Shanghai Hansoh BioMedical Co., Ltd.

A Randomized, Controlled, Double-Blind, Multicenter, Phase III Study to Assess the Efficacy and Safety of HS-10296 Versus Gefitinib as First-Line Treatment in Patients with EGFR Mutation [Positive], Locally Advanced or Metastatic NSCLC

Statistical Analysis Plan (SAP)

Protocol No.: HS-10296-03-01
Version: V 1.1
SAP version date: 10/21/2020

Status:	Approved
Protocol version date:	12/10/2019
Statistical unit:	Shanghai Hansoh BioMedical Co., Ltd.
Protocol version	V 3.0

Criteria: The implementation of the clinical trial described in this report was carried out in compliance with the principles of Good Laboratory Practice (GCP).

Signature and approval page

Shanghai Hansoh BioMedical Co., Ltd.

Sponsor

[redacted]	[signature]	[hw:] *10/21/2020*
Shanghai Hansoh BioMedical Co., Ltd. Statistician	Signature	Date

[redacted]	[signature]	[hw:] *10/21/2020*
Shanghai Hansoh BioMedical Co., Ltd. Senior Medical Manager	Signature	Date

[redacted]	[signature]	[hw:] *10/21/2020*
Shanghai Hansoh BioMedical Co., Ltd. Director of Quantitative Science	Signature	Date

Table of Contents

Revision of History

As compared with Version 1.0 (Version 10/10/2020), the modified content in this V1.1 version is briefly described as follow

Page of original version	Brief description of modification
12	Estimating 25%, median, and 75% quantile of this indicator➔ (changed to, the same below) Estimating 1/4 quantile, median and 3/4 quantile of this indicator
16	As "Date of adverse event outcome" was used in the study, some related description of "Missing start date of adverse event" is deleted.
17	Statement of "Missing start date of past concomitant medications" is modified: 1) 01/01 of the year of start date ➔1) If the year of start date is not that of initial medication, use 01/01 of the year of start date
18	The following statement in the section of "Missing end date of past and concomitant medications" is deleted, as it's not filled in under such condition in 3): 4) If the year, month, and day are all missing and [the answer] to whether it is continuing is not "yes", the start date serves as the end date. If the answer to whether it is continuing is "yes," the data cutoff date serves as the end date
18	Expression approaches are unified: The rules for filling in concomitant and subsequent anti-tumor treatment➔ Missing start date of concomitant and subsequent anti-tumor treatment 4) End date of concomitant and subsequent anti-tumor treatment➔ Missing end date of concomitant and subsequent anti-tumor treatment
18	The date of death was missing when calculating the overall survival, rules for filling in "Missing date of death" are added
20	The conditions of subjects who terminated treatment for reasons other than disease progression after randomization are given in a list. ➔The conditions of subjects who terminated treatment after enrolled and randomized are given in a list
21	The frequencies and percentages of past and concomitant medications are descriptively summarized by coded ATC3 category and treatment group. ➔For past and concomitant medications, the frequencies and percentages of subjects by treatment group based on the coded ATC3 category and ATC1 category, ATC3 and preferred term are given separately.
23	More specific statement is made for Table 4.1-1: Date of imaging examination during which new lesions were found (if the criterion for progression is new lesions) ➔ Date of imaging examination during which new lesions were first found (if the criterion for progression is new lesions) Date of imaging examination during which the first disease progression of non-target lesions was found➔ Date of last imaging examination during which progression of non-target lesions was first found Date of last imaging examination during which disease progression of target lesions was confirmed➔ Date of last imaging examination during which progression of target lesions was first confirmed
28	Definition of "Related to investigational drug" is added, to make the definition of "Related to investigational drug" clearer.
29	All abnormal physical examination results with clinical significance are given in a list. ➔All physical examination results are given in lists.
30	All abnormal LVEF results of each subject will be presented by list. ➔All LVEF results of each subject will be presented by list Abnormal ophthalmological examination results with clinical significance are given in a list. ➔ophthalmological examination results are given in a list.
32	Some literal expressions in "Statistical analysis charts" is modified, list number is adjusted to add some chart items generated in the original plan to make the results more perfect.

1. Brief Introduction

The statistical analysis plan provides descriptions of the statistical analysis methods and data processing principles for the analysis and reporting of data related to this study. This statistical analysis plan (SAP) is exclusively for clinical study HS-10296-03-01 of Shanghai Hansoh BioMedical Co., Ltd., and is based on version 03 of the clinical study protocol (December 10, 2019).

1.1. Study Objectives

1.1.1. Primary objective

To compare the progression-free survival (PFS) of HS-10296 and gefitinib in the first-line treatment of locally advanced or metastatic NSCLC with EGFR sensitivity mutations.

1.1.2. Secondary objectives

1) To compare the other anti-tumor efficacy of HS-10296 treatment versus gefitinib treatment: Overall survival (OS), objective response rate (ORR), duration of response (DoR), disease control rate (DCR), and depth of response (DepOR).
2) To compare the safety of HS-10296 and gefitinib treatment.

1.2. Study Design

1.2.1. Overall Design

This study is a randomized, controlled, double-blind, multicenter, phase III clinical trial to evaluate the efficacy and safety of first-line treatment with HS-10296 versus gefitinib in treatment-naïve subjects with NSCLC with EGFR sensitivity mutations. Patients are randomly assigned to the HS-10296 treatment group or the gefitinib treatment group at a ratio of 1:1 and take HS-10296 or gefitinib by oral administration once a day. This study plans to enroll 410 subjects. The study process is shown in Figure 2.4-1.

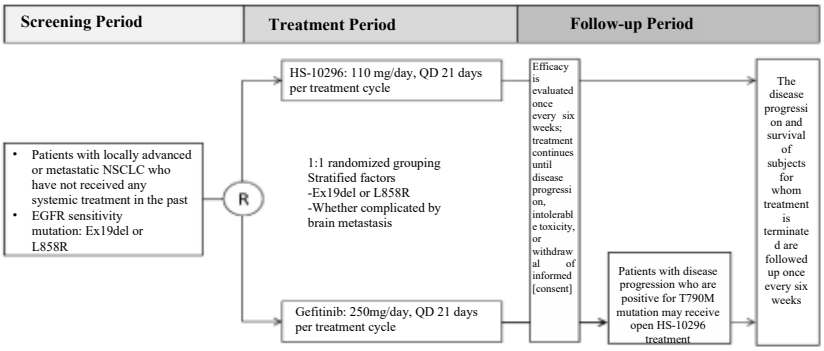

Figure 2.4-1 Study Flowchart

1.2.2. Study procedure

The following sections describe the study procedures and the data to be collected. For each procedure, each patient should be assessed by the same investigator or site personnel whenever possible. Refer to Appendix B of the study protocol for the overall follow-up arrangements.

1.2.2.1. Screening Period (D-28–D-1)

- Prior to any study procedure, subjects must be adequately informed and sign the ICF
- Tumor tissue samples or blood samples after diagnosis with locally advanced or metastatic NSCLC are submitted for EGFR mutation testing
- Collection of demographic data (including date of birth or age, sex, ethnicity, smoking status, etc.) and comprehensive medical history (treatment history, surgical history, allergy history, etc.)
- Comprehensive physical examination (including body weight), vital sign check (blood pressure, heart rate, respiratory rate, and body temperature), and height check
- ECOG PS score
- For premenopausal women, blood or urine pregnancy testing is performed within 3 days prior to the start of the first treatment with the investigational drug
- Collection of blood and urine samples for laboratory testing (clinical biochemistry, blood, and urine testing)
- 12-lead ECG examination and echocardiography examination (the echocardiography results within 28 days before enrollment is valid, and is not limited by the time of knowledge)
- Comprehensive ophthalmological examination, including best corrected vision exam, intraocular pressure examination, fundi examination, and slit-lamp examination
- Baseline tumor assessment is performed according to RECIST 1.1 criteria (the result within 28 days before enrollment is valid, and is not limited by the time of knowledge)
- Eligibility evaluated against the inclusion and exclusion criteria
- Record anti-tumor and surgical treatments
- Record adverse events (start recording from the signing of the informed consent form)
- Record concomitant medications (record starting 28 days prior to enrollment)

1.2.2.2. Treatment period (C1-C7+, D1-D127+)

1.2.2.2.1. Treatment protocol (C1-C7+, D1-D127+)

One cycle (C1-C7+) of treatment is defined as 21 days. Oral HS-10296 or gefitinib is given each day. Subjects are randomly grouped on C1D1 and will continue to receive the investigational treatment until the investigator assesses disease progression based on the RECIST 1.1 criteria. Or even if the patient is with disease progression, yet the investigator judges that the subject can still benefit from the treatment; in this case the study treatment can be carried out continuously.

