STATISTICAL ANALYSIS PLAN

Study Protocol Number:	BGB-A317-Sitravatinib-301
Study Protocol Title:	A Randomized Phase 3 Study of Tislelizumab in Combination with Sitravatinib in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer That Progressed on or After Platinum-Based Chemotherapy and Anti-PD-(L)1 Antibody
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ADA	Anti-drug antibody
ADI	Actual dose intensity
AE	Adverse event
AUC	Area under the concentration-time curve
BLQ	Below the assay quantification limit
BOR	Best overall response
BSA	Body surface area
CI	Confidence interval
CR	Complete response
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DCR	Disease Control Rate
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EORTC	European Organization for Research and Treatment of Cancer
FDA	Food and Drug Administration
HRQoL	Health Related Quality of Life
imAE	Immune-mediated adverse event
IRC	Independent Review Committee
IRR	Infusion-Related Reactions
IRT	Interactive Response Technology
ITT	Intent to Treat
LS-SCLC	Limited-Stage Small Cell Lung Cancer
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PD-L1	Programmed cell death protein-ligand 1
PK	Pharmacokinetic
PFS	Progression-free survival

PR	Partial response
PT	Preferred term
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TCM	Traditional Chinese Medication
TEAE	Treatment-emergent adverse event
TTD	Time to Deterioration
TTR	Time to Response
VAS	Visual Analog Scale
WHO DD	World Health Organization Drug Dictionary

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for BGB-A317-Sitravatinib-301: A Randomized Phase 3 Study of Tislelizumab in Combination with Sitravatinib in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer That Progressed on or After Platinum-Based Chemotherapy and Anti-PD-(L)1 Antibody. This SAP is developed based on BGB-A317-Sitravatinib-301 Protocol Amendment 3.0, dated on Aug 09, 2022. BeiGene decided to terminate the study on Sep 25, 2023 based on the recommendations from Independent Data Monitoring Committee (IDMC) given the new safety finding of pulmonary hemorrhage in the investigational arm. After the review of the available clinical data, the IDMC assessed that the overall risk-benefit assessment is unfavorable. Due to the early termination of the study, the enrollment is not completed and efficacy data is not matured. The focus of this SAP is to briefly analyze the primary endpoints (overall survival [OS] and progression-free survival [PFS] assessed by independent review committee [IRC]) and some secondary endpoints including PFS assessed by investigator, objective response rate (ORR) assessed by IRC and TEAE in the study protocol.

2 STUDY OVERVIEW

This is an open-label, randomized, multicenter, Phase 3 clinical study evaluating the efficacy and safety of tislelizumab in combination with sitravatinib compared with docetaxel in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have disease progression following platinum-based chemotherapy and anti-programmed cell death protein-1 (PD-1)/programmed cell death ligand-1 (PD-L1) antibody, with the anti-PD-(L)1 antibody administered in combination with, or sequentially before or after the platinum-based chemotherapy.

Patients must have received no more than 2 lines of prior systemic therapy for locally advanced and unresectable or metastatic disease. Furthermore, patients must have had radiographic progression per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 on or after anti-PD-(L)1 containing therapy for locally advanced and unresectable or metastatic NSCLC. If anti-PD-(L)1 containing therapy is not the most recent systemic treatment, patients should also have radiographic progression per RECIST v1.1 on or after the most recent systemic treatment. Adjuvant or neo-adjuvant chemotherapy will be counted as a prior line of chemotherapy if the disease progressed on or within 6 months after the completion of the last dose. In locally advanced and unresectable NSCLC, disease progression on or within 6 months of the end of prior curatively intended multimodal therapy will be counted as a prior line of systemic therapy. If chemoradiation is followed by planned systemic therapy without documented progression between chemoradiation and systemic therapy, the entire treatment course counts as 1 line of therapy (patients who received anti-PD-(L)1 antibody as consolidation treatment following definitive chemoradiation for unresectable Stage III NSCLC can be enrolled immediately after disease progression, if the disease progression occurred within 6 months after the end of platinum-based chemotherapy component of the definitive chemoradiation). Maintenance therapy following platinum-based chemotherapy is not considered as a separate line of therapy, and no other prior immunotherapies with antibody or drug specifically targeting T-cell

costimulation or checkpoint pathways, including but not limited to anti-TIGIT, anti-OX40, and anti-CD137, will be allowed (prior anti-CTLA4 used in combination with anti-PD-(L)1 is permitted). No prior anticancer therapy having the same mechanism of action as sitravatinib (eg, tyrosine kinase inhibitor with a similar target profile or VEGF- or VEGFR inhibitor) will be allowed either.

