Title: A Randomized, Parallel-Controlled, Multicenter Phase II/III Clinical Study Evaluating Anti-PD-1 Antibody SHR-1210 in Patients with Advanced Hepatocellular Carcinoma (HCC) Who Have Previously Received Systemic Therapy
Clinical trial registration number: NCT02989922
Version Date: 8 Jan., 2019

A RANDOMIZED, OPEN-LABEL, MULTI-CENTER, PHASE II CLINICAL STUDY EVALUATING ANTI-PD-1 ANTIBODY SHR-1210 IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA WHO HAVE PREVIOUSLY RECEIVED SYSTEMIC THERAPY

Statistical Analysis Plan

(SAP)

Author: [redacted]

Company: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Version: 3.0/Final

Date: 8 Jan., 2019

This statistical analysis plan will be reviewed by the following personnel prior to its approval and taking effect.

Functional Role	Name of Reviewer
[redacted]	[redacted]
[redacted]	[redacted]

ABBREVIATIONS

Abbreviations and Terms	Explanation
BOR	Best overall response
DCR	Disease control rate
DoR	Duration of response
ECG	Electrocardiogram
ES	Evaluable set
FAS	Full analysis set
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PPS	Per-protocol set
QD	Quaque die (once a day)
SD	Standard deviation
SS	Safety set
TEAE	Treatment-emergent adverse event
TTP	Time to progression
TTR	Time to response

TABLE OF CONTENTS

1. REVISION

This version is formulated in accordance with the protocol numbered SHR-1210-II/III-HCC (Version 5.0, 3 Apr., 2018).

Contents	Before	After	Reason for Revision
Cover Page	1. Version Number: 2.0 2. Version Date: 16 Jul., 2018	1. Version Number: 3.0 2. Version Date: 16 Sep., 2018	Version upgrade
5.1.4 Definition of subgroup populations		The population is classified in accordance with the type of previous therapy and number of treatment lines: Subgroup A: subjects previously treated with at least one standard treatment Subgroup B: subjects previously treated with sorafenib Subgroup C: subjects treated with sorafenib only Subgroup D: subjects previously treated with only one standard treatment Subgroup E: subjects previously treated with two or more lines of treatment	Comparison with the other drugs is required by medicine based on the efficacy in the subgroup populations
4.1.4 Progression-free survival	If a subject misses ≥ 2 consecutive scheduled imaging assessments (16 weeks), then the date to be censored will be the date of last objective tumor response evaluation prior to missing.	If a subject misses ≥ 2 consecutive scheduled imaging assessments (24 weeks after 12 months from the first dose, 14 weeks before 12 months) before disease progression or death, then the date to be censored will be the date of last objective tumor response evaluation prior to the missing.	It was modified due to the change of frequency of response evaluation after the 12 months of first dose.
4.1.5 Time to progression	If a subject misses ≥ 2 consecutive scheduled imaging assessments (16 weeks), then the date to be censored will the date of last objective tumor response evaluation prior to the missing.	If a subject misses ≥ 2 consecutive scheduled imaging assessments (24 weeks after 12 months from the first dose, 14 weeks before 12 months) before disease progression, then the date to be censored will be the last objective tumor response evaluation prior to the missing.	It was modified due to the change of frequency of response evaluation after the 12 months of first dose.
4.17 6/9/12-Month Overall Survival Rate	6-Month Overall Survival Rate	6/9/12-month Overall Survival Rate	The 9- and 12-month overall survival rates were added as required by medicine.

Contents	Before	After	Reason for Revision
5.4 Efficacy Analysis		Efficacy evaluations will be performed on each subgroup population. Reconciliation for BOR and for CR/PR	The efficacy analysis in subgroup population is required. The reconciliation between the investigator-assessed and the IRC-assessed BOR and CR/PR is required.
5.5.2 Adverse events		Selected related adverse events (endocrine, gastrointestinal, liver, lung, kidney, hypersensitivity/infusion reaction, and skin);	Missing description
5.4 Efficacy Analysis		The analytical method for inter-group comparison was detailed and that statistical inference will not be conducted was expounded.	Detailed analytical method
4.1 Efficacy Endpoints		The start date used to calculate efficacy endpoints was changed from the date of randomization to the date of first dose.	The calculation should be started from the date of first dose for single-arm study.

