BeiGene

# STATISTICAL ANALYSIS PLAN

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| **Study Protocol Number:** | BGB-A317-309 |
| **Study Protocol Title:** | A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-controlled Study to Compare the Efficacy and Safety of Tislelizumab (BGB-A317) Combined With Gemcitabine Plus Cisplatin Versus Placebo Combined With Gemcitabine Plus Cisplatin as First-Line Treatment for Recurrent or Metastatic Nasopharyngeal Cancer |
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## SIGNATURE PAGE

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## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| ADA | antidrug antibody |
| AE | adverse event |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| BICR | Blinded Independent Central Review |
| CI | confidence interval |
| CL | clearance |
| CNS | central nervous system |
| CR | complete response |
| CSR | Clinical Study Report |
| CT | computed tomography |
| CPI | checkpoint inhibitor |
| CYP | cytochrome P-450 |
| DCR | disease control rate |
| DOR | duration of response |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report form |
| EDC | electronic data capture (system) |
| EORTC QLQ-C30 | European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 |
| EORTC QLQ-H&N35 | European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Head and Neck-35 modules |
| FDG | fluorodeoxyglucose |
| FFPE | formalin-fixed paraffin-embedded |
| GFR | Glomerular Filtration Rate |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HR | hazard ratio |

| Abbreviation | Definition |
|---|---|
| ICF | informed consent form |
| ICH | International Council for Harmonisation |
| IDMC | Independent Data Monitoring Committee |
| IEC | Independent Ethics Committee |
| IgG | immunoglobulin G (eg, IgG1, IgG2, IgG3, IgG4); other types of immunoglobulins include IgD and IgM |
| imAE | immune-mediated adverse event |
| IRB | Institutional Review Board |
| IRC | Independent Review Committee |
| IRT | Interactive Response Technology |
| ITT | intent-to-treat |
| IV | intravenous(ly) |
| MRI | magnetic resonance imaging |
| NCI-CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| NPC | nasopharyngeal cancer |
| NSCLC | non-small cell lung cancer |
| ORR | objective response rate |
| OS | overall survival |
| PBMC | peripheral blood mononuclear cells |
| PD-1 | programmed cell death protein-1 |
| PD-L1 | programmed cell death protein ligand-1 |
| PET | positron emission tomography |
| PFS | progression-free survival |
| PK | pharmacokinetic(s) |
| PR | partial response |
| PS | performance status |
| Q2W | once every 2 weeks |
| Q3W | once every 3 weeks |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| SAE | serious adverse event |

| Abbreviation | Definition |
|---|---|
| SD | stable disease |
| SOC | system organ class |
| $t_{1/2}$ | half-life |
| TEAE | treatment-emergent adverse event |
| TTR | time to response |
| ULN | upper limit of normal |

# 1 INTRODUCTION

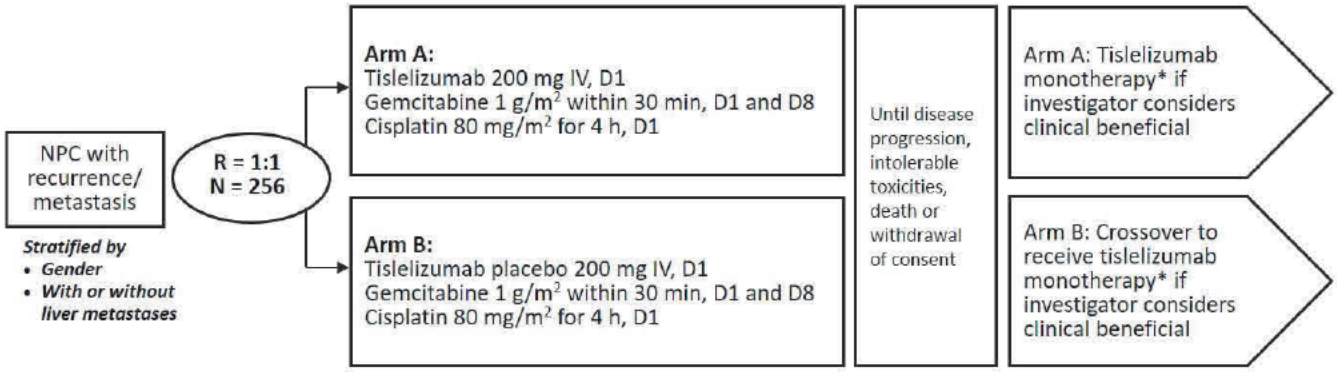
The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for BGB-A317-309: A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-controlled Study to Compare the Efficacy and Safety of Tislelizumab (BGB-A317) Combined With Gemcitabine Plus Cisplatin Versus Placebo Combined With Gemcitabine Plus Cisplatin as First-Line Treatment for Recurrent or Metastatic Nasopharyngeal Cancer. The focus of this SAP is for the planned interim analysis and the final analysis specified in the study protocol. This SAP is based on BGB-A317-309 Original Protocol dated on 28 November 2018.

The analysis details for Pharmacokinetic (PK), Pharmacodynamics, Pharmacogenomics and Biomarker analyses are not described within this SAP. Separate analysis plans may be completed for these analyses and will be attached to the clinical study report when applicable.

# 2 STUDY OVERVIEW

## 2.1 STUDY DESIGN

This is a double-blind, placebo-controlled, randomized, multicenter Phase 3 study designed to compare the efficacy and safety of tislelizumab combined with gemcitabine + cisplatin (Arm A) versus placebo + gemcitabine + cisplatin (Arm B) as first-line treatment in approximately 256 patients who have recurrent or metastatic NPC. The study design schema is as follows:




Abbreviations: D, Day; DOR, duration of response; h, hour; IV, intravenously; min, minutes; N, number of patients; NPC, nasopharyngeal cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2, progression-free survival after next line of treatment; QOL, quality of life; R, randomization ratio.