The study will be conducted at approximately 100 centers globally. The study will consist of a screening period, a treatment period, and a long-term follow-up period. Approximately 420 patients with locally advanced or metastatic NSCLC will be enrolled and randomized in a 1:1 ratio to receive either tislelizumab in combination with sitravatinib or docetaxel monotherapy.

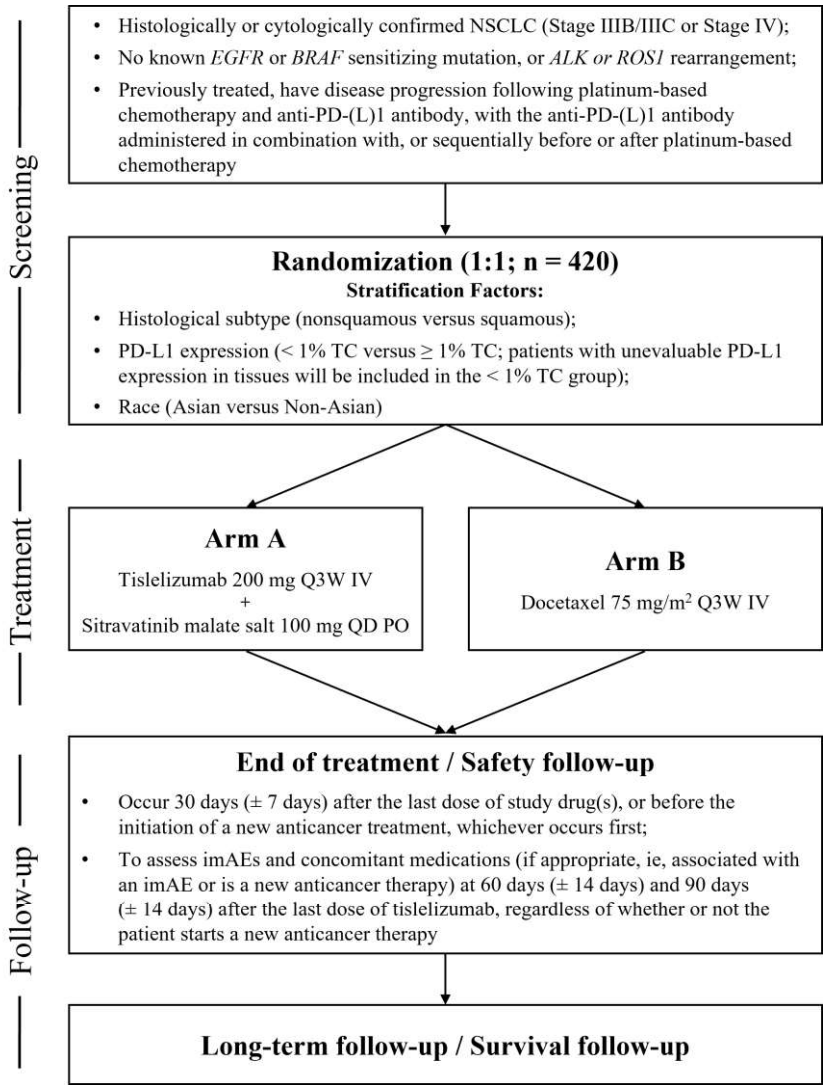
Patients will be stratified by histological subtype (nonsquamous versus squamous), PD-L1 expression (< 1% TC versus ≥ 1% TC by the Ventana SP263 assay; patients whose tissues are unevaluable for PD-L1 expression will be included in the < 1% TC group), and race (Asian versus non-Asian) to receive one of the following treatment regimens:

Arm A: tislelizumab 200 mg intravenously once every 3 weeks in combination with sitravatinib 100 mg orally once a day

Arm B: docetaxel 75 mg/m^2 intravenously once every 3 weeks

The study design schema is presented in Figure 1.