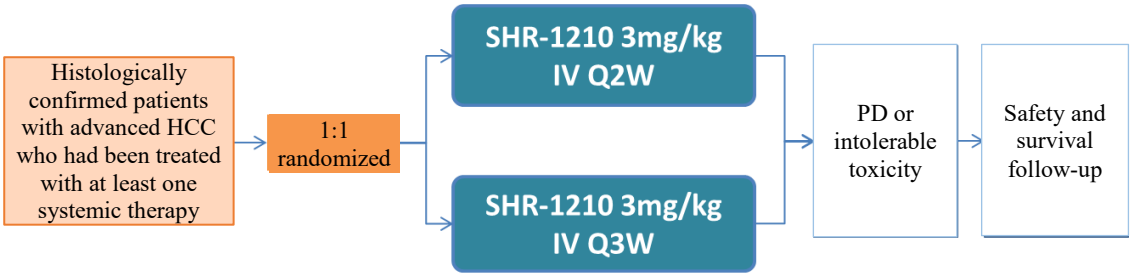
2. INTRODUCTION

This is a phase II clinical study to explore and assess the efficacy and safety of SHR-1210 in treatment of hepatocellular carcinoma (HCC).

2.1. Study Design

This is a randomized, open-label, multi-center, phase II study. The primary objective is to evaluate the efficacy and safety of SHR-1210 in subjects with advanced HCC after failure of previous systemic treatment. A total of 220 subjects will be enrolled and randomized in a 1:1 ratio to receive SHR-1210 3 mg/kg, I.V., Q2W (once every two weeks) or SHR-1210 3 mg/kg, I.V., Q3W (once every three weeks) group, in 42-day cycles.

The study design schematic is presented in the following figure:



2.2. Study Objectives

To evaluate the efficacy and safety of anti-PD-1 antibody SHR-1210 in subjects with advanced hepatocellular carcinoma (HCC) who have received previous systemic treatment.

2.3. Sample Size

Referring to the study results on similar products, assuming the ORR is 15% for SHR-1210 in treatment of target population of this study, and the lower limit of 95% confidential interval of ORR obtained from this study is >7%, it can be considered as effective. 154 subjects need to be enrolled to obtain 90% power at a one-sided significance level of 0.025. Further assuming evaluable cases accounting for 80% of the enrolled subjects, 194 subjects are required to be enrolled.

Assuming the survival rate at 6 months is 80% for SHR-1210 in treatment of target population, and the lower limit of 95% confidential interval is >70%, this therapy can be considered to have advantage in efficacy. 200 subjects need to be enrolled to obtain 90% power at a one-sided significance level of 0.025. Considering the drop-out rate of 10%, a total of 220 subjects are required to be enrolled.

Considering the above two points, a total of 220 subjects will be enrolled in the study.

3. STATISTICAL HYPOTHESIS

All analyses will be primarily based on descriptive statistical summary by group and overall. No formal statistical hypothesis testing will be performed. The overall 95% CIs of the two primary study endpoints, ORR and 6-month OS rate, will be calculated. The lower limit of the overall 95% CI of ORR is > 7% and the lower limit of the overall 95% CI of 6-month OS rate is >70% indicate that the drug is effective.

4. STUDY ENDPOINTS

4.1. Efficacy Endpoints

4.1.1. Objective response rate (ORR)

Defined as the percentage of subjects with confirmed complete response or partial response (CR or PR) from the first dose of the investigational drug to PD assessed using RECIST 1.1 or start of new anti-cancer therapy.

4.1.2. Duration of response (DoR)

Defined as the period from the first documentation of CR or PR to the first documentation of PD or to death due to any reason in subjects with confirmed CR or PR. If no PD or death occurs, it will be censored at the last tumor assessment.

4.1.3. Disease control rate (DCR)

Defined as the percentage of subjects with CR, PR or stable disease (SD) for ≥ 6 weeks. A subject with missing or unknown evaluations is deemed not evaluable (NE). This subject will be included in the denominator to calculate percentage.

