Title: A single-arm, open-label, multi-center, phase II clinical study of anti-PD-1 antibody SHR-1210 in recurrent/metastatic nasopharyngeal carcinoma subjects who have received previous at least two lines of chemotherapy

Clinical trial registration number: NCT03558191

Date: 2 Mar., 2020

A Single-Arm, Open-Label, Multi-Center, Phase II Clinical Study of Anti-PD-1 Antibody SHR-1210 in Recurrent/Metastatic Nasopharyngeal Carcinoma Patients Who Have Received Previous at Least Two Lines of Chemotherapy

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
Senior Medical Director	Qing Yang
Associate Director of 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
PFS	Progression-free survival
PR	Partial response
PPS	Per-protocol set
SD	Stable disease
SS	Safety set
TEAE	Treatment-emergent adverse event

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1 REVISION

None

2 INTRODUCTION

This is a phase II clinical study to investigate and evaluate the efficacy and safety of anti-PD-1 antibody SHR-1210 in patients with recurrent/metastatic nasopharyngeal carcinoma who have failed at least two lines of chemotherapy.

This statistical analysis plan is written based on the final version of its study protocol (version: 1.0, version date: 20 Apr., 2018).

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

2.1 Study Design

This is a single-arm, open-label, multi-center phase II clinical study to investigate and evaluate the efficacy and safety of anti-PD-1 antibody SHR-1210 in subjects with recurrent/metastatic nasopharyngeal carcinoma who have failed at least two lines of chemotherapy. A total of 155 subjects will be enrolled.

After being fully informed and providing a written informed consent form, eligible subjects will receive SHR-1210 200 mg IV, q2w, in treatment cycles of 4 weeks. Treatment will continue until the criteria for treatment discontinuation as specified in the protocol are met. After the end of treatment, subjects will continue safety follow-ups and survival follow-ups. Subjects who discontinue the treatment due to reasons other than progressive disease will also be followed for progressive disease after discontinuation. SHR-1210 is an immune checkpoint inhibitor and, according to the experience of similar drugs, some subjects may experience delayed or early tumor pseudo progression after receiving immunotherapy drugs. Therefore, the benefits of immunotherapy drugs may be underestimated based on RECIST 1.1 only. As a result, it is suggested in this study to carry out imaging evaluation based on both RECIST 1.1 and iRECIST. For subjects who are clinically stable after the first occurrence of PD, the investigator may decide to allow the subjects to continue using SHR-1210 and undergo imaging examination again after 4-6 weeks. If the subsequent imaging examination confirms PD, the subjects should discontinue SHR-1210 treatment unless the investigator believes that the subjects can continue to gain clinical benefit from the SHR-1210 treatment, which should be decided upon discussion with the sponsor.

After subjects are enrolled in the study, safety follow-ups will be conducted before administration of SHR-1210 on D1 and D15 of each treatment cycle. After treatment begins, response will be assessed once every 2 cycles (8 weeks) until the end of treatment, withdrawal of informed consent, or death.

The schedule of activities is detailed in the protocol.

2.2 Study Objectives

- **Primary objective:**

To evaluate the objective response rate (ORR) of SHR-1210 in subjects with recurrent/metastatic nasopharyngeal carcinoma who have failed at least two lines of chemotherapy by independent review committee (IRC).

- **Secondary objective:**

To evaluate the efficacy and safety of SHR-1210 in subjects with recurrent/metastatic nasopharyngeal carcinoma who have failed at least two lines of chemotherapy.

- **Exploratory objectives:**

To evaluate the relationship between PD-L1 expression in tumor tissues and efficacy of SHR-1210; to evaluate the immunogenicity of SHR-1210 in subjects with recurrent/metastatic nasopharyngeal carcinoma; and to investigate the correlation between immunogenicity and efficacy/safety.

3 STATISTICAL HYPOTHESIS

The primary endpoint of this study is the ORR. The ORR of the investigational drug is compared with the ORR of 15% for the monotherapy (refer to the ORR in the single-arm study of pembrolizumab in the treatment of head and neck squamous cell carcinoma for which the drug is approved by the FDA). The hypotheses are as follows:

H0: The ORR of the investigational drug = 15%

H1: The ORR of the investigational drug ≠ 15%

α level: 0.05 (two-sided).

If the lower limit of the 95% CI for the ORR of the investigational drug exceeds 15%, the investigational drug is considered effective compared with historical control data.

4 STUDY ENDPOINTS

4.1 Primary Endpoint

IRC-assessed ORR of SHR-1210 in subjects with recurrent/metastatic nasopharyngeal carcinoma who have failed at least two lines of chemotherapy.

4.2 Secondary Endpoints

4.2.1 Efficacy

- Investigator-assessed ORR
- Duration of response (DoR)
- Disease control rate (DCR)
- Time to response (TTR)
- Progression-free survival (PFS) as per RECIST 1.1
- Overall survival (OS)

4.2.2 Safety

The following safety data will be collected and summarized following the study protocol (see the study protocol for the endpoints and collection time in details).