1.2.2.2.2. Treatment visit (C1-C7+, D1-D127+)

Treatment visit (C1-C7, D1-D127)

Treatment period visits are performed on the first day (CnD1, N = 1-7) of the first 7 cycles of treatment (C1-C7). During the first cycle, in addition to C1D1, two visits are added on C1D8 and C1D15. The specific visit process follows:

- Administered once a day
- Comprehensive physical examinations, body weight checks, ECOG PS scoring, vital sign checks, laboratory testing (clinical biochemistry, hematology, and urine testing), and 12-lead ECGs are performed once every 3 weeks (CnD1)
- Two examinations are added on C1D8 and C1D15: Including vital sign checks, laboratory testing (clinical biochemistry, hematology, and urine testing), and 12-lead ECGs
- Throughout the treatment period, ophthalmological examinations are performed as clinically needed. The examination items are determined by the investigator or specialist based on the patient's condition
- Echocardiography is performed once every 12 weeks (and as clinically needed) from the first administration
- Solid tumor efficacy evaluation is performed once every 6 weeks according to RECIST 1.1
- Record adverse events and concomitant medications

Treatment visits (C7+, D127+)

Treatment visits after the 7th treatment cycle are performed in accordance with the following process:

- Administered once a day
- Comprehensive physical examinations, body weight checks, ECOG PS scoring, vital sign checks, laboratory testing (clinical biochemistry, blood, and urine testing), and 12-lead ECGs are performed once every 6 weeks (C1-D21) or 12 weeks (C23 and subsequently)
- Throughout the treatment period, ophthalmological examinations are performed as clinically needed. The examination items are determined by the investigator or specialist based on the patient's condition
- Echocardiography is performed once every 12 weeks (and as clinically needed)
- Evaluation of solid tumor efficacy is performed based on RECIST 1.1 every 6 weeks (C1-C21) or 12 weeks (C23 and after)
- Record adverse events and concomitant medications

1.2.2.3. Follow-up Period

1.2.2.3.1. End of treatment follow-up

The end of treatment follow-up refers to the visit procedure that the subject must complete when completely stopping the investigational drug treatment and specifically includes the following content:

- Comprehensive physical examinations, body weight checks, ECOG PS scoring, vital sign checks, laboratory testing (clinical biochemistry, blood, and urine testing), 12-lead ECGs, and echocardiography
- When the disease progresses, tumor and/or blood samples are collected according to the subject's wishes (optional), and genetic testing after disease progression is performed to guide further treatment
- Solid tumor efficacy is evaluated based on RECIST 1.1
- Record adverse events and concomitant medications

At the end of treatment visit, if safety examination results (comprehensive physical examination, weight examination, ECOG PS score, vital signs examination, laboratory test, and 12-lead ECG examination) within the previous 7 days are available, there is no need to repeat the examinations; if RECIST efficacy evaluation and echocardiography examination results within the previous 4 weeks are available, there is no need to repeat the examinations.

1.2.2.3.2. Safety follow-up (follow-up for 28 days)

Safety follow-up refers to the visit procedures that should be completed by the subject 28 days after the end of treatment with the investigational drug (end of the use of the investigational drug). The patient is contacted by telephone to collect new AEs or to follow up on AEs experienced during the end of treatment. This also includes all concomitant drugs, including anti-tumor therapy. If possible, follow-up should be conducted until the SAE has an outcome. Specifically, this include the following:

- Recording of adverse events (new AEs or follow-ups of AEs experienced when treatment was terminated)
- Recording of concomitant medications (all concomitant medications including anti-tumor treatment)

1.2.2.3.3. Progression follow-up

Progression follow-up refers to the visit procedures that should be completed by the subject when treatment is terminated for reasons other than disease progression. Subjects are evaluated by RECIST 1.1 and ECOG PS score every 6 weeks (C1-C21) or 12 weeks (C23 and after) (relative to the date of randomization). After progression, subjects who continue to receive treatment because of possible clinical benefit will continue to undergo tumor evaluations. Specifically, this include the following:

Progression follow-up for subjects who terminate treatment for reasons other than disease progression:

- Solid tumor efficacy evaluation is performed once every 6 weeks (C1-C21) or 12 weeks (C23 and after) until the investigator evaluates disease progression based on RECIST 1.1
- ECOG PS scoring is performed once every 6 weeks (C1-C21) or 12 weeks (C23 and after) until the investigator evaluates disease progression based on RECIST 1.1
- Recording of concomitant medications: Only the detailed information of subsequent anti-tumor treatment is recorded until disease progression
- Subjects with disease recurrence before the completion of the 28-day safety follow-up after discontinuation of treatment should continue the safety follow-up until 28 days after discontinuation of treatment.

Progression follow-up of subjects who continue to receive the investigational treatment (compassionate treatment) after disease progression:

- It is recommended to conduct tumor evaluation based on RECIST 1.1 once every 6 weeks (C1-C21) or 12 weeks (C23 and after) until the investigator judges progression after compassionate treatment or medication is terminated before progression (for safety reasons or based on the investigator's judgment or the subject's decision)
- ECOG PS scoring is performed once every 6 weeks (C1-C21) or 12 weeks (C23 and after) until the investigator judges further progression or medication is terminated before progression (for safety reasons or based on the investigator's judgment or the subject's decision)
- Recording of concomitant medications: All concomitant medications, including anti-tumor therapy, until 28 days after the drug is terminated, after which only anti-tumor therapy is collected
- Recording of adverse events: For subjects who continue to receive the investigational treatment after progression, continue to collect their AEs and SAEs until 28 days after the drug is terminated, after which only AEs with no outcome and SAEs related to the investigational drug are collected.

1.2.2.3.4. Survival follow-up

After disease progression (the date of first disease progression if non-compassionate treatment, the date of clinical progression if compassionate treatment), the patient, the patient's dependents, or the patient's current doctor must be contacted every 6 weeks to obtain survival information; if the progression follow-up is not completed according to the trial procedure and the date of disease progression is missing, then the recorded date of refusal of progression follow-up/acceptance of the survival follow-up will be the starting point. The detailed information about the subsequent treatment program (treatment received since withdrawal of the investigational drug) and unresolved AEs (unless the subject withdraws informed consent) must be collected, regardless of the date of the last contact. Specifically, this include the following:

- Follow-up is performed every 6 weeks to document details of subsequent anti-tumor therapy
- Follow up every 6 weeks to record consequent response/progress data
- Follow up every 6 weeks to record survival status

Continue to collect survival follow-up data until subject death.

1.2.3. Sample size estimation

This study is a randomized, controlled, double-blind, multicenter, superior effect-designed phase III clinical study.

Assuming that the PFS hazard ratio (HR) of HS-10296 versus gefitinib is 0.67 (if the data conform to an exponential distribution and the statistical model satisfies the proportional hazards assumption, median PFS improves from 10 months to 15 months), the enrollment ratio is 1:1, the enrollment time is 8 months, the longest observation time after the enrollment of the first subject is 23 months, and α is two-sided 0.05. With a confidence of 90%, 262 events can be used to test the statistical differences between the groups and approximately 410 subjects need to be enrolled. The software nQuery Advisor 8.0 is used for sample size calculation.

1.2.4. Randomization

This study is a randomized, controlled, double-blind, multicenter clinical study. This trial adopts a central randomization system (IWRS) to randomize the patients into groups for competitive enrollment at each center. EGFR mutation status (Ex19del vs. L858R) and brain metastasis status (present vs. absent) at the time of enrollment are stratifying factors. Subjects are randomly assigned to the test group (HS-10296) and control group (gefitinib) at a ratio of 1:1.

Subjects who pass the screening receive a unique random number on the day of the first time they receive the investigational drug treatment (day 1 of the first treatment cycle, C1D1). The investigator assigns all subjects who pass the screening and are suited for the study a random number and drug number after randomization. If multiple subjects are scheduled to participate in randomized grouping on the same day, subjects should be randomized in the order in which they arrive, not in order of screening number. If subjects' drugs are damaged during the course of the study, the investigator can acquire new drug numbers through the IWRS to continue the clinical trial. If a subject does not accept randomized grouping, the reason why the subject was not enrolled in the study must be recorded.

The subjects start the investigational treatment on the day of randomization.

1.2.5. Stratification

EGFR mutation status (Ex19del vs. L858R) and brain metastasis status (present vs. absent) at the time of random enrollment are the stratifying factors.

1.2.6. Blinding

This trial adopts a double-blind design. From the start of randomization until the investigator evaluates disease progression based on the RECIST 1.1 criteria, the true status of treatment will be kept blinded from the subjects, the investigator, the data analysts, the sponsor, and all medical personnel involved in treatment or clinical evaluation.