4.1.4. Progression-free survival (PFS)

Defined as the period from the date of first dose to the first documentation of PD in accordance with RECIST 1.1 or death due to any reason, whichever comes first. If a subject still shows no PD or does not die at the end of study, this period will be censored. The rules for PFS censoring are as below:

- If there is no tumor assessment at baseline, the date of censoring is the date of the first dose of study treatment.
- If there is no tumor assessment after baseline, the date of censoring is the date of the first dose of study treatment.
- If no RECIST 1.1 progression or death is recorded, the date of censoring is the date of the last tumor assessment.
- If no radiological progression or death is recorded prior to initiation of subsequent therapy, the date of censoring is the date of the last tumor assessment prior to the subsequent therapy.
- If subjects miss 2 or more consecutive planned tumor assessments prior to progression or death (12 weeks within 12 months from the first dose of study treatment, 24 weeks after 12 months from taking first dose), the date of censoring will be the date of the last tumor assessment.

4.1.5. Time to progression (TTP)

Defined as the period from first dose to PD. Rules for TTP censoring are as follows:

- If there is no tumor assessment at baseline, the date of censoring is the date of the first dose of study treatment.
- If there is no tumor assessment after baseline, the date of censoring is the date of the first dose of study treatment.
- If no RECIST 1.1 progression or death is recorded, the date of censoring is the date of the last tumor assessment.
- If subjects die before the onset of disease progression, the date of censoring will be the date of the last tumor assessment.

- If no radiological progression or death is recorded prior to initiation of subsequent therapy, the date of censoring is the date of the last tumor assessment prior to the subsequent therapy.
- If subjects miss 2 or more consecutive planned tumor assessments prior to progression or death (12 weeks within 12 months from the first dose of study treatment, 24 weeks after 12 months from the first dose of study treatment), the date of censoring will be the date of the last tumor assessment.

4.1.6. Overall survival (OS)

Defined as the period from first dose to death due to any reason. It will be censored if no death occurs.

Rules for OS censoring are as below:

- If death is not obtained, the date of censoring will be the date of the last follow-up who are known to be alive.
- If the subject withdraws from the study and the date of death is not obtained, the date of censoring will be the last date who are known to be alive.

4.1.7. 6/9/12-month overall survival rate

Defined as the survival rate at 6/9/12 months after the date of first dose, which will be based on the Kaplan-Meier estimate.

4.1.8. Time to response (TTR)

Time to response is defined as the period from the first dose to the first documentation of CR or PR (whichever occurs first). Tumor response refers to the confirmed response. The date of response is the date of first documented response rather than the date of confirmation.

4.2. Safety Endpoints

The following safety data will be collected and summarized in accordance with the study protocol (details will be elucidated in subsections):

- Adverse events
- Laboratory test data
- Vital signs data
- Electrocardiogram (ECG)
- Physical examination

4.2.1. Adverse events

Any adverse event occurring after signing of informed consent form and enrollment into the study will be collected.

Any adverse event occurring after treatment or occurring prior to treatment but being exacerbated after treatment will be counted as treatment emergent adverse event (TEAE). The following cases include but are not limited to:

- Medical condition/diseases present before starting the investigational drug that worsen after starting study treatment.
- Any new adverse event after starting study treatment.
- Abnormal laboratory measurements or test results with clinical significance occurring after starting study treatment.

If an event occurs in non-treatment period (e.g., dose interruption period or follow-up period after treatment discontinuation), this event will still be counted as a TEAE and attributed to previous treatment.

4.2.2. Laboratory test

The laboratory test data, including hematology, blood biochemistry, and urinalysis, will be collected at the visits specified in the protocol.

4.2.3. Vital signs

Vital signs, including blood pressure, heart rate, temperature, and respiratory rate, will be collected at the predefined time points in the protocol.

4.2.4. Electrocardiogram

Heart rate, PR, QT, and QTc will be collected at the predefined time points in the protocol.

4.2.5. Physical examination

Physical examination includes general condition, head, heart, lungs, abdomen, four limbs, skin, mucosa, lymph node, among others. These data will be collected at the visits/time points specified in the protocol.

4.2.6. Other safety endpoints

Other safety data to be collected according to the protocol

4.3. Pharmacokinetic Endpoints

None.

4.4. Pharmacodynamics Endpoints

None.