- Adverse events
- Laboratory tests
- Vital signs
- 12-Lead ECG
- Physical examination

4.3 Exploratory Endpoints

- To evaluate the relationship between PD-L1 expression and efficacy of SHR-1210
- To investigate the anti-SHR-1210 antibodies (ADAs) in subjects after injection of SHR-1210

5 STATISTICAL ANALYSIS

5.1 General Considerations

5.1.1 Analysis sets

- Full analysis set (FAS): all enrolled subjects who have received at least one dose of the investigational drug. The FAS is the primary analysis set for the efficacy analysis of this study.
- Per-protocol set (PPS): a subset defined in the FAS, excluding subjects with important protocol deviations that have a significant impact on efficacy.

- Safety set (SS): all enrolled subjects who have received at least one dose of the investigational drug.
- Slice-testing biomarker analysis set (SBAS): all enrolled subjects who have received at least one dose of the investigational drug and have at least one slice-testing biomarker data for PD-L1.
- ADA analysis set (ADAS): all enrolled subjects who have received at least one dose of the investigational drug and have at least one ADA assessment data.

5.1.2 General analytical method

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 formulas:

- If an examination/event occurs before the start of the study, days = examination date - study start date;
- If an examination/event occurs after the start of the study, days = examination date - study start date + 1.

General analysis

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

- Measurement data will be summarized using number of subjects, mean, standard deviation, median, maximum, and minimum;
- Count data will be summarized using frequency and percentage;
- For time-to-event data, Kaplan-Meier method will be used to estimate the survival function and median time to event onset, and a survival curve will be plotted.

Number of decimal places

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

- The decimal places of the minimum and maximum will remain the same as those of the raw data to be acquired. Mean and median should have one more decimal place than those of the raw data, and the standard deviation should have 2 more decimal places than that of the raw data. However, there can only be at most 4 decimal places.
- The percentage will be rounded to 1 decimal place. If the frequency is 0, the percentage is not displayed.
- The P value will retain 4 decimal places. If the P value is < 0.0001, it will be expressed as "< 0.0001"; if the P value is > 0.9999, it will be reported as "> 0.9999".
- The 95% CI, if being a decimal, will retain at least 2 decimal places, up to 4 decimal places.
- Time to event (in months) will be rounded to one decimal place.
- Hazard ratio will be rounded to two decimal places.

Analysis software

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

5.1.3 Covariates and subgroups

Subgroups include but are not limited to the following: gender (male/female), age (< 50 years old or ≥ 50 years old), baseline anti-tumor treatment (2 lines, 3 lines or more), baseline ECOG PS (0 and 1), number of organs with metastases (2 and ≥ 3), PD-L1 expression level in tumor tissues (< 1% and ≥ 1%, < 5% and ≥ 5%, or < 10% and ≥ 10%), and baseline EBV-DNA (negative or positive).

5.1.4 Analysis window

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

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.

5.1.5 Missing data

Missing dates that are incalculable shall be imputed as follows. However, the listings are still presented with actual records.

5.1.5.1 Medical history

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

- If the day is missing, it will be imputed with 1 of that month.
- If both month and day are missing while the year precedes the year of the first dose, the date will be imputed with 1 Jan.
- If both month and day are missing while the year is the same as the year of the first dose, the date will be imputed with 1 Jan.
- Completely missing dates will not be imputed.

5.1.5.2 Adverse events

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

- If the start date of an AE is completely missing, it will be imputed with the date of the first dose.
- If only the day of the start date of an AE is missing, while the year and month are the same as those of the first dose, the day will be imputed with the day of the first dose.
- If both month and day of the start date of an AE are missing, while the year is the same as that of the first dose, they will be imputed with the month and day of the first dose.
- In other cases when the month or day of the start date of an AE is missing, it will be imputed with 1.
- If only the day of the end date of an AE is missing, it 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 when the end date of an AE is missing, it will not be imputed. If the end date of an AE is later than the end date of study and if the outcome of the AE is ongoing, the end date of the study will be used as the end date of the AE.

5.1.5.3 Concomitant medication

If the date related to the concomitant medication is missing, the rules for imputing are as follows:

- If the start date of the concomitant medication is completely missing, it will be imputed with the date of the first dose.
- If only the day of the start date of the concomitant medication is missing, while the year and month are the same as those of the first dose, the day will be imputed with the day of the first dose.
- If both month and day of the start date of the concomitant medication are missing, while the year is the same as that of the first dose, they will be imputed with the month and day of the first dose.

- In other cases when the month or day of the start date of the concomitant medication is missing, it will be imputed with 1.
- If only the day of the end date of the concomitant medication is missing, it 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 when the end date of the concomitant medication is missing, it will not be imputed.