In this study, randomization numbers and drug numbers will be obtained through the IWRS. The double-dummy technique is adopted to control the blinding of the drug. HS-10296 tablets and HS-10296 dummy tablets (as well as gefitinib tablets and gefitinib dummy tablets) will use completely identical packaging, administration methods, labeling, appearances, flavors, and odors to conceal the truth about the investigational drug. HS-10296 tablets and gefitinib dummy tablets are packaged together and gefitinib tablets and HS-10296 dummy tablets are packaged together. After uniform packaging, they are given drug numbers uniformly. The blind codes are stored in the IWRS and with the randomization specialist.

1.2.7. Unblinding

This study is a double-blind design, and the study should be kept as blind as possible.

1.2.7.1. Unblinding after disease progression and process

For patients with disease progression, the subject can be unblinded according to the unblinding process if the investigator needs to know the patient's randomized drug treatment information, in order for selection of subsequent treatments:

1) The investigator immediately informs the sponsor's inspector;

2) Complete the EDC entry of the efficacy and safety data generated from the subject;

3) Perform source data verification (SDV) and data cleanup on the data entered in the EDC;

4) After data cleanup is completed, unblind the subject.

1.2.7.2. Emergency unblinding

Emergency unblinding of an individual patient is only applicable if urgent medical intervention is necessary by the investigator and continued blinding of the patient will affect the development of the best medical management for the investigator.

If emergency unblinding is required, the investigator will notify the Sponsor's medical monitor immediately to request unblinding (the investigator may perform unblinding before informing the Sponsor only if emergency treatment for the patient might be delayed). After the sponsor agrees and authorizes the IWRS, the investigator will unblind the patient. The investigator should note that the occurrence of SAEs is not a prerequisite for routine immediate unblinding. The sponsor, investigator and ethics committee of each site must be notified of the above process as soon as possible, and the unblinding time, reason and result must be recorded in the source file.

1.2.8. Central review

All imaging data collected during the study, including those obtained in unscheduled visit examinations, should be subject to independent central review (ICR) by a qualified independent review committee (IRC) in accordance with the independent imaging reading regulations. The results of this independent evaluation by the IRC will not be returned to the investigator. Efficacy endpoints derived from the IRC evaluation will be used only for sensitivity analysis.

1.3. Endpoint indicators

1.3.1. Primary efficacy indicators

The primary endpoint of this study is PFS derived by the investigator based on the RECIST V1.1 evaluation ratings. PFS is defined as the time from the start of randomization until objective tumor progression as evaluated by the investigator or death (using the date of the first event).

1.3.2. Secondary efficacy indicators

1) Objective response rate (ORR): As in RECIST 1.1, this is defined as the percentage of patients with at least 1 CR or PR before progression. CR and PR here do not need to be reconfirmed based on RECIST V1.1.

2) Duration of response (DoR): This is defined as the time from the first date on which response is met to the date of disease progression or death from other causes. The response termination date is consistent with the date used for the PFS endpoint. The start date of response time is defined as the most recent date of the first visit that meets the PR or CR criteria. If a subject does not progress after response, the duration of response will be the PFS cut-off time.
3) Disease control rate (DCR): Disease control rate is defined as the proportion of the subjects whose best overall response is CR, PR, or SD. Considering the 7-day visit window, the requirement for the evaluation of SD is that the time from the first medication to the final overall efficacy evaluation result of SD prior to progression be at least 35 days.
4) Depth of response (DepOR): As a continuous variable, this refers to the change in the sum of the length of the longest diameter of the target lesion as defined by RECIST 1.1 when no new lesions appear or there is no progression of non-target lesions versus baseline. The change in tumor size of a subject during a visit includes absolute change (mm) and relative change (%). The percentage change in tumor size of the subjects with measurable lesions at baseline will be calculated based on the percentage changes in the total diameters of target lesions compared with those measured at baseline at each visit. The optimal value of depth of response will be generated from all of the efficacy evaluations before progression or before the start of subsequent anti-tumor treatment. The calculation formulae for absolute change and relative change are as follows:
    a) Absolute change in tumor size = the sum of the longest diameters of all of the subject's measurable target lesions at the visit (if the target lesion site is a lymph node, use the maximum short diameter) - the sum of the longest diameters of all target lesions at baseline (if the target lesion site is a lymph node, use the maximum short diameter)
    b) Percentage change in tumor size relative to baseline = (the sum of the longest diameters of all of the subject's measurable target lesions at the visit (if the target lesion site is a lymph node, use the maximum short diameter) - the sum of the longest diameters of all target lesions at baseline (if the target lesion site is a lymph node, use the maximum short diameter)) / the sum of the longest diameters of all target lesions at baseline (if the target lesions site is a lymph node, use the maximum short diameter) * 100%
    c) Optimal value of depth of response = minimum value of percentage change in tumor size versus baseline

5) Overall survival (OS): This is defined as the time from the start of randomization to the date of death from any cause.

1.3.3. Safety Evaluation Indicators

The safety endpoints include:

1) Adverse events and serious adverse events
2) Laboratory testing
   - Clinical blood biochemistry: Albumin, ALT, AST, alkaline phosphatase, bilirubin, total bilirubin, calcium, total blood calcium, creatinine, creatine kinase, glucose, LDH, HbA1C, magnesium, potassium, sodium, urea nitrogen or urea (pick one of two)
   - Hematology: Hemoglobin, white blood cells, hematocrit, red blood cell count (RBC), absolute white blood cell count (neutrophils, lymphocytes, monocytes, basophils, eosinophils), platelet count, reticulocyte count
   - Urinalysis: Glucose, urine protein, blood in urine
3) Vital signs: Pulse, sitting systolic and diastolic blood pressure, respiratory rate, and body temperature.
4) Physical examination: Including general condition, skin and mucous membranes, lymph nodes, head, neck, chest, abdomen, spine, and limbs or other examinations.
5) Weight
6) 12-lead electrocardiogram (ECG): Heart rate (beats/minute), QRS duration (ms), PR interval (ms), RR interval (ms), QT and QTcF intervals (ms), and clinical classification of normal/abnormal ECG.
7) ECOG Performance Status Score
8) LVEF Measured With Echocardiography or MUGA
9) Changes of ophthalmological examination

2. General analysis definition

2.1. Statistical analysis software

Shanghai Hansoh BioMedical Co., Ltd., is responsible for the statistical analysis of this trial. SAS 9.4® or a newer version of the software is adopted for the statistical analysis.

2.2. General principles and analytical definitions

The biostatistician and principal investigator formulate the statistical analysis plan, which is finalized before data are locked, based on the study protocol.

1) For the time interval, days are converted into months at one month = 30.4375 days.
2) Efficacy analysis is performed in the full analysis set (FAS) and the per-protocol set (PPS). The results are based on the full analysis set. Safety analysis is performed in the safety set (SS).
3) Except for special circumstances, the statistical diagrams are only for planned visit points, while the data sheets list all visits, including unplanned visits.

2.2.1. Descriptive statistics

For continuous variables, arithmetic mean, standard deviation (SD), median, minimum, and maximum are used to describe the data. The number of decimal places for minimum and maximum will be consistent with the raw data recorded in the database. Mean and median will keep one more decimal place than the raw data recorded in the database. Standard deviation will keep two more decimal places than the raw data recorded in the database.

Categorical variables will be listed in the form of frequency tables (frequency and percentage). Percentages will be rounded to one decimal place. When the frequency is 0, frequency (composition ratio) will not be shown.

For time outcome endpoint indicators, the number of people who reached the event endpoint, the number of people censored, and the estimated 25%, median, and 75% quantiles of the indicators and their 95% confidence intervals will be given and the Kaplan-Meier curves of the two treatment groups will be drawn.

2.2.2. Hypothesis testing

Otherwise specified, all statistical inferences are tested using a two-tailed test or two one-tailed tests, with a statistical significance level of $\alpha = 0.05$, and the interval of the parameters is estimated using 95% confidence interval. The p value will retain 4 decimal places, and when the p value is less than 0.0001, it is recorded as "< 0.0001". 95% confidence interval will keep one more decimal place than the raw data recorded in the database. The confidence interval of rates is estimated with the exact probability test.

2.2.3. Definition of subgroups

The main efficacy indicators will undergo subgroup analysis based on the following subgroups.

Table 2.2.3-1 Subgroups in the study

Subgroup	Definition
Sex	• Male • Female
Age grouping	• <65 years old • ≥ 65 years old
Baseline brain metastasis status	• Present • None
History of smoking	• Yes • None
EGFR gene mutation type	• Ex19del • L858R
Baseline ECOG PS score	• 0 • 1

2.2.4. Random stratification error

If a stratifying factor entered into the IWRS randomization system is inconsistent with the actual stratification information during the screening period, the inconsistent information should be recorded and listed. Subjects receive treatment in accordance with their existing randomized grouping results. Subjects' actual stratification information during the screening period is used for statistical analysis.

