STATISTICAL ANALYSIS PLAN

Study Protocol Number:	BGB-A317-Sitravatinib-203
Study Protocol Title:	A Phase 2, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sitravatinib in Combination With Tislelizumab in Patients With Locally Advanced Unresectable or Metastatic Esophageal Squamous Cell Carcinoma That Progressed on or After Anti-PD-(L)1 Antibody Therapy
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SIGNATURE PAGE

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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-203: a Phase 2, randomized, open-label study to investigate the efficacy and safety of Sitravatinib in combination with tislelizumab in patients with locally advanced unresectable or metastatic esophageal squamous cell carcinoma that progressed on or after anti-PD-(L)1 antibody therapy. This SAP is developed based on BGB-A317-Sitravatinib-203 protocol amendment 2.0, dated on Jul 10, 2023. BeiGene decided to terminate the study on Oct 9, 2023 based on the modifications of company development strategy. 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 and secondary efficacy endpoints and treatment emergent adverse events (TEAE) in the study protocol.

2 STUDY OVERVIEW

This is an open-label, randomized, multicenter, Phase 2 study to investigate the efficacy and safety of sitravatinib in combination with tislelizumab given as a second or third line treatment in patients with locally advanced unresectable or metastatic ESCC whose disease progressed after prior systemic chemotherapy, which is platinum-based chemotherapy doublet and anti-PD-(L)1 antibody therapy, with the anti-PD-(L)1 antibody administered in combination with or sequentially following the platinum-based chemotherapy.

The study will be conducted at approximately 25 centers in Mainland China. Approximately 100 patients with locally advanced unresectable or metastatic ESCC whose disease progressed on or after platinum-based chemotherapy doublet and anti-PD-(L)1 antibody therapy will be randomized to receive either sitravatinib plus tislelizumab (Arm A), sitravatinib monotherapy (Arm B), or ICC (Arm C). Patients must have received ≤ 2 lines of prior systemic therapy for locally advanced unresectable or metastatic disease. Other prior immunotherapeutic agents specifically targeting T-cell costimulation or checkpoint pathways (eg, anti-TIGIT antibody) are allowed if it was administered in combination with an anti-PD-(L)1 antibody. The choice of chemotherapy must be determined before randomization at the investigator's discretion, either docetaxel or irinotecan. Randomization will be stratified by PD-L1 expression status (assessed by the Ventana PD-L1 [SP263] assay: Tumor Area Positivity [TAP] score ≥ 10% versus TAP score < 10%) in a 2:1:2 ratio to receive 1 of treatment regimens:

- Arm A: Sitravatinib 100 mg orally once daily plus tislelizumab 200 mg intravenously once every 3 weeks
- Arm B: Sitravatinib 100 mg orally once daily
- Arm C: Docetaxel 75 mg/m^2 intravenously on Day 1 of every 21-day cycle **OR** irinotecan 125 mg/m^2 intravenously on Days 1 and 8 of every 21-day cycle

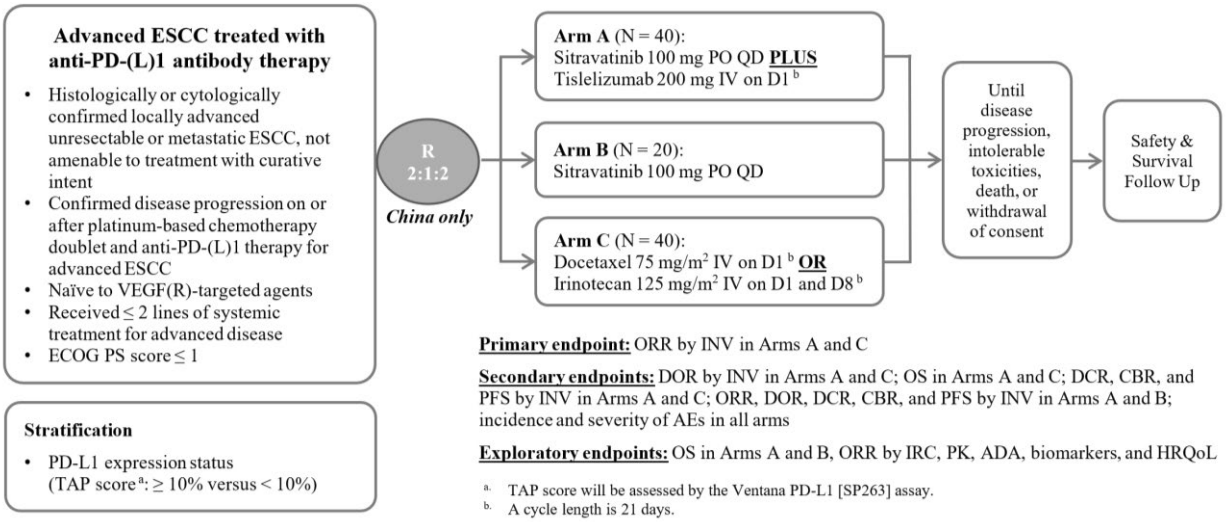
Switching of chemotherapeutic agent or cross-over between treatment arms will not be allowed during the study.