5.1.5.4 Drug exposure

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

- If the date of the last dose is completely missing while the date of death and CRF page for treatment discontinuation are absent, the subject is considered to be under continuous administration and the date of the last dose will be imputed with the end date of the study.
- If the date of the last dose is completely or partially missing while the date of death or CRF page for treatment discontinuation is present (both are before the end date of the study), the date of the last dose will be imputed as follows:

  = 31-12-YYYY (if the year YYYY is known, and if YYYY < min (year) [date of treatment discontinuation, date of death])

  = The last day of the month (if both the year and month are not missing, and if YYYY < min (year) [date of treatment discontinuation, date of death])

  = The last day of the month (if both the year and month are not missing, and if YYYY = min (year) [date of treatment discontinuation, date of death], and MM < min (month) [date of treatment discontinuation, date of death])

  = min (date of treatment discontinuation, date of death), other cases.

5.1.5.5 Rules for imputing the last survival date and the start date of a new anti-tumor treatment

5.1.5.5.1 Last survival date

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

- All dates of examinations and evaluations of the subjects (tumor response evaluation, blood tests (laboratory, PK), vital signs, physical examination, ECOG PS, pregnancy test, urinalysis, and routine stool test)

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

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

5.1.5.5.2 Date of death

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

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

  - Day is missing: 01-MM-YYYY
  - Month and day are missing: 01-01-YYYY

5.1.5.5.3 Start date of a new anti-tumor treatment

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

- If the end date of a new anti-tumor treatment is partially missing or not missing, it will be used to derive the start date of the new anti-tumor treatment.
  - If the month and day of the end date of the new anti-tumor treatment are missing while the year is not missing, 31 Dec. will be used as the end date of the new anti-tumor treatment.

- If only the day of the end date of the new anti-tumor treatment is missing, the last day of the month will be used as the end date of the new anti-tumor treatment.

- If the start date of a new anti-tumor treatment is completely missing or only the year is not missing, it will be derived and imputed according to the following rules:
  - If the start date of the new anti-tumor treatment is completely missing, the start date imputed = min [max (PD date + 1, date of last dose + 1), end date of new anti-tumor treatment]
  - Only the year (YYYY) of the start date of the new anti-tumor treatment is not missing
    1) If YYYY < min (year) [max (PD date + 1, date of last dose + 1), end date of new anti-tumor treatment], the date will be imputed as 31-12-YYYY.
    2) In other cases, if YYYY = min (year) [max (PD date + 1, date of last dose + 1), end date of new anti-tumor treatment], the date imputed = min [max (PD date + 1, date of last dose +1), end date of new anti-tumor treatment].
    3) In other cases, if YYYY > min (year) [max (PD date + 1, date of last dose + 1), end date of new anti-tumor treatment], the date imputed = 01-01-YYYY.

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

5.2 Sample Size

Efficacy hypothesis:

According to study SHR-1210-101, the ORR of all dose groups (n = 93) of NPC subjects was 29.0%, and the ORR of the 200 mg dose group (n = 68) was 36.8%. In the subgroup analysis, the ORR of all dose groups (n = 58) of subjects who had failed at least two lines of chemotherapy was 27.6%, and the ORR of the 200 mg dose group (n = 43) was 37.2%. Also, referring to the efficacy results of similar drugs, the intended study for registration will use a dose of 200 mg, and a conservative estimate of the upper limit of ORR is set at 26%.

Pembrolizumab for the treatment of head and neck squamous cell carcinoma was approved by the FDA with an ORR of 16% in a single-arm study. Therefore, it is stipulated that the lower limit of the 95% confidence interval for the ORR for this study should not be less than 15%.

Sample size calculation:

According to the above efficacy hypothesis (ORR = 26%), with a one-sided alpha = 0.025, enrolling 139 subjects can achieve a power of 90% that the lower limit of 95% confidence interval for ORR is not less than 15%. In order to ensure that the 139 subjects are included in the evaluation, assuming a dropout rate of 10%, 155 subjects should be enrolled.

5.3 Subject Description

5.3.1 Subject distribution

The descriptive statistics of the screening status of the subjects, including the number and percentage of subjects failing the screening, will be summarized based on the signing of informed consent form and categorized by the reasons for screening failure. The enrolled subjects receiving or not receiving the study treatment will be described, and the reasons for not receiving the study treatment or discontinuing the study treatment will be descriptively summarized with a detailed list.

Subjects included in each analysis set will be descriptively summarized, and the reasons for being excluded from the FAS, PPS, SS, SBAS, and ADAS will be listed in detail.

5.3.2 Demographics and other baseline characteristics

The gender, age, age stratification [< 50 years old and ≥ 50 years old] (those ≥ 50 years old can be further divided into ≥ 50 to < 65 vs. ≥ 65), ethnicity, height (cm), weight (kg), and body mass index BMI (kg/m^2) of the subjects will be summarized using descriptive statistics. Demographic characteristics will be described based on the FAS.

