Official Title: Phase IV, open-label, multi-center, single-arm study of the safety and efficacy of everolimus (Afinitor) in adult patients with locally advanced, unresectable or metastatic, well differentiated progressive pancreatic neuroendocrine tumors (pNET) in China.

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Statistical Analysis Plan

Phase IV, open-label, multi-center, single-arm study of the safety and efficacy of everolimus (Afinitor) in adult patients with locally advanced, unresectable or metastatic, well differentiated progressive pancreatic neuroendocrine tumors (pNET) in China

Study drug:	Everolimus (Afinitor®)
Comparator:	None
Indication:	Chinese adult patients with unresectable, locally advanced or metastatic, G1 or G2 progressive pancreatic neuroendocrine tumors (pNET) (WHO 2010)
Phase:	IV
Authors:	[redacted]
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Statistical Analysis Plan Signature Page

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Amendment Record			
Version No.	**Effective Date**	**Modification/Amendment Rationale**	**Substituted Version**
Final Version 1.1	May 22, 2017	Added analysis of laboratory tests and adverse events of special interest based on comments from the sponsor	Final Version 1.0
Final Version 1.2	June 14, 2017	Protocol was updated to add analysis of AE as required by sponsor's Medical Writer and Clinical Lead	Final Version 1.1
Final Version 2.0	July 14, 2017	1. Title was updated in accordance with the latest Chinese protocol 2. Protocol was updated involving violation analysis to tabulate only major protocol violations	Final Version 1.2
Final Version 3.0	May 12, 2021	1. Updated PFS censoring rules; 2. Added imputation rules regarding dates of death in Section 5.4.2.4.1 3. Added Section 5.5.5 Additional Analysis for Assessment the Impact of COVID-19 4. Added imputation rules on the end date of administration in Section 5.4.1 5. In Section 5.4.2, added the description of "In the causality assessment between the investigational drug and the adverse event, if the result is missing or unknown, that AE will be assessed as "suspected to be related to the investigational drug" " 6. The Chinese name of “progressive pancreatic neuroendocrine tumor” was unified throughout the document	Final Version 2.0
Final Version 3.1	October 11, 2023	1. Based on Novartis SOP requirements, the definitions of full analysis set and safety set were updated to align with the protocol	Final Version 3.0
Final Version 3.2	April 12, 2024	1. Section 5.4.2, updated the determination principle of the period to which adverse events fall into 2. Section 5.3.5, added imputation rules for start date and end date of concomitant drugs 3. Section 5.4.2.4.1, added last known alive date definition. 4. Section 5.5.2, added the definition of new anticancer therapy 5. Update case 5 of the censoring rules for PFS in Table 2, the censoring date of new anticancer therapy was adjusted from “date of last adequate tumor assessment prior to initiation of subsequent anticancer therapy” to	Final Version 3.1

		"date of last adequate tumor assessment prior to initiation of subsequent anticancer therapy (start date of the study treatment if there is no post-baseline imaging examination)".	
Final Version 4.0	May 13, 2024	Finalized Version	Final Version 3.2

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Abbreviations

AE	Adverse event
ATC	Anatomical therapeutic chemical
CR	Complete response
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CTCAE	Common Terminology Criteria for Adverse Events
FAS	Full Analysis Set
MedDRA	Medical Dictionary for Regulatory Activities
OS	Overall survival
PD	Progression of disease
PFS	Progression-free survival
pNET	Pancreatic neuroendocrine tumors
PR	Partial response
PT	Preferred Term
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SD	Stable Disease
SMQ	Standard MedDRA query
SOC	System organ class
WHO	World Health Organization

1 Project Introduction

The Statistical Analysis Plan (SAP) provides and describes the statistical analysis methods and data processing principles for the Phase IV clinical study (protocol number: CRAD001PCN31) sponsored by Novartis Pharma AG to analyze and report on the efficacy and safety of this study. This SAP was formulated based on the revised clinical study protocol of version 01 (version date: May 31, 2017).

2 Study objectives and study endpoints

2.1 Primary study objective

- To evaluate the safety of treatment with Afinitor in Chinese adult patients with well differentiated progressive pancreatic neuroendocrine tumors (pNET).

2.2 Secondary study objective

- To evaluate the overall efficacy of treatment with Afinitor in Chinese patients with well differentiated progressive pNET.

2.3 Primary study endpoints

- Incidences of adverse events (AEs), AEs suspected to be related to Afinitor, Grade 3 or 4 AEs and serious adverse events (SAEs);
- AEs of special interest: Non-infectious pneumonitis.
- Other safety endpoints.

2.4 Secondary study endpoints

- Overall Survival (OS): defined as time from the start of study treatment to death due to any cause;
- Progression Free Survival (PFS): defined as time from the start of study treatment to progression or death due to any cause.