Cisplatin: 80 mg/m$^2$, Day 1, administrated as an IV infusion over 4 hours if possible or with proper infusion time based on local clinical guidelines or clinical practice according to the treating physician's clinical judgment

Gemcitabine: 1 g/m$^2$, Day 1 and Day 8, administered as an IV infusion within 30 minutes

Administration of 4 to 6 cycles will be at the investigator's discretion. Chemotherapy will be administered on a 3-week cycle until one of the following occurs (whichever occurs first): 1) completion of administration of 4 to 6 cycles; 2) unacceptable toxicity; or 3) documented disease progression per RECIST v1.1.

All patients will undergo tumor assessments at baseline and every 6 weeks (± 7 days) for the first 6 months, every 9 weeks (± 7 days) for the remainder of Year 1, and every 12 weeks (± 7 days) from Year 2 onwards based on RECIST v1.1, regardless of dose delays to manage toxicities. After completion of the Week 52 tumor assessment, tumor assessment will continue every 12 weeks. Patients will undergo tumor assessments until radiographic disease progression per RECIST v1.1, loss of clinical benefit (for tislelizumab-only patients who continue treatment after radiographic disease progression according to RECIST v1.1), withdrawal of consent, study termination by sponsor, start a new anticancer therapy, or death, whichever occurs first.

### 2.2 Study Assessments

Tumor imaging will be performed within 28 days before randomization. Results of standard of care tests or examinations performed prior to obtaining informed consent and ≤ 28 days prior to randomization may be used for the purposes of screening rather than repeating the standard of care tests. During the study, tumor imaging will be performed approximately every 6 weeks (± 7 days) for the first 6 months, every 9 weeks (± 7 days) for the remainder of Year 1, every 12 weeks (± 7 days) from Year 2 onwards based on RECIST v1.1.

Response will be assessed by IRC and the investigator using RECIST v1.1. The same evaluator should perform assessments, if possible, to ensure internal consistency across visits.

After informed consent has been signed but prior to the administration of the study drug, only SAEs should be reported.

After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until either 30 days after last dose of study treatment or initiation of new anticancer therapy, whichever occurs first. An imAE (serious or nonserious) should be reported until 90 days after the last dose of tislelizumab (or placebo), regardless of whether or not the patient starts a new anticancer therapy. All SAEs considered related to the study drug(s) that are brought to the attention of the investigator should be reported regardless of time since the last dose of treatment.

Safety and efficacy monitoring will be performed by an Independent Data Monitoring Committee (IDMC). The IDMC may recommend modifications to the study, including termination due to safety and/or efficacy concerns. The functions and membership of the IDMC will be described in the IDMC Charter.

## 3 STUDY OBJECTIVES

### 3.1 Primary Objectives

- To compare the progression-free survival as assessed by the Independent Review Committee per RECIST v1.1 in an Intent-to-Treat analysis set between tislelizumab combined with gemcitabine + cisplatin and placebo + gemcitabine + cisplatin in patients with recurrent or metastatic nasopharyngeal cancer.

## 3.2 SECONDARY OBJECTIVES

- To compare objective response rate as assessed by the Independent Review Committee per RECIST v1.1 between tislelizumab combined with gemcitabine + cisplatin and placebo + gemcitabine + cisplatin.
- To compare duration of response as assessed by the Independent Review Committee per RECIST v1.1 between tislelizumab combined with gemcitabine + cisplatin and placebo + gemcitabine + cisplatin.
- To compare overall survival between tislelizumab combined with gemcitabine + cisplatin and placebo + gemcitabine + cisplatin in an Intent-to-Treat analysis set.
- To compare progression-free survival as assessed by the investigator per RECIST v1.1 between tislelizumab combined with gemcitabine + cisplatin and placebo + gemcitabine + cisplatin in an Intent-to-Treat analysis set.
- To evaluate the progression-free survival after next line of treatment as assessed by the investigator per RECIST v1.1 between patients who cross over to subsequent tislelizumab monotherapy after initial progression of disease and patients who do not cross over to subsequent tislelizumab monotherapy or other anti- PD-1/PD-L1 agents for patients who are randomized to placebo + gemcitabine + cisplatin arm.
- To compare health-related quality of life between tislelizumab combined with gemcitabine + cisplatin and placebo + gemcitabine + cisplatin.
- To evaluate the safety and tolerability of tislelizumab combined with gemcitabine + cisplatin compared with placebo + gemcitabine + cisplatin.

## 3.3 EXPLORATORY OBJECTIVES

- To compare objective response rate as assessed by the investigator per RECIST v1.1 between tislelizumab combined with gemcitabine + cisplatin and placebo + gemcitabine + cisplatin.
- To compare duration of response as assessed by the investigator per RECIST v1.1 between tislelizumab combined with gemcitabine + cisplatin and placebo + gemcitabine + cisplatin.
- To compare tumor assessment outcomes (eg, disease control rate, time to response) between tislelizumab combined with gemcitabine + cisplatin and placebo + gemcitabine + cisplatin assessed by the investigator per RECIST v1.1.
- To evaluate the correlation between PD-L1 expression levels by immunohistochemistry and antitumor activity of tislelizumab combined with gemcitabine + cisplatin compared with placebo + gemcitabine + cisplatin
- To assess tumor and blood-based biomarkers of tislelizumab response, resistance and patient prognosis. To explore potential predictive biomarkers including any association with response to study treatment and mechanism(s) of resistance.

- To characterize the pharmacokinetics of tislelizumab when given in combination with gemcitabine + cisplatin.
- To assess host immunogenicity to tislelizumab.

# 4 STUDY ENDPOINTS

## 4.1 PRIMARY ENDPOINTS

- Progression-free survival as assessed by the Independent Review Committee: the time from randomization to the first objectively documented disease progression, or death from any cause, whichever occurs first, as assessed by the Independent Review Committee per RECIST v1.1 in an Intent-to-Treat analysis set.