Figure 1: Study Schema



Abbreviations: ALK, anaplastic lymphoma kinase; BRAF, B-Raf proto-oncogene; EGFR, epidermal growth factor receptor; imAE, immune mediated adverse event; IV, intravenously; NSCLC, non-small cell lung cancer; PD-(L)1, programmed cell death protein-1/programmed cell death protein ligand-1; PO, orally; ROS1, ROS proto oncogene 1; QD, once a day; Q3W: every 3 weeks; TC, tumor cells

3 STUDY OBJECTIVES

3.1 Primary Objective

- To compare the OS of tislelizumab and sitravatinib combination therapy with that of docetaxel monotherapy.
- To compare the PFS of tislelizumab and sitravatinib combination therapy with that of docetaxel monotherapy, as assessed by the IRC.

3.2 Secondary Objective

- To compare the PFS of tislelizumab and sitravatinib combination therapy with that of docetaxel monotherapy, as assessed by the investigator.
- To compare the confirmed overall response rate (ORR) of tislelizumab and sitravatinib combination therapy with that of docetaxel monotherapy as assessed by the IRC.
- To evaluate the safety and tolerability of tislelizumab and sitravatinib combination therapy with that of docetaxel monotherapy.

4 STUDY ENDPOINTS

4.1 Primary Endpoints

- OS, defined as the time from randomization to death from any cause.
- PFS, defined as the time from randomization to the first occurrence of disease progression as determined by the IRC based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, or death from any cause, whichever occurs first.

4.2 Secondary Endpoints

- PFS, defined as the time from randomization to the first occurrence of disease progression as determined by the investigator based on RECIST v1.1, or death from any cause, whichever occurs first.
- ORR, defined as the proportion of patients with partial response (PR) or complete response (CR) as determined by the IRC based on RECIST v1.1.
- Incidence and severity of TEAEs graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0.

5 SAMPLE SIZE CONSIDERATIONS

The sample size calculation is based on the primary efficacy analysis of OS in the Intent-to-Treat (ITT) analysis set.

The hazard ratio of OS is assumed to be 0.70, with a median OS of 14.3 months in the treatment arm and 10.0 months in the control arm. The dropout hazard rate for OS is assumed to be 0.004 per month which accounts for approximately 5% overall dropout during the study. The maximum enrollment rate is assumed to be 28 patients per month and a ramp-up period is 6 months. A total of 420 patients will be enrolled in a 1:1 randomization over 18 months. Approximately 289 OS events are planned for the final analysis, to have a power of 85% with an alpha of 0.024. A group sequential testing of OS will be performed with an interim analysis planned when 68% of total events are reached.

The hazard ratio assumption of PFS is 0.63 with a median PFS of 5.4 months in the treatment arm and 3.4 months in the control arm. Approximately 332 PFS events are expected to occur at

the final analysis of PFS (ie, at the time of interim OS analysis), to have a power of 87% with an alpha of 0.001.

However, due to the early termination of this study, the enrollment is not completed and finally 377 patients were enrolled in this study.

6 STATISTICAL METHODS

6.1 Analysis Sets

The Intent-to-Treat (ITT) analysis set consists of all the patients who were randomized to a treatment arm. All patients will be grouped by the assigned treatment at randomization. The ITT analysis set will be used for efficacy analyses.

The Safety analysis set includes all patients who were randomized and received any dose of any study drug, and patients will be grouped by actual treatment received, where actual treatment received is defined as (i) the intended treatment if it was received at least once, or (ii) the first treatment received when starting therapy with study medication if intended treatment is never received. Each patient will be classified into and analyzed consistently within one (and only one) treatment arm. The safety analysis set is used for all safety analyses.

6.2 Data Analysis General Considerations

6.2.1 Definitions and Computations

Study drugs include sitravatinib, tislelizumab, and docetaxel.

Study day will be calculated in reference to the first dose date for safety analysis. For assessments conducted on or after the first dose date, the study day will be calculated as the assessment date – first dose date + 1. For assessments conducted before the first dose date, study day is calculated as the assessment date – first dose date. There is no study day 0. In the situation where the event date is partial or missing, the date will appear partial or missing in the listings. Study day and any corresponding durations will be presented based on the imputations specified in 0.

To derive the duration of any efficacy endpoint, the reference date will be the date of randomization.