3 Study design

This is an open-label, multi-center, single-arm study of the safety and efficacy of Afinitor in adult patients with locally advanced, well differentiated progressive pNET in China.

Patient who are eligible will be provided with everolimus by sponsor to treat pancreatic neuroendocrine tumors and will follow the visit schedule in Appendix 1 Visit Evaluation Schedule to collect safety and efficacy data until disease progression, unacceptable toxicity, death, visit deviation or other reason that may lead to discontinuation before the end of study.

All patients will be followed-up for survival status every 6 months by the investigator until death, lost to follow-up, withdrawal of consent for survival or end of study.

4 Sample size calculation

The sample size was determined based on feasibility rather than statistical considerations.

Based on pre-marketing field survey, each year, approximately 6 to 10 patients at each of the 5 to 10 study sites selected for this study will be newly diagnosed as 'locally advanced or metastatic, well differentiated pancreatic neuroendocrine tumor', about 10% to 20% of diagnosed patients will be eligible and agree to participate the study. Approximately 30 patients were initially planned to be enrolled, and approximately 60 patients are now planned to be enrolled after further communication with the Center for Drug Evaluation. Due to the uncertainties during the enrollment, the actual number of patients may differ from estimations.

5 Statistical Analysis

5.1 General Principle

All statistical analysis were done by using SAS 9.4 or updated version.

In general, continuous variables were descriptively summarized using number of subjects, mean, median, SD, minimum and maximum. Categorical variables and rank variables were descriptively summarized using the frequency and percentage under each category or rank. Unless otherwise specified, missing data were not included for the calculation of percentage.

The analytical method of this study was predominantly descriptive, without predetermined hypothesis test regarding the comparison of various observation periods.

5.1.1 Visit Window

Treatment day is defined as the number of days on which safety/efficacy assessments are performed relative to the initiation of study drug treatment. The day on which the study drug treatment is initiated will be recorded as Study Treatment Day 1. Treatment day will be calculated as follows:

- Treatment day = date of assessment − date of initiation of study drug treatment + 1 (assessment occurs after study drug treatment)
- Treatment day = date of assessment − date of initiation of study drug treatment (assessment occurs before study drug treatment).

Since there may be deviations from the visit schedule during the actual trial operation, visit windows were created based on the scheduled treatment day of the visits in order that these deviated data could also be included in the visits for pooled analysis. If multiple assessments fall into the same visit window, the assessment closest to the scheduled treatment day in the visit window will be used in the pooled analysis. If there are multiple assessments that are equally close to the scheduled treatment date, the latest assessment will be used in the pooled analysis. The table below defines the scheduled treatment days and the width of window for visits at different assessment endpoints:

(I) Safety assessment endpoints (vital signs, laboratory tests)

Scheduled visits	Visit labels in tables/lists	Scheduled treatment days	Visit window (days)
Screening/Baseline, Visit 1	Baseline	1	≤ 1
Visit 2	Week 4	29	2 - 57
Visit 3	Week 12	85	58 - 127
Visit 4	Week 24	169	128 - 211
Visit 5	Week 36	253	212 - 295
Visit 6	Week 48	337	296 - 379
….	...		
Visit n	Week 12* (n-2)	12 * (n - 2) * 7 + 1	12 * (n - 2) * 7 + 1 - 41 - 12 * (n - 2) * 7 + 1 + 42

(II) Tumor assessments (only for division of the analysis visits for summary of the diameters of target lesions)

Scheduled visits	Visit labels in tables/lists	Scheduled treatment days (Day)	Visit window (days)
Screening/Baseline, Visit 1	Baseline	1	≤ 1
Visit 3	Week 12	85	2 - 127
Visit 4	Week 24	169	128 - 211
Visit 5	Week 36	253	212 - 295
Visit 6	Week 48	337	296 - 379
….	….		
Visit n	Week 12* (n-2)	12 * (n - 2) * 7 + 1	12 * (n - 2) * 7 + 1 - 41 - 12 * (n - 2) * 7 + 1 + 42

5.2 Analysis Population

- Full Analysis Set (FAS): including all patients who received at least one study treatment. Patients will be analyzed according to the treatment they received. The FAS will be the primary population in the assessment of efficacy.
- Safety Analysis Set (SS): same as FAS. All safety analyses will be analyzed using the Safety Set.

5.3 Study Participants

5.3.1 Patient Distribution

All patients will be summarized according to the analysis datasets. The number and percentage of patients in the FAS and SAF will be summarized separately.

The number of patients undergoing treatment, and in the FAS, the number and percentages of patients who ended the treatment and who ended the treatment for different reasons, and the numbers and percentages of patients who ended the trial and who ended the trial for different reasons will be separately summarized. The total number of patients screened in each study site and the number of patients in the different analysis sets will also be summarized separately.