2.2.5. Study date and relative date of visit

For the summarization of effectiveness data, the first day of the study is defined as the date of randomization. If the date of the visit (or event) occurs on or after the date of randomization, the number of days of the study is defined as the date of the visit (or event) - the date of randomization + 1; if the date of the visit is before the date of randomization, the number of days of the study is defined as the date of the visit (or event) - the date of randomization.

For the summarization of safety data, the first day of the study is defined as the date of first medication. If the date of the visit (or event) occurs on or after the date of first medication, the number of days of the study is defined as the date of the visit (or event) - the date of first medication + 1; if the date of the visit is before the date of first medication, the number of days of the study is defined as the date of the visit (or event) - the date of first medication.

2.2.6. Analysis visit window

Subjects may not undergo visits on the dates stipulated by the protocol for various reasons during the trial. Therefore, during analysis, it is necessary to designate the corresponding analysis visits for the observation values of different indicators during each visit based on the examination dates.

Safety data such as vital signs, laboratory testing, ECG, LVEF, ECOG, and physical examinations will be analyzed during the analysis visits defined in Table 2.2.6-1 (analysis visits determined based on subjects' first medication dates and actual examination dates). The upper limit of the analysis visit window after C1D1 will be set based on the sum of half of the difference between the scheduled study date of the visit and the number of days from adjacent visits.

The summary analysis by visit follows the following rules:

1) If a subject has 2 or more visit records during the same visit window as defined above, the results recorded from the visit closer to the planned study date serve as the assessment values for the visit window. The other visits will not be analyzed in the summary table. If two visits are the same distance from the planned study date of the visit window, the earlier visit is used for the evaluation in the visit window.
2) For summarization at the individual level, all data of the subject should be included in the analysis, regardless of whether the measurement is from a planned visit or an unplanned visit, including the maximum values of statistics derived on the individual level.

The visit data of the subjects at all time points will be presented as a list.

Table 2.2.6-1 Definition of analysis visit window

Serial number	Analysis visit name	Scheduled study date	Lower limit of the window	Upper limit of the window
1	Screening period	1	-28	1
2	C1D8	8	2	11
3	C1D15	15	12	18
4	C2D1	22	19	32
5	C3D1	43	33	53
6	C4D1	64	54	74
7	C5D1	85	75	95
8	C6D1	106	96	116
9	C7D1	127	117	148
10	C9D1	169	149	190
11	C11D1	211	191	232
12	C13D1	253	233	274
13	C15D1	295	275	316
14	C17D1	337	317	358
15	C19D1	379	359	400
16	C21D1	421	401	442

17	C23D1	463	443	484
18	C25D1	505	485	526
19	C27D1	547	527	568
20	C29D1	589	569	610
21	C31D1	631	611	652
22	C33D1	673	653	694
23	C35D1	715	695	736

2.2.7. Definition of baseline

Unless specifically indicated, the baseline values of the effectiveness endpoints of this study are defined as the last valid measurement of the endpoint before randomization. The baseline values of safety endpoints are defined as the last valid measurement before the first use of the investigational drug, including the day of medication.

Change from baseline will be calculated based on the measurement after baseline minus the measurement at baseline, or measurement after baseline - measurement at baseline.

2.2.8. Missing data processing

In general, missing values are not filled in unless specifically indicated.

2.2.8.1. Main efficacy data

The primary endpoint of this study is the time outcome variable. When tumor efficacy assessment results are missing from a visit point, refer to Table 4.1-2 and Table 4.2-1 for the handling rules.

2.2.8.2. Laboratory test values

If laboratory test values are recorded as lower than (and equal to) or higher than (and equal to) the test range values (for example, $< x, \leq x, > x, \geq x$), when summarizing descriptive statistics, this is handled based on the test range value (that is = x). However, in data lists, the result recorded in the CRF will still be listed; that is, list "< x," "≤ x," "> x," or "≥ x."

2.2.8.3. Partial missing dates

For missing dates of adverse events and past and concomitant medications or past and concomitant treatments (partially or completely missing), if not specifically indicated, judgment is made after filling in the missing dates in the following ways:

Missing start dates of adverse events

If only the "day" is missing from the start date of the adverse event, the rules for filling it in are as follows:

1) If the start date (month/year) of the adverse event is different from the date of first medication (month/year), fill in the first day of the month with the start date of the adverse event;
2) If the start date (month/year) of the adverse event is the same as the date of first medication (month/year) and is different from the date of outcome of the adverse event (month/year), fill in the "day" part of the date of first medication;

3) If the start date (month/year) of the adverse event is the same as the date of first medication (month/year) and is the same as the date of outcome (month/year) of the adverse event, fill in the "day" part of the date of first medication or the "day" part of the date of outcome of the adverse event, whichever is earlier.

If only the "month" and "day" are missing from the start date of the adverse event, fill in the earliest of the following dates:

1) The start date of the adverse event is January 1st of the year (if this date is not earlier than the date of first medication);
2) The "month" and "day" parts of the date of first medication (if the year of the start date of the adverse event is the same as the year of the date of first medication);
3) The last day of the year of the start date of the adverse event (if the year of the start date of the adverse event is earlier than the year of the first medication);
4) The date of outcome of the adverse event.

If the "year," "month," and "day" of the start date of the adverse event are all missing, do not fill them in.

Missing dates of outcome of adverse events

1) If only "date" of date of outcome of adverse event is missing, then fill in the last date of

   the month or the date of death (for deceased subjects), whichever is earlier
2) If both the "month" and "day" of the date of outcome of the adverse event are missing, fill in December 31 of the year or the date of death (for deceased subjects) as the "month" and "day" parts of the date of outcome of the adverse event, whichever is earlier;
3) If the "year," "month," and "day" of the date of outcome of the adverse event are all missing, do not fill them in

The start date of the adverse event (if missing, then the date after supplementation) is compared with the date of first medication to determine whether the adverse event is an adverse event that occurred during treatment.

Missing start dates of past concomitant medications

If the "year," "month," and "day" of the start date of the past concomitant medication are all missing, do not fill them in. If only the "day" is missing from the start date of the past and concomitant medication, the rules for filling it in are as follows:

1) If the start date (month/year) is different from the date of first medication (month/year), fill in the first day of the month of the start date
2) If the start date (month/year) is the same as the date of first medication (month/year) and different from the end date (month/year): If before the first medication (cmprior = "Y"), fill in the first day of the month; otherwise, fill in the "day" part of the date of first medication;
3) If the start date (month/year) is the same as the date of first medication (month/year) and the same as the end date (month/year): If before the first medication (cmprior = "Y"), fill in the first day of the month; otherwise, fill in the "day" part of the date of first medication or the "day" part of the end date, whichever is earlier.

If only the "month" and "day" are missing from the start date, fill in the earliest of the

following dates:

1） If the year of the start date differs from the year of the date of first medication, January 1 of the year of the start date;

2） If the year of the start date is the same as the year of the date of first medication: If before the first medication (cmprior = "Y"), then fill in January 1 of the year of the start date; otherwise, fill in the "month" and "day" parts of the date of first medication.

Missing end dates of past and concomitant medications

If the end date of past concomitant medication is missing, the rules for filling it in are as follows:

1） If only "day" is missing for the end date, fill in the last day of the month of the end date or the date of death (for deceased subjects) as the day part, whichever is earlier
2） If the "month" and "day" are both missing from the end date, fill in December 31 of the year of the end date or the date of death (for deceased subjects), whichever is earlier, as the "month" and "day" parts
3） If the "year," "month," and "day" of the end date are all missing, do not fill them in

The start date of concomitant and subsequent anti-tumor treatment is missing

If the "year," "month," and "day" of the start date of concomitant and subsequent anti-tumor [therapy] are all missing, do not fill them in.

If only the "day" is missing from the start date of concomitant and subsequent anti-tumor [therapy], the rules for filling it in are as follows:

1) If the start date (month/year) is different from the date of first medication (month/year), fill in the first day of the month of the start date
2) If the start date (month/year) is the same as the date of first medication (month/year) and different from the end date (month/year), fill in the "day" part of the date of first medication;
3) If the start date (month/year) is the same as the date of first medication (month/year) and the same as the end date (month/year), fill in the "day" part of the date of first medication or the "day" part of the end date, whichever is earlier.

If only the "month" and "day" are missing from the start date, fill in the earliest of the following dates:

1) 01/01 of the year of start date

2) If the year of the start date is the same as the year of the date of first medication, fill in the "month" and "day" parts of the date of first medication
3) If the year of the start date is earlier than the year of the date of this first medication, fill in December 31 of the year of the start date

End dates of concomitant and subsequent anti-tumor therapy are missing

If the end date of concomitant and subsequent anti-tumor therapy is missing, the rules for filling it in follow:

1) If only "day" is missing for the end date, fill in the last day of the month of the end date or the date of death (for deceased subjects) as the day part, whichever is earlier
2) If the "month" and "day" are both missing from the end date, fill in December 31 of the year of the end date or the date of death (for deceased subjects), whichever is earlier,

as the "month" and "day" parts

3) If the "year," "month," and "day" of the end date are all missing, do not fill them in

The date of death is missing

For subjects who are confirmed dead, if the complete date of death cannot be known, use the date of death after filling it in or the known last date of survival + 1, whichever is later, as the date of death. The rules for filling in the date of death are as follow:

1) If only the "day" is missing, fill in the 1st date of the month;
2) If "month" and "day" are missing, fill in January 1 of the year.