4.5. Other Endpoints

PD-L1 expression level (< 1% or ≥ 1%, based on staining percentage). It will be used to explore the relationship with the efficacy (ORR and 6-month OS%). The efficacy in subjects with PD-L1 expression level < 1% or ≥ 1% will be tabulated.

5. STATISTICAL ANALYSIS

5.1. General Considerations

5.1.1. Analysis sets

Full analysis set (FAS)

Full analysis set includes all the randomized subjects who have received at least one dose of the investigational drug. Based on the analysis in the FAS, subjects belong to their allocated group as randomized rather than the actual medication group.

Per-protocol set (PPS)

It is a subset of the FAS. The PPS forms by excluding subjects with protocol deviation that has important effect on the study results from the FAS. Analysis based on the PPS, as supportive analysis, will be used as a supplement to the analysis based on the FAS. The PPS must be determined by the medical team and the statistical team of the project prior to database lock for the final analysis. All protocol deviations, including those that are judged to have major effect on the study results, will be presented in study report in a form of listing.

Evaluable set (ES)

Evaluable set is also a subset of the FAS and defined as the subjects with at least one post-baseline tumor evaluation in the FAS.

Safety set (SS)

Safety set includes all the subjects who have received at least one dose of the investigational drug. Based on the analysis in SS, subjects belong to the actual medication group (as treated). The safety set is the primary set for the safety analyses.

PD-L1 set (PD-L1)

PD-L1 set of this study comprises of all subjects who have been randomized and have received at least one dose of the investigational drug, and have provided tumor biopsy samples.

Table 1. Correspondence between study endpoints and analysis sets

Endpoints	Analysis Sets				
	FAS	PPS	ES	SS	PD-L1
ORR (%)	X	X	X		X
6/9/12-month OS rate (%)	X	X			X
TTP (months)	X				
PFS (months)	X				
DoR (months)	X				
DCR (%)	X	X	X		
OS (months)	X				
TTR (months)	X				
Safety (AE, LAB, VS, ECG, PE)				X	

5.1.2. General rule and analysis

Baseline

Unless otherwise specified, the "baseline" in this study is defined as the last non-missing measurement prior to the first dose of the investigational drug, including the measurement on the day of the first dose, but prior to the first dose.

Study days

Study days for examinations or events will be calculated using following formulas:

If the date of examination/event is before the date of first dose, study days = date of examination – date of first dose;

If the date of examination/event is on or after the date of first dose, study days = date of examination – date of first dose + 1.

General analysis

Unless otherwise specified, the following descriptive statistical summaries will be provided by the type of variables:

- The continuous variables will be summarized by mean, standard deviation, median, maximum, and minimum.
- The categorical variables will be summarized by frequency and percentage.

For time-event data, Kaplan-Meier method is used to estimate the median time of survival function and event occurrence, and the survival curve will be plotted.

Decimal places

Unless otherwise specified, the decimal places in study report will be presented using the following rules:

The decimal places of minimum and maximum will be kept consistent with that of the original data to be collected, those of mean and median will be kept one more place than the original data, and that of standard deviation will be kept two places more than the original data; however, at most 4 decimal places will be reserved.

Percentages will be presented with 2 decimal places of precision. If the frequency is 0, no percentage will be shown.

Four decimal places will be reserved for P value. If the P value is < 0.0001, it will be presented as "< 0.0001", and if the P value is > 0.9999, it will be presented as "> 0.9999".

If there is decimal for 95% CI, at least two and at most four decimal places will be reserved.

Analysis software

All the statistical analyses will be performed using statistical analysis software SAS® v9.4 or later version.

5.1.3. Derived variables

SHR-1210-Q2W group:

Duration of exposure (days) = date of last dose + 14 – date of first dose + 1

Duration of exposure (months) = (date of last dose +14 – date of first dose + 1) / 30.4375

Planned number of dosing = duration of drug exposure (days) / 14

Planned total dose (mg) = weight at baseline (kg) × 3 mg/kg × planned number of dosing

SHR-1210-Q3W group:

Duration of exposure (days) = date of last dose +21 – date of first dose + 1.

Duration of exposure (months) = (date of last dose +21 – date of first dose + 1) / 30.44.