The disposition of all patients in the FAS set will be tabulated.

5.3.2 Protocol Violations

Protocol violations of patients in the FAS analysis set will be tabulated for analysis. In addition, major protocol violations will also be tabulated for analysis.

5.3.3 Demographic and Baseline Characteristics

Demographic characteristics and baseline characteristics will be summarized and tabulated based on the FAS.

The following demographic characteristics and baseline characteristics will be summarized and tabulated separately:

Demographic characteristics

- Age and age group (18 to < 65 years, ≥ 65 years)
- Gender
- Height
- Weight
- Body mass index (weight (kg) / (height (cm) / 100) ^{2})

Baseline disease characteristics

- Type according to histological diagnosis
- Tumor staging
- Duration of illness (years, time from initial diagnosis to start of study treatment): if the day is missing in the patient's initial diagnosis date (year and month known), it will be imputed using the median value of the dates in that month, i.e., it will be imputed as 15th if that month consists of 30 days, or as 16th if that month consists of 31 days; if the month and day are missing in the patient's initial diagnosis date (year known), it will be imputed with June 30 of that year.

In addition, the following baseline tumor lesion examinations will be summarized by means of contingency tables or descriptive statistics (number of cases, mean, median, standard deviation, minimum, and maximum) according to the distribution of data types:

- Total number of lesions, number of target lesions, and number of non-target lesions (1, 2, 3, 4, 5 and > 5)
- Number of organs affected (1, 2 and ≥ 3)
- Distribution of organs affected
- Type of lesion (only target lesion, both target lesions and non-target lesions)
- Diameter of target lesion (short diameter of the nodular lesion or the longest diameter of other target lesions)

5.3.4 Medical History

The medical history will be summarized and listed based on the FAS.

The medical history will be coded using the Medical dictionary for regulatory activities (MedDRA) 23.0 or the latest version of the coding dictionary before database lock. The number and percentage of patients with at least 1 history will be summarized by System Organ Class (SOC) (in alphabetical order) and Preferred Term (PT) (in descending frequency).

All medical history was tabulated by patient.

5.3.5 Concomitant medications

Combined medications will be summarized and listed based on the SAF.

Combined medications will be using the latest version of World Health Organization (WHO) dictionary and Anatomical Therapeutic Chemical (ATC) codes prior to database lock. Combined medications will be categorized into prior and concomitant medications based on whether they are used at the start of study treatment:

- Prior medications, refer to medications used only prior to study treatment (i.e., medications ended before the start of study treatment)
- Concomitant medications, refer to medications used concurrently during study treatment (i.e., medications received at or after the start of study treatment, or medications used prior to the start of study treatment and continued after the start of study treatment). If the time of a combined medication relative to the start of study treatment cannot be determined, it will be considered concomitant.

If the start date of a combined medication is missing, it will be imputed according to the following rules:

- Missing days only: if the year and month are the same as the first dose of study drug, the date of the first dose of study drug will be used, otherwise it will be imputed with the first day of that month
- Missing month and day: if the year is the same as the first dose of study drug, the date of the first does of study drug will be used, otherwise it will be imputed as January 1
- If the year, month, and day are all missing, it will be imputed directly with the date of the first dose of study drug

If the end date of a combined medication is missing and it is unknown if the combined medication is still in use at the end of study treatment, it will be imputed according to the following rules:

- Missing days only: impute with the last day of the month
- Missing month and day: impute with December 31
- If the year, month, and day are all missing, it will be imputed with the date of the last dose of study drug

For concomitant medications, the number and percentage of patients using at least 1 dose will be summarized according to ATC 2nd level (in alphabetical order) and Preferred Term (in descending frequency). Concomitant medications will be listed. Prior medication was only tabulated.

5.4 Safety Analysis (Primary Analysis)

All safety analyses were based on SAF.

5.4.1 Drug administration

Duration of study treatment exposure, cumulative dose, dose intensity, and relative dose intensity were summarized descriptively. Where:

- Dose intensity (mg/day) = cumulative dose (mg) / duration of exposure (days), where duration of exposure (days) = time of last dose of Afinitor − time of first dose of Afinitor + 1.
- Relative dose intensity (%) = dose intensity / planned daily dose (10 mg/day) × 100%.

Patients with a certain duration of exposure (< 12 weeks, 12 - < 24 weeks, 24 - < 36 weeks, 36 - < 48 weeks, 48 - < 60 weeks, 60 - < 72 weeks, 72 - < 84 weeks, and ≥ 84 weeks) were summarized; patients with certain relative dose intensity (0 - < 50%, 50% - < 70%, 70% - < 90%, 90% - < 110%, and ≥ 110%) were summarized.

