1, the date of last administration + 1), the ending date of new anti-cancer treatment];
3) If YYYY > min (year) [max (first PD date + 1, the date of last administration + 1), the ending date of new anti-cancer treatment], the starting date will be imputed with 1 Jan., YYYY.

- The year (YYYY) and month (MM) of the starting date of new anti-cancer treatment are not missing

1) If YYYY = min (year) [max (first PD date + 1, the date of last administration + 1), the ending date of new anti-cancer treatment] and MM < min (month) [max (first PD date + 1, the date of last administration + 1), the ending date of new anti-cancer treatment], the starting date will be imputed with the last day of MM-MM-YYYY;

2) If YYYY = min (year) [max (first PD date + 1, the date of last administration + 1), the ending date of new anti-cancer treatment] and MM = min (month) [max (first PD date + 1, the date of last administration + 1), the ending date of new anti-cancer treatment], the starting date will be imputed with min [max (first PD date + 1, the date of last administration + 1), the ending date of new anti-cancer treatment];

3) If YYYY = min (year) [max (first PD date + 1, the date of last administration + 1), the ending date of new anti-cancer treatment] and MM > min (month) [max (first PD date + 1, the date of last administration + 1), the ending date of new anti-cancer treatment], the starting date will be imputed with 01-MM-YYYY;

4) If YYYY < min (year) [max (first PD date + 1, the date of last administration + 1), the ending date of new anti-cancer treatment], the starting date will be imputed with the last day of MM-MM-YYYY;

5) If YYYY > min (year) [max (first PD date + 1, the date of last administration + 1), the ending date of new anti-cancer treatment], the starting date will be imputed with 01-MM-YYYY.

5.1.6.5. Date of death

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

- If the date of death is completely missing, the last date of survival + 1 is used to impute the date of death
- If the day or both month and day are missing, the date of death = max (the last date of survival + 1, the following date imputed)
  - The day is missing: 01-MM-YYYY
  - The month and day are missing: 01-01-YYYY

5.2. Study Subjects

The population involved in the statistical analysis in the study subjects section is based on all populations who have and have not received systemic first-line treatment, as well as all enrolled subjects.

5.2.1. Disposition of subjects

For all subjects who have signed the informed consent and participated in screening period, descriptive summary will be conducted to summarize the screening status of population subjects, including the number and percentage of screening failures, which will be categorized by the reasons of screening failure.

All enrolled subjects are summarized using frequency and percentage, based on the population who have and have not received systemic first-line treatment, as well as the total population.

In addition, in the disposition of subjects, the frequency and percentage will be summarized for the following information according to the grouped population and the total population:

- Number of enrolled subjects (number of subjects receiving the treatment/number of subjects not receiving the treatment);
- Number of subjects discontinuing the treatment/reasons for treatment discontinuation;
- Number of subjects discontinuing the study/reasons for study discontinuation;
- Number of subjects in each analysis set (full analysis set, safety analysis set, evaluable analysis set, and PD-L1 analysis set).

5.2.2. Demographics

Descriptive statistical summary is conducted by age, gender, ethnicity, body height [cm], weight [kg], body mass index (BMI) [kg/m^2], and others of subjects. A detailed listing is provided.

The continuous variables such as age, body height, weight, and BMI are summarized by using descriptive statistics such as the number of evaluable subjects (n), mean, standard deviation, median, minimum (min), maximum (max), and quartile (Q1 and Q3).

Gender, ECOG PS, Child-Pugh score classification (5 and 6 points), HBV infection (baseline positive HBsAg), baseline alpha fetoprotein level (< 200 ng/mL and ≥ 200 ng/mL; < 400 ng/mL and ≥ 400 ng/mL), drinking history (yes, no, unknown), and other categorical variables are descriptively summarized by using the number of evaluable subjects and the percentage of corresponding total number of subjects.

Descriptive statistics such as median, quartile (Q1 and Q3), maximum, and minimum of baseline sum of target lesion diameter values (IRC assessment) and baseline sum of target lesion diameter values (investigator assessment) are summarized.

The age will be calculated as the number of full years between the date of birth and the signing date of the informed consent. Age (years) = (date of singing the informed consent - date of birth) / 365.25, and one decimal place will be reserved.

The BMI calculation formula is: BMI (kg/m^2) = baseline weight (kg) / baseline body height (m^2).

5.2.3. Tumor diagnosis

Related descriptive statistics are used to summarize the following tumor indexes: the number and percentage of subjects under each disease name/symptom. In addition, number of subjects and percentage of the degree of differentiation, presence of extrahepatic metastasis, presence of vascular invasion, Barcelona stage, presence of cirrhosis of liver, clinical T/N/M stage, and course of disease (month) in each group will be summarized separately. A detailed list of subjects for tumor diagnosis is provided.