Baseline Measurements:

- For efficacy evaluation: a baseline value is defined as the last non-missing value collected prior to the randomization.
- For safety: a baseline value is defined as the last non-missing value prior to the first study drug administration.

Study Follow-up Duration (SFD): Study follow-up duration is defined as the duration from the randomization date to the study discontinuation date (e.g. death, consent withdrawal, lost to follow-up) or to the cutoff date if a patient is still ongoing.

All calculations and analyses will be conducted using SAS® Version 9.4 or higher.

6.2.2 Conventions

Unless otherwise specified, the following conventions will be applied to all analyses:

- 1 year = 365.25 days. Number of years is calculated as (days/365.25) rounded up to 1 significant digit.
- 1 month = 30.4375 days. Number of months is calculated as (days/30.4375) rounded up to 1 significant digit.
- BMI (kg/m^2) will be calculated as Weight(kg)/(Height(cm)/100)^2.
- P-values will be rounded to 4 decimal places. P-values that are less than 0.0001 will be presented as '< 0.0001' and p-values that are larger than 0.9999 will be presented as '> 0.9999'.
- Duration of image-based event endpoints (such as PFS) will be based on the actual date the radiograph was obtained rather than the associated visit date.
- For continuous endpoints, summary statistics will include n, mean, standard deviation, median, Q1, Q3 and range (minimum and maximum).
- For discrete endpoints, summary statistics will include frequencies and percentages.

6.2.3 Handling of Missing Data

Handling of missing data related to primary endpoints will be further elaborated in Section 6.4.1. Missing dates or partially missing dates will be imputed conservatively for adverse events and prior/concomitant medications/procedures. Specific rules for the handling of missing or partially missing dates for adverse events prior/concomitant medications/procedures, and subsequent anti-cancer therapies, etc. are provided in 0. Other missing data will not be imputed unless otherwise specified elsewhere in this SAP.

By-visit endpoints will be analyzed using observed data unless otherwise specified. For observed data analyses, missing data will not be imputed, and only the observed records will be included.

6.3 Patient Characteristics

6.3.1 Patient Disposition

The number (percentage) of patients who signed informed consent, enrolled in the study, and screen-failure including re-screened will be summarized. The number (percentage) of screen failure reasons will also be summarized.

The number (percentage) of patients randomized, treated, discontinued from the study, reasons for discontinued from the study, and the duration of study follow-up will be summarized in the ITT analysis set. The patients who discontinued treatment and the primary reason for the end of treatment will be summarized among patients who were treated. The reasons for treatment/study discontinuation related to COVID-19 impact will also be summarized.

6.3.2 Protocol Deviations

Important protocol deviation criteria will be established, and patients with important protocol deviations will be identified and documented. Important protocol deviations will be summarized

for all patients in the ITT analysis set. Deviation categories are not mutually exclusive. Multiple deviations within the same category are counted once per patient.

6.3.3 Demographic and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized using descriptive statistics in the ITT analysis set, including the following variables:

- Age (continuously and by categories [≤65 or >65 years])
- Sex
- Race
- Weight (kg)
- BMI (kg/m^2)
- ECOG performance score
- Smoking status
- Ethnicity
- Country

In addition, the stratification factors per Interactive Response Technology (IRT) and per eCRF will be summarized based on the ITT population:

- Race (Asian versus non-Asian)
- Histology (non-squamous versus squamous)
- PD-L1 expression (< 1% TC versus ≥ 1% TC)

6.3.4 Disease History

The number (percentage) of patients reporting a history of disease and characteristics, as recorded on the eCRF, will be summarized in the ITT analysis set. Disease characteristics include time from the initial diagnosis to study entry, clinical stage at study entry, time from diagnosis of metastatic disease to study entry, metastasis status and site, etc.

6.3.5 Prior Anticancer Drug Therapies

Prior anti-cancer drug therapies, prior anti-cancer radiotherapy will be summarized in the ITT analysis set.

The variables include the number of patients with any prior systemic anticancer therapy, number of lines of prior systemic therapy, type of last-line systemic therapy, best response to last-line systemic therapy, duration of last-line systemic therapy, treatment setting of last-line systemic therapy, type of anti-PD(L)1 therapy for the prior systemic therapy, time from end of last-line systemic therapy to study entry, time from last disease progression to study entry for prior anti-cancer drug therapies, number of patients with any prior radiotherapy. The therapies with the same sequence/regimen number are counted as one prior therapy.