In addition, the number and percentage of patients with dose adjustments/dose interruptions (1 and ≥ 2) were summarized, and the reasons for dose adjustments were summarized by number and percentage of patients.

If the end date is missing, the following rules are used to impute:

- Missing days only: if the year and month are the same as the last visit, the date of the last visit will be used, otherwise it will be imputed with the last day of that month
- Missing month and day: if the year is the same as the last visit, the date and month of the last visit will be used, otherwise it will be imputed as December 31. If the imputed date is later than the withdrawal date, the end-of-medication date is adjusted to withdrawal date - 1 day.
- If all year, month and day are missing, it will be imputed directly with the date of the last visit

Drug administration was tabulated by patient.

5.4.2 Adverse events (AEs)

Adverse events (AEs) were coded according to the latest version of MedDRA prior to database lock.

If an outcome is missing and there is no outcome date, the outcome of that adverse event will be considered "ongoing". In the causality assessment between the investigational drug and the adverse event, if the result is missing or unknown, that AE will be assessed as "suspected to be related to the investigational drug". Other missing data will be treated as missing.

Adverse events were classified by onset time of AE relative to start time of study treatment as:

- Pre-treatment period: from day of patient’s informed consent to the day before first dose of study medication;

- On-treatment period: from day of first dose of study medication to 30 days after last dose of study medication;
- Post-treatment period: starting from 30 + 1 days after last dose of study medication.

In addition to the overview of adverse events, only treatment-emergent adverse events were summarized by the number and percentage of patients with AEs. However, all AEs (including pre-treatment and post-treatment AEs) were tabulated with data indicating whether the AE occurred before or during or after the treatment period. For AE with missing dates, the available information should be used as much as possible when determining the period to which the AE belongs. If it is still impossible to distinguish, please refer to Table 1.

Table 1 Handling of missing adverse event onset date

Known date information	Missing date information	Case	Period belonging to
[None]	DDMMYYYY		Treatment period
DDMM	YYYY		Treatment period
YYYY	DDMM	If year < year of time of the first dose of the study drug	Pre-treatment
		If year ≥ year of time of the first dose of the study drug and ≤ year of time of the lase dose of the study drug	Treatment period
		If year > year of time of the lase dose of the study drug	Post-treatment
MMYYYY	Day	If year < year of time of the first dose of the study drug	Pre-treatment
		If year = year of time of the first dose of the study drug, and month < month of time of the first dose of the study drug	Pre-treatment
		If year = year of time of the first dose of the study drug and month ≥ month of time of the first dose of the study drug	Treatment period
		If year > year of time of the first dose of the study drug and < year of time of the lase dose of the study drug	Treatment period
		If year = year of time of the last dose of the study drug and month ≤ month of time of the last dose of the study drug + 2	Treatment period
		If year > year of time of the lase dose of the study drug	Post-treatment
		If year = year of time of the last dose of the study drug and month > month of time of the last dose of the study drug + 2	Post-treatment
DDYYYY	Month	If year < year of time of the first dose of the study drug	Pre-treatment
		If year ≥ year of time of the first dose of the study drug and ≤ year of time of the lase dose of the study drug	Treatment period

Known date information	Missing date information	Case	Period belonging to
		If year > year of time of the lase dose of the study drug	Post-treatment
Note: If the end date of the adverse event is prior to the first dose, the adverse event is a pre-treatment adverse event, even if the onset date of the adverse event is missing.			

5.4.2.1 Overview of adverse events

The overview of adverse events included the number and percentage of patients with the following AE (reported by all grades and Grade 3/4, respectively):

- All death events
- Treatment-emergent deaths (all grades only reported)
- Treatment-emergent AE
- AE suspected to be related to the study drug
- Treatment-emergent SAE
- SAE suspected to be related to the study drug
- AE leading to discontinuation of medication
- AE leading to discontinuation of medication, suspected to be related to the study drug
- Other significant treatment-emergent AE (AE leading to interruption or change in dose or frequency of Afinitor, AE requiring additional treatment)

5.4.2.2 All treatment-emergent adverse events

The number and percentage of patients with treatment-emergent AE (including all grades and Grade 3/4) (regardless of study drug-related or not) were summarized by SOC (in descending order of incidence).

The number and percentage of patients with treatment-emergent AE (including all grades and Grade 3/4) (regardless of study drug-related or not) were summarized by PT (in descending order of incidence).

The number and percentage of patients with common treatment-emergent AE (incidence ≥ 5%) were summarized by PT (in descending order of incidence).

The number and percentage of patients with treatment-emergent AE (regardless of study drug-related or not) were summarized by PT (in descending order of incidence) and CTCAE grade (Grade 1, Grade 2, Grade 3, Grade 4, and Grade 3/4). A patient would be categorized and analyzed based on the most severe one if he/she experiences an AE of different severities for many times.