Other missing time data are not processed.

Note: In the data list, listing is still based on the original collected data.

2.2.9. Impact of the COVID-19 Epidemic

The COVID-19 epidemic has had a certain impact on data collection during the trial and subsequent statistical analysis. The COVID-19 epidemic may cause subject tumor efficacy evaluations to be regarded as "missing" or "NE" in planned visits. When handling the efficacy data, it is treated as "missing" in accordance with established event censorship rules. This handling method is relatively conservative in the estimation of PFS.

For subjects whose evaluation results before progression as "NE" because of the epidemic, sensitivity analysis will be performed on the date when PFS is censored to the final assessment result of "NE" before disease progression.

For safety variables, descriptive summarization is performed based on the analysis visit window.

The COVID-19 epidemic also has an impact on the execution of clinical studies. Serious protocol deviations have occurred because of the epidemic. Therefore, this study will separately summarize the included and excluded serious protocol deviations caused by the epidemic.

If there are other conditions affected by the epidemic, they will also be analyzed.

2.3. Statistical analysis set

Screened subjects are patients who signed the informed consent form and participated in the screening process of this study. Random subjects are patients who received randomization and were assigned random numbers.

2.3.1. Full analysis set (FAS)

Based on the principle of intention-to-treat (ITT), the FAS is defined as all patients who were randomly enrolled and received the investigational drug treatment at least once. Comparisons between treatment groups will be based on the randomized grouping results, regardless of whether the group's drug treatment was actually received.

2.3.2. Per protocol set (PPS)

As a subset of the FAS, the PPS is defined as all of the patients who satisfied the trial protocol, had good compliance, and did not have serious protocol deviations that significantly affected efficacy evaluation.

Baseline and demographic characteristics will be analyzed using the FAS and the primary efficacy evaluation will be based on the FAS and the PPS simultaneously, with results being obtained primarily from the FAS.

2.3.3. Safety set (SS)

The safety set (SS) will include all randomized patients who received the investigational drug treatment at least once, but comparisons between treatment groups will be summarized based on the treatment group that was actually received. For example, for patients who receive the wrong treatment: The randomly assigned treatment group is A and treatment B is actually received. The safety data should be counted in group B. The safety evaluation will be performed based on the SS.

3. Subject information

Unless specifically stipulated, all enrolled subjects undergo descriptive summarization based on randomized treatment group and in total.

3.1. Failure in Screening

The causes of subject screening failure are descriptively summarized. In the calculation of composition ratio, the number of subjects who signed the informed consent form is the denominator.

Subject screening failure is shown as a list.

3.2. Condition of enrolled subjects

The completion of enrolled and randomized subjects is descriptively summarized. In the calculation of composition ratio, the number of randomized subjects is the denominator.

The summarization of the number and percentage of subjects includes the following information:

- Subjects who received at least one study drug treatment
- Subjects still continuing the investigational drug treatment at the time of data cutoff
- Subjects who terminated treatment and reasons

The conditions of subjects who terminated treatment after enrolled and randomized are given in a list.

3.3. Distribution of Subjects in Each Analysis Set

The distribution of subjects in each analysis set is summarized based on all enrolled and randomized subjects. The numbers and percentages of subjects are summarized based on the reasons for exclusion from each analysis set. In the calculation of composition ratio, the number of randomized subjects is the denominator.

The descriptive summaries of the subjects enrolled in each analysis set will be performed based on treatment group and as a whole.

The conditions of subjects excluded from the FAS and PPS are given in a list.

A list of subjects with random stratification errors will be given.

3.4. Protocol Deviations

All serious protocol deviations in the randomized, double-blind treatment stage based on the FAS will be summarized by treatment group and as a whole.

Considering the impact of the epidemic, in addition, summaries of excluded serious protocol deviations due to the impact of the epidemic will be given.

All serious protocol deviations of subjects in the full analysis set are given in a list.

3.5. Demographic data and baseline characteristics

The following demographic indicators and baseline characteristics are summarized based on the FAS and PPS by treatment group:

Age (years), height (cm), weight (kg), body mass index (BMI) (kg/m^2), age group (< 65, ≥ 65 years old), sex (male, female), ethnicity (Han, other), and smoking history (present, absent).

At the same time, the following baseline disease characteristics are summarized:

Pathological type (adenocarcinoma, squamous cell carcinoma, large cell carcinoma, other), diagnostic staging (IIIB, IV), relapse status (yes, no), ECOG PS score (0 points, 1 point), EGFR gene mutation type (Ex19del, L858R), T790M mutation (yes, no), and brain metastasis (yes, no).

The demographic data, the baselines, and the above baseline disease characteristics of all subjects are given in a list.

3.6. Past Medical History

Subjects' past medical histories are coded with MedDRA 23.0 or a higher version.

Subjects' past medical histories are summarized and described based on the FAS by treatment group and system organ classification/preferred term (SOC/PT).

The details of all subjects' past medical histories are listed.

3.7. Ophthalmological examination, Surgical History, and Allergy History

The ophthalmological examination results, surgical histories, and allergy histories of all subjects are given separately in lists.

3.8. Subject Exposure and Medication Compliance

Exposure to and compliance with the investigational drug are summarized based on the safety set by treatment group.

Exposure time is calculated as follows:

Total exposure time (days) = (date of last dose - date of first dose) + 1;

Cumulative exposure time (days) = total exposure time - cumulative number of days without medication;

Medication compliance = cumulative exposure time / total exposure time * 100%;

The details of subject medication are listed.

3.9. Past and concomitant medications

In this study, past medications and concomitant medications will be coded with WHO Drug 2020Q1 or a newer version.

Past medications are non-investigational drugs whose medication start dates are before the first medication.

Concomitant medications are drugs that started to be taken after the first medication or were taken before the first medication but continued to be used subsequently.

For past and concomitant medications, the frequencies and percentages of subjects by treatment group based on the coded ATC3 category and ATC1 category, ATC3 and preferred term are given separately.

The past and concomitant medications of all subjects are given in a list.

3.10. Concomitant and Subsequent Anti-Tumor Therapies

The concomitant and subsequent anti-tumor therapies in this study will be coded with WHO Drug 2020Q1 or a higher version.

Concomitant anti-tumor therapies are other anti-tumor therapies used during medication with the investigational drug.

Subsequent anti-tumor therapies are other anti-tumor therapies used after the last use of the investigational drug.

The frequencies and percentages of concomitant and subsequent anti-tumor therapies are descriptively summarized by treatment group and coded ATC3 category.

The concomitant and subsequent anti-tumor therapies of all subjects are given in a list.

4. Analysis of efficacy

4.1. Primary Efficacy Endpoint Analysis

The primary efficacy endpoint of this study is PFS as evaluated by the investigator. The primary analysis is based on the full analysis set. For the rules for determining the dates of progression when the subjects have disease progression during treatment, see Table 4.1-1. For the primary event censoring rules, see Table 4.1-2.

Table 4.1-1 Rules for determining the date of progression when there is disease progression

	Description of situation	Outcome (occurrence of event or censoring)	Date of occurrence of PFS event or end date
Progression confirmed during treatment	New lesions	Progression	Date of imaging examination during which new lesions were first found (if the criterion for progression is new lesions)
	Non-target lesions	Progression	Date of last imaging examination during which progression of non-target lesions was first found
	Target lesions	Progression	Date of last imaging examination during which progression of target lesions was first confirmed
When two or more are present, the corresponding dates are determined based on the above principles and compared. Finally, the earliest examination date is taken as the date of disease progression			

Table 4.1-2 PFS event censoring rules 1 (primary event censoring rules)

Situation	Date	Outcome
No baseline or post-baseline imaging evaluation results	Date of randomization	Censored
No progression or death before data cutoff	Date of the last valid imaging examination before data cutoff	Censored
Treatment terminated or new systemic tumor therapy started before non-imaging disease progression	Date of the last valid imaging examination before the termination of treatment or the start of new systemic anti-tumor therapy	Censored
Disease progression or death before data cutoff (including occurrence during a missing visit or unplanned visit)	Examination date of first imaging disease progression or date of death	Progression or death

Progression or death occurred before data cutoff but two or more consecutive visits are missing or evaluation could not be performed before progression or death	Date of last valid imaging examination before progression or death	Censored
Note: No baseline is when there are no baseline examination records or baseline target lesion examinations are missing.		