Planned number of dosing = duration of drug exposure (day) / 21

Planned total dose (mg) = weight at baseline (kg) × 3 mg/kg × planned number of dosing

Cumulative dose (mg) = total dose during drug exposure

Dose intensity (mg/month) = cumulative dose/duration of drug exposure (months)

Compliance (%) = (cumulative dose/planned total dose) ×100%

5.1.4. Covariates and subgroups

This study will include the following subgroups:

- Gender (male vs. female)
- Age (< 65 vs. ≥ 65 years)
- Use of local therapy (yes/no)
- ECOG PS (0 points vs. 1 point): grouped by baseline ECOG PS
- Weight (< 60 kg vs. ≥ 60 kg vs. ≤ 55 kg vs. 55–70 kg vs. ≥ 70 kg)
- Baseline AFP level (< 200 ng/mL vs. ≥ 200 ng/mL, < 400 ng/mL vs. ≥ 400 ng/mL)
- Etiology (hepatitis B vs. non-hepatitis B): hepatitis B can be determined when the surface antigen or HBV-DNA is positive at baseline or HBV-DNA can be detected.
- BCLC stage (stage B vs. stage C)
- New anti-cancer therapy (yes vs. no): whether received other anti-cancer therapies during survival follow-up period.

Sub-populations will be classified in accordance with the type of previous therapy and number of treatment lines:

- Subgroup A: subjects previously treated with at least one standard treatment (sorafenib or oxaliplatin-based chemotherapy)
- Subgroup B: subjects previously treated with sorafenib
- Subgroup C: subjects treated with sorafenib only
- Subgroup D: subjects previously treated with only one standard treatment
- Subgroup E: subjects previously treated with two or more lines of treatment

5.1.5. Analysis window

Summary will be based on the visits filled in eCRF according to protocol predefined, with no need to consider unscheduled visits.

In the case that the scheduled protocol visit is missing, or one examination is missing within the scheduled visit or the result is invalid, the unscheduled visit closest to the scheduled protocol visit will be considered as the protocol visit. If the time to the scheduled visit is equal for two unscheduled visits, the later scheduled visit will be used as the protocol visit. All the protocol visits will be scheduled in order. Once one unscheduled actual visit has been defined as one protocol visit, it will be no more defined for the other protocol visit. When analyzing by visit, the statistical analysis will be performed in accordance with the time point for the scheduled protocol visits, i.e., there is no need to present the time points for unscheduled visits.

5.1.6. Processing of missing date and missing data

Except for special circumstances, the following rules for imputation are applicable to the absence of event date for safety data.

If the date of an event is totally absent, it will not be imputed. If the date is missing, but the year and the month are consistent with that of study treatment, it will be imputed with the date of the first dose of the investigational drug, or first day of that month for other conditions; if the date of the end day is missing, but the year and the month are consistent with that of the end of treatment, the date of the end of event will be imputed with the date of the end of study treatment, or the last day of that month for other conditions.

If the month and the date of an event are missing, but the year is consistent with that of study treatment, they will be imputed with those of the start of study treatment, or 1 Jan. for other conditions.

All the dates imputed must precede the dates of withdrawal of informed consent form, lost to follow-up or death.

Missing data on laboratory tests, ECG, and vital signs will not be imputed.

5.2. Study Subjects

All summaries will be performed by group and overall.

5.2.1. Disposition of subjects

The number and percentage of subjects will be summarized, the number and percentage of subjects included in each analysis set will be summarized, and the number and percentage of subjects in each period during the study will be summarized, for example, the number of subjects enrolled after randomization, number of subjects who have completed the study, as well as the number and percentage of subjects who interrupt treatment and withdraw from the study prematurely for various reasons.

5.2.2. Demographics

Age, gender, ethnicity, height, weight, and body mass index of subjects will be descriptively summarized. Continuous variables, including age, height, weight, and body mass index, will be summarized with descriptive statistics, including number of evaluable subjects (n), mean, standard deviation, median, minimum (Min), and maximum (Max). Categorical variables, including gender and ethnicity, will be descriptively summarized with the number of evaluable subjects in each category and corresponding percentage in the total number. Baseline characteristics are also summarized for sub-populations.