## 4.2 SECONDARY ENDPOINTS

- Overall response rate as assessed by the Independent Review Committee: the proportion of patients who had complete response or partial response as assessed by the Independent Review Committee per RECIST v1.1 in all randomized patients with measurable disease at baseline.
- Duration of response as assessed by the Independent Review Committee: the time from the first occurrence of a documented objective response to the time of relapse, or death from any cause, whichever comes first, as assessed by the Independent Review Committee per RECIST v1.1 in all randomized patients with documented objective responses.
- Overall survival: the time from the date of randomization to the date of death due to any cause in an Intent-to-Treat analysis set.
- Progression-free survival as assessed by the investigator: the time from randomization to the first objectively documented disease progression, or death from any cause, whichever occurs first, as assessed by the investigator per RECIST v1.1 in an Intent-to-Treat analysis set.
- Progression-free survival after next line of treatment as assessed by the investigator: the time from randomization to second/subsequent disease progression after initiation of new anticancer therapy, or death from any cause, whichever occurs first.
- Health-related quality of life: measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Head and Neck-351 modules and Core 30 as presented in patient-reported outcomes.
- Incidence and severity of treatment-emergent adverse events graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, v5.0.

[1] EORTC QLQ-H&N43 is an updated version of EORTC QLQ-H&N35 and currently under validation at the time of the protocol finalization. Once formally released, EORTC QLQ-H&N43 will be used in the study to replace EORTC QLQ-H&N35.

### 4.3 EXPLORATORY ENDPOINTS

- Overall response rate as assessed by the investigator: the proportion of patients who had complete response or partial response as assessed by the investigator per RECIST v1.1 in all randomized patients with measurable disease at baseline.
- Duration of response as assessed by the investigator: the time from the first occurrence of a documented objective response to the time of relapse, or death from any cause, whichever comes first, as assessed by the investigator per RECIST v1.1 in all randomized patients with documented objective responses.
- Disease control rate: the proportion of patients who had complete response, partial response, or stable disease as assessed by the investigator per RECIST v1.1.
- Time to response: the time from randomization to the first occurrence of a documented objective response as assessed by the investigator per RECIST v1.1.
- Evaluate biomarkers from patient derived tumor tissue(s) and/or blood (or blood derivatives) samples obtained before, during and/or after treatment. Candidate biomarkers may include, but are not limited to, PD-L1 expression, cytokines and soluble proteins in peripheral blood, immune cells subpopulation analysis in peripheral blood and tumor tissues, tumor mutation analysis and gene expression profiling.
- Levels of circulating EBV DNA level as potential surrogate biomarker for anti-tumor efficacy prediction with EBV positive disease.
- Summary of serum concentrations of tislelizumab.
- Assessments of immunogenicity of tislelizumab by determining the incidence of antidrug antibodies.

## 5 SAMPLE SIZE CONSIDERATIONS

The sample size calculation is based on the number of PFS events required to demonstrate the PFS superiority of Arm A to Arm B in the ITT analysis set. Exponential distribution is assumed for PFS. The estimates of the number of events required to demonstrate efficacy with regard to PFS based on the following assumptions:

1 Median PFS of 7 months in the Arm B.

2 At a one-sided α of 0.025, 82% power to detect a difference, assuming a HR of 0.65, corresponding to an improvement in median PFS from 7 months to 10.8 months, in the PFS of A versus B comparison.

3 Randomization ratio: 1:1.

4 PFS evaluation dropout rate of 5% per 12 months.

5 A steady-state enrollment rate of 20 patients per month and enrollment ramp up duration of three months, ie, enrollment rate of 5 patients per month from study month 0 to month

1, 10 patients per month from month 1 to 2, 15 patients per month from month 2 to month 3, and 20 patients per month afterwards.

6 One interim analysis is planned when approximately 70% of total PFS events occurred, with Lan-DeMets O'Brien-Fleming approximation spending function.

With these assumptions, a total of 181 PFS events is required for final analysis of PFS.

Assuming 256 patients are to be enrolled over a 14.3-month period, the final analysis will occur at approximately 21.5 months after first patient randomized.

Sample size is calculated by EAST (version 6.0).

# 6 INTERIM ANALYSIS

There will be one interim efficacy analysis of PFS performed in the ITT analysis set. The interim efficacy analysis will be performed when approximately 127 PFS events (70% of the target number of 181 PFS events) are observed. It is estimated that it will take approximately 15.6 months to reach time of interim analysis. The interim boundary is based on Lan-DeMets O'Brien-Fleming approximation spending function. The planned interim and final analysis timing, and stopping boundaries are summarized in Table 1 below. The actual boundaries will be calculated based on the actual number of events observed at interim.

**Table 1. Analysis Timing and Stopping Boundaries for PFS in Each of the Primary Tests at a One-sided $\alpha = 0.025$**

| Type of analysis | Time (months) | Number of events | Testing boundary | |
|---|---|---|---|---|
| | | | P-value boundary | Approximate hazard ratio threshold |
| Interim analysis | 15.6 | 127 | 0.007 | 0.649 |
| Final analysis | 21.5 | 181 | 0.023 | 0.743 |

# 7 STATISTICAL METHODS

## 7.1 Analysis Sets

- The ITT analysis set includes all randomized patients. Patients will be analyzed according to their randomized treatment arms. This will be the primary analysis set for all efficacy analysis, including analyses of PFS and OS endpoints.
- Per-Protocol analysis set (PP) includes patients in the ITT analysis set who had no critical protocol deviations. Critical protocol deviations are a subset of major protocol deviations impacting efficacy analysis. Criteria for exclusion from the PP will be determined and documented before the database lock for the primary analysis. This will be the secondary analysis set for efficacy analysis when there are over 10% ITT patients who had critical protocol deviations.