The number and percentage of patients with treatment-emergent AE suspected to be related to the study drug were summarized by PT (in descending order of incidence) and CTCAE grade (Grade 1, Grade 2, Grade 3, Grade 4, and Grade 3/4). A patient would be categorized and analyzed based on the most severe one if he/she experiences an AE of different severities for many times.

The number and percentage of patients with treatment-emergent AE (regardless of study drug-related or not) were summarized by SOC (in descending order of incidence) and CTCAE grade (Grade 3, Grade 4, and Grade 3/4). A patient would be categorized and analyzed based on the most severe one if he/she experiences an AE of different severities for many times.

The number and percentage of patients with common treatment-emergent AE (incidence ≥ 5%) (regardless of study drug-related or not) were summarized by PT (in descending order of incidence) and CTCAE grade (Grade 3, Grade 4, and Grade 3/4). A patient would be categorized and analyzed based on the most severe one if he/she experiences an AE of different severities for many times.

The number and percentage of patients with treatment-emergent AE suspected to be related to the study drug were summarized by PT (in descending order of incidence) and CTCAE grade (Grade 3, Grade 4, and Grade 3/4). A patient would be categorized and analyzed based on the most severe one if he/she experiences an AE of different severities for many times.

The number and percentage of patients with treatment-emergent AE (excluding SAE) (regardless of study drug-related or not) were summarized by SOC (in alphabetical order) and PT (in descending order of incidence).

The number and percentage of patients with treatment-emergent AE (regardless of study drug-related or not) were summarized by SOC (in alphabetical order), PT (in descending order of incidence), and CTCAE grade (all grades). A patient would be categorized and analyzed based on the most severe one if he/she experiences an AE of different severities for many times.

5.4.2.3 Adverse events of special interest

Adverse events of special interest in this study included: non-infectious pneumonitis, stomatitis/oral mucositis, hepatitis B virus reactivation and cardiac disease: heart failure; ejection fraction decreased.

For non-infectious pneumonitis, SMQ (standard MedDRA query) (broad) "interstitial lung disease" was used to help retrieve relevant adverse events in the database.

For stomatitis/oral mucositis, the following terms were used as preferred terms to identify adverse events in the database.

- Mucosal inflammation
- Lip ulceration
- Glossitis
- Gingival ulceration
- Gingival swelling
- Mucosal ulceration
- Tongue ulceration
- Gingival pain
- Glossodynia
- Stomatitis
- Mouth ulceration

- Aphthous ulcer

For hepatitis B virus reactivation, the following terms were used as preferred terms to identify adverse events in the database.

- Hepatitis viral test positive
- Hepatitis B
- Infection reactivation
- Hepatitis B antibody
- Hepatitis B surface antibody positive
- Hepatitis B virus test positive
- Viral hepatitis carrier

For cardiac diseases: heart failure and the ejection fraction decreased, SMQ (narrow) "cardiac failure" was used to help retrieve relevant adverse events in the database.

The number and percentage of patients with non-infectious pneumonitis were tabulated and summarized by:

- At least one non-infectious pneumonitis
- Non-infectious pneumonitis suspected to be related to the study drug
- At least one severe (Grade 3 or 4) non-infectious pneumonitis
- Severe (Grade 3 or 4) non-infectious pneumonitis suspected to be related to the study drug.

In addition, the following AE was individually tabulated and summarized by the number and percentage of patients:

- Non-infectious pneumonitis, regardless of study drug-related or not graded by CTCAE
- Non-infectious pneumonitis leading to discontinuation of treatment, interruption or change in dose or frequency of Afinitor, suspected to be related to the study drug

Non-infectious pneumonitis was tabulated by patient.

Similar methods were used for analysis of stomatitis/oral mucositis, hepatitis B virus reactivation and cardiac diseases: heart failure; ejection fraction decrease.

5.4.2.4 Death, SAE and other significant AE

5.4.2.4.1 Death

The number and percentage of patients who died during different time periods were summarized, and the causes of deaths during treatment were summarized:

- All deaths
- Treatment-emergent deaths, defined as deaths that occurred between the start of study treatment and within 30 days after the end of treatment
- Deaths during the follow-up period, defined as those that occurred at or after 30 + 1 days after the end of study treatment.

In addition, deaths due to AE were summarized by MedDRA SOC (in alphabetical order) and PT (in descending order of incidence).

For confirmed deaths only, the date of death is imputed with the following rules:

- If the year is missing (or all missing), it is imputed with the last known survival date + 1;
- If the month and day are missing, they are imputed with January 1st of the current year;
- If only the day is missing, it is imputed with the 1st of the current month.