6.3.6 Prior and Concomitant Medications

Prior medications are defined as medications that stopped before the first dose of study drug. Concomitant medications are defined as medications that are (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 days after the patient's last dose.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO DD) drug codes (Version B3 March 1, 2022 or higher). They will be further classified to the appropriate Anatomical Therapeutic Chemical (ATC) code.

6.3.7 Medical History

Medical History will be coded using Medical Dictionary for Regulatory Activities (MedDRA) (Version 25.0 or higher). The number (percentage) of patients reporting a history of any medical condition, as recorded on the CRF, will be summarized by system organ class and preferred term in the safety analysis set.

6.4 Efficacy Analysis

Since the study is early terminated, the enrollment is not completed and follow-up time is limited. No inferential hypothesis testing will be performed in the efficacy analysis.

6.4.1 Primary Efficacy Endpoints

Overall Survival

OS is defined as the time from randomization date to the documented death date for patients who died prior to or on the clinical cutoff date. For patients who are alive by the clinical cutoff date, OS will be censored at the last known alive date (LKADT). The last known alive date will be defined as either the clinical data cutoff date for patients who are still on treatment, or last available date showing patients alive or cut-off date whichever comes first for other alive patients.

Every effort should be made to ensure complete death dates. In the rare case, if day of death date is missing, death date is imputed as the max (last available date showing patients alive + 1, first day of year/month of death date). The patient with imputed death date will be considered as an event for OS analysis.

The HR and its 2-sided 95% CI will be estimated from a stratified Cox regression model with the stratification factors (squamous vs non-squamous, PD-L1 expression <1% (including unevaluable) vs >=1%, and Asian vs non-Asian) in IRT system. The distribution of OS, including median, Q1 and Q3, and event-free rates every 3 months if estimable, will be estimated using the Kaplan-Meier method for each treatment group. Ninety-five percent CIs for median and Q1 and Q3 of OS will be estimated using the method of Brookmeyer and Crowley (Brookmeyer & Crowley, 1982). And 95% CIs for event-free rates will be estimated using Greenwood's formula (Greenwood, 1926).

Progression-Free Survival by IRC

PFS by IRC is defined as the time from randomization to the first occurrence of disease progression as determined by the IRC based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, or death from any cause, whichever occurs first.

The HR and its 2-sided 95% CI will be estimated from a stratified Cox regression model with the same stratification factors as for OS. The distribution of PFS, including median, Q1 and Q3, and event-free rates every 3 months if estimable, will be estimated using the Kaplan-Meier method for each treatment group. Ninety-five percent CIs for median and Q1 and Q3 of PFS will be estimated using the method of Brookmeyer and Crowley (Brookmeyer & Crowley, 1982). And 95% CIs for event-free rates will be estimated using Greenwood's formula (Greenwood, 1926).

The censoring rules for the primary analysis of PFS are presented in Table 1.

Table 1: Censoring Rules for Progression-Free Survival per RECIST Version 1.1

	Derivation rules	**Outcome**
No progression at the time of data cut-off or withdrawal from study or lost to follow up	Date of last adequate radiologic assessment prior to or on date of data cut-off or withdrawal from study or lost to follow up	Censored
New anticancer therapy started	Last adequate radiological assessment before the new anticancer therapy	Censored
No baseline or post-baseline tumor assessments without death within 13 weeks after randomization	Date of randomization	Censored
No baseline or post-baseline tumor assessments with death within 13 weeks after randomization	Date of death	Event
Death or progression after more than one missed visit	Date of last adequate radiologic assessment before missed tumor assessments	Censored
Death prior to progression	Date of death	Event

6.4.2 Secondary Efficacy Endpoints

PFS by INV

The PFS by investigators is defined as the time from randomization to the first documented disease progression, as assessed by the investigators based on RECIST v1.1, or death from any cause, whichever comes first. The PFS by INV will be analyzed similarly as the primary analysis of PFS by IRC.

Objective Response Rate by IRC (ORR by IRC)

The best overall response (BOR) is defined as the confirmed best response observed from the date of randomization until disease progression, death, cut-off date or initiation of subsequent anticancer therapy, whichever occurs first. BOR will be summarized with descriptive statistics for each treatment arm.