- The Safety analysis set includes all randomized patients who received any dose of any component of study drug; it will be the analysis set for the safety analyses. Patients will be analyzed according to the actual treatment regimen received. For first line treatment, patients who randomized to arm B but took any dose of Tislelizumab will be included in arm Tislelizumab + Gemcitabine + Cisplatin in SAF. Patients who randomized to arm A but did not take any dose of Tislelizumab will be included in Placebo + Gemcitabine + Cisplatin in SAF.
- The HRQoL analysis set includes all randomized patients who received any dose of study drug and completed at least one HRQoL assessment. This will be the analysis set for HRQoL analysis.
- The PK analysis set includes all patients who receive ≥ 1 dose of tislelizumab per the protocol, for whom any postdose PK data are available.
- The immunogenicity (ADA) analysis set includes all patients who receive at least 1 dose of tislelizumab for whom both baseline ADA and at least 1 post-baseline ADA results are available.

## 7.2 Data Analysis General Considerations

Statistical programming and analyses will be performed using SAS® (SAS Institute, Inc., Cary, NC, USA), version 9.3 or higher, and/or other validated statistical software as required.

All descriptive statistics for continuous variables will be reported using mean, standard deviation (SD), median, 25 percentile (Q1), 75 percentile (Q3), minimum (Min), maximum (Max) and n. Categorical variables will be summarized as number (percentage) of patients.

The study Table Listing Graph shells will be in a separate document, which will show the content and format of all tables, listings, and graphs in detail.

### 7.2.1 Definitions and Computations

Baseline: Unless otherwise specified, a baseline value for ITT analysis set is defined as the last non-missing value collected before or at the time of randomization date, if not available, defined as last non-missing value collected before or at the time of first dose date. A baseline value for safety analysis set is defined as the last non-missing value collected before or at the time of first dose date.

Retests and Unscheduled Visits: Unscheduled measurements will not be included in by-visit table summaries and graphs but will contribute to best/worst case value where required (e.g. shift table). Listings will include scheduled, unscheduled and retest data.

### 7.2.2 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.
- Age will be calculated as the integer part of (date of informed consent – date of birth + 1)/365.25
- P-values will be rounded to 4 decimal places. P-values that round to 0.0000 will be presented as '< 0.0001' and p-values that round to 1.000 will be presented as '> 0.9999'.
- For laboratory results collected as < or >, a numeric value, 0.0000000001 will be subtracted or added, respectively, to the value.
- For by-visit observed data analyses, percentages will be calculated based on the number of patients with non-missing data as the denominator, unless otherwise specified.
- For continuous endpoints, summary statistics will include n, mean, standard deviation, median, Q1, Q3 and range (minimum and maximum).

### 7.2.3 Handling of Missing Data

Missing data will not be imputed unless otherwise specified elsewhere in the SAP. Missing dates or partially missing dates will be imputed conservatively for adverse events and prior or concomitant medications/procedures.

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.

### 7.2.4 Adjustments for Covariates

The actual value of the pooled stratification factors used at randomization (collected in eCRF), including gender (male; female) and metastatic status (liver versus other organ) will be used in stratified log-rank test and stratified Cox proportional hazard model for primary endpoint PFS, key secondary endpoint OS and other secondary endpoints. The value of the stratification factors (IWRS) and other baseline factors may be used in the model as covariates as supportive analyses for endpoints.

### 7.2.5 Multiplicity Adjustment

Multiplicity adjustment of interim analysis has been described in section 6.

### 7.2.6 Data Integrity

Before pre-specified interim or final statistical analysis begins, the integrity of the data should be reviewed to assure fit-for-purpose. The data set for analysis should be an accurate and complete representation of the subjects' relevant outcomes from the clinical database. All data should be

complete and reviewed up to a pre-specified cutoff date. Consistency checks and appropriate source data verification should be complete.

## 7.3 Subject Characteristics

### 7.3.1 Subject Disposition

The number and percentage of patients randomized, treated, permanently discontinued from study treatment, remained on treatment, discontinued from study, and remained on study will be summarized in the ITT analysis set. The primary reasons for study treatment discontinuation and study discontinuation will be summarized according to the categories in the CRF. Study follow-up time and primary reason for screen failure will be summarized.

### 7.3.2 Protocol Deviations

Critical protocol deviation criteria will be established and subjects with critical protocol deviations will be identified and documented before the database lock. Critical protocol deviations will be summarized for all patients in the ITT analysis set. They will also be listed by each category.

### 7.3.3 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics of the ITT analysis set will be summarized using descriptive statistics.
Continuous demographic and baseline variables include age, BMI (in $kg/m^2$) and body weight (in kg); categorical variables include sex, age group (<65 years, ≥65 years), ECOG performance status at baseline, smoking status, EBV DNA level (< 500 IU/ml, >= 500 IU/ml), PD-L1 expression in tumor cell (Positive: >=10%, Negative <10%, NA) and stratification factors.

### 7.3.4 Disease History and Baseline Disease Characteristics

The number (percentage) of patients reporting a history of disease and characteristic, as recorded in CRF, will be summarized in the ITT analysis set. Disease characteristics includes time from initial diagnosis to study entry, time from recurrent to study entry, time from metastatic disease diagnosis to study entry, and histology. A subject data listing of disease history will be provided.

### 7.3.5 Prior Anti-Cancer Drug Therapies, Radiotherapies, and Surgeries

The number of subjects receiving prior anti-cancer drug therapies, prior anti-cancer radiotherapy and prior anti-cancer surgeries will be summarized in the ITT analysis set. The therapies and surgeries with the same sequence/regimen number are counted as one prior therapy/surgery.

### 7.3.6 Prior and Concomitant Medication and Therapy

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO DD) of the version currently in effect at BeiGene at the time of database lock, and will be further classified to the appropriate Anatomical Therapeutic Chemical (ATC) code.

