Title: An Open-Label, Single Arm, Multi-Center, Phase 2 Study of PD-1 Antibody SHR-1210 in Subjects with Relapsed or Refractory Classic Hodgkin's Lymphoma

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AN OPEN-LABEL, SINGLE ARM, MULTI-CENTER, PHASE II STUDY OF PD-1 ANTIBODY SHR-1210 IN SUBJECTS WITH RELAPSED OR REFRACTORY CLASSIC HODGKIN'S LYMPHOMA

Statistical Analysis Plan

(SAP)

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This SAP has been reviewed by the following personnel before being approved and effective.

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

ABBREVIATIONS

Term	Definition
CR	Complete response
DCR	Disease control rate
DoR	Duration of response
ECG	Electrocardiogram
FAS	Full analysis set
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PE	Physical examination
PFS	Progression-free survival
PR	Partial response
PPS	Per-protocol set
SD	Stable disease
SS	Safety set
TEAE	Treatment-emergent adverse event
TTP	Time to progression
TTR	Time to response

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1. REVISION

Updated to Version 3.0 on 30 Aug. 2020. Formulated with reference to the protocol No. SHR-1210-II-204 (Version 3.0, 19 Jul., 2017).

Content	Before	After
Cover	1. The version number is 2.0 2. The version date is 4 Apr., 2018	1. The version number is 3.0 2. The version date is 30 Aug., 2020
Definition of FAS	Full Analysis Set (FAS): eligible subjects who have received the investigational drug and meet the following requirements. (1) Subjects who have received rescue autologous stem cell transplant after chemotherapy, and then have recurrence or progression; (2) Subjects who have not received autologous stem cell transplant are required to have received the following treatment: The first-line chemotherapy must be systemic multi-drug combination chemotherapy. For subsequent chemotherapy, it is required that at least one line of chemotherapy is systemic multi-drug combination chemotherapy. Patients with refractory disease are patients who did not achieve PR after ≥ 2 treatment cycles or CR after ≥ 4 treatment cycles, or patients who developed progressive disease, regardless of number of treatment cycles. Patients with relapsed disease are patients who were recently treated with at least second-line chemotherapy prior to recurrence.	Full Analysis Set (FAS): eligible subjects who have received the investigational drug.
5.1.4 Covariates and subgroups	Subjects who received the highest number of lines of prior chemotherapy or autologous stem cell transplant but achieved non-CR/non-PR are classified as subjects with refractory diseases, and others are classified as subjects with relapsed diseases.	Relapsed: Best overall response to the last chemotherapy/transplant is CR or PR, and time from the end of chemotherapy/transplant to progression is > 6 months. Refractory: 1. Best overall response to the last chemotherapy/transplant is CR, PR, or not evaluated, and time from the end of chemotherapy/transplant to progression is ≤ 6 months. Or, 2. Best overall response to the last chemotherapy/transplant is PD or SD. Missing: Response to the last chemotherapy/transplant is not evaluated, and time from the end of last chemotherapy/transplant to progression is > 6 months.

2. INTRODUCTION

This study is a phase II clinical study evaluating the efficacy and safety of SHR-1210 in the treatment of patients with refractory or relapsed classic Hodgkin's lymphoma.

2.1. Study Design

This study adopts a multi-center, open-label, single-arm design to evaluate the efficacy and safety of SHR-1210 in patients with relapsed or refractory classic Hodgkin's lymphoma and the PK parameters of 12 subjects at the same time. Sixty subjects who meet the eligibility criteria will be enrolled and given SHR-1210 at 200 mg/dose on day 1 of each 2-week cycle, until the following condition occurs: progressive disease (PD), intolerable toxicity, or other reasons specified in the protocol. After treatment, the subjects entered the follow-up period would receive safety follow-up or survival follow-up.

2.2. Study Objectives

2.2.1. Primary objective

To evaluate the efficacy, namely objective response rate (ORR), of PD-1 antibody SHR-1210 in the treatment of relapsed or refractory classic Hodgkin's lymphoma.

2.2.2. Secondary objectives

- To observe and evaluate the duration of response (DoR), progression-free survival (PFS), time to response (TTR), and overall survival (OS) of PD-1 antibody SHR-1210 in the treatment of patients with relapsed or refractory classic Hodgkin's lymphoma (cHL).
- To evaluate the safety of PD-1 antibody SHR-1210 in patients with relapsed or refractory classic Hodgkin's lymphoma (cHL).