Efficacy and safety will be assessed between Arm A and Arm C, while efficacy between Arm A and Arm B will only be assessed for efficacy contribution analysis of tislelizumab in the combination treatment.

Study treatment will be administered until disease progression as assessed by the investigator per RECIST v1.1, unacceptable toxicity, withdrawal of consent, or another treatment discontinuation criterion is met, whichever occurs first.

The study design schema is presented in Figure 1.

Figure 1: Study Schema



Abbreviations: CBR, clinical benefit rate; D, Day; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ESCC, esophageal squamous cell carcinoma; HRQoL, health-related quality of life; INV, investigator; IRC, Independent Review Committee; IV, intravenously; N, number of patients; ORR, overall response rate; OS, overall survival; PD-1, programmed cell death protein-1; PD-(L)1, programmed cell death protein (ligand)-1; PFS, progression-free survival; PK, pharmacokinetic(s); PO, orally; QD, once daily; R, randomization ratio; TAP, Tumor Area Positivity; VEGF(R), vascular endothelial growth factor (receptor).

3 STUDY OBJECTIVES

3.1 Primary Objective

- To assess the overall response rate (ORR) by the investigator per Response Evaluation Criteria in Solid Tumors (RECIST) Version (v) 1.1 in the Intention-to-Treat (ITT) Population between Arm A (sitravatinib plus tislelizumab) and Arm C (investigator-chosen chemotherapy)

3.2 Secondary Objective

- To evaluate the duration of response (DOR) as assessed by the investigator per RECIST v1.1 in Arm A and Arm C
- To assess the efficacy between Arm A and Arm C through overall survival (OS)

- To assess the efficacy between Arm A and Arm C through disease control rate (DCR), clinical benefit rate (CBR), and progression-free survival (PFS) as assessed by the investigator per RECIST v1.1
- To assess the efficacy of Arm A and Arm B (sitravatinib monotherapy) through ORR, DOR, DCR, CBR, and PFS as assessed by the investigator per RECIST v1.1
- To assess the safety and tolerability of sitravatinib as monotherapy and in combination with tislelizumab

4 STUDY ENDPOINTS

4.1 Primary Endpoints

- ORR as assessed by the investigator, defined as the proportion of patients with a confirmed complete response (CR) or partial response (PR) per RECIST v1.1, in Arms A and C in the ITT Analysis Set

4.2 Secondary Endpoints

- DOR as assessed by the investigator, defined as the time from the first confirmed objective response until the first documentation of disease progression or death, whichever comes first, in Arms A and C in the ITT Analysis Set
- OS, defined as the time from the date of randomization until the date of death from any cause, in Arms A and C in the ITT Analysis Set
- DCR as assessed by the investigator, defined as the proportion of patients who achieve CR, PR, or stable disease, in Arms A and C in the ITT Analysis Set
- CBR as assessed by the investigator, defined as the proportion of patients who achieve CR, PR, or durable stable disease (stable disease $\geq$ 24 weeks), in Arms A and C in the ITT Analysis Set
- PFS as assessed by the investigator, defined as the time from the date of randomization to the date of first documentation of disease progression or death, whichever occurs first, in Arms A and C in the ITT Analysis Set
- ORR, DOR, DCR, CBR, PFS as assessed by the investigator, in Arms A and B in the ITT Analysis Set