Formula of BMI calculation: Baseline weight (kg)/Baseline height (m^2).

The tumor histological classification, metastasis, number of organs with distant metastases, location of metastases, clinical stage before enrollment, course of disease, and time from the date of last progression/recurrence to the randomization will be summarized. A detailed listing of subjects for tumor diagnosis will be provided.

Course of disease (month) is defined as the time from the date of first pathological diagnosis to the date of first dose, and its formula of calculation is as follows: (Date of first dose - Date of first pathological diagnosis + 1)/30.4375.

The calculation formula for the time (month) from the date of last progression/recurrence to the date of first dose is as follows: (Date of first dose - Date of last progression/recurrence + 1)/30.4375.

Calculation of the number of organs with distant metastasis: the number of metastasis site checked in EDC (excluding the nasopharynx and neck; "other" is counted only once)

5.3.3 Medical history and cancer surgery history

If permitted, medical history and cancer surgery history will be coded per the latest version of MedDRA, categorized by PT and SOC, and summarized. In addition, a detailed list of medical history will also be provided.

5.3.4 History of anti-tumor treatment

For the history of anti-tumor treatment, the following descriptive statistics will be provided:

- Number of lines of previous anti-tumor treatment summarized by categorical variables
- Number and percentage of subjects who have received platinum-based medications
- Number and percentage of subjects who have received radiotherapy to the primary tumor lesion (nasopharynx)
- Summary of type of treatment (chemotherapy, targeted therapy, others) and purpose of treatment (neoadjuvant therapy, adjuvant therapy, others).

A detailed listing will be provided for the history of anti-tumor treatment; a detailed listing will also be provided for the cancer surgery history, history of other surgeries, and history of radiotherapy.

5.3.5 History of drug allergy

A detailed listing of subjects with history of drug allergies will be provided.

5.3.6 Past medication and concomitant medication

Past medications are defined as drugs whose use has been completed before the first dose of the investigational drug. Concomitant medications are defined as drugs that are used after the first dose of the investigational drug, or drugs that are used before the first dose of the investigational drug but are continued to be used during the treatment period.

The past and concomitant medications will be classified and summarized according to ATC level 2 and PT. In the summary description, if a subject uses the same drug (classified by ATC) more than once, it is counted only once.

A listing of all past and concomitant medications will be provided.

5.3.7 Subsequent anti-tumor treatment

The number and percentage of subjects who have subsequently received new anti-tumor treatments will be summarized by the type and purpose of treatments, and a detailed listing will be provided.

5.3.8 Protocol deviation

Prior to database locking, the investigator and the sponsor will discuss and determine protocol deviations. Protocol deviations can be classified as "major" or "minor".

Based on the FAS, all major protocol deviations will be descriptively summarized by type, and be tabulated for analysis. In addition, a detailed listing of protocol deviations will be provided. The listing will include all major and minor protocol deviations.

5.4 Compliance

The descriptive statistics of treatment compliance will be analyzed based on SS.

The duration of drug exposure, drug exposure, number of treatment cycles, frequency of doses, frequency of and reason for dose interruption, frequency of and reason for dose delay, and the compliance rate of the subjects receiving camrelizumab will be summarized using descriptive statistics.

Since camrelizumab is administered twice in one treatment cycle, the treatment cycle is considered completed providing that at least one administration is completed in the cycle.

The duration of exposure to the investigational drug (weeks) is defined as: (date of last dose - date of first dose + 1)/7.

Drug exposure is defined as the cumulative amount of investigational drug received by the subject.

Planned exposure to the investigational drug (mg) = (Date of last dose - Date of first dose + 14)/ 14 ×200

Compliance rate% = (Actual cumulative exposure (mg)/Planned cumulative exposure (mg)) ×100%.

A detailed listing will be provided for the administration of camrelizumab.

In addition, the follow-up time of the subjects and the number and percentage of subjects who continue camrelizumab medication after PD will be counted.

Follow-up time (months) = (Date of last contact or date of death (whichever occurs first) - date of first dose + 1)/12

5.5 Efficacy Analysis

5.5.1 Primary efficacy analysis

The primary endpoint is the IRC-assessed ORR, which will be analyzed based on the FAS.

The ORR refers to the objective tumor response as per RECIST 1.1 and is obtained by dividing the number of subjects whose best overall response (BOR) during the trial is complete response (CR) or partial response (PR) by the number of subjects included in the FAS. Any CR or PR after the new anti-tumor treatment will not be included in the ORR calculation.

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

The above analyses will be repeated in the PPS.

5.5.2 Secondary efficacy analysis

The secondary efficacy endpoints of this study include the investigator-assessed ORR, duration of response (DoR), disease control rate (DCR), time to response (TTR), progression-free survival (PFS), and overall survival. The secondary efficacy analysis will be based on the FAS only. The consistency between IRC-assessed and investigator-assessed PD/non-PD, BOR, and CR/PR will be analyzed using Amit's method.