2.3. Sample Size

This study adopts a single-arm design. The primary objective is to evaluate the efficacy of SHR-1210 in the treatment of relapsed or refractory cHL. The study endpoint is ORR. Based on historical research data and research results of similar products, combined with current clinical practice requirements, only when the lower limit of the 95% confidence interval for ORR obtained from the study is greater than 40%, it can be considered as effective. Therefore, the sample size for this study is determined based on the following 2 points: 1. the exact method (Clopper-Pearson) is used to calculate the 95% confidence interval for ORR; 2. the lower limit of the confidence interval is greater than 40%. Assume that the ORR of SHR-1210 in the treatment of relapsed or refractory cHL reaches 65%, a power of 92.90% can be obtained with 50 subjects. Combined with a dropout rate of 20%, this study intends to enroll 60 subjects.

3. STATISTICAL HYPOTHESES

Hypotheses of ORR are as follows:

H_0: ORR = 40%

H_a: ORR ≠ 40%

$\alpha = 0.05$ (two-sided)

4. STUDY ENDPOINTS

4.1. Efficacy Endpoints

Primary efficacy endpoint:

Objective response rate (ORR) assessed by the independent review committee (IRC), including the proportion of complete response (CR) and partial response (PR).

Secondary efficacy endpoints:

- Objective response rate (ORR) assessed by the investigators, including the proportion of complete response (CR) and partial response (PR)
- Duration of response (DoR)
- Progression-free survival (PFS): The date of first PD documented after CR, PR, or SD is used as the date of progression; if the subject does not achieve CR, PR, or SD following PD, then the date of initial PD is used as the date of progression.
- Time to response (TTR)
- Overall survival (OS)
- Time to progression (TTP)

4.2. Safety Endpoints

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

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

4.2.1. Adverse events

Including any AE occurring after signing the informed consent form (ICF) and being enrolled in the study.

Any AE occurring after the treatment or occurring prior to the treatment but worsening after the treatment will be considered as a treatment-emergent AE (TEAE). Including but not limited to the followings:

- Worsening of pre-existing (prior to start of study treatment) medical conditions/diseases after the start of investigational drug administration.
- Any new AE occurring after the start of study treatment.
- Clinically significant abnormal laboratory findings or results occurring after the start of study treatment.

If an event occurs during non-treatment period (e.g., treatment interruption or follow-up period after treatment discontinuation), then this event will still be considered to be treatment emergent and attributed to previous therapy.

4.2.2. Laboratory test

Laboratory measurements including hematology, hepatic and renal function, urinalysis and fecal occult blood, blood electrolytes, coagulation function, and thyroid function will be collected at the visit time points specified in the study protocol.

4.2.3. Vital signs

Vital signs such as blood pressure, heart rate, body temperature, and respiratory rate will be collected at time points predetermined in the study protocol.

4.2.4. Electrocardiogram (ECG)

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

4.2.5. Physical examination

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

4.2.6. Other safety endpoints

Assessment of B symptoms, IPS score, and ultrasound ECG.

4.3. Pharmacokinetic Endpoints

Not included in this SAP. See "PK Statistical Analysis Plan" provided by the vendor.

4.4. Pharmacodynamic Endpoints

None. This study does not involve PD endpoints.

4.5. Other Endpoints

None.

5. STATISTICAL ANALYSIS

5.1. General Considerations

5.1.1. Analysis sets

This study will involve the following analysis sets or populations:

- **Informed Consent Set (ICS)**
  All subjects who have signed the informed consent form.
- **Full Analysis Set (FAS)**
  Eligible subjects who have received the investigational drug.
- **Per-Protocol Set (PPS)**
  A subset of the FAS, defined as subjects in the FAS who have experienced no important protocol deviations.
- **Safety Set (SS)**
  All enrolled subjects who have received the investigational drug and have post-administration safety evaluation. The SS is the primary analysis set for safety analysis.

Table 1. Analysis sets and corresponding endpoints.

Endpoint	Analysis Sets		
	FAS	PPS	SS
ORR (%)*	X	X	
TTR (Month)	X		
TTP (Month)	X		
PFS (Month)	X		
DoR (Month)	X		
DCR (%)	X		
OS (Month)	X		
Safety (AE, LAB, VS, ECG, and PE)			X

*: Assessed by the investigator and independent review committee, respectively.

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 investigational drug, including the measurements taken on the day of and prior to the first dose.

Study days

The day of the first dose is defined as the start day of the study. Then, based on the start day of the study, the number of days of study corresponding to test or event is calculated by the following formula:

- Study days = examination date - start date of the study, if the date of an examination/event is before the start date of study;
- Study days = examination date - start date of the study + 1, if the date of an examination/event is on or after the start day of study.

General analysis

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

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

Number of decimal places

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

- The decimal places of the minimum and maximum will remain the same as that 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 2 decimal places. If the frequency is 0, the percentage is not displayed.

- The 95% CI, if being a decimal, will retain at least 2 decimal places, up to 4 decimal places.
- Time to event (in months) will be rounded to one decimal place.