5 SAMPLE SIZE CONSIDERATIONS

This exploratory study is not powered for the hypothesis testing between treatment arms but rather to obtain preliminary efficacy and safety data for sitravatinib in combination with tislelizumab and sitravatinib monotherapy for patients with locally advanced unresectable or metastatic ESCC that progressed on or after anti-PD-(L)1 antibody therapy. This study will enroll approximately 100 patients into 3 arms, with approximately 40, 20, and 40 patients in Arms A, B, and C, respectively. The efficacy of tislelizumab in combination with sitravatinib

versus chemotherapy will be demonstrated by descriptive analysis of ORR, PFS, OS, DCR, CBR, and DOR as assessed by the investigator in the assessment between Arms A and C. The contribution of adding tislelizumab to sitravatinib monotherapy will be demonstrated by similarly descriptive analysis in the assessment of Arms A and B. With a sample size of 40 patients in Arm A (sitravatinib plus tislelizumab), the binomial probabilities of detecting ≥ 1 TEAE with a frequency of 5% and 1% are approximately 0.87 and 0.33, respectively.

6 STATISTICAL METHODS

6.1 Analysis Sets

The ITT Analysis Set includes all patients randomly assigned to a treatment arm. Patients' data will be analyzed according to their randomized treatment arm. This will be the primary analysis population for all efficacy analyses.

The Safety Analysis Set includes all patients who receive at least 1 dose of any component of study treatment, 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 will be the population for all the safety analyses..

6.2 Data Analysis General Considerations

6.2.1 Definitions and Computations

Study drugs include sitravatinib, tislelizumab, docetaxel and Irinotecan.

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 Appendix 1.

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.
- 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 Appendix 1. 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 screened failure including re-screened will be summarized. The 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.

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
- Ethnicity
- Geographic Region

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

- PD-L1 TAP score (< 10% versus ≥ 10%)

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 clinical stage at initial diagnosis, time from diagnosis of metastatic/locally advanced disease to randomization date, primary site of esophageal cancer, metastasis status and site, etc.

6.3.5 Prior Anticancer Drug Therapies

Prior anti-cancer drug therapies, prior anti-cancer local therapy (including surgery and radiotherapy) will be summarized in the ITT analysis set.

The variables include the number of patients with any prior anticancer drug therapies, number of prior lines, type of prior anticancer drug therapies, best response to last anticancer drug therapy, treatment setting of last line, time from end of last anticancer drug therapy to randomization date, time from last disease progression to randomization date for prior anti-cancer drug therapies, and number of patients with any prior radiotherapy, treatment intent, treatment setting of last regimen and time from end of last prior radiotherapy to randomization date for prior anti-cancer radiotherapy, number of patients with any prior curative anticancer surgery. The therapies with the same sequence/regimen number are counted as one prior therapy.

6.3.6 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 ITT Analysis Set.

6.4 Efficacy Analysis

Due to the exploratory purpose of this study, all the below efficacy analyses are descriptive and exploratory; no formal testing is designed.

6.4.1 Primary Efficacy Endpoints

ORR as assessed by the investigator is defined as the proportion of patients with a confirmed CR or PR assessed by investigator per RECIST v1.1. Patients without any postbaseline response assessment (for any reason) will be considered nonresponders.

The crude odds ratio and risk difference of ORR, along with their exact 95% CIs (Thomas 1971; Chan and Zhang 1999) will be calculated between Arms A and C. The ORR rate and its Clopper-Pearson 95% CI will be calculated for each arm.

ORR based on unconfirmed PR or CR will also be summarized.