The course of disease (month) is defined as the time from the date of first pathological diagnosis to the date before first administration. The calculation formula is: (The date of first administration - the date of first pathological diagnosis + 1) / 30.4375.

5.2.4. Medical history

Medical history is summarized separately according to populations. In addition, a detailed list of subjects is provided.

5.2.5. Tumor treatment history

Tumor treatment history mainly includes history of tumor surgery, radiotherapy, interventional therapy, local ablation therapy, other local treatments and systemic treatment.

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 any local treatments (surgery, radiotherapy, interventional therapy, local ablation or other local treatments)
- Number and percentage of subjects who have previously received any local treatments (radiotherapy, interventional therapy, local ablation or other local treatments)
- Number and percentage of subjects who have previously received any local treatments (surgery, interventional therapy, and local ablation)
- Number and percentage of subjects who have previously received tumor surgery

- Number and percentage of subjects who have previously received radiotherapy
- Number and percentage of subjects who have previously received interventional therapy
- Number and percentage of subjects who have previously received local ablation therapy
- Number and percentage of subjects who have previously received systemic therapy
- Number and percentage of subjects who have previously received other local treatments
- Number and percentage of subjects who have previously received systemic therapy with different treatment outcomes (outcomes of first use of sorafenib)

In addition, a detailed list of subjects is provided.

5.2.6. Prior therapy and concomitant medication

All previous medication, concomitant medication, and concomitant non-drug therapy are listed. ATC1 and verbatim terms are summarized separately according to the coded information of prior and concomitant medication.

5.2.7. Protocol deviations

All protocol deviations are recorded, classified, and summarized in a list. Prior to database locking, all protocol deviations are reviewed and discussed by relevant researchers and investigators of the sponsor project team.

Protocol deviations are classified as "critical", "major", and "general".

Critical and major protocol deviations are summarized according to the types of deviations and the enrolled population. Protocol deviations will also be listed in detail by subject.

5.3. Treatment Compliance

The use of study drugs SHR-1210 and apatinib in the treatment period is summarized by descriptive statistics. Treatment compliance is summarized by using indexes such as relative dose intensity value.

5.4. Efficacy Analysis

ORR and DCR are analyzed based on FAS and ES. Other efficacy analyses are performed based on FAS.

All efficacy analyses are performed according to the following populations (population with systemic first-line treatment, population without systemic first-line treatment, and total population).

5.4.1. Primary efficacy analysis

The primary efficacy endpoint in this study is objective response rate (ORR) assessed by IRC based on RECIST v1.1. Full analysis set is the primary analysis set.

5.4.1.1. Objective response rate (ORR)

See Section 4.1.1 for the definition of objective response rate.

For the primary endpoint ORR, the proportion of all enrolled subjects whose best overall response (BOR) is assessed as complete response (CR) or partial response (PR) as per RECIST v1.1 is descriptively summarized. The ORR is calculated along with the corresponding two-sided 95% CI calculated using the Clopper-Pearson method. Data of best overall response evaluation will be listed and summarized.

5.4.2. Secondary efficacy analysis

5.4.2.1. Objective response rate (ORR)

For secondary endpoints, ORRs assessed by investigators based on RECIST v1.1 and by IRC based on mRECIST are analyzed by using the aforementioned statistical methods for primary efficacy analysis.

5.4.2.2. Progression-free survival (PFS)

See Section 4.1.2.6 for the definition of progression-free survival (PFS).

Secondary endpoint PFS is calculated in months by using the following formula: (PFS event date/censoring date - date of first administration + 1) / 30.4375.

Kaplan-Meier method is used to analyze PFS, and the median time (month) of PFS is calculated. Brookmeyer-Crowley method is used to estimate the two-sided 95% CI of median time, and the PFS curve is drawn. The 6/9/12-month PFS rates are estimated by Kaplan-Meier method, and the corresponding 95% CIs are calculated using the log-log transformation according to normal distribution approximation with back transformation to CIs on the untransformed scale. The number and percentage of subjects with PFS of at least 6/9/12 months are calculated.

At the same time, the number and percentage of PFS events as well as the censoring number and percentage are calculated and classified according to the reason for censoring.

5.4.2.3. Time to response (TTR)

See Section 4.1.2.3 for the definition of time to response (TTR).

The calculation of secondary endpoint TTR only includes subjects showing a response. TTR is calculated in months by using the following formula: (TTR event date - date of first administration + 1) / 30.4375.

TTR (month) is described by mean, standard deviation, median, maximum, minimum, and quartile (Q1 and Q3) according to the population.

5.4.2.4. Time to progression (TTP)

See Section 4.1.2.4 for the definition of time to progression (TTP).

Secondary endpoint TTP is calculated in months by using the following formula: (TTP event date/censoring date - date of first administration + 1) / 30.4375.

Kaplan-Meier method is used to analyze TTP, and the median time (month) of TTP is calculated. Brookmeyer-Crowley method is used to estimate the two-sided 95% CI of median time, and the survival curve is drawn. The number and percentage of subjects with TTP of at least 6/9/12 months are calculated.