Analysis software

All statistical analyses will be conducted using SAS® 9.4 or above.

5.1.3. Derived variables

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

Time from initial pathological diagnosis to enrollment (month) = (date of enrollment - date of initial pathological diagnosis + 1)/30.44

Time from final dose to enrollment (month) = (date of enrollment - last date of any previous anti-tumor therapy + 1)/30.44

Duration of drug exposure (month) = (date of last dose +14 - date of first dose + 1)/30.44

5.1.4. Covariates and subgroups

This study includes the following subgroups:

- Age (≤ 45 years old and > 45 years old)
- IPS score (≤ 3 points and > 3 points)
- Baseline Disease Status (Relapsed and Refractory):
  - Relapsed: Best overall response to the last chemotherapy/transplant is CR or PR, and time from the end of chemotherapy/transplant to progression is > 6 months.
  - Refractory: 1. Best overall response to the last chemotherapy/transplant is CR, PR, or not evaluated, and time from the end of chemotherapy/transplant to progression is ≤ 6 months. Or, 2. Best overall response to the last chemotherapy/transplant is PD or SD.
  - Missing: Response to the last chemotherapy/transplant is not evaluated, and time from the end of last chemotherapy/transplant to progression is > 6 months.

5.1.5. Analysis window

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

When a planned visit is missing, or one of the test items in the planned visit is missing or its results are invalid, the unplanned visit closest to the planned visit will be considered as the protocol visit. If the time of two unplanned visits is equally close to the time of planned visit, the later unplanned visit will be selected as the protocol visit. All visits in the protocol will be sorted chronologically. In addition, once an unplanned visit is defined in one protocol, it will no longer be defined in other protocols. In the analysis carried out by visits, the statistical analysis will be performed according to the planned time points in the protocol, i.e., the time points of unplanned visits do not need to be shown.

5.1.6. Missing data

If the missing date and month needs to be imputed, they will be imputed in accordance with the imputation rules of Hengrui date-type data. If not recorded in events, the time-event data will be right-censored. See appendix for information on how to judge censoring and calculate censored date. Other missing data will not be handled.

5.2. Study Subjects

Demographics and baseline characteristics will be analyzed based on FAS, and medical history and prior therapy will be analyzed based on SS.

5.2.1. Disposition of subjects

The number of screened subjects, number of enrolled subjects, number and percentage of treated subjects, number and percentage of subjects in the analysis sets, number of subjects who discontinue study/treatment, and number and percentage of corresponding subjects to the reasons for discontinuation.

5.2.2. Demographics and baseline characteristics

Age, gender, ethnicity, height, IPS score, B symptoms, and the occurrence of pulmonary involvement and mediastinal lesions of the subjects are summarized using descriptive statistics, respectively. Continuous variables such as age and body height are summarized using descriptive statistics, such as number of evaluable subjects (n), mean and standard deviation, median, min and max. Categorical variables such as gender and ethnicity will be summarized using descriptive statistics, including number of evaluable subjects per category and corresponding percentage in total population.

5.2.3. Medical history

The analysis of tumor diagnosis includes time to first pathological diagnosis, pathological classification, and Ann Arbor staging.

5.2.4. Prior therapy and concomitant medication

The analyses of previous therapies include time from the last dose to enrollment (< 3 months, 3–6 months, > 6 months), previous therapies (brentuximab vedotin, autologous stem cell transplant, and radiotherapy), and analysis of chemotherapy history (chemotherapy and autologous stem cell transplant) which includes the number of therapy line (1, 2, 3, 4, ≥ 5) and baseline disease status (relapsed/refractory). These analyses will be summarized using frequency and percentage. The number of therapy line (continuous variable) and time from the last dose to enrollment (month) will be summarized using descriptive statistics, such as mean, standard deviation, median, min, and max.

All prior concomitant medications, concomitant medications, and concomitant non-drug therapy will be listed.

5.2.5. Protocol deviations

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

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

Important protocol deviations include but are not limited to the following:

- Serious violation of the inclusion/exclusion criteria;
- Meeting the withdrawal criteria but the subject did not withdraw from the study;
- Use of medication prohibited by the protocol.

5.3. Treatment Compliance

The use of investigational drug during the treatment period is summarized using descriptive statistics by cycles. All study drugs will be listed by subject code, treatment stage, dosing date, and use of medications.

5.4. Efficacy Analysis

Primary efficacy analysis

The primary efficacy endpoint of the study is IRC-assessed ORR. Analysis will be based on results assessed by IRC and the investigator, respectively. The primary analysis of ORR is based on IRC assessment. ORR will be calculated and the 95% confidence interval will be calculated using the Clopper-Pearson method. The analysis will be based on FAS and PPS (mainly on the FAS).