The log-rank test stratified by EGFR mutation type and brain metastasis status will be used to compare the PFS distributions of the HS-10296 group and the gefitinib group to determine whether there are statistical differences. This test is a two-tailed test with a level of significance of 0.05. The results will be given as test p values.

Kaplan-Meier plots of the two treatment groups are drawn and the 1/4 quantile, median value, and 3/4 quantile of the PFS of the two treatment groups as well as the 95% confidence intervals for each quantile are given. The Kaplan-Meier estimates of progression-free survival at 6, 12, 18, and 24 months as well as the 95% confidence intervals corresponding to the K-M estimates based on Greenwood's standard error estimation method are given.

The stratified Cox proportional hazards model is used to estimate the PFS hazard ratio (HR) of the two treatment groups and the 95% confidence intervals corresponding to the estimates are given. The reasonableness of the proportional hazards assumption in this model will be tested.

The above two tests use subjects' actual stratification information during the screening period for analysis.

4.2. Sensitivity Analysis of the Primary Efficacy Endpoint

The following sensitivity analysis is performed on the primary efficacy endpoint:

- Considering the presence of primary resistance to EGFR TKI in non-small cell lung cancer patients with sensitive EGFR mutations, the early progression data may not satisfy the statistical assumptions of proportional hazards. The primary event censoring rules will be adopted to analyze the data of patients with primary drug resistance removed from the primary efficacy endpoint (progression within 3 months) in the full analysis set
- The primary event censoring rules are used for analysis of the main efficacy endpoint in the per-protocol set
- The primary event censoring rules are used for analysis of the main efficacy endpoint minus 42 days of patients with disease progression after 15 months in the full analysis set
- The primary event censoring rules are used for re-analysis of the main efficacy endpoint based on the full analysis set
- The primary event censoring rules are used for analysis of the PFS results derived by IRC evaluation based on the full analysis set
- Based on the primary event censoring rules, subjects for whom the main efficacy endpoint is evaluated as "NE" before progression because of the epidemic are censored to the date on which the evaluation result before disease progression is "NE" for sensitivity analysis

Table 4.2-1PFS event censoring rules 2 (secondary event censoring rules)

Situation	Date	Outcome
No baseline or post-baseline imaging evaluation results	Date of randomization	Censored

No progression before data cutoff	Date of the last valid imaging examination before data cutoff	Censored
Progression or death before data cutoff	Examination date of first imaging disease progression or date of death	Progression or death

4.3. Subgroup Analysis of Primary Efficacy Endpoint

The subgroup analysis in this chapter will adopt the primary event censoring rules. Subgroup analysis is expressed as follows:

1) Based on the full analysis set, the following analysis is performed on the subgroup level in the two subgroups of EGFR gene mutation type and brain metastasis status based on PFS as evaluated by the investigator:
   Kaplan-Meier plots are drawn for the two treatment groups and the median and 95% confidence interval of PFS in the two treatment groups are given.
2) The above analysis is repeated based on PFS as evaluated by the IRC.
3) In addition, based on the full analysis set, the Cox proportional hazards model is adopted for subgroup analysis of the subgroups defined in Section 2.2.3 based on PFS as evaluated by the investigator. The HR and 95% confidence interval of the PFS comparison between the two treatment groups on the subgroup level are given.
   The HR and corresponding 95% confidence interval calculated in different subgroups will be displayed as a forest plot and the above analysis results will be displayed in the plot.
   Note: For subgroups with too few events (that is, the number of events on the subgroup level is lower than 20), the analysis results for the subgroup will not appear in the forest plot.

4.4. Secondary Efficacy Endpoint Analysis

4.4.1. Objective response rate (ORR)

The following analysis of the endpoint will be performed based on the FAS:

1) The number and percentage of best tumor response results based on treatment group are summarized as follows: Complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), and not evaluable (NE).
2) The number of cases that achieved an objective response and the objective response rate (as a percentage) as well as the 95% Clopper-Pearson confidence interval for the response rate in each treatment group are calculated and summarized. In ORR analysis, evaluations performed after subject progression are not included in the analysis. If a subject uses other non-investigational drugs for anti-tumor therapy after terminating the investigational drug treatment, any CR or PR occurring from the time of use will not be included in the numerator of the ORR calculation.
3) A logistic regression model stratified by EGFR mutation type and brain metastasis status is used for the Wald Chi-squared test to compare the objective response rates of the two treatment groups. The odds ratio (OR) estimate and 95% confidence interval calculated based on the Wald method are given.

4.4.2. Duration of response (DoR)

The following analysis of the endpoint is performed on all subjects with an objective response based on the FAS:

The same method as the primary endpoint PFS is adopted for analysis. The Kaplan-Meier estimates of progression-free response rate at 6, 9, 12, 15, and 18 months as well as the 95% confidence intervals corresponding to the K-M estimates based on Greenwood's standard error estimation method are given.

4.4.3. Disease Control Rate (DCR)

The following analysis of DCR based on the FAS will be performed:

1) Descriptive summarization of DCR by treatment group is performed. The DCR estimate and 95% Clopper-Pearson confidence interval of each treatment group is estimated.
2) A logistic regression model stratified by EGFR mutation and brain metastasis status is adopted to compare the DCR of the two treatment groups. The estimated odds ratio (OR), 95% confidence interval, and test p value of DCR of the two treatment groups are given.

4.4.4. Depth of response (DepOR)

The following analysis of this indicator is performed based on the FAS.

1) Based on visit, the number of subjects included in the calculation and absolute change and relative percentage change in tumor size versus baseline in the two treatment groups are descriptively summarized. At the same time, the means, standard deviations, 1/4 quantiles, medians, 3/4 quantiles, minimums, and maximums are also given.
2) The best percentage of tumor response by treatment group is summarized. The number of subjects included in the calculation and the mean, standard deviation, minimum, maximum, and median of the best percentage in each treatment group are given; and the numbers and proportions of subjects who achieved a 30%, 50%, and 75% tumor response are calculated.
3) The ANCOVA model is adopted for comparison of best percentage of tumor response between groups. The covariates in the model include EGFR mutation type, brain metastasis status, the sum of the diameters of all evaluable target lesions at baseline (mm), and the time interval from the baseline scan date to the date of randomization (days). The analysis results provide the number of subjects included in the calculation, the corrected mean best percentage, and the corresponding 95% confidence interval of each treatment group. At the same time, the estimated least squares mean of the comparison between the two groups, the 95% confidence interval, and the test p value are given (level of significance of 0.05).
4) Waterfall plots of best percentage of tumor response by treatment group are drawn. In the plots, two reference lines of the best percentage are marked: 20% (indicating a 20% increase in tumor size versus baseline, corresponding to disease progression as defined by RECIST V1.1) and -30% (indicating a 30% decrease in tumor size versus baseline, corresponding to partial response as defined by RECIST V1.1).

4.4.5. Overall survival (OS)

Overall survival OS is performed separately in the FAS and PPS.

If the subject's date of survival or death is confirmed to be later than the data cutoff date, the survival period of the subject is censored to the data cutoff date. If it is not known whether the subject has died, it will be censored to the latest known date of survival recorded in the EDC.

1) The same method as the primary endpoint PFS is adopted for analysis. The Kaplan-Meier estimates of overall survival rate at 12, 24, and 36 months and corresponding 95% confidence intervals are given.
2) If the data are mature, the same subgroup analysis method as PFS will be adopted for analysis of OS.

5. Safety Analysis

All safety analysis will be based on the safety set.

5.1. Adverse events

Adverse events will be coded with MedDRA 23.0 or a higher version.

CTCAE (4.03) will be obtained for the rating of the seriousness of adverse events. AEs that occur from the start of treatment to within 28 days after the last treatment will be summarized in the safety evaluation. AEs occurring prior to treatment initiation and AEs occurring within 28 days after the last treatment are tabulated separately and will not be included in summary tables for AEs.

General principles to follow when summarizing adverse events:

1) Adverse events are summarized by treatment group and system organ class/preferred time (SOC/PT).

2) If the same subject has the same adverse event multiple times, the one with the highest correlation with the investigational drug will be used to summarize the investigational drug-related AE and the one with the highest severity will be used for the summary of adverse event seriousness.

3) Only adverse events during the randomized, double-blind treatment stage and not during the cross-treatment stage are included.

All of the AEs of each subject will be presented in a list.

Related to the investigational drug refers to "definitely related," "possibly related," and "unable to be determined."

Serious adverse events will be summarized and tabulated individually.