The number and percentage of patients who took prior and concomitant medications will be summarized respectively by ATC medication class and WHO DD preferred term (PT) in the

safety analysis set. Prior medications will be defined as medications that received within 30 days before randomization and stopped before the day of first dose of study drug. Concomitant medications will be defined as medications that 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 (as of the Safety Follow-up visit). In addition, telephone contacts with patients should be conducted to assess imAEs and concomitant medications (if appropriate, ie, associated with an imAE or is a new anticancer therapy) at 60 and 90 days (± 14 days) after the last dose of study drugs regardless of whether or not the patient starts a new anticancer therapy.

### 7.3.7 Medical History

Medical History will be coded using MedDRA codes of the version currently in effect at Beigene at the time of database lock. 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. A listing of medical history will be provided.

## 7.4 Efficacy Analysis

### 7.4.1 Primary Efficacy Analysis

**PFS per the IRC in ITT Analysis Set:**

PFS is defined as the time from randomization to the first documented disease progression as assessed by the IRC with the use of RECIST v1.1, or death from any cause, whichever occurs first.

PFS assessed by IRC per RECIST v1.1 will be compared between tislelizumab with gemcitabine + cisplatin (Arm A) and placebo + gemcitabine + cisplatin (Arm B), using stratified log-rank test in the ITT analysis set. The hypothesis test is formed as follows:

The null hypothesis to be tested is:

$$H_0: \text{PFS in Arm A} \leq \text{PFS in Arm B}$$

Against the alternative hypothesis:

$$H_a: \text{PFS in Arm A} > \text{PFS in Arm B}$$

The p-values from a stratified log-rank test will be presented using stratification factors with actual values as recorded in the electronic data capture (EDC) at randomization in the ITT analysis set. PFS will be estimated using the Kaplan-Meier method in the ITT analysis set. Their 95% CI will be constructed using Greenwood's formula (Greenwood, 1926). The median PFS and the cumulative probability of PFS at every 6 months, if estimable, will also be estimated using the Kaplan-Meier method. A two-sided 95% CIs of the corresponding median PFS and the cumulative probability of PFS at every 6 months, if estimable, will be constructed with a generalized Brookmeyer and Crowley method (Brookmeyer and Crowley 1982). The PFS censoring rule will follow the FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (FDA, 2007).

Kaplan-Meier survival probabilities for each arm will be plotted over time. The HR of PFS will be estimated using a Cox proportional hazard model with Efron's method of tie handling, with treatment arm as a factor and stratified by the pooled stratification factors at randomization. The 95% CI for the HR will be provided. Unstratified analysis will also be presented.

In order to evaluate the robustness of the PFS per IRC, we will perform possible sensitivity analyses with different censoring rules if the number of patients with censor reason (i.e. the specific situation in Appendix 10.1) is greater than or equal to 5% of patients in the ITT analysis set. If the patient met multiple situations in Appendix 10.1, the censor reason will be the earliest situation.

The sensitivity analysis 1 is the same as the primary analysis except that it progressed at date of documented progression with protocol specified continued follow-up in all treatment arms or died at date of death whichever is earlier when new anticancer therapy was started.

The sensitivity analysis 2 is the same as the primary analysis except that it progressed at date of documented progression or died at date of death whichever is earlier after ≥2 missed tumor assessment.

When there are over 10% ITT patients who had critical protocol deviations, sensitivity analysis 3 in PP analysis set will be implemented using primary PFS censoring rule.

Sensitivity analysis 4 in ITT analysis set will be implemented using primary PFS censoring rule when randomization error in stratification factor from IWRS is high.

If necessary, restricted mean survival time (RMST, Uno H, Claggett B, Tian L, Inoue E, et al. 2014), Max-combo (Satrajit R, Keaven A, Jiabu Y, Pralay M, 2019) will be performed to account for the possible non-proportional hazard effects.

**Subgroup Analysis for PFS per the IRC**

Subgroup analysis of primary endpoint of PFS per the IRC will be conducted to determine whether the treatment effect is consistent across various subgroups, and the HR estimates of PFS and its 95% CI will be estimated and plotted within each category of the following variables: metastatic status (liver versus other organ), ECOG performance status (0 versus 1), age (< 65 versus >= 65 years), gender (female versus male), smoking status (never versus former versus current), EBV DNA level (>= 500 IU/ml vs < 500 IU/ml), PD-L1 expression in tumor cell (Positive: >=10% vs Negative: <10% vs NA), etc.

### 7.4.2 Secondary Efficacy Endpoints

**Overall Survival**

OS is defined as the time from randomization to death from any cause. Data for patients who are not reported as having died at the time of analysis will be censored at the date last known to be alive. Data for patients who do not have postbaseline information will be censored at the date of randomization.

Similar methodology used to evaluate PFS per the IRC will be applied to OS analysis.

Sensitivity analysis may be performed for OS analyses to adjust for the crossover effect if necessary and when data maturity allows.

**Progression-Free Survival per Investigator**

PFS assessed by the investigator is defined as the time from randomization to the first objectively documented disease progression, or death from any cause, whichever occurs first per RECIST v1.1 in the ITT analysis set. PFS by investigator per RECIST v1.1 will be analyzed similarly in the ITT analysis set as described in the primary efficacy analysis for PFS per IRC.

**Objective Response Rate per the IRC**

ORR is the proportion of patients
who had a CR or PR as determined per the IRC per RECIST v1.1 in ITT analysis set. Patients without any post-baseline assessment will be considered non-responders. Similar methodology used to evaluate ORR per the IRC will be applied to analysis of ORR per the investigator.

**Duration of Response per the IRC**

Duration of response (DOR) per the IRC is defined as the time from the first documented objective response to documented disease progression as assessed by the IRC per RECIST v1.1, or death from any cause, whichever occurs first.