In addition, the consistency between IRC-assessed and investigator-assessed PD and non-PD, CR + PR, and non-CR + PR will be analyzed using Amit's method based on the FAS.

Secondary efficacy analysis

Identical to the primary efficacy analysis, the secondary efficacy analysis will be performed based on IRC-assessed and investigator-assessed results, respectively. However, the secondary efficacy analysis will be based on FAS only.

Among the secondary efficacy endpoints in this study, time-event endpoints such as DoR, PFS, TTP, and OS will be analyzed using the Kaplan-Meier method, and TTR will be summarized using descriptive statistics. Survival curves could be plotted if needed.

The secondary efficacy endpoint of DCR will be analyzed using the same statistical method as for ORR.

In addition, best overall response will be summarized using descriptive statistics.

5.4.1. Exploratory analyses

None.

5.4.2. Subgroup analysis

The ORR analysis will be based on FAS. The ORR in subgroups and the corresponding 95% confidence interval will be analyzed. See 5.1.4 for subgroups and the definitions.

5.4.3. Other analysis

None.

5.5. Safety Analyses

All safety analyses will be conducted based on SS.

5.5.1. Extent of exposure

Duration of drug exposure and number of doses received will be summarized.

5.5.2. Adverse events

TEAE is any adverse event after treatment with the investigational drug. AEs will be summarized using descriptive statistics according to Hengrui's Statistical Analysis Reporting Standards, including but not limited to:

- Overview of AEs (of all causes and treatment-related);
- Summary of SAEs;

- Incidence and severity of AEs (of all-cause and treatment-related);
- Causality assessment of AEs;
- Analysis of adverse events of special interest (AESIs).

AESIs mainly include the following:

- Haemangioma (time to onset and duration)
- Grade ≥ 3 infusion reaction
- Grade ≥ 2 diarrhoea/colitis, uveitis, interstitial pneumonia
- Grade ≥ 3 other immune-related adverse events: skin, digestive tract, lungs, endocrine (by system organ class)
- Hepatic enzyme abnormalities: ALT, AST and total bilirubin are abnormal against baseline
- Grade 4 amylase or lipase increased.

For AEs occurring after the start of study treatment, treatment-related AEs include those whose causality with the investigational drug is related, possibly related, unlikely related, or unassessable; if the causality assessment is missing, then the AE will be deemed treatment-related for analysis.

5.5.3. Laboratory evaluations

The baseline is defined as the last measurement before the first dose. Data will be summarized using descriptive statistics according to Hengrui Statistical Analysis Reporting Standards, including but not limited to:

- Incidence of abnormal measurements and parameters;
- Shift tables and listings of changes in measurements, visits, and parameters from baseline (normal/abnormal).
- Shift tables of CTCAE grades before and after treatment.

Listings of abnormal laboratory will be provided.

5.5.4. Vital signs

The baseline is defined as the last measurement before the first dose. Data will be summarized using descriptive statistics according to Hengrui Statistical Analysis Reporting Standards, including but not limited to: descriptive statistics and categorical analysis of absolute values and changes from baseline at scheduled visits in the protocol. Blood pressure and heart rate will be summarized. See Appendix B for classification criteria.

5.5.5. Electrocardiogram (ECG)

ECG results will be listed.

5.5.6. Physical examination

Data will be summarized using descriptive statistics according to Hengrui Statistical Analysis Reporting Standards, including but not limited to: descriptive statistics of absolute values at scheduled visits in the protocol.

5.5.7. Other safety measures

Baseline ECOG PS and post-baseline changes will be summarized by visit. B symptom scores will be summarized by visit and analyzed using frequency and percentages (according to categorical variables).

Echocardiography results will be listed.

5.6. Pharmacokinetic Analysis

PK analysis is provided by the vendor and not included in this SAP.

5.7. Pharmacodynamics Analysis

Not involved.

5.8. Other Analysis

None.

6. INTERIM ANALYSIS

No routine interim analysis.

7. REFERENCES

None.

8. APPENDIX

Appendix 1.1. Definition of progression-free survival (PFS).

No.	Situation	Date of Progression/ Censoring	Handling
1	No baseline assessment	Date of first dose	Censoring
2	No post-baseline assessment, and no death	Date of first dose	Censoring
3	Any death (except #5)	Date of death	Event
4	Progressive disease during study (including after missing one assessment)	Date of progressive disease	Event
5	Death or progressive disease after 2 consecutive missing tumor assessments	Date of last tumor assessment before missing	Censoring
6	Withdrawal from the study due to toxicity or other reasons without PD or death record	Date of last tumor assessment before study withdrawal	Censoring
7	No progressive disease or death recorded before the initiation of new anti-cancer treatment	Date of last recorded objective tumor assessment as no PD before the initiation of new anti-tumor treatment	Censoring