5.2.3. Medical history

The previous history of tumors (extrahepatic metastasis, HBV infection, Child-Pugh score (5, 6, 7), AFP ≥ 200 NG/mL or AFP < 200 NG/mL, AFP ≥ 400 NG/mL or AFP < 400 NG/mL, and BCLC stage) and history of treatment will be statistically described correspondingly by treatment group.

All the previous history of general diseases will be listed.

5.2.4. Prior therapy and concomitant medication

These will be summarized based on the classification of clinical departments. Prior anti-cancer therapy: surgical therapy, local therapy, radiotherapy, systemic therapy (1 line, 2 lines, ≥ 3 lines of therapies); the systemic treatment includes systemic chemotherapy and targeted therapy.

The systemic treatment will be classified and tabulated by the type of therapy and generic name.

All prior and concomitant medications will be classified and tabulated by the type of therapy and generic name.

5.2.5. Protocol deviations

Before the database is locked, all subjects' data on the CRF will be checked for important protocol deviations. All possible critical or major protocol deviations will be evaluated by the investigator and the sponsor.

All critical or major protocol deviations will be summarized and described by types, and analyzed in listing.

Critical or major protocol deviations include, but are not limited to:

- Serious violation of the eligibility criteria;
- Wrong assignment into treatment groups;
- Use of prohibited drug during treatment;
- Poor compliance (compliance rate < 50%).

5.3. Treatment Compliance

The use of the investigational drug will be descriptively summarized.

All subjects will be listed by treatment groups. The contents to be listed include but are not limited to treatment period, date of administration, and actual dose administered.

5.4. Efficacy Analysis

The efficacy analysis will be performed separately by group and overall.

Efficacy analysis will be based on IRC-assessed data and investigator-assessed data, with the former as the primary analysis.

Based on the FAS, PPS, and ES, ORR and 95% CI will be calculated separately by group and overall. The CI will be calculated using the Clopper-Pearson method. In addition, the difference in ORR will be calculated between the two groups, and Wald method will be used to estimate the 95% CI of the difference, and the nominal P value will be calculated based on Pearson Chi-square test.

In addition, based on the FAS, Amit method will be used to analyze the discrepancy between IRC-assessed and investigator-assessed PD/non-PD, BOR, and CR/PR.

Based on the FAS and PPS, Kaplan-Meier method will be used to calculate the 6/9/12-month OS% and the corresponding 95% CIs will be calculated.

Based on the FAS, the secondary efficacy endpoint PFS (including the 6/9/12-month PFS rate), TTP, OS, and DoR will be analyzed using Kaplan-Meier method. TTR will be descriptively summarized. When applicable, the survival curve will be plotted by endpoints. For PFS, TTP, OS, and DoR, the hazard ratios between groups and their 95% CIs will be computed using the COX proportional hazards model and nominal P values will be calculated using the log-rank test.

For the secondary efficacy endpoint DCR, the same statistical method with ORR will be used for analysis based on the FAS, the PPS, and the ES.

The best overall response (BOR) will be summarized.

5.4.1. Exploratory analyses

Based on PD-L1 analysis set, ORR will be estimated by groups of different PD-L1 expression levels (PD-L1 $\geq$ 1% vs. PD-L1 < 1) (point estimate and 95% CI estimate). The 6/9/12-month survival rate will be estimated by groups of different PD-L1 expression levels (point estimate and 95% CI estimate). BOR will be summarized by the occurrence of capillary endothelial proliferation (with vs. without).

5.4.2. Subgroup analysis

Based on the FAS, subgroup analysis will be conducted merely on OS. The median OS and their 95% CIs will be provided for each subgroup. Forest plot will be prepared when necessary. The definition of subgroup is presented in section 5.1.4.

Based on the FAS, relevant efficacy endpoint analyses will be performed for sub-populations A, B, C, D, and E, with the same analytical method as above. The objective response swimmer plot and survival curves will be plotted for each sub-population.

5.4.3. Other analysis

In accordance with the tumor evaluation by IRC and investigators, the categories of the sum of diameter of the target lesions increased in the first evaluation of tumor response from baseline will be analyzed; the criteria on category are ≥ 100% vs. ≥ 50% and < 100% vs. ≥ 20% and < 50% vs. > 0% and < 20%.