ORR by IRC is defined as the percentage of patients whose BOR is confirmed CR or PR as determined by the IRC based on RECIST v1.1. Patients with no post-baseline response assessment (due to any reason) will be considered as non-responders. ORR will be summarized by treatment arms and its Clopper-Pearson 95% confidence interval (CI) will be calculated.

6.4.3 Subgroup Analyses

Subgroup analyses of OS and PFS by the IRC will be conducted in ITT analysis set, to explore the consistence of efficacy across variety of subgroups. Subgroup variables may include, but not limited to,

- PD-L1 expression: (>=1% TC, <1% TC, Not Evaluable)
- Race: (Asian, non-Asian)
- Histological subtype: (non-squamous, squamous)
- Country: (China, Australia)
- ECOG performance status: (0, 1)
- Age group: (< 65 years, >= 65 years)
- Sex: (Male, Female)
- Smoking status: (former/current smoker, non-smoker)
- Disease status at study entry: (locally advanced, metastatic)
- Number of lines of prior systemic therapy: (1, 2)

For OS and PFS, KM estimates by treatment arm, and the estimation of unstratified hazard ratio and their 95% CI will be provided for the subgroups. If any subgroup with a number of patients in it less than 10, the hazard ratio and its 95% CI of that subgroup will not be reported.

6.4.4 Post and during-treatment Anti-Cancer Therapy

Post treatment anti-cancer therapy is defined as the anti-cancer therapy started after the last dose of study drug(s). During-treatment anti-cancer therapy is defined as the anti-cancer therapy started after randomization and before the last dose of study drug(s). Subsequent anti-cancer therapy contains post and during-treatment anti-cancer therapy.

Separate flags of start date of new anti-cancer therapy for efficacy and safety analyses are derived individually.

- As for efficacy analysis, start date of new anti-cancer therapy will be the earliest date of prohibited anti-cancer therapy taken during treatment, date of the post-treatment systemic anti-cancer therapy and date of other anti-cancer therapy such as post-treatment surgery and radiotherapy as deemed appropriate.

- The start date of new anti-cancer therapy in defining TEAE for safety is always the first date of new systemic anti-cancer therapy taken after the last study treatment.

Tumor response per RECIST or event driven endpoints have not been commonly used for the efficacy evaluation of the traditional Chinese medicine (TCM). ORR, PFS or OS benefit of Chinese herbal medicines or Chinese patent medicines has not yet been established. Therefore, they will not be taken into account as the new anti-cancer therapy in the efficacy and safety analyses.

6.5 Safety Analyses

All safety analyses will be performed by treatment arms based on the safety analysis set. Safety and tolerability will be assessed, where applicable, by incidence and severity for AEs.

6.5.1 Extent of Exposure

The following measures of the extent of exposure will be summarized with descriptive statistics for each study drug in the safety analysis set. One cycle is defined as 21 days of treatment.

- Duration of exposure (months) for tislelizumab or docetaxel: defined as (last date of exposure - first dose date + 1) / 30.4375. For treatment ongoing patients, use cutoff date as the 'last date of exposure'; for patients discontinued from treatment, 'last date of exposure' is defined as the earliest date of cutoff date, death date and last dose date + 20.
- Duration of exposure (months) for sitravatinib: defined as (last date of exposure - first dose date + 1) / 30.4375. For treatment ongoing patients, use cutoff date as the 'last date of exposure'; for patients treated with sitravatinib and discontinued from treatment, use last dose date as 'last date of exposure'.
- Number of treatment cycles received: defined as the total number of treatment cycles in which at least one dose of the study drug is administered.
- Total dose received per patient: For tislelizumab or sitravatinib (mg), it is defined as the cumulative dose of the study drug during the treatment period of the study up to clinical cutoff date. For the docetaxel, the total dose received per patient (mg/m^2) is defined as the cumulative dose of the docetaxel during the treatment period of the study divided by body surface area (BSA), where the BSA is defined as the square root of weight * height /3600. The BSA is derived at each visit to use baseline weight unless weight change for one visit is at least 10% greater compared to baseline weight.
- Actual dose intensity for tislelizumab (mg/cycle) or docetaxel (mg/m^2/cycle) is defined as the cumulative dose received by a patient / (last dose date prior to cut off date – first dose date + 21)/21). Actual dose intensity for sitravatinib (mg/day) is defined as the total cumulative dose (mg) / (last dose date prior to or on cutoff date – first dose date +1 (days)).
- Relative dose intensity (%): defined as the ratio of the actual dose intensity and the planned dose intensity. The planned dose intensity is 200 mg/cycle for tislelizumab, 75 mg/m^2/cycle for docetaxel and 100 mg/day for sitravatinib.
- Number (%) of patients with dose reductions and number of dose reductions per patient
- Number (%) of patients with dose interruptions
- Number (%) of patients with dose delay