At the same time, the number and percentage of TTP events as well as the censoring number and percentage are calculated and classified according to the reason of censoring.

5.4.2.5. Duration of response (DOR)

See Section 4.1.2.5 for the definition of duration of response (DOR).

Secondary endpoint DOR is calculated in months by using the following formula: (DOR event date/censoring date - date of first response + 1) / 30.4375.

DOR is analyzed only in subjects who have the best overall response of tumor response after treatment. The ending date of response must be consistent with the date of PD of PFS or death. Kaplan-Meier method is used to calculate the median DOR in each treated population. Brookmeyer-Crowley method is used to estimate the two-sided 95% CI of median time, and the survival curve is drawn. The 6/9/12-month DOR rates are estimated by Kaplan-Meier method, and the corresponding 95% CIs are calculated using the log-log transformation according to normal distribution approximation with back transformation to CIs on the untransformed scale. The response date is the date of the first observed response.

In addition, descriptive statistics such as the number of subjects, minimum, maximum, and quartile (Q1 and Q3) are used to summarize the DOR data. If the maximum values are the censoring data, they will be displayed in the form of "xx+". The number and percentage of subjects with DOR of at least 6/9/12 months are calculated. At the same time, the number and percentage of DOR events as well as the censoring number and percentage are calculated and classified according to the reason of censoring.

5.4.2.6. Disease control rate (DCR)

See Section 4.1.2.2 for the definition of disease control rate (DCR).

The analysis method of secondary endpoint DCR is the same as that of ORR.

5.4.2.7. Overall survival (OS)

See Section 4.1.2.7 for the definition of overall survival (OS).

OS is calculated in months by using the following formula: (OS event date/censoring date - date of first administration + 1) / 30.4375.

Kaplan-Meier method is used to analyze OS, and the median survival time of each treated population is calculated. Brookmeyer-Crowley method is used to estimate the two-sided 95% CI of median time, and the overall survival curve is drawn. Follow-up time (month) is described by the number of subjects, median, maximum, minimum, and quartile (Q1 and Q3) according to the population. If the maximum values are the censoring data, they will be displayed in the form of "xx+".

At the same time, the number and percentage of OS events as well as the censoring number and percentage are calculated and classified according to the reason of censoring.

5.4.2.8. Overall survival rate (OS%)

See Section 4.1.2.8 for the definition of 6/9/12/15/18-month survival rates.

The 6/9/12/15/18-month survival rates are analyzed by Kaplan-Meier method, and the corresponding 95% CIs are calculated using the log-log transformation according to normal distribution approximation with back transformation to CIs on the untransformed scale.

5.4.2.9. Time to treatment failure (TTF)

See Section 4.1.2.9 for the definition of time to treatment failure (TTF).

Secondary endpoint TTF is calculated in months by using the following formula: (TTF event date/censoring date - date of first administration + 1) / 30.4375.

Kaplan-Meier method is used to analyze TTF, and the median TTF (month) is calculated. Brookmeyer-Crowley method is used to estimate the two-sided 95% CI of median time, and the survival curve is drawn.

At the same time, the number and percentage of TTF events as well as the censoring number and percentage are calculated.

5.4.3. Exploratory analyses

See Section 5.4.5.

5.4.4. Subgroup analysis

In order to evaluate whether the efficacy of this study is consistent among various subgroups, ORR, PFS (evaluated by IRC based on RECIST v1.1), and OS in the following subgroups are analyzed based on FAS. ORR, PFS, OS and 95% CI of each subgroup are estimated, and forest plot of ORR is drawn. The analysis method is the same as those in Sections 5.4.1 and 5.4.2:

- Age (< 65 years, ≥ 65 years)
- Gender (male, female)
- Baseline ECOG PS (0 points, 1 point)
- Extrahepatic metastasis (yes, no)
- Vascular invasion (yes, no)
- Child-Pugh score (5 points, 6 points)
- BCLC stage (stage B, stage C)
- Weight (< 60 kg, ≥ 60 kg)
- HBV infection (yes, no)
- Baseline alpha fetoprotein level (< 400 ng/mL, ≥ 400 ng/mL)
- Baseline alpha fetoprotein level (< 200 ng/mL, ≥ 200 ng/mL)

5.4.5. Other analyses

Based on FAS, the best post-baseline changes in the sum of target lesion diameter values from baseline over time is plotted (i.e. waterfall plot, which is grouped by the best overall response).

Based on FAS, the swimmer plots of objective response and disease control are drawn. A swimmer plot of treatment and survival status of subjects who continue treatment after PD is drawn.

Based on FAS, the consistency of imaging PD events in each group is analyzed according to the consistency analysis of IRC and investigator assessment (LE) among different populations. Similar analyses are carried out for CR/PR consistency and BOR consistency of imaging assessment in each group.