6.4.2 Secondary Efficacy Endpoints

DOR as assessed by investigator

DOR as assessed by the investigator is defined as the time from the first confirmed objective response until the first documented disease progression or death date, whichever occurred first. All the censoring rules for PFS will be applied to DOR. Only patients who have achieved objective responses will be included in the analysis of DOR. Kaplan-Meier methodology will be used to estimate median or other quartiles of DOR along with its 95% CI by using Brookmeyer and Crowley method (Brookmeyer & Crowley, 1982) for Arms A and C. Event-free rate at selected timepoints will be estimated with 95% CI estimated using Greenwood formula (Greenwood, 1926). No assessment of DOR between Arm A and C will be performed as it would be based on non-randomized subgroups.

OS

OS is defined as the time from randomization date until the date of death from any cause. 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.

Kaplan-Meier methodology will be used to estimate median or other quartiles of OS along with its 95% CI by using Brookmeyer and Crowley method (Brookmeyer & Crowley, 1982) for Arms A and C. Kaplan-Meier curves will be constructed to provide a visual description of the OS distribution. Event-free rate at selected timepoints (eg, 6 months and 12 months) will be estimated with 95% CI estimated using Greenwood formula (Greenwood, 1926). The HR of OS between Arms A and C will be estimated using a stratified Cox regression model with PD-L1 TAP score (≥ 10% versus < 10%) collected from IRT system as strata. The 95% CI for the HR will be provided. Unstratified analysis will also be presented.

PFS as assessed by investigator

PFS assessed by the investigator is defined as the time from the randomization date to the first documented disease progression, as assessed by the investigators based on RECIST v1.1 or death, whichever occurs first.

The censoring rules for the 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

Similar methodology used to evaluate OS between Arms A and C will be applied to the analysis of PFS for the assessment between Arms A and C.

DCR and CBR as assessed by investigator

DCR as assessed by the investigator is defined as proportion of patients with PR or CR or a stable disease per RECIST v1.1.

CBR as assessed by the investigator is defined as proportion of number of patients with PR or CR or a durable stable disease per RECIST v1.1.

Similar methodology used to evaluate ORR between Arms A and C in the primary analysis will be applied to the analysis of DCR and CBR for the assessment between Arms A and C.

Besides, ORR, DOR, DCR, CBR, PFS as assessed by the investigator will also be analyzed in Arms A and B in the ITT Analysis Set using similar methodology as the above analyses of ORR, DOR, DCR, CBR and PFS in Arms A and C.

6.4.3 Subgroup Analyses

Subgroup analysis on ORR by investigator will be conducted in ITT analysis set, to evaluate the uniformity of treatment effect across variety of subgroups. Subgroup variables may include, but not limited to:

- Age group (< 65 years, >= 65 years)
- Sex (Male, Female)
- ECOG performance status (0, 1)
- PD-L1 expression (>=10% TAP, <10% TAP)
- Disease status at study entry (metastatic, locally advanced)
- Number of lines of prior systemic therapy (1, 2)

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 or irinotecan: 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 (tislelizumab or docetaxel) or 13 (irinotecan).

- 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 or irinotecan, the total dose received per patient (mg/m^2) is defined as the cumulative dose of the docetaxel or irinotecan 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 using baseline weight at each visit 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 irinotecan (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 + 14)/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, 125×2 mg//m^2/cycle for irinotecan 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, and treatment-related version of any of the above categories will be provided in the safety analysis set. Treatment-related AEs include those events considered by the investigator to be related to any of the study drugs 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, and 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. Immune mediated AEs will be identified from all AEs 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 90 days after the last dose of study drug, regardless of whether the patient starts a new anticancer therapy. 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

No formal interim analyses will be conducted; administrative interim analysis is allowed. Summaries of efficacy and safety data may be generated to inform subsequent clinical development planning or to address emergent safety concerns.

8 CHANGES IN THE PLANNED ANALYSIS

Because of the early termination of the study, the planned statistical analysis in PA2.0 is condensed. No supplementary or sensitivity analysis is planned for the primary analysis. All the exploratory analyses, laboratory analyses, vital signs, pharmacokinetic and immunogenicity analyses are removed.

9 REFERENCES

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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.