- Investigator-assessed ORR

Analyzed using the same method as that for the primary efficacy endpoint. In addition, the consistency between IRC-assessed and investigator-assessed PD/non-PD, BOR, and CR/PR will be analyzed using Amit's method based on the FAS.

- Duration of response (DoR)

DoR refers to the time from the first PR or CR to the subsequent first PD or death.

DoR will only be assessed in subjects with a BOR after treatment. The end date of tumor response must be consistent with the PD date of PFS or the date of death. The Kaplan-Meier product-limit method will be used to estimate the median survival, and its 95% CI will be calculated. If possible, the 6- and 12-month DoRs and their 95% CIs will be estimated. BOR of tumor response indicates CR or PR. The date of response is the date when response is first observed. The assessments by the investigator and the IRC will be analyzed separately.

Note: For subjects with pseudo progression, such as subjects who have PR or SD after PD, the DoR event is the first PD after this PR.

Censoring rules: Follow the method for PFS (see PFS Analysis).

- Disease control rate (DCR)

DCR refers to the proportion of subjects whose BOR is CR, PR, or SD (SD ≥ 8 weeks (± 7 days)). DCR is defined as a parameter of best response starting from the date of first dose to the date of objective documentation of PD or subsequent anti-tumor treatment (whichever occurs first). For subjects with no record of PD or subsequent anti-tumor treatment, the DCR will be determined based on all results of response assessment.

DCR will be analyzed using the same method as that for ORR. The IRC- and investigator-assessed results will be summarized separately.

- Time to response (TTR)

TTR is the time from the first dose to the first occurrence of CR/PR.

TTR will only be measured in subjects with a BOR after treatment. The date of response is the date of first documented response instead of the date of confirmation. TTR will be statistically described by the number of subjects, mean, standard deviation, median, minimum, and maximum. The assessments by the investigator and the IRC will be analyzed separately.

- Progression-free survival (PFS)

PFS is the time from the first dose to the first occurrence of PD.

The Kaplan-Meier method will be used to estimate the PFS, plot the survival curve, and estimate the median PFS, and its 95% CI will be calculated (using the Brookmeyer-Crowley method with log-log transformation). The IRC- and investigator-assessed PFS will be summarized separately.

The censoring rules are as follows:

- If there is no baseline tumor assessment, the date of first dose will be censored.
- If there is no post-baseline objective tumor response evaluation or death, the date of first dose will be censored.
- If there is no PD or death as per RECIST 1.1, the date of the last objective tumor response evaluation will be censored.
- If there is no imaging PD or death before the start of any new anti-tumor treatment, then the date of the last objective tumor response assessment prior to the start of a new anti-tumor treatment will be censored.
- If the subject misses ≥ 2 planned imaging assessments in a row before PD or death (i.e., the time between PD or death and prior tumor assessment is ≥ 126 days), the censoring date is the date of the last objective tumor imaging assessment carried out before the

missing imaging assessments; if no tumor assessments are carried out after the first dose, the time interval from the date of baseline tumor imaging assessment to the date of the event will be calculated. If it exceeds 126 days, it is recorded as censored data and is censored to the date of the first dose.

Definition of the date of tumor PD/non-PD:

- For PD, it is the earliest of the dates of imaging examination of progression.
- For non-PD, it is the latest of the dates of imaging examination.

- Overall survival (OS)

OS is defined as the time from the first dose to the death of the subject due to any cause.

The Kaplan-Meier method will be used to estimate the OS, plot the survival curve, and estimate the median OS, and its 95% confidence interval will be calculated (Brookmeyer-Crowley method: log-log transformation, standard error calculated using the Greenwood formula).

Censoring rules:

- If there is no death during the study, the survival will be censored on the date of the last survival follow-up.
- If a subject is lost to follow-up, the survival will be censored on the date of the last survival follow-up before lost to follow-up.

5.5.3 Subgroup analysis

The ORR, DoR, DCR, PFS, and OS will be analyzed according to the following factors (including but not limited to).

Stratification factors: gender (male/female), age (< 50 years old or ≥ 50 years old), baseline anti-tumor treatment (2 lines, 3 lines or more), baseline ECOG PS (0 and 1), number of organs with metastases (2 and ≥ 3), PD-L1 expression level in tumor tissues (< 1% and ≥ 1%, < 10% and ≥ 10%, or < 20% and ≥ 20%), and baseline EBV-DNA (negative or positive).

If possible, a subgroup analysis will also be conducted on the ORR and PFS by the presence or absence of capillary hyperplasia.

5.6 Safety Analysis

Safety analysis will be based on the safety set. Unless otherwise stated, safety will be summarized using descriptive statistics.

5.6.1 Drug exposure

See the Compliance section.