Based on FAS, the change of target lesions of subjects with best overall response of CR/PR/SD (assessed by IRC based on RECIST v1.1) from baseline over time is plotted (i.e., spider plot).

Based on FAS, the change of target lesions of subjects who continue study drug therapy after PD (assessed by investigators based on RECIST v1.1) from baseline against time is plotted (i.e., spider plot).

Based on FAS, HBsAg loss is defined as the number and percentage of subjects who have positive baseline value and any negative post-baseline test values.

Based on FAS, the overall survival curve is plotted according to different populations and grouped by CR + PR, SD, and PD according to best overall response (best overall response is assessed by IRC based on RECIST v1.1, excluding subjects with the best overall response of NE).

The information of subsequent post-withdrawal anti-cancer therapy (including chemotherapy, radiotherapy, target therapy, surgery, interventional procedure, traditional Chinese medicine, and other categories) used after treatment discontinuation is summarized to analyze whether the anti-cancer therapy used after treatment discontinuation in each population is balanced, and listed. In addition, the duration (month) of a particular category of subsequent post-withdrawal anti-cancer therapy (chemotherapy, target therapy, and immunotherapy) after treatment discontinuation is summarized by using descriptive statistics such as number of subjects (n), mean, standard deviation, median, quartile (Q1 and Q3), minimum (min), and maximum (max).

5.5. Safety Analysis

All safety analyses are conducted based on safety analysis set.

5.5.1. Extent of exposure

Extent of exposure mainly for drug exposure duration, planned treatment time, cycle length, actual cumulative dose per cycle, actual cumulative doses of all cycles, actual dose intensity per cycle, actual dose intensity, relative dose intensity per cycle, and relative dose intensity of SHR-1210 and apatinib is summarized by using mean, standard deviation, median, maximum, minimum, and quartile, and the medication intensity per cycle and overall medication intensity for each subject are listed.

In addition, only the number of use of SHR-1210 is calculated and summarized by using mean, standard deviation, median, maximum, and minimum. The number and percentage of subjects who receive SHR-1210 treatment for ≥ 6 months and ≥ 12 months and subjects who receive apatinib treatment for ≥ 6 months and ≥ 12 months are calculated, respectively.

See Table 1 for the specific definition rules of derived variables of study drugs SHR-1210 and apatinib.

Table 1. Derived variables of SHR-1210 and Apatinib

Variable	SHR-1210	Apatinib
Protocol-specified method of administration	Administration once per two weeks, 200 mg or 3 mg/kg each time, and every 4 weeks for a cycle	Administration once per day, 250 mg each time, and every 4 weeks for a cycle
Duration of drug exposure (days)	Date of last administration - date of first administration + 14	Date of last administration - date of first administration + 1
Planned duration of treatment (days)	Date of last administration - date of first administration + 14	Date of last administration - date of first administration + 1
Cycle length (weeks)	Except for the last cycle: (Actual starting date of next cycle - 1 - actual starting date of the cycle + 1) / 7; Last cycle: (Date of last administration + 14 - actual starting date of the cycle) / 7	Except for the last cycle: (Actual starting date of next cycle - 1 - actual starting date of the cycle + 1) / 7; Last cycle: (Date of last administration + 1 - actual starting date of the cycle) / 7
Actual cumulative dose per cycle (mg)	Actual administration dose (mg) during a cycle is summarized, and each actual administration dose is recorded in CRF	
Actual cumulative doses of all cycles (mg)	Actual administration doses (mg) during all cycles are summarized	
Planned cumulative dose per cycle (mg)	200 (mg) ×2 = 400 (mg)*	250 (mg) ×28 = 7000 (mg)*
Actual dose intensity per cycle (mg/4-week cycle)	Actual cumulative dose per cycle (mg) / [cycle length (weeks) / 4]	
Actual dose intensity (mg/4-week cycle)	Actual cumulative doses of all cycles (mg) / [planned treatment time (weeks) / 4]	
Planned dose intensity per cycle (mg/4-week cycle)	Planned cumulative dose per cycle (mg) / [1 (4-week cycle)] = 400 (mg/4-week cycle)**	Planned cumulative dose per cycle (mg) / [1 (4-week cycle)] = 7000 (mg/4-week cycle)
Planned dose intensity (mg/4-week cycle)	400 (mg/4-week cycle)***	7000 (mg/4-week cycle)
Relative dose intensity per cycle (%)	100 ×[Actual dose intensity per cycle (mg/4 -week cycle)] / [Planned dose intensity per cycle (mg/4-week cycle)]	
Relative dose intensity (%)	100 ×[Actual dose intensity (mg/4 -week cycle)] / [Planned dose intensity (mg/4-week cycle)]	

*: If the baseline weight of the subject is < 50 kg, the planned cumulative dose per cycle (mg) = 3 (mg/kg) × baseline weight (kg) ×2 = 6 ×baseline weight (mg);

**: If the baseline weight of the subject is < 50 kg, the planned dose intensity per cycle (mg/4-week cycle) = 6 × baseline weight (mg/4-week cycle)

***: If the baseline weight of the subject is < 50 kg, the planned dose intensity (mg/4-week cycle) = 6 ×baseline weight (mg/4-week cycle).