The following summary results will be given:

1) Summary of all adverse events

2) All adverse events summarized by system organ class and preferred term

3) Investigational drug-related adverse events summarized by system organ class and preferred term

4) All common adverse events summarized by system organ class and preferred term

5) All common investigational drug-related adverse events summarized by system organ class and preferred term

6) Adverse events of CTCAE grade ≥ 3 summarized by system organ class and preferred term

7) Investigational drug-related adverse events of CTCAE grade ≥ 3 summarized by system organ class and preferred term

8) Serious adverse events (SAEs) summarized by system organ class and preferred term

9) Investigational drug-related serious adverse events (SAEs) summarized by system organ class and preferred term

10) Adverse events leading to permanent discontinuation summarized by system organ class and preferred term

11) Investigational drug-related adverse events leading to permanent discontinuation summarized by system organ class and preferred term

12) Adverse events leading to suspension of medication summarized by system organ class and preferred term

13) Investigational drug-related adverse events leading to suspension of medication summarized by system organ class and preferred term

14) Adverse events leading to dose reduction summarized by system organ class and preferred term

15) Investigational drug-related adverse events leading to dose reduction summarized by system organ class and preferred term

16) All adverse events leading to death summarized by system organ class and preferred term

17) All adverse events and serious adverse events are given in the list of all investigational drug-related adverse events leading to death summarized by system organ class and preferred term.

5.2. Laboratory testing

In accordance with the study protocol, laboratory testing was performed during specific visit periods in this study. For the specific examination items, refer to Section 1.3.3.

Laboratory test data will be divided into continuous variables and categorical variables, which will be analyzed by group as follows:

1) For quantitative results, the actual measurements and their change from baseline will be descriptively summarized by visit;
2) For qualitative results, the results for the judgment of the clinical significance of the laboratory test data and the numbers and ratios of subjects with clinically significant abnormalities by visit will be presented in cross table form.
3) For qualitative results, the numbers and ratios of subjects with results that were normal or abnormal without clinical significance at baseline but turned abnormal with clinical significance after treatment are summarized.

All laboratory test data and the results for the judgment of clinical significance are presented in list form.

5.3. Vital Signs

The measurement results and changes versus baseline of each vital sign indicator during each visit are summarized and described by treatment group, including temperature (oral temperature, ear temperature, or axillary temperature, expressed in degrees Celsius), blood pressure (systolic and diastolic pressure), pulse (heart rate per minute), respiratory rate, and weight.

All vital sign check results, weight, and ECOG PS scores are listed separately.

5.4. Physical Examination

All physical examination results are given in lists.

5.5. 12-lead ECG

Because each ECG examination in this study is repeated 3 times, the average ECG results of each examination serve as the ECG values for the examination in the following analysis:

1) The changes versus baseline of various ECG indicators (heart rate (beats/minute), PR

(ms), QRS duration (ms), RR interval (ms), QT, and QTcF (ms)) at each visit and each post-treatment visit are summarized by treatment group and visit.

2) The proportions of ≤ 450 ms, 450-480 ms, 480-500 ms, and > 500 ms are described for the absolute values at baseline and during post-treatment visits of QT interval and QTcF interval by treatment group and visit and the proportions of change versus baseline during post-treatment visits at ≤ 30 ms, 30-60 ms, and > 60 ms are given.
3) The changes versus baseline in the clinical significance of the 12-lead ECG examination results (normal, abnormal without clinical significance, and abnormal with clinical significance) are summarized with cross tables by visit and treatment group.

A list is made of all of the ECG examination results.

"Abnormal and clinically significant" above is an EDC-collected value.

5.6. LVEF measured with echocardiography or MUGA

The following will be summarized by treatment group at each visit and after treatment:

- Summary of the proportion of subjects with LVEF value < 50% and decrease versus baseline ≥ 10%

- Summary of the proportion of subjects with LVEF value ≥ 50% and decrease versus baseline ≥ 15%.

All LVEF results of each subject will be presented by list.

5.7. Ophthalmological examination

ophthalmological examination results are given in a list.

6. Modifications to the Analysis Plan

In accordance with the NMPA anti-tumor drug clinical trial endpoint technical guidelines, the definition of overall survival is modified from “the time between the first medication date and the date of patient death from any cause” to “the time from the start of randomization to death from any cause.” This modification will not affect the primary efficacy endpoint results.

7. Statistical Analysis Form

The list of statistical analysis charts follows:

14.1 Subject Information
14.1.1 Distribution of subjects
Table 14.1.1.1 Summary of screening failures-all screened subjects
Table 14.1.1.2 Subject distribution-all randomized subjects
Table 14.1.1.3 Distribution of subjects in each analysis set-all randomized subjects
14.1.2 Protocol Deviations
Table 14.1.2.1 Summary of serious protocol deviations during the randomized, double-blind treatment stage-full analysis set
Table 14.1.2.2 Summary of serious protocol deviations during the randomized, double-blind treatment stage (excluding those caused by the epidemic)-full analysis set
14.1.3 Demographic data and baseline data
Table 14.1.3.1 Summary of subject demographic data and baseline characteristics-full analysis set
Table 14.1.3.2 Summary of subject demographic data and baseline characteristics-per-protocol set
Table 14.1.3.3 Summary of subject baseline disease characteristics-full analysis set
Table 14.1.3.4 Summary of subject baseline disease characteristics-per-protocol set
14.1.4 Past medical history
Table 14.1.4.1 Summary of past medical history-full analysis set
14.1.5 Past concomitant medications
Table 14.1.5.1 Summary of past medications by ATC3 and PT-full analysis set
Table 14.1.5.2 Summary of past medications by ATC1 and ATC3-full analysis set
Table 14.1.5.3 Summary of concomitant medications by ATC3 and PT-full analysis set
Table 14.1.5.4 Summary of concomitant medications by ATC1 and ATC3-full analysis set
14.1.6 Past, concomitant and subsequent anti-tumor therapy
Table 14.1.6.1 Summary of past anti-tumor treatment by treatment category and treatment type-full analysis set
Table 14.1.6.2 Summary of concomitant anti-tumor medications by ATC3 and PT-full analysis set
Table 14.1.6.3 Summary of subsequent anti-tumor treatment by ATC3 and PT-full analysis set
14.1.7 Subject exposure and medication compliance
Table 14.1.7.1 Summary of drug exposure time and compliance-safety set
14.2 Efficacy evaluation
14.2.1 Analysis based on endpoint PFS as evaluated by the investigator (primary event censoring rules)-full analysis set
Table 14.2.1.1 Statistical analysis based on PFS as evaluated by the investigator (primary event censoring rules)-full analysis set
Figure 14.2.1.1 Kaplan-Meier curve based on PFS as evaluated by the investigator (primary event censoring rules)-full analysis set
14.2.2 Analysis based on endpoint PFS as evaluated by the investigator (primary event censoring rules and considering primary drug resistance)-full analysis set
Table 14.2.2.1 Statistical analysis based on PFS as evaluated by the investigator-full analysis set (excluding subjects with primary drug resistance)
Figure 14.2.2.1 Kaplan-Meier curve based on PFS as evaluated by the investigator-full analysis set (excluding subjects with primary drug resistance)
14.2.3 Analysis based on endpoint PFS as evaluated by the investigator (primary event censoring rules)-per-protocol set
Table 14.2.3.1 Statistical analysis based on PFS as evaluated by the investigator (primary event censoring rules) - per-protocol set
Figure 14.2.3.1 Kaplan-Meier curve based on PFS as evaluated by the investigator (primary event censoring rules)-per-protocol set
14.2.4 Analysis based on endpoint PFS as evaluated by the investigator (secondary event censoring rules)-full analysis set
Table 14.2.4.1 Statistical analysis based on PFS as evaluated by the investigator (secondary event censoring rules)-full analysis set
Figure 14.2.4.1 Kaplan-Meier curve based on PFS as evaluated by the investigator (secondary event censoring rules)-full analysis set
14.2.5 Analysis based on endpoint PFS as evaluated by the IRC (primary event censoring rules)-full analysis set
Table 14.2.5.1 Statistical analysis based on PFS as evaluated by the IRC (primary event censoring rules)-full analysis set
Figure 14.2.5.1 Kaplan-Meier curve based on PFS as evaluated by the IRC (primary event censoring rules)-full analysis set
14.2.6 Analysis based on endpoint PFS as evaluated by the investigator (primary event censoring rules and considering the impact of the COVID-19 epidemic)-full analysis set