5.6.2 Adverse events

Safety information should be collected from the subject's signing of the informed consent form to 90 days after the last dose or the start of new anti-tumor treatments (if the anti-tumor treatment starts within 30 days after the last dose, the subject should be followed up until at least 30 days after the last dose; if the tumor treatment starts beyond 30 days after the last dose, the subjects should be followed up until the start of the new anti-tumor treatment).

A treatment-emergent adverse event (TEAE) is defined as an AE that occurs on or after the first dose of the investigational drug but no later than 90 days after the last dose of the investigational drug (an AE that occurs more than 90 days after the last dose and is judged to be definitely or possibly related to the investigational drug will also be included in the analysis). Causality with the investigational drug consists of "definitely related, possibly related, and indeterminable"; if the causality is missing, the AE will be considered treatment-related for analysis. SAE refers to a medical occurrence during the clinical study that results in hospitalization, prolonged hospitalization, disability, incapacity, life-threatening or death, or congenital malformation. See the protocol for the definition of AE of special interest. The immune-related AEs per the investigator's judgment are those whose CRF option for immune-related AEs is shown as yes, undeterminable, or missing.

Attention should be paid to immune-related AEs, including immune-related pneumonia, immune-related diarrhea and colitis, immune-related hepatitis, immune-related myocarditis, immune-related nephritis, immune-related endocrine diseases, immune-related cutaneous adverse drug reactions, and infusion reactions.

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

The incidence of AEs will be sorted from high to low based on their corresponding SOC and treatment groups, and the incidence of AEs in each SOC will be sorted from high to low based on their PT. If the incidences of ≥ 2 PT are equal, the AEs will be sorted alphabetically.

TEAEs will be statistically described by frequency and percentage. These include but are not limited to:

- Overview of AEs (AEs/treatment-related AEs, Grade ≥ 3 AEs/treatment-related AEs, AEs/treatment-related AEs resulting in treatment interruption, AEs/treatment-related AEs resulting in treatment discontinuation, AEs/drug-related AEs resulting in death, SAEs/treatment-related SAEs, SAEs/treatment-related SAEs resulting in treatment interruption/discontinuation, SAEs/treatment-related SAEs resulting in death, AESIs, irAEs per the investigator's judgment, irAEs resulting in death per the investigator's judgment; subjects with the highest CTC Grade: 1-5)

- AEs will be summarized by SOC, PT, and CTCAE grade
- Treatment-related AEs will be summarized by SOC, PT, and CTCAE grade
- Grade ≥ 3 AEs will be summarized by SOC and PT
- Grade ≥ 3 treatment-related AEs will be summarized by SOC and PT
- AEs with an incidence of ≥ 5% will be summarized by SOC and PT
- Treatment-related AEs with an incidence of ≥ 5% will be summarized by SOC and PT
- AEs resulting in treatment interruption will be summarized by SOC and PT
- Treatment-related AEs resulting in treatment interruption will be summarized by SOC and PT
- AEs resulting in treatment discontinuation will be summarized by SOC and PT
- Treatment-related AEs resulting in treatment discontinuation will be summarized by SOC and PT
- AEs resulting in death will be summarized by SOC and PT
- Treatment-related AEs resulting in death will be summarized by SOC and PT
- SAEs will be summarized by SOC and PT
- Treatment-related SAEs will be summarized by SOC and PT
- SAEs resulting in treatment interruption will be summarized by SOC and PT
- SAEs resulting in treatment discontinuation will be summarized by SOC and PT
- SAEs resulting in death will be summarized by SOC and PT
- Treatment-related SAEs resulting in death will be summarized by SOC and PT
- AESIs will be summarized by SOC and PT
- AESIs resulting in treatment interruption will be summarized by SOC and PT
- AESIs resulting in treatment discontinuation will be summarized by SOC and PT
- Outcomes and corrective treatment of AESIs will be summarized by SOC and PT
- irAEs per the investigator's judgment will be summarized by SOC and PT
- irAEs per the investigator's judgment resulting in treatment interruption will be summarized by SOC, PT, and CTCAE grade
- irAEs per the investigator's judgment resulting in treatment discontinuation will be summarized by SOC, PT, and CTCAE grade

- irAEs per the investigator's judgment resulting in death will be summarized by SOC, PT, and CTCAE grade
- irAEs resulting in death will be summarized by the classification of irAEs and PT
- The number and percentage of subjects experiencing at least one irAE of special interest will be summarized by the classification of irAEs and PT; these irAEs will be summarized according to the highest CTCAE severity grade
- irAEs of special interest resulting in treatment interruption/discontinuation will be summarized by the classification of irAEs
- The number and percentage of subjects experiencing irAEs of special interest will be summarized by the classification of irAEs
- Reactive capillary endothelial proliferation will be summarized (including location, concomitance, infection, ulceration, pain, bleeding, treatment)

All collected AEs, AEs resulting in treatment interruption, AEs resulting in treatment discontinuation, AEs resulting in death, SAEs, and reactive capillary endothelial proliferation will be listed.