5.5.2. Adverse events

All AEs are encoded by using MedDRA v24.0 and graded using NCI-CTCAE v4.03. For the same SOC and/or PT, multiple cases of the same events occurred 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.

Treatment-emergent adverse events (TEAEs) are defined as any adverse events (AEs) that are new or worse than those at baseline (before treatment) after initiation of the study drugs. Only TEAEs will be summarized, and all AEs will be listed.

Drug-related TEAE (ADR) is defined as TEAE having the causal relationship of *"treatment-related"* with study drugs. In this trial, the definition of *"treatment-related"* is as follows: It refers to the relationship with the study drugs: related, possibly related, and unassessable. If the relationship between the AE and the study drugs is missing, the AE will be considered as an ADR.

AEs will be ranked from high to low according to the proportion of SOC/Cluster occurrence (total populations receiving the treatment), from high to low according to the proportion of PT under SOC (total populations receiving the treatment), and in alphabetical order if the incidences of at least 2 PTs are equal. If there is no AE under an SOC/Cluster or PT, the analysis will not be performed. Refer to Appendices 4 and 5 for the definition of Cluster classification.

In AE summary table, AEs after study drug treatment are analyzed according to the population, and the frequency and proportion are used for statistical description. AEs will be summarized using descriptive statistics according to Hengrui's Statistical Analysis Reporting Standards, including but not limited to the following contents:

- Any TEAE
- Treatment-related TEAE
- Any TESAE
- Treatment-related TESAE
- Grade ≥ 3 TEAE according to CTCAE grading
- Grade ≥ 3 treatment-related TEAE according to CTCAE grading
- Any TEAE ≥ 5%
- Treatment-related TEAE ≥ 5%
- TEAE leading to SHR-1210 treatment discontinuation and interruption

- TEAE leading to apatinib treatment discontinuation, treatment interruption, and dose reduction
- TEAE leading to death
- TEAE of special interest (AESI, the preferred term for AE provided by medical monitor, see Appendix 2 for details; other Grade ≥ 3 immune-related adverse events (irAEs): meeting irAE definition requirements and Grade ≥ 3 according to CTCAE v4.03)
- Immune-related TEAE (irAE, including two categories: 1) AE that the investigators determine to be related to SHR-1210 (including definitely related, possibly related, and indeterminable) and corrected with glucocorticoid drugs (except reactive capillary endothelial proliferation); 2) other irAEs that the investigators determine to be related to SHR-1210 without the use of glucocorticoids, with the preferred term for AE provided by medical monitor, see Appendix 3 for details)
- The selected TEAE (the preferred term for AE provided by medical monitor, see Appendix 4 for details)
- The selected TEAE that the investigators determine to be related to SHR-1210 (the preferred term for AE provided by medical monitor, see Appendix 5 for details) and glucocorticoid utilization rate
- No subject with TEAE leading to interruption, dose reduction, and termination of two drugs
- TEAE leading to treatment interruption (apatinib or SHR-1210)
- TEAE leading to treatment termination of two drugs

The incidence of AE is calculated based on the number of subjects having an AE, instead of the number of AE episodes.

AESIs include:

- Grade ≥ 3 infusion reaction
- Grade ≥ 2 diarrhea/colitis, uveitis, and interstitial pneumonia
- Other Grade ≥ 3 irAEs
- Liver enzyme abnormal event: ALT, AST, and total bilirubin (TBIL) are abnormal against baseline
- Grade 4 amylase or lipase increased
- Reactive capillary endothelial proliferation

Among them, the specific definition of liver enzyme abnormal events is as follows:

Baseline Period	Normal (AST/ALT and TBIL)	Abnormal (AST/ALT/TBIL)
Treatment Period	ALT or AST ≥ 3 × ULN with TBIL ≥ 2 × ULN and ALP ≤ 2 × ULN and without hemolysis	AST or ALT ≥ 2 × baseline level, and ≥ 3 × ULN or AST or ALT ≥ 8 × ULN with TBIL increase ≥ 1 × ULN or TBIL ≥ 3 × ULN

The selected AEs are analyzed separately. For each selected AE, the time to first event (weeks) is summarized in the form of continuous variables, that is, mean, standard deviation, median, maximum, minimum, and quartile (Q1 and Q3) are used for the summary. The greatest grade and the measures taken to study drugs are summarized in the form of categorical variables. The events are also summarized according to factors such as TEAE severity and TEAE occurrence cycle, respectively. The number and percentage of subjects who experience each selected AE and have been resolved are summarized.