DOR will be estimated using Kaplan-Meier methodology in the responders.

**Second Progression-free Survival per the Investigator**

Analysis of PFS after next line of treatment (PFS2) per the investigator, defined as the time from randomization to second/subsequent disease progression after initiation of new anticancer therapy, or death from any cause, whichever occurs first, will be carried out. Patients alive and for whom a second objective disease progression has not been observed will be censored at the last time known to be alive and without second objective disease progression.

**Health-Related Quality of Life**

All HRQoL analyses will be in the HRQoL analysis set, unless otherwise specified. Observed values and changes from baseline in global health status/quality of life (GHS/QoL) and functional/symptom scales of QLQ-C30 and the symptom scales and index score of H&N35 will be descriptively summarized by visit and by treatment arm.

Compliance for the QLQ-C30 and QLQ-H&N35 modules, defined as the proportion of questionnaires actual received out of the expected number (i.e, number of patients on treatment), in the HRQoL analysis set will be summarized by visit and by treatment arm.

Time to deterioration (TTD) is defined as the time from randomization to first onset time at which deterioration is clinically meaningful that is confirmed at a subsequent clinically meaningful deterioration. The minimum important clinically meaningful difference change in symptoms of QLQ-C30 and QLQ-H&N35 is defined as ≥10 points increase from baseline (Osoba et al 1998; King, 1996; Maringwa et al 2011). The clinically meaningful deterioration is defined as ≥10 points decrease from baseline in the GHS/QoL of QLQ-C30 and QLQ-H&N35 index score. TTD will be calculated using Kaplan-Meier estimates, and presented with 2-sided 95% CIs.

Details of HRQoL scoring are specified in Appendix 10.2 according to the algorithm described in the EORTC QLQ-C30 and EORTC QLQ-H&N35 scoring manual (Fayers 2001).

### 7.4.3 Exploratory Efficacy Analyses

**Objective Response Rate per the Investigator**

ORR is the proportion of patients who had CR or PR as assessed by the investigator per RECIST v1.1 in all randomized patients with measurable disease at baseline. Patients without any postbaseline assessment will be considered nonresponders. Similar methodology used to evaluate ORR per the IRC will be applied to analysis of ORR per the investigator.

**Duration of Response per the Investigator**

Similar methodology used to evaluate DOR per the IRC will be applied to analysis of DOR per the investigator.

**Disease Control Rate per the Investigator**

DCR is defined as the proportion of patients with objective response (CR or PR) or SD maintained for ≥ 6 weeks as assessed by the investigator using RECIST v1.1. The analysis methods for DCR will be similar as those for ORR per the investigator.

**Time to Response per the Investigator**

Time to Response (TTR) by investigator per RECIST v1.1 will be analyzed using sample statistics such as mean, median and standard deviation in the responders.

**PD-L1 Expression as a Predictive Biomarker for Response**

PD-L1 expression level will be examined in the ITT analysis set. Association between PD-L1 expression and treatment effect over control (PFS, OS, ORR, DOR, DCR) will be explored if applicable.

**EBV DNA level as a Predictive Biomarker for Response**

Distribution of EBV DNA level will be examined in the ITT analysis set. Association between EBV DNA level and tislelizumab treatment effect over control (PFS, OS, ORR, DOR, DCR) will be explored if applicable.

## 7.5 SAFETY ANALYSES

Safety will be assessed by monitoring and recording of all AEs graded by NCI-CTCAE v5.0. Laboratory values (e.g., hematology, clinical chemistry), vital signs, ECGs, and PEs, will also be used in determining safety. Descriptive statistics (e.g., n, mean, standard deviation, median, Q1, Q3, minimum, maximum for continuous variables; n [%] for categorical variables) will be used to analyze all safety data in the safety analysis set.

Safety analyses of patients who crossover to receive tislelizumab monotherapy may be separately summarized if data allows. When crossover rate (the rate among the patients who crossed over to receive at least one dose of tislelizumab monotherapy) is equal to or larger than 10% among the patients who actually randomized into Arm B, additional analysis for patients who crossed over will be provided, including but not limited to tislelizumab extent of exposure, overall summary of TEAE and concomitant medication.

### 7.5.1 Extent of Exposure

Extent of exposure to each study drug will be summarized descriptively by the following variables:

- Number of treatment cycles
- Duration of exposure (weeks) is defined as:

  (date of last dose of study drug + 21 days – date of first dose of study drug)/7, with censored by death date and cutoff date, without censoring when calculating actual dose intensity.

- Cumulative dose (mg): the sum of all actual dose of study drug, given from first to last administration
- Actual dose intensity (ADI) in mg/cycle is defined as

  Cumulative dose (mg) received by a patient / Duration of exposure (cycles)

- Relative dose intensity (RDI) in % is defined as:

$$100 \times \frac{\text{ADI (mg/cycle)}}{\text{Planned Dose Intensity (mg/cycle)}}$$

  Where planned dose intensity (PDI) of tislelizumab equals to 200mg/cycle and for other chemotherapy, PDI is protocol defined full dose.

### 7.5.2 Adverse Events

AEs will be graded by the investigators using CTCAE version 5.0 and coded using the Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at BeiGene at the time of database lock.

A treatment-emergent AE (TEAE) is defined as an AE that had an onset date or a worsening in severity from baseline (pre-treatment) on or after the first dose of study drug up to 30 days after the last dose of study drug or initiation of new anticancer therapy, whichever occurs first. For tislelizumab arm, the TEAE classification also applies to imAEs that are recorded up to 90 days after the last dose of tislelizumab, regardless of whether the patient starts a new anticancer therapy. 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. AEs that were treatment emergent for patients who crossover to receive tislelizumab monotherapy may be separately summarized if data allows.