- Number (%) of patients with dose modifications, including dose reductions, dose delays and dose interruptions.

6.5.2 Adverse Events

AEs will be graded by the investigators using NCI-CTCAE version 5.0. The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using MedDRA. Adverse events will be coded to the MedDRA (Version 25.0 or higher) lowest level term closest to the verbatim term, along with the linked MedDRA preferred term (PT) and primary system organ class (SOC).

6.5.2.1 Treatment Emergent Adverse Event

A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to 30 days following study drug discontinuation or initiation of new anticancer therapy, whichever occurs first. Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in patient data listings.

An AE overview table, including the number and percentage of patients with TEAEs, treatment-emergent serious adverse events (SAEs), TEAEs with Grade 3 or above, TEAEs that led to death, TEAEs that led to treatment discontinuation, TEAEs that led to dose modification, treatment-related TEAEs, treatment-related version of any of the above categories, infusion-related reactions, infusion-related reaction with Grade 3 or above will be provided in the safety analysis set. Treatment-related AEs include those events considered by the investigator to be related to study drug or with a missing assessment of the causal relationship.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by PT. A patient will be counted only once by the highest severity grade within a PT, even if the patient experienced more than 1 TEAE within a specific PT. The number (percentage) of patients with TEAEs, treatment-emergent SAEs, TEAEs with grade 3 or above, treatment-related TEAEs, treatment-related SAEs, treatment-related TEAEs with grade 3 or above, TEAEs that led to death, treatment-related TEAEs that led to death, TEAEs that led to treatment discontinuation, treatment-related TEAEs that led to treatment discontinuation, TEAEs that led to dose modification, and treatment-related TEAEs that led to dose modification, will be summarized by PT.

6.5.2.2 Immune-Mediated Adverse Event

Immune-mediated adverse events (imAEs) are of special interest and summarized by category within a pre-defined list. The identification of immune-mediated adverse events is described in immune-mediated adverse event charter version 1.2. If an imAE occurs outside of the above-mentioned TEAE window, it will not be classified as a TEAE.

The number (percentage) of patients with imAEs will be summarized by category and PT.

6.5.2.3 Death

All deaths and causes of death will be summarized by treatment arms, including those occurred within 30 days after the last dose and those reported after 30 days after the last dose.

7 INTERIM ANALYSES

The pre-planned efficacy interim analysis is aborted due to early termination.

An early futility analysis based on PFS by IRC was performed based on data with cut-off date Jun 13, 2022, when 62 PFS events assessed by IRC are documented in the ITT analysis set. The non-binding futility boundary is specified at a one-sided p-value of 0.4662, as is determined by a Hwang-Shih-DeCani (HSD) beta spending function with parameter 1.

8 CHANGES IN THE PLANNED ANALYSIS

Because of the early termination of the study, the planned statistical analysis in PA3.0 is substantially condensed. No official hypothesis testing will be performed. For the primary endpoints, the supplementary and sensitivity analysis are removed. The analysis of the secondary endpoints including PFS assessed by investogators and ORR assessed by IRC are kept, while the analysis for DOR, DCR, HRQOL and PK for sitravatinib are removed. The immunogenicity and exploratory anaslysis will not be performed. The pre-planned efficacy interim analysis is aborted too.

9 REFERENCES

Brookmeyer, R., & Crowley, J. (1982). A Confidence Interval for the Median Survival Time. *Biometrics*, *38*(1), 29. https://doi.org/10.2307/2530286

Greenwood, M. (1926). A Report on the Natural Duration of Cancer. *A Report on the Natural Duration of Cancer.*, *33*.