The last known survival date is defined as the latest of the following dates:

- All test/examination dates including all laboratory tests, vital sign tests, imaging examinations
- Treatment dates including the date of treatment with the investigational drug, concomitant drugs, concomitant non-drugs
- Onset date of adverse event and end date of adverse event with an outcome other than death
- Date of last survival in which the subject's status is not "dead" on the Survival Follow-up page
- The study completion date on the end of study page or the withdrawal date for which the reason for the withdrawal is not "lost to follow-up" and "death"

If the imputed date of death is before the last known survival date, the imputed date is modified to the last known survival date + 1. If the imputed date of death is after the referencable date of death (date of follow-up visit in which the survival follow-up status is “dead”), the imputed date is modified to the referencable date of death - 1.

5.4.2.4.2 SAE

The number and percentage of patients with following SAE were tabulated and summarized separately by SOC (in alphabetical order) and PT (in descending order of incidence):

- Treatment-emergent SAE regardless of whether related to the study drug or not
- Treatment-emergent SAE suspected to be related to the study drug
- SAE leading to withdrawal, regardless of whether related to the study drug or not.

The number and percentage of patients with following SAE were tabulated and summarized separately by PT (in descending order of incidence) and CTCAE grade (Grade 3/4):

- Treatment-emergent SAE regardless of whether related to the study drug or not
- Treatment-emergent SAE suspected to be related to the study drug
- SAE leading to withdrawal, regardless of whether related to the study drug or not.

A patient would be categorized and analyzed based on the most severe one if he/she experiences an AE of different severities for many times.

The number and percentage of patients with following SAE were tabulated and summarized separately by SOC (in alphabetical order), PT (in descending order of incidence), and CTCAE grade (all grades):

- Treatment-emergent SAE regardless of whether related to the study drug or not
- Treatment-emergent SAE suspected to be related to the study drug
- SAE leading to withdrawal, regardless of whether related to the study drug or not.

A patient would be categorized and analyzed based on the most severe one if he/she experiences an AE of different severities for many times.

5.4.2.4.3 Other significant AE

Other significant AE included: AE leading to discontinuation of medication, AE leading to withdrawal from the trial, and AE leading to interruption or changes in dose or frequency of Afinitor.

The number and percentage of patients with following significant AE were tabulated and summarized separately by SOC (in alphabetical order) and PT (in descending order of incidence):

- AE leading to discontinuation of medication, regardless of whether related to the study drug or not
- AE leading to withdrawal, regardless of whether related to the study drug or not
- AE leading to interruption or changes in dose or frequency of Afinitor, regardless of whether related to the study drug or not

The number and percentage of patients with following significant AE were tabulated and summarized separately by PT (in descending order of incidence) and CTCAE grade (Grade 3/4):

- AE leading to discontinuation of medication, regardless of whether related to the study drug or not
- AE leading to withdrawal, regardless of whether related to the study drug or not
- AE leading to interruption or changes in dose or frequency of Afinitor, regardless of whether related to the study drug or not

A patient would be categorized and analyzed based on the most severe one if he/she experiences an AE of different severities for many times.

The number and percentage of patients with following significant AE were tabulated and summarized separately by SOC (in alphabetical order), PT (in descending order of incidence), and CTCAE grade (all grades):

- AE leading to discontinuation of medication, regardless of whether related to the study drug or not
- AE leading to withdrawal, regardless of whether related to the study drug or not
- AE leading to interruption or changes in dose or frequency of Afinitor, regardless of whether related to the study drug or not

A patient would be categorized and analyzed based on the most severe one if he/she experiences an AE of different severities for many times.

5.4.3 Laboratory tests

Baseline is defined as the last valid assessment value prior to dosing.

Laboratory test results were converted to International Standard Units and values were graded for severity, if applicable, using commonly used toxicity criteria (CTCAE version 4.03).

Grade 3, grade 4 and all grade tables of all laboratory test abnormal values were provided, and the number and percentage of subjects corresponding to the grade of each test value were calculated.

Shift tables of CTCAE grades from baseline to each visit during treatment, last result during treatment, and the worst case during treatment were provided. In the shift table, the total number of patients and the number and percentage of patients with a change in CTCAE grade at each visit were tabulated.

Those laboratory test values that could not be evaluated by CTCAE grading were analyzed using "low", "normal" and "high" based on the range of normal values provided by the local laboratory, giving a shift table from baseline to each visit during the treatment period.

All laboratory test values were tabulated separately for each laboratory parameter by patient and visit. All test values outside the laboratory normal range were tabulated separately.

5.4.4 Vital signs

Baseline is defined as the last valid assessment value prior to dosing.