An overview table of patients with at least one TEAE will be presented with the incidence of:

- patients with any TEAE
- patients with any ≥ grade 3 TEAE
- patients with any serious TEAEs
- patients with any TEAE leading to death
- patient with any TEAE leading to permanent discontinuation of any component of study treatment
- patients with any TEAE related to any component of study treatment
- patients with any TEAE related to tislelizumab
- patients with any TEAE related to tislelizumab and ≥ grade 3
- patients with any TEAE ≥ grade 3 and related to any component of study treatment
- patients with any serious TEAEs and related to any component of study treatment
- patients with any infusion-related reaction
- patients with any imTEAE

Treatment-related TEAEs include those events considered by the investigator to be related or with missing assessment of the causal relationship. For patients with multiple occurrences of the same event will be counted only once, and the maximum grade per CTCAE v5.0 will be used.

If the grade is missing for one of the treatment-emergent occurrences of an adverse event, the maximal grade on the remaining occurrences with the same preferred term of the same patient will be used. If the patient has no other TEAE with the same preferred term, then impute as the maximum grade on all TEAE with the same preferred term; If the grade is missing for all the

occurrences, do not impute, a "missing" category will be added in the summary table.

The incidence of following TEAEs will be reported by SOC and PT, sorted by decreasing frequency of the SOC and PT:

- TEAE by maximum grade
- TEAE leading to permanent discontinuation of any component of study treatment
- TEAE leading to death
- ≥ grade 3 TEAE
- TEAE related to any component of study treatment
- Serious TEAE

All deaths and cause of death will be summarized, including those occurred during the study treatment period and those reported during the survival follow-up period after treatment discontinuation.

### 7.5.3 Laboratory Analyses

Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) for selected laboratory parameters described in Table 2 and their changes from baseline will be summarized by visit.

Selected laboratory parameters that are graded in NCI-CTCAE v5.0 will be summarized by shift from baseline CTCAE grades to maximum post-baseline grades, parameters with CTCAE grading in both high and low directions will be summarized separately.

Patient data listings of selected laboratory parameters will be provided.

**Table 2 Clinical Laboratory Tests**

| Serum Chemistry | Hematology | Thyroid Function |
|---|---|---|
| Alanine aminotransferase (ALT) | Hemoglobin | Free Triiodothyronine (FT3) |
| Aspartate aminotransferase (AST) | White blood cell (WBC) count | Free Thyroxine (FT4) |
| Creatinine | Neutrophil (Absolute) | Thyroid Stimulating |
| Potassium | Platelet count | Hormone (TSH) |
| Sodium | | |
| Creatine kinase (CK) | | |
| Creatine kinase-cardiac muscle isoenzyme (CK-MB) | | |

Hy's Law for liver injury will also be summarized by visit.

### 7.5.4 Vital Signs

Descriptive statistics for vital sign parameters (systolic and diastolic blood pressure, heart rate, respiratory rate, temperature, weight) and changes from baseline will be presented by visit for all visits. Vital signs will be listed by patient and visit.

### 7.5.5 Electrocardiograms (ECG)

ECG will be performed during baseline and multiple time post-baseline points (refer the time points to the protocol study assessments and procedures schedule). Postbaseline abnormal QTc observations will be summarized.

### 7.5.6 ECOG

A shift table from baseline to worst post-baseline in ECOG performance score will be summarized.

## 7.6 Pharmacokinetic Analyses

PK samples will be collected only in patients randomized to receive tislelizumab. Tislelizumab post-dose and Ctrough (pre-dose) will be tabulated and summarized for each cycle at which these concentrations are collected. Descriptive statistics will include means, medians, ranges, standard deviations, coefficient of variation (CV%), geometric mean and geometric CV%, as appropriate.

Additional PK analyses, including population PK analyses and exposure-response (efficacy, safety endpoints) analyses may be conducted as appropriate and the results from these analyses will be reported separately from the CSR.

## 7.7 Immunogenicity Analyses

Human anti-drug antibodies (ADA) to tislelizumab will be assessed during the study as defined in the protocol.

ADA attributes:

- Treatment boosted ADA is defined as ADA positive at baseline that was boosted to a 4-fold or higher level following drug administration.
- Treatment-induced ADA is defined as ADA negative at baseline and ADA positive post-baseline.
- Persistent ADA response is defined as Treatment-induced ADA detected at 2 or more time points during treatment or follow-up, where the first and last ADA positive samples are separated by 16 weeks or longer; or detected in the last time point.

- Transient ADA response is defined as Treatment-induced ADA detected only at 1 time point during treatment or follow-up, excluding last time point; or detected at 2 or more timepoints during treatment or follow-up, where the first and last positive samples (irrespective of any negative samples in between) are separated by less than 16 weeks and the last time point is negative. Transient ADA is a treatment-induced response that is not considered persistent.
- Neutralizing ADA is defined as ADA that inhibits or reduces the pharmacological activity.

ADA response endpoints:

- ADA incidence is defined as sum of treatment-emergent ADA, which include both treatment-induced and treatment-boosted ADA-positive patients, as a proportion of the ADA evaluable population.
- ADA prevalence is defined as proportion of all patients that are ADA positive, including pre-existing ADA, at any time point.

The immunogenicity results will be summarized using descriptive statistics by the number and percentage of patients who develop detectable ADA. The incidence of positive ADA and neutralizing ADA will be reported for evaluable patients. The effect of immunogenicity on PK, efficacy, and safety may be evaluated if data allow.

# 8 CHANGES IN THE PLANNED ANALYSIS

If the SAP needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

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# 10 APPENDIX

## 10.1 PFS CENSORING RULES

Definition of Progression Date: Progression date is assigned to the first time when tumor progression was documented.

The PFS derivation rules in this SAP follow the Table C1 and C2 described in Appendix C of Food and Drug Administration (FDA) "Guidance for Industry Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics (2015)", which includes documented progression only.

Censoring rules for primary and sensitivity analyses are summarized in Table 3.