The calculation method for the cycle length of TEAE which occurs is:

(Starting date of TEAE - date of first administration + 1) / 28 + 1, and the integer part will be retained;

Time to first event (weeks) = (date of first event occurrence - date of first administration + 1) / 7.

All AEs will be listed. Treatment-related AEs, AEs that result in treatment termination, AEs that result in treatment delay or dose reduction, and death will be listed separately.

5.5.3. Laboratory evaluations

Baseline laboratory test is defined as the latest non-missing test result prior to the first dose of the study drugs.

The worst grades (normal, abnormal without clinical significance, and abnormal with clinical significance) of baseline and post-baseline laboratory tests in hematology, blood biochemistry, blood lipase, blood amylase, urinalysis, stool routine, coagulation function test, thyroid function test, myocardial zymogram, pituitary adrenal axis test, and alpha fetoprotein are summarized by using shift table. 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. For continuous variables, the laboratory tests and changes from baseline values will be summarized by scheduled time point using descriptive statistics, such as number of subjects (n), arithmetic mean, standard deviation (SD), median, minimum (Min), and maximum (Max).

All laboratory measurements will be listed by subject ID, among which, abnormal values will be marked with H/L and indicated for clinical significance if any.

Virological examination and pregnancy test results will be listed.

Unplanned single test result will be listed.

5.5.4. Vital signs

Vital signs will be summarized using descriptive statistics.

All vital signs will be listed in detail.

5.5.5. Electrocardiogram

If 12-lead ECG at baseline is abnormal, it will be performed multiple times a day, and mean will be used as the baseline value. Investigation items of ECG include: HR (beats/min), PR interval (ms), QT interval (ms), QTc (ms), and QRS (ms).

The analysis of worst grades of the measurements at baseline and post-baseline or clinical significance will be summarized by shift table. Clinical significance includes normal, abnormal without clinical significance, and abnormal with clinical significance.

The observed values of each ECG variable at each test time point are analyzed by using descriptive statistics.

Test Item	Unit		Criteria for Abnormality
PR	ms	Post-baseline maximum	max. ≥ 300
		Change from baseline	Baseline > 200 and maximum increase from baseline ≥ 25%, or, baseline ≤ 200 and maximum increase from baseline ≥ 50%
QTcF	ms	Post-baseline maximum	max. < 450 450 ≤ max. < 480 480 ≤ max. < 500 max. ≥ 500
		Change from baseline	max. < 30 30 ≤ max. < 60 max. ≥ 60

For ECG parameters such as heart rate, PR interval, QT interval, and QTcF, the results at each test time point are summarized descriptively.

Detailed test results of ECG will be listed.

5.5.6. ECOG PS

The baseline and post-baseline maximum grades of ECOG PS are summarized and the ECOG PS at each visit is summarized.

All ECOG PS scores are reported in a list.

5.5.7. Physical examination

Data of physical examination are listed.

5.5.8. Other safety measures

Data of echocardiogram and other laboratory tests are listed.

5.6. Exploratory Analyses

5.6.1. Immunogenicity

None.

5.6.2. Quality of life index

None.

5.6.3. Other exploratory analysis

Based on the PD-L1 analysis set, grouping is performed according to different expression levels of PD-L1 (based on the staining ratio < 1% or ≥ 1%) to explore the relationship with efficacy (number of objective response and PFS events), and *P* values are calculated based on chi-square tests. In addition, the efficacy data of patients with expression level of PD-L1 of < 1% or ≥ 1% are listed.

5.7. Pharmacokinetics and Pharmacodynamics

None. If applicable, PK parameters and drug exposure-response are analyzed and reported separately by the department of clinical pharmacology.

6. INTERIM ANALYSIS

None.

7. REFERENCES

None.

8. APPENDICES

Appendix 1.1 Time Point Response: Subjects with Target Lesions (Including or Excluding Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response at the Time Point
CR	CR	Non	CR
CR	Non-CR/Non-PD	Non	PR
CR	Not evaluable	Non	PR
PR	Non-PD or not all evaluable	Non	PR
SD	Non-PD or not all evaluable	Non	SD
Not all evaluable	Non-PD	Non	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable

If the tumor efficacy evaluation at a visit is completed within several days, and if the evaluation result of the visit is PD, the efficacy evaluation date is the earliest imaging examination date of PD among the target lesion, non-target lesion, and new lesion. If the evaluation result of this visit is non-PD (CR/PR/SD/NE), then the date of efficacy evaluation is calculated according to the latest imaging examination date of this visit.