The measured values of each of vital signs at baseline and different time points after baseline were described and analyzed, and the changes in measured results of each vital sign at different time points after baseline relative to baseline were given.

Results for vital signs were tabulated separately for each vital sign parameter by patient and visit.

5.4.5 Other safety measurements

Other safety measurements were collected according to clinical indications. However, only pulmonary function test and chest CT assessment data were recorded in CRF, and other data was only be kept in the source file.

The assessment data of pulmonary function test and chest CT were tabulated by patient only and not summarized in tables.

5.5 Efficacy analyses (secondary analyses)

All efficacy analyses were based on FAS.

5.5.1 Overall Survival (OS)

Overall survival is defined as time from study treatment to death due to any cause.

If a patient was alive at the data cutoff, the last known survival date was used as the censored date for analysis. The definition of the last known survival date is detailed in Section 5.4.2.4.1.

If the data permits, the Kaplan-Meier method was used to obtain the survival function estimate and the median OS estimate, the survival curve was plotted, and the error of the survival function was estimated using the Greenwood formula [1], resulting in a 95% confidence interval

of the median OS. In addition, the survival probabilities and their 95% confidence intervals at different time points such as at Month 3 and Month 6 were also calculated.

5.5.2 Progression-Free Survival (PFS)

Progression-free survival is defined as time from the start of study treatment to progression of disease (PD) or death due to any cause (whichever occurs first).

Time to progression of disease is defined as the time when progression is first observed:

- At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of 5 mm;

Or

- Unequivocal progression of existing non-target lesions;

Or

- Emergence of new lesions.

The calculation of PFS was based on the date of the imaging examination, not the date of the RECIST tumor evaluation or the date of the visit.

For calculation of PFS, if imaging examinations were completed on multiple dates, the progression date or censored date was determined according to the following rules:

- For patients with progression of disease, the date of progression is defined as the earliest date when it is assessed that there is progression.
- For patients without progression of disease, the censored date is defined as the date of the latest imaging examination within the visit.

If the patient was alive and progression-free at the time of data cutoff, the date of the last imaging examination of the measurable lesion was used as the date of the last evaluation in the PFS analysis, i.e., the censored date. If the patient had no PFS data available or was missing baseline data assessment and was still alive at the data cutoff, the study treatment start date was used as the censored date in the PFS analysis. Detailed censoring rules for PFS are shown in Table 2.

Table 2 Censoring rules for PFS

#	Situation	Progression or censored date	Result
1	No baseline or post-baseline tumor assessment	Study treatment start date	Censored
2	Documented progression of disease	Progression date	Progression
3	No progression based on RECIST assessment (i.e. clinical progression based on investigator's assessment) leading to end of treatment	Date of discontinuation of treatment	Progression
4	No events occurred	Date of last adequate tumor assessment	Censored
5	Initiation of new anti-cancer therapy	Date of last adequate tumor assessment prior to initiation of subsequent anticancer therapy (start date of the	Censored

		study treatment if there is no post-baseline imaging examination)	
6	Death [a]	Date of death	Progression
7	Event [b] documented after two or more missing tumor assessments	Date of last adequate tumor assessment prior to two or more consecutive tumor assessments not performed as per protocol	Censored
Note 1: Adequate assessment included tumor assessment in the following situations: CR, PR, SD, PD Note 2: [a] Including cases where no tumor evaluation was conducted after enrollment and death occurred during two consecutive scheduled tumor evaluation visits (i.e., date of death is less than or equal to 24 weeks + 2 weeks from the start date of study treatment). Note 3: [b] Indicating that the date of death or progression of disease is greater than 24 weeks + 2 weeks from the last tumor assessment.			

New anticancer therapy is defined as the following drugs received at or after the start of study treatment:

- The name of the drug is Capecitabine, Temozolomide, or Sandostatin LAR
- Indication or reason for administration is chemotherapy or anti-tumor

Baseline is defined as the last RECIST1.1 assessment prior to the start of study treatment.

PFS was analyzed using statistical methods similar to those used for OS analysis.

5.5.3 Overall response assessment

The number and percentage of patients with complete response, partial response, stable disease, and progression of disease were summarized according to the best response determined by the investigator.

5.5.4 Tumor assessment

The sum of the diameters of target lesions at baseline and at different visits after baseline was summarized by descriptive statistics (number, mean, median, standard deviation, minimum, and maximum). 1) the change from baseline in the sum of diameters at different visits after baseline and 2) the relative change in the sum of diameters at different visits after baseline from the minimum value of the sum of diameters among previous visits were summarized by descriptive statistics, respectively.

Tumor assessments were tabulated by patient and visit.