In addition, for irAEs of special interest (classified per irAEs), the time to the occurrence of AEs, the time to the occurrence of Grade ≥ 3 AEs, the duration of AEs, the duration of Grade ≥ 3 AEs, the response time of AEs, and the response time of Grade ≥ 3 AEs will be summarized.

The time (day) to the occurrence of AE is defined as the time from the date of the first administration of investigational drug to the date of the first occurrence of the AE. If one subject has experienced multiple times of one AE, the date of the first occurrence of the AE will be used for calculation regardless of the AE grading. The formula is as follows: Start date of AE - Date of the first dose of investigational drug + 1.

The time (day) to the occurrence of Grade ≥ 3 AE is defined as the time from the date of the first administration of investigational drug to the date of the first occurrence of the Grade ≥ 3 AE. The calculation method is similar to the time to the occurrence of AE.

The response time of AE (day) is defined as the date from the start to the end of the AE, and the calculation formula is as follows: End date of AE - Start date of AE + 1. If one subject has experienced multiple times of one AE, the cumulative time of the AE will be calculated, but the time overlapping of multiple times of the AE should be avoided in the calculation. If an AE is not relieved by the cut-off point of analysis or the end of the study (the response of the AE will be judged by the last outcome information of the AE, and the responses include AE outcome of recovered/resolved, recovered/resolved with sequelae, and alleviated), the end date of the AE will be used for censoring. If the end date of the AE is missing, the date will be imputed

according to Section 5.1.5 before censoring. If one AE category (such as the category of immune-related AE) contains more than one AEs (by PT) and one of these AEs is not relieved, this AE category will be judged as not relieved.

The duration of AE is defined similarly to the response time of AE, with the difference that the duration of AE does not need to consider the state of censoring.

Time to the occurrence of AE, time to the occurrence of Grade ≥ 3 AE, response time of AE, and response time of Grade ≥ 3 AE will only be calculated for the population who have experienced AE, and the corresponding median time and 95% confidence interval will be estimated by the Kaplan-Meier product limit method. For duration of AE and duration of Grade ≥ 3 AE, a descriptive summary will be provided as measurement data.

For irAEs of special interest (by irAEs), listing of subjects receiving high-dose corticosteroids (defined as at least one dose or a single daily dose of ≥ 40 mg of the equivalent dose of prednisone), the starting dose of corticosteroids, and the duration of dosing will also be provided. The dosage of different hormonal drugs will be converted into the equivalent dose of prednisone according to the following formula: 0.75 mg of dexamethasone = 5 mg of prednisone = 5 mg of prednisolone = 4 mg of methylprednisolone = 20 mg of hydrocortisone = 0.8 mg of betamethasone = 5 mg of prednison.

If one subject experiences one AE and receives two or more hormones during the presence of the AE, the starting dose of the hormone used first will be involved in the statistics of starting doses (i.e., the starting dose(s) of subsequent hormone therapy/therapies will not be involved in the statistics of starting doses). Then, the cumulative duration of the use of multiple hormones (time overlapping of hormone therapies should be avoided in the calculation) will be summarized as the duration of dosing. If one AE category (such as the category of immune-related AE) contains more than one AEs (by PT), this AE category will be treated as one AE when being summarized. When the starting dose is summarized, if the dosing frequency of hormones is more than once a day, it will be converted into a single daily dose before being summarized.

A detailed listing of AEs, SAEs, AEs resulting in treatment interruption/discontinuation, and deaths will be provided.

5.6.3 Laboratory tests

For blood routine, blood biochemistry, urinalysis, and thyroid function, a crossover table will be used to descriptively summarize the number and percentage of subjects showing most significant changes from baseline after the first administration. Among them, the statistics of the most severe grading will be calculated for indicators whose toxicity grading can be carried out by CTCAE. The statistics of the most severe clinical significance (grading of clinical severity: abnormal with clinical significance > abnormal with no clinical significance > normal) will also be provided for the above indicators.

In addition, for the judgment of clinical significance of blood routine, blood biochemistry, urinalysis, and thyroid function, a crossover table will be used to descriptively summarize the number and percentage of subjects showing changes from baseline.

The judgment of clinical significance of test indicators such as blood routine, blood biochemistry, urinalysis, thyroid function, coagulation function, fecal occult blood, and virology will be provided with a detailed listing of various laboratory test items. The listing will include at least name of visit, date of sampling, number of days of study, measurement and unit (if applicable), and judgment of clinical significance (if applicable).

5.6.4 ECOG (performance status assessment)

ECOG PS will be treated as a categorical variable, and a crossover table will be used to summarize the number and percentage of subjects showing changes in the highest ECOG PS from baseline after the first dose according to treatment groups. In addition, a detailed listing of ECOG will also be provided. The listing will include at least name of visit, date of scoring, number of days of study, and ECOG PS.