Appendix 1.2 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

Overall Response at First Time Point	Overall Response at Subsequent Time Point	Best Overall Response

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 disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD is met. However, sometimes CR may be claimed but subsequent scans suggest small lesions were likely still present, so in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Appendix 2

List of Preferred Terms for Adverse Events of Special Interest

Event of Special Interest	Classification	Preferred Term of AE
Grade 4 amylase or lipase increased	Amylase	Amylase increased
Grade 4 amylase or lipase increased	Lipase	Lipase increased
Reactive capillary endothelial proliferation		Reactive capillary endothelial proliferation
Grade ≥ 3 infusion reaction		Infusion related reaction
Grade ≥ 2 diarrhea/colitis	Colitis	Immune-mediated enterocolitis
Grade ≥ 2 diarrhea/colitis	Colitis	Colitis
Grade ≥ 2 diarrhea/colitis	Diarrhea	Diarrhea
Grade ≥ 2 uveitis		Eye pain
Grade ≥ 2 interstitial pneumonia		Interstitial lung disease
Grade ≥ 2 liver enzyme abnormal event		Hepatic enzyme abnormal

Appendix 3

PT Term List of Immune-Related Adverse Events

Cluster Term	PT Term
Selected endocrine-related adverse events (SHR-1210 related)	Hyperglycemia
Selected endocrine-related adverse events (SHR-1210 related)	Diabetes mellitus
Selected endocrine-related adverse events (SHR-1210 related)	Ketoacidosis
Selected endocrine-related adverse events (SHR-1210 related)	Thyroid function test abnormal
Selected endocrine-related adverse events (SHR-1210 related)	Thyroxine increased
Selected endocrine-related adverse events (SHR-1210 related)	Glucose urine present
Selected endocrine-related adverse events (SHR-1210 related)	Tri-iodothyronine decreased
Selected endocrine-related adverse events (SHR-1210 related)	Blood thyroid stimulating hormone decreased

Cluster Term	PT Term
Selected endocrine-related adverse events (SHR-1210 related)	Blood thyroid stimulating hormone increased
Selected endocrine-related adverse events (SHR-1210 related)	Blood glucose increased
Selected endocrine-related adverse events (SHR-1210 related)	Thyroxine free increased
Selected endocrine-related adverse events (SHR-1210 related)	Tri-iodothyronine free decreased
Selected endocrine-related adverse events (SHR-1210 related)	Tri-iodothyronine free increased
Selected endocrine-related adverse events (SHR-1210 related)	Primary hypothyroidism
Selected endocrine-related adverse events (SHR-1210 related)	Hypothyroidism
Selected endocrine-related adverse events (SHR-1210 related)	Hyperthyroidism
Selected endocrine-related adverse events (SHR-1210 related)	Thyroiditis
Selected endocrine-related adverse events (SHR-1210 related)	Lymphocytic hypophysitis
Selected endocrine-related adverse events (SHR-1210 related)	Immune-mediated endocrinopathy

Appendix 4

Preferred Term List of Selected Treatment-Related Adverse Drug Reaction

Cluster Term	MedDRA Preferred Term
Reactive capillary endothelial proliferation	Reactive capillary endothelial proliferation
Selected endocrine-related adverse events (drug related)	Adrenal insufficiency
Selected endocrine-related adverse events (drug related)	Cortisol increased
Selected endocrine-related adverse events (drug related)	Diabetes mellitus
Selected endocrine-related adverse events (drug related)	Blood glucose increased
Selected endocrine-related adverse events (drug related)	Hyperglycemia
Selected endocrine-related adverse events (drug related)	Ketoacidosis
Selected endocrine-related adverse events (drug related)	Lymphocytic hypophysitis
Selected endocrine-related adverse events (drug related)	Hypophysitis
Selected endocrine-related adverse events (drug related)	Thyroiditis
Selected endocrine-related adverse events (drug related)	Thyroid function test abnormal
Selected endocrine-related adverse events (drug related)	Lymphocytic hypophysitis
Selected endocrine-related adverse events (drug related)	Immune-mediated endocrinopathy
Selected endocrine-related adverse events (drug related)	Primary hypothyroidism
Selected endocrine-related adverse events (drug related)	Hypothyroidism
Selected endocrine-related adverse events (drug related)	Hyperthyroidism
Selected endocrine-related adverse events (drug related)	Blood thyroid stimulating hormone increased
Selected endocrine-related adverse events (drug related)	Thyroxine free decreased