5.5.5 Additional analysis for assessment the impact of COVID-19

Considering that the outbreak of COVID-19 in 2020 has affected the work of each study site to varying degrees, protocol deviations due to COVID-19 were collected for this study, including visit assessments completed at other hospitals, visit assessments and tests not completed or out-of-window due to COVID-19, changes in drug supply methods, interruption or discontinuation of study drug treatment, etc. Patients seriously affected by COVID-19 were identified at the data review meeting, and patients whose response was seriously affected by COVID-19 were excluded from the sensitivity analysis of efficacy, with the purpose of exploring the potential impact of COVID-19 on the efficacy assessment results of this study.

6 Interim analysis

Interim analysis was conducted during the study as needed. In order to obtain an outline of the data submitted to the China Food and Drug Administration when the drug license was renewed in February 2018, the project team planned to conduct the first interim analysis around July 2017. Moreover, during the study, based on the requirements of the Center for Drug Evaluation, clinical data was submitted every 5 years for license renewal, so the project team planned to conduct the second interim analysis in February 2021.

The contents of the interim analysis included all primary and secondary endpoints covered by the statistical analysis plan. The analytical methods of this study are predominantly descriptive, so alpha spending function is not applicable. For interim analysis, data will be analyzed according to the content and methods of analysis described in this SAP, and there is no plan to formulate a separate SAP of interim analysis.

7 Modification of the Analytical Method for the Protocol Plan

None.

8 Statistical Analysis Form Template Statistics

The analysis form template will be provided in a separate document.

9 Reference

1. Collett, D. (2003), Modeling Survival Data in Medical Research, Second Edition, London: Chapman & Hall.

10 Appendix

Appendix 1 Visit Evaluation Schedule

	Category	Screening/Baseline (-28 - 0 day)	Visit 1 (day 1)	Visit 2 (day 28 ± 2 d)	Visit 3 (week 12 ± 1 wk)	Subsequent visits (every 12 wk ± 1 wk)	End of study treatment (EOT)	30-day Safety Follow-up	Survival follow up (every 6 months)
Obtain Informed Consent	D	X							
Patient medical history	D	X							
Demography	D	X							
Inclusion/exclusion criteria	D	X							
Relevant medical history/current medical conditions	D	X							
Diagnosis of cancer	D	X							
Prior/concomitant medications	D	X	X	X	X	X	X		
Physical examination	S	X	X	X	X	X	X		
Vital signs	D	X	X	X	X	X	X		
Height/Weight	D	X							
Laboratory assessments									
Hematology [a]	D	X	X	X	X	X	X		
Liver function tests [b]	D	X		X	X	X	X		
Coagulation	S	X		X	X	X	X		
Other laboratory test [c]	S		Only to be done if clinically indicate						
Urinalysis [c]	S	X	Only to be done if clinically indicate						
Pregnancy test [d]	D	X					X		

	Category	Screening/Baseline (-28 - 0 day)	Visit 1 (day 1)	Visit 2 (day 28 ± 2 d)	Visit 3 (week 12 ± 1 wk)	Subsequent visits (every 12 wk ± 1 wk)	End of study treatment (EOT)	30-day Safety Follow-up	Survival follow up (every 6 months)
Tumor assessment (MRI or CT) [e]	D	X			X	X			X [f]
Pulmonary function tests, Chest CT [g]	D		Only to be done if clinically indicate						
Adverse event	D	X	Continuously					X	
Study Drug administration	D		X	X	X	X	X		
Reason for discontinuation/withdrawal	D						X		
Survival follow-up	D								X

a. Fasting hematology include: hemoglobin, hematocrit, platelets, red blood cell count (RBC) total white blood cell count (WBC), absolute & differentiated cells including lymphocytes, monocytes, eosinophils and basophils. Absolute Neutrophil Count (ANC) will be calculated by the laboratory.

b. Liver function tests include: AST, ALT, total bilirubin, alkaline phosphatase, serum albumin.

c. Clinically significant findings will be noted in the Medical history/Current medical condition pages or Adverse Events pages. Urinalysis assessment could include but not limited to: pH, protein, glucose, occult blood, ketones, and leukocytes. Other laboratory test could include but not limited to: total LDH, GGT, fasting glucose, fasting serum lipid, sodium, magnesium, phosphate, potassium, chloride, bicarbonate, creatinine, BUN, total protein, uric acid, calcium.

d. A serum pregnancy test will be conducted locally at screening/baseline in all females of child-bearing potential, urine pregnancy test will be conducted at the end of treatment visit.

e. Repeat scans (multiphase MRI or triphasic CT) at baseline and every 12 weeks thereafter. The same type of scan should be used at baseline and follow-up.

f. Efficacy assessment will be collected until progression of disease (PD).

g. If an investigator suspects a patient may be developing non-infectious pneumonitis, investigations such as pulmonary function tests, CT chest and referral to a pulmonologist should be considered.