Subjects with initial progression will be classified according to treatment continuation or treatment discontinuation, and the overall duration of treatment (months), overall survival (months), and 6-month survival rate after initial progression will be analyzed. Tumor assessments of subjects who continue treatment beyond investigator-assessed progression will be listed (including subject ID, dose group, assessment visit, date of assessment (presented by the earliest date of occurrence), sum of target lesion diameters and its change (%) from baseline, non-target lesion assessments, presence of new lesions, and the overall assessment). Subjects who continue treatment beyond disease progression and have > 30% reduction in target lesion relative to baseline (reduction or continuous reduction of target lesion after disease progression) will be listed (subject ID, dose group, largest change in target lesion from baseline (%), duration of treatment after PD (months)). Changes in target lesion from baseline (%) vs. time will be plotted for subjects who continue treatment beyond disease progression.

5.5. Safety Analysis

Unless otherwise specified, the safety analysis will be descriptively summarized and listed by treatment group. All safety analyses will be based on the safety set.

5.5.1. Extent of exposure

The extent of drug exposure will be summarized by duration of drug exposure (months), number of dosing, cumulative dose, and drug intensity mainly for different dose group and overall, using mean, standard deviation, median, maximum, and minimum.

5.5.2. Treatment-emergent adverse events (TEAEs)

Adverse events will be summarized using descriptive statistics according to Hengrui's Statistical Analysis Reporting Standards, including but not limited to:

- Overview of adverse events (all-cause and treatment-related);
- Summary of serious adverse event;
- Incidence and severity of adverse event (all-cause and treatment-related);

- Causality between adverse event and investigational drug;
- Selected related adverse events (endocrine, gastrointestinal, liver, lung, kidney, hypersensitivity/infusion reaction, and skin);
- Adverse events of special interest.

Adverse events of special interest mainly include:

- Hemangioma (time to event and duration of event, outcome, recovery, or remission)
- Grade ≥ 3 infusion reaction
- Grade ≥ 2 diarrhea/colitis, uveitis, and interstitial pneumonia
- Grade ≥ 3 other immune related adverse events: skin, gastrointestinal, lung, endocrine (by system organ class)
- Abnormal hepatic enzyme: abnormal ALT, AST, and total bilirubin from baseline
- Grade 4 amylase or lipase increased

5.5.3. Laboratory evaluations

Baseline is defined as the last measurement prior to first dose. The laboratory data will be summarized using descriptive statistics according to Hengrui's Statistical Analysis Reporting Standards, including but not limited to:

- Incidence of abnormities by item and parameter;
- Shift table and listing of changes from baseline (normal/abnormal) by item, visit, and parameter;
- Shift table of changes in greatest grade from baseline for parameters that can be graded as per CTCAE.

Laboratory abnormalities will be listed.

5.5.4. Vital signs

Baseline is defined as the last measurement prior to first dose. Vital signs will be summarized using descriptive statistics according to Hengrui's Statistical Analysis Reporting Standards, including but not limited to: descriptive summaries of absolute value and change from baseline at the scheduled visits in the protocol.

5.5.5. Electrocardiogram

The listing of ECG results will be provided.

5.5.6. Physical examination

Physical examination results will be summarized using descriptive statistics according to Hengrui's Statistical Analysis Reporting Standards, including but not limited to: descriptive summary of absolute value at the scheduled visits in the protocol.

5.5.7. Other safety measures

The ECOG PS at baseline and change from baseline will be analyzed by visit and group. Child-Pugh score will be summarized by visit and group (as continuous variable), and analyzed for frequency and percentage (as categorical variable).

The listing of echocardiography results will be provided.

The categories of the greatest post-baseline HBV-DNA values (< 500, 500–2000, and ≥ 2000 IU/mL) will be summarized. The proportion of subjects with ≥ 100-fold (2log10) maximum change in the greatest post-baseline HBV-DNA values relative to baseline will be summarized and the maximum rate of change from baseline will be descriptively summarized. AEs and efficacy in subjects with post-baseline HBV-DNA ≥ 2000 IU/mL will be summarized.

5.6. Pharmacokinetic Analysis

None.

5.7. Pharmacodynamics Analysis

None.

6. REFERENCES

None.

7. APPENDIX

None.