5.6.5 Vital signs

The vital signs to be collected in this study will include body temperature, heart rate, respiration, diastolic blood pressure, and systolic blood pressure. The number and incidence of subjects with clinically significant abnormalities after the first administration will be descriptively summarized (refer to the following criteria for determining clinically significant abnormalities in vital signs), along with the results obtained at various time points.

In addition, a detailed listing of vital signs will also be provided. The listing will include at least the name of the visit, the date of the examination, number of days of study, the results of various examination items of vital signs, and the signs of clinically significant abnormalities.

Table 5.6.5-1. Criteria for determining clinically significant abnormalities of vital signs

Test Item	Unit	Low	High
Body Temperature	℃	≤ 35 °C and change from baseline ≤ -1.1 ℃	≥ 38.3 °C and change from baseline ≥ 1.1 °C
Heart Rate	bpm	< 40 bpm	> 120 bpm
Respiration	breaths/min	< 12 breaths/min	> 24 breaths/min
Systolic Blood Pressure	mmHg	< 90 mmHg or change from baseline ≤ -30 mmHg	change from baseline ≥ 30 mmHg
Diastolic Blood Pressure	mmHg	< 50 mmHg or change from baseline ≤ -20 mmHg	change from baseline ≥ 20 mmHg

5.6.6 ECG

The descriptive statistics of the number and percentage of subjects based on the most severe cases after the first administration will be provided by clinical significance judgment, i.e., normal, abnormal with no clinical significance, and abnormal with clinical significance (grading of clinical severity: abnormal with clinical significance > abnormal with no clinical significance > normal). The clinical significance judgment will also be descriptively summarized by test time.

For PR interval and QTcF, the incidence of each category defined in the table below after the first administration will be descriptively summarized. In addition, the incidence will be summarized by test time points.

Table 5.6.6-1. Classification criteria of PR and QTcF

Test Item	Unit		Criteria for Abnormality
PR	ms	Absolute value	max ≥ 300
		Change from baseline	Baseline > 200 and change from baseline ≥ 25%, or baseline ≤ 200 and change from baseline ≥ 50%
QTcF	ms	Absolute value	450 ≤ max < 480
			480 ≤ max < 500
			max ≥ 500
		Change from baseline	30 ≤ max < 60
			max ≥ 60

For ECG parameters such as heart rate, PR interval, QT interval, and QTcF, the results obtained at various time points will be descriptively summarized.

The calculation formula for QTcF: QTcF = QT $\sqrt[3]{RR}$, where RR = 60/heart rate

5.6.7 Physical examination

Physical examinations will be listed only.

5.6.8 Other safety analyses

Other safety parameters will be listed only.

5.7 Statistical analysis of PK

A descriptive statistical analysis will be performed on the drug concentration of concurrent immunogenic blood samples.

5.8 Statistical analysis of PD

This study does not involve PD analysis.

5.9 Immunogenicity (ADA) Analysis

The number and percentage of subjects with ADA positive at baseline, ADA negative at baseline and positive post baseline, and at least one ADA positive at baseline or post baseline will be summarized.

For the population with negative baseline results and positive post-baseline results, the following items will be analyzed: the time to the first positive ADA result (i.e., time to the first positive ADA result (days) = date of the first positive ADA result - date of first dose + 1), the number and percentage of subjects with transient positive post-baseline results (transient ADA positive is defined as the subjects who are negative at baseline and have only one ADA-positive sample post baseline before the last sample and are not persistent ADA positive), the number and percentage of subjects with persistent positive post-baseline results (persistent ADA positive can be divided to two categories: 1) negative at baseline, there are at least two positive samples post baseline, where the first and last ADA-positive samples are separated by a period >16 weeks, or 2) negative at baseline, the last post-baseline sample is positive, or the last post-baseline sample is negative and the second last post-baseline sample is positive), and the number and percentage of subjects with other positive post-baseline results (Other ADA positive is defined as the subjects who are negative at baseline, have at least two ADA positive samples post baseline, but not persistent ADA positive, and the last sample is negative) will be summarized using descriptive statistics.

In addition, the efficacy and safety of ADA-positive and negative subjects will be analyzed so as to investigate the effects of ADA on efficacy and safety. ADA-positive subjects refer to subjects with post-baseline ADA-positive samples, mainly including: a. the subjects who have the baseline negative and post-baseline positive samples, or b. the subjects who have both baseline and post-baseline positive samples, and the titer of the post-baseline samples is ≥ 4-fold of the baseline titer. ADA-negative subjects are those who are not ADA positive.

The number and percentage of subjects with neutralizing antibodies (Nabs) positive will be summarized.

Immunogenicity raw data will be reported in the form of listing.

5.10 Other Analyses

N/A

6 INTERIM ANALYSIS

No routine interim analysis.

7 REFERENCES

None