Cluster Term	MedDRA Preferred Term
Selected endocrine-related adverse events (drug related)	Blood thyroid stimulating hormone decreased
Selected endocrine-related adverse events (drug related)	Thyroxine free increased
Selected liver-related adverse events (drug related)	Aspartate aminotransferase increased
Selected liver-related adverse events (drug related)	Alanine aminotransferase increased
Selected liver-related adverse events (drug related)	Hepatic function abnormal
Selected liver-related adverse events (drug related)	Bilirubin conjugated increased
Selected liver-related adverse events (drug related)	Hyperbilirubinemia
Selected liver-related adverse events (drug related)	Blood bilirubin unconjugated increased
Selected liver-related adverse events (drug related)	Liver injury
Selected liver-related adverse events (drug related)	Blood bilirubin abnormal
Selected liver-related adverse events (drug related)	Bilirubin total increased
Selected liver-related adverse events (drug related)	Blood bilirubin increased
Selected liver-related adverse events (drug related)	Hepatic failure
Selected liver-related adverse events (drug related)	Hepatic enzyme increased
Selected liver-related adverse events (drug related)	Hepatic enzyme abnormal
Selected liver-related adverse events (drug related)	Immune-mediated hepatitis
Selected liver-related adverse events (drug related)	Immune-mediated hepatic disorder
Selected skin-related adverse events (drug related)	Rash
Selected skin-related adverse events (drug related)	Macule
Selected skin-related adverse events (drug related)	Rash papular
Selected skin-related adverse events (drug related)	Alopecia
Selected skin-related adverse events (drug related)	Drug eruption
Selected skin-related adverse events (drug related)	Eczema
Selected skin-related adverse events (drug related)	Rash maculo-papular
Selected skin-related adverse events (drug related)	Skin exfoliation
Selected skin-related adverse events (drug related)	Dermatitis
Selected skin-related adverse events (drug related)	Pruritus
Selected digestive tract-related adverse events (drug related)	Diarrhea
Selected digestive tract-related adverse events (drug related)	Colitis
Selected digestive tract-related adverse events (drug related)	Mouth ulceration
Selected digestive tract-related adverse events (drug related)	Stomatitis
Selected digestive tract-related adverse events (drug related)	Immune-mediated enterocolitis

Cluster Term	MedDRA Preferred Term
Selected infusion reaction-related adverse events (drug related)	Infusion related reaction
Selected infusion reaction-related adverse events (drug related)	Hypersensitivity
Selected lung-related adverse events (drug related)	Pneumonitis
Selected lung-related adverse events (drug related)	Interstitial lung disease
Selected lung-related adverse events (drug related)	Immune-mediated lung disease
Selected myocarditis-related adverse events (drug related)	Myocarditis
Selected kidney-related adverse events (drug related)	Blood creatinine increased
Selected kidney-related adverse events (drug related)	Glomerular filtration rate decreased
Selected kidney-related adverse events (drug related)	Renal impairment

Appendix 5

Preferred Term List of Selected SHR-1210-Related Adverse Drug Reaction

Cluster Term	MedDRA Preferred Term
Selected endocrine-related adverse events (SHR-1210 related)	Diabetes mellitus
Selected endocrine-related adverse events (SHR-1210 related)	Hyperglycemia
Selected endocrine-related adverse events (SHR-1210 related)	Lymphocytic hypophysitis
Selected endocrine-related adverse events (SHR-1210 related)	Ketoacidosis
Selected endocrine-related adverse events (SHR-1210 related)	Primary hypothyroidism
Selected endocrine-related adverse events (SHR-1210 related)	Hypothyroidism
Selected endocrine-related adverse events (SHR-1210 related)	Hyperthyroidism
Selected endocrine-related adverse events (SHR-1210 related)	Thyroiditis
Selected liver-related adverse events (SHR-1210 related)	Aspartate aminotransferase increased
Selected liver-related adverse events (SHR-1210 related)	Alanine aminotransferase increased
Selected liver-related adverse events (SHR-1210 related)	Hepatic function abnormal
Selected liver-related adverse events (SHR-1210 related)	Bilirubin conjugated increased
Selected liver-related adverse events (SHR-1210 related)	Hyperbilirubinemia
Selected liver-related adverse events (SHR-1210 related)	Blood bilirubin unconjugated increased
Selected liver-related adverse events (SHR-1210 related)	Blood bilirubin increased
Selected liver-related adverse events (SHR-1210 related)	Hepatic enzyme abnormal
Selected liver-related adverse events (SHR-1210 related)	Immune-mediated hepatitis

Cluster Term	MedDRA Preferred Term
Selected liver-related adverse events (SHR-1210 related)	Hepatic failure
Selected liver-related adverse events (SHR-1210 related)	Immune-mediated hepatic disorder
Selected skin-related adverse events (SHR-1210 related)	Rash
Selected skin-related adverse events (SHR-1210 related)	Rash maculo-papular
Selected skin-related adverse events (SHR-1210 related)	Rash papular
Selected skin-related adverse events (SHR-1210 related)	Drug eruption
Selected skin-related adverse events (SHR-1210 related)	Eczema
Selected digestive tract-related adverse events (SHR-1210 related)	Diarrhea
Selected digestive tract-related adverse events (SHR-1210 related)	Colitis
Selected digestive tract-related adverse events (SHR-1210 related)	Immune-mediated enterocolitis
Selected lung-related adverse events (SHR-1210 related)	Pneumonitis
Selected lung-related adverse events (SHR-1210 related)	Interstitial lung disease
Selected lung-related adverse events (SHR-1210 related)	Immune-mediated lung disease