APPENDIX 1 IMPUTATION OF MISSING OR PARTIALLY MISSING DATES

In general, missing or partial dates will not be imputed at the data level. The following rules will apply for the specific analysis and summary purposes mentioned below only. The last known alive date only is based on complete dates without imputation.

1. **Prior/Concomitant Medications/Procedures**

When the start date or end date of medication is partially missing, the date will be imputed to determine whether the medication is prior or concomitant. The following rules will be applied to impute partial dates for medications:

If the start date of medication is partially missing, impute as follows:

- If both month and day are missing, then set to January 01.
- If only day is missing, then set to the first of the month.
- If the imputed start date > min(death date, end of study date) then set to min(death date, end of study date).

If the end date of medication is partially missing, impute as follows:

- If both month and day are missing, then set to December 31.
- If only day is missing, then set to last day of the month.
- If the imputed end date > min(death date, end of study date), then set to min(death date, end of study date).

If start date or end date of medication is completely missing, do not impute.

2. **Adverse Events**

The imputation rule for the safety analyses will be used to address the issues with partial dates. When the start date or end date of an adverse event is partially missing, the date will be imputed to determine whether the adverse event is treatment-emergent. When in doubt, the adverse event will be considered treatment-emergent by default. If year of the start date is missing or start date is completely missing, do not impute. Impute AE end date first if both AE start date and end date are partially missing. The following rules will be applied to impute partial dates for adverse events:

If the end date of an AE is partially missing, impute as follows:

- If both month and day are missing, then set to December 31.
- If only day is missing, then set to last day of the month.
- If the imputed end date > min(death date, end of study date), then set to min(death date, end of study date).

If the year of the end date or end date is completely missing, do not impute.

If start date of an adverse event is partially missing, impute as follows:

- If both month and day are missing and year = year of treatment start date, then set to treatment start date
- If both month and day are missing and year ≠ year of treatment start date, then set to January 01
- If day is missing and month and year = month and year of treatment start date, the set to treatment start date
- If day is missing and month and year ≠ month and year of treatment start date, the set to first of the month
- If the imputed AE start date is after AE end date (maybe imputed), then update AE start date with AE end date as final imputed AE start date
- If the imputed start date > min(death date, end of study date), then set to min(death date, end of study date)

3. **Subsequent Anti-cancer Therapies**

If the start date of subsequent anti-cancer therapy is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month
- If the imputed start date > min (death date, data cutoff date, study discontinuation date, start date of the next subsequent therapy), then set it as min (death date, data cutoff date, study discontinuation date, start date of the next subsequent therapy)

If stop date of is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month
- If the imputed stop date > min (death date, study discontinuation date, start date of the next subsequent therapy), then set it as min (death date, study discontinuation date, start date of the next subsequent therapy)

The (imputed) stop date must be after or equal to the (imputed) start date. If year of the start date/stop date is missing, do not impute.

4. **Diagnosis**

If date of initial diagnosis is partially missing, impute as follows:

- If both month and day are missing, then set to January 01
- If only day is missing, then set to the first of the month
- If the imputed date > randomization date, then set to randomization date – 1

If diagnosis date of metastatic disease/locally advanced is partially missing, impute as follows:

- If both month and day are missing, then set to January 01
- If only day is missing, then set to the first of the month
- If the imputed date > randomization date, then set to randomization date – 1

- If the imputed date < (imputed) date of initial diagnosis date, then set to initial diagnosis date.

If a diagnosis date is completely missing, do not impute.

5. **Prior Therapy/Response to Prior Therapy**

The following rules will be applied to impute partial dates for prior therapy and response to prior therapy. Impute end date of prior therapy first if both start date and end date of prior therapy are partially missing.

If end date of a disease history or prior therapy is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month
- If the imputed end date > randomization date, then set to randomization date -1

If start date of a disease history or prior therapy is partially missing, impute as follows:

- If both month and day are missing, then set to January 01
- If only day is missing, then set to the first of the month
- If the imputed start date > end date, then set to end date

If the date of disease progression to prior therapy is partially missing, impute as follows:

- If both month and day are missing, then set to January 01
- If only day is missing, then set to the first of the month
- If the imputed date > randomization date, then set to randomization date – 1
- If the imputed date < the start date of prior therapy, then set to the start date of prior therapy +1.