Table 14.3.1.8 Summary of common (≥ 10%) adverse events by system organ class and preferred term-safety set
Table 14.3.1.9 Summary of common (≥ 10%) investigational drug-related adverse events by system organ class and preferred term-safety set
Table 14.3.1.10 Summary of adverse events causing the suspension of medication by system organ class and preferred term-safety set
Table 14.3.1.11 Summary of investigational drug-related adverse events causing the suspension of medication by system organ class and preferred term-safety set
Table 14.3.1.12 Summary of adverse events causing dose reduction by system organ class and preferred term-safety set
Table 14.3.1.13 Summary of investigational drug-related adverse events causing dose reduction by system organ class and preferred term-safety set
Table 14.3.1.14 Summary of adverse events causing permanent discontinuation by system organ class and preferred term-safety set
Table 14.3.1.15 Summary of investigational drug-related adverse events causing permanent discontinuation by system organ class and preferred term-safety set
Table 14.3.1.16 Summary of adverse events causing death by system organ class and preferred term-safety set
Table 14.3.1.17 Summary of investigational drug-related adverse events causing death by system organ class and preferred term-safety set
Table 14.3.1.18 Summary of all adverse events and adverse events of CTCAE grade ≥ 3 by system organ class and preferred term-safety set
Table 14.3.1.19 Summary of all investigational drug-related adverse events and adverse events of CTCAE grade ≥ 3 by system organ class and preferred term-safety set
Table 14.3.1.20 Summary of adverse events of CTCAE grade ≥ 3 and investigational drug-related adverse events of CTCAE grade ≥ 3 by system organ class and preferred term-safety set
Table 14.3.1.21 Summary of common (≥ 10%) adverse events and adverse events of CTCAE grade ≥ 3 (incidence rate ≥ 2%) by system organ class and preferred term-safety set
Table 14.3.1.22 Summary of investigational drug-related common (≥ 10%) adverse events or adverse events of CTCAE ≥ grade 3 adverse events (incidence rate ≥ 2%) by system organ class and PT class-safety set
Table 14.3.1.23 Summary of adverse events by system organ class, preferred term, and drug relation-safety set
Table 14.3.1.24 Summary of adverse events by system organ class, PT and severity (CTCAE grade)-safety set
Table 14.3.1.25 Summary of investigational drug-related adverse events by system organ class, preferred term, and seriousness (CTCAE grade)-safety set
Table 14.3.1.26 Summary of adverse events causing permanent discontinuation and investigational drug-related adverse events causing permanent discontinuation by system organ class and preferred term-safety set
Table 14.3.1.27 Summary of serious adverse events and investigational drug-related serious adverse events by system organ class and preferred term-safety set
14.3.2 Laboratory Tests
Table 14.3.2.1 Summary of laboratory test values before and after treatment and changes versus baseline by visit (routine blood)-safety set
Table 14.3.2.2 Summary of laboratory test values before and after treatment and changes versus baseline by visit (blood chemistry)-safety set
Table 14.3.2.3 Summary of subjects with clinically significant abnormal laboratory tests by visit (routine blood)-safety set
Table 14.3.2.4 Summary of subjects with clinically significant abnormal laboratory tests by visit (blood chemistry)-safety set
Table 14.3.2.5 Summary of subjects with clinically significant abnormal laboratory tests by visit (routine urine)-safety set
Table 14.3.2.6 Cross table of laboratory tests before and after treatment by (routine blood)-safety set
Table 14.3.2.7 Cross table of laboratory tests before and after treatment (blood chemistry)-safety set
Table 14.3.2.8 Cross table of laboratory tests before and after treatment (routine urine)-safety set
Table 14.3.2.9 Summary of normal or abnormal [tests] without clinical significance at baseline that turned to abnormal with clinical significance after treatment (routine blood)-safety set
Table 14.3.2.10 Summary of normal or abnormal [tests] without clinical significance at baseline that turned to abnormal with clinical significance after treatment (blood chemistry)-safety set
Table 14.3.2.11 Summary of normal or abnormal [tests] without clinical significance at baseline that turned to abnormal with clinical significance after treatment (routine urine)-safety set
14.3.3 12-lead ECG
Table 14.3.3.1 Summary of ECG values before and after treatment and changes versus baseline by visit-safety set
Table 14.3.3.2 Summary of QT and QTcF by visit-safety set
Table 14.3.3.3 Cross table of ECGs before and after treatment-safety set
Table 14.3.3.4 Summary of the classification of the maximum absolute value or the maximum change versus baseline of QTcF after treatment-safety set
Table 14.3.3.5 Summary of normal or abnormal [tests] without clinical significance at baseline that turned to abnormal with clinical significance after treatment (ECG)-safety set

14.3.4 Vital signs
Table 14.3.4.1 Summary of vital sign values before and after treatment and changes versus baseline by visit-safety set
Table 14.3.4.2 Summary of ECOG PS score distribution by visits-safety set
14.3.5 LVEF
Table 14.3.5.1 Summary of LVEF abnormalities by visit-safety set
Table 14.3.5.2 Summary of LVEF abnormalities after treatment-safety set
14.3.6 Physical examination
Table 14.3.6.1 Cross table of physical examination results before and after treatment-safety set
Table 14.3.6.2 Summary of normal or abnormal [tests] without clinical significance at baseline that turned to abnormal with clinical significance after treatment (physical examination)-safety set
16.2 Subject lists
16.2.1 Distribution of subjects
List 16.2.1.1 List of subject screening failures-all subjects
List 16.2.1.2 List of the details of the distribution of subjects-all randomized subjects
List 16.2.1.3 List of the discontinuation of treatment by subjects-all randomized subjects
List 16.2.1.4 List of subjects with random stratification errors-all randomized subjects
List 16.2.1.5 List of subjects not included in the per-protocol set-full analysis set
16.2.2 Serious protocol deviations
List 16.2.2.1 List of serious protocol deviations during the study-full analysis set
16.2.3 Demographic data and baseline data
List 16.2.3.1 List of demographic information and baseline characteristics-full analysis set
List 16.2.3.2 List of baseline disease characteristics-full analysis set
List 16.2.3.3 List of past medical histories-full analysis set
List 16.2.3.4 List of past medications-full analysis set
List 16.2.3.5 List of concomitant medications-full analysis set
List 16.2.3.6 List of surgical histories-full analysis set
List 16.2.3.7 List of allergy histories-full analysis set
List 16.2.3.8 List of past anti-tumor therapies-full analysis set
List 16.2.3.9 List of concomitant anti-tumor therapies-full analysis set
List 16.2.3.10 List of subsequent anti-tumor therapies-full analysis set
16.2.4 Drug exposure and compliance
List 16.2.4.1 List of subject drug exposure and medication-safety set
16.2.5 Efficacy data-progression-free survival and overall survival
List 16.2.5.1 Progression-free survival (as evaluated by the investigator)-full analysis set
List 16.2.5.2 Progression-free survival (as evaluated by the IRC)-full analysis set
List 16.2.5.3 Overall survival-full analysis set
16.2.6 Efficacy data-lists of tumor measurements and evaluations
List 16.2.6.1 List of tumor response as evaluated by the investigator based on RECIST 1.1-full analysis set
List 16.2.6.2 List of tumor response as evaluated by the IRC based on RECIST 1.1-full analysis set
List 16.2.6.3 List of target lesions measurements and total diameters by visit (as evaluated by the investigator)-full analysis set
List 16.2.6.4 List of duration of response as evaluated by the investigator-full analysis set
List 16.2.6.5 List of objective response rate and disease control rate as evaluated by the investigator-full analysis set
16.2.7 Lists of adverse events
List 16.2.7.1 List of all adverse events (during treatment and 28 days after the last medication)-safety set
List 16.2.7.2 List of all adverse events (before the first medication)-safety set
List 16.2.7.3 List of all adverse events (28 days after the last medication)-safety set
List 16.2.7.4 List of all serious adverse events-safety set

List 16.2.7.5 List of adverse events leading to death-safety set
16.2.8 Laboratory tests, ECGs, LVEF, ECOG PS scores, etc.
List 16.2.8.1 List of laboratory test results (routine blood)-safety set
List 16.2.8.2 List of laboratory test results (blood chemistry)-safety set
List 16.2.8.3 List of laboratory tests (routine urine)-safety set
List 16.2.8.4 List of examination results of vital signs (including weight and ECOG PS score)-safety set
List 16.2.8.5 List of physical examination results-safety set
List 16.2.8.6 List of 12-lead ECG examination results-safety set
List 16.2.8.7 List of LVEF test results-safety set
List 16.2.8.8 List of ophthalmological examination results-safety set

References

1. NMPA: Good Clinical Practice (GCP) 2020
2. NMPA: Technical Guideline for Endpoints in Clinical Trials of Anti-Tumor Drugs 2020
3. NMPA: Guidelines for the Management of Drug Clinical Trials During the COVID-19 Epidemic (Pilot) 2020
4. ICH: STATISTICAL PRINCIPLES FOR CLINICAL TRIALS 1998
5. FDA: STATISTICAL CONSIDERATIONS FOR CLINICAL TRIALS DURING COVID-19 2020
6. CFDA: Biostatistics Guidelines for Drug Clinical Trials 2016
7. CFDA: Technical Guidelines for Clinical Trial Data Management 2016
8. CFDA: “Guidelines for Planning and Reporting of Data Management and Statistical Analysis of Drug Clinical Trials”, 2016