**Table 3 Censoring Rules for Primary and Sensitivity Analysis of PFS Per RECIST version 1.1**

| No. | Situation | Primary Analysis | Sensitivity Analysis |
|---|---|---|---|
| 1 | Incomplete or no baseline tumor assessments | Censored at randomization date | |
| 2 | No postbaseline tumor assessment and no death | Censored at randomization date | |
| 3 | No postbaseline tumor assessment and death | Died at date of death | |
| 4 | Progression documented between scheduled visits | Progressed at date of documented progression | |
| 5 | No progression | Censored at date of last adequate tumor assessment with no documented progression | |
| 6 | New anticancer treatment started | Censored at date of last adequate tumor assessment before date of new anticancer treatment | Progressed at Date of documented progression with protocol specified continued follow-up in all treatment arms or died at date of death whichever is earlier |
| 7 | Death between adequate assessment visits | Died at date of death | |
| 8 | Death or progression after ≥2 missed tumor assessment visit | Censored at date of last adequate tumor assessment prior to the ≥2 missed tumor assessments | progressed at date of documented progression or Died at date of death whichever is earlier |

### 10.2 Health Related Quality of Life

The QLQ-C30 consists of thirty questions that are associated with five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The QLQ-H&N35 consists of thirty-five questions that are associated with eighteen symptom scales (pain, swallowing, senses, speech, social eating, social contact, sexuality, problem with teeth, problem opening mouth, dry mouth, problem with sense smell, cough, felt ill, pain med, nutritional supplements, feeding tube, weight loss and weight gain). Additionally the QLQ-H&N35 index score based on the eighteen symptom scales will also be calculated. QLQ-C30 and QLQ-H&N35 scale scores will be calculated as described below.

*Scoring Process*
The principle for scoring applies to all scales/scores: Raw scores are calculated as the average of the items that contribute to the scale.

A linear transformation to standardize the raw scores is utilized, so that the scores are ranged from 0 to 100. Increases in scores for functional domains (e.g., physical, role, social, emotional, etc.) are improvements while increases in scores for symptoms (e.g., fatigue, vomiting and nausea, diarrhea, pain, etc.) are deteriorations.

*Missing Items*
If at least half of the items for a scale are answered, then all the completed items are used to calculate the score. Otherwise, the scale score is set to missing.

In practical terms, if items $I_1$, $I_2$, ... $I_n$ are included in a scale, the procedure is as follows:

*Raw Score*
For all scores, the raw score (RS), is the mean of the component items
$RS = (I_1+I_2+\ldots+I_n)/n$

*Derived Scale*
The derived scales are obtained from the raw scores as defined in the EORTC manual. The derived scales have a more intuitive interpretation: larger function scale or global health status / QoL are improvements while larger symptom scales (e.g., pain, nausea, etc.) are deteriorations.

The derivation formulas are as follows:

**Linear transformation**

Apply the linear transformation to 0-100 to obtain the score $S$,

Functional scales: $S = \left\{1 - \frac{(RS-1)}{range}\right\} \times 100$

Symptom scales / items: $S = \{(RS-1)/range\} \times 100$

Global health status / QoL: $S = \{(RS-1)/range\} \times 100$

*Derived QLQ-H&N35 index score:*

Derived QLQ-H&N35 index score is equal to the average of the eighteen symptom's derived scales from QLQ-H&N35

**Table 4 Scoring of QLQ-C30**

| | Scale | Number of items | Item range | Item Numbers |
|---|---|---|---|---|
| **Global health status/ QoL**<br>Global health status/QOL | QL2 | 2 | 6 | 29,30 |
| **Functional Scales** | | | | |
| Physical functioning | PF2 | 5 | 3 | 1, 2, 3, 4, 5 |
| Role functioning | RF2 | 2 | 3 | 6, 7 |
| Emotional functioning | EF | 4 | 3 | 21, 22, 23, 24 |
| Cognitive functioning | CF | 2 | 3 | 20, 25 |
| Social functioning | SF | 2 | 3 | 26, 27 |
| **Symptom Scales/ items** | | | | |
| Fatigue | FA | 3 | 3 | 10, 12, 18 |
| Nausea and vomiting | NV | 2 | 3 | 14, 15 |
| Pain | PA | 2 | 3 | 9, 19 |
| Dyspnoea | DY | 1 | 3 | 8 |
| Insomnia | SL | 1 | 3 | 11 |
| Appetite loss | AP | 1 | 3 | 13 |
| Constipation | CO | 1 | 3 | 16 |
| Diarrhoea | DI | 1 | 3 | 17 |
| Financial Difficulties | FI | 1 | 3 | 28 |

**Table 5 Scoring of QLQ-H&N35**

| | Scale | Number of items | Item range | Item Numbers |
|---|---|---|---|---|
| Pain | HNPA | 4 | 4 | 31, 32, 33, 34 |
| Swallowing | HNSW | 4 | 4 | 35, 36, 37, 38 |
| Senses | HNSE | 2 | 4 | 43, 44 |
| Speech | HNSP | 3 | 4 | 46, 53, 54 |
| Social eating | HNSO | 4 | 4 | 49, 50, 51, 52 |
| Social contact | HNSC | 5 | 4 | 48, 55, 56, 57, 58 |
| Sexuality | HNSX | 2 | 4 | 59, 60 |
| Problem with teeth | HNTE | 1 | 4 | 39 |
| Problem opening mouth | HNOM | 1 | 4 | 40 |
| Dry mouth | HNDR | 1 | 4 | 41 |
| Problem with sense smell | HNSS | 1 | 4 | 42 |
| Cough | HNCO | 1 | 4 | 45 |
| Felt ill | HNFI | 1 | 4 | 47 |
| Pain med | HNPK | 1 | 2 | 61 |
| Nutritional supplements | HNNU | 1 | 2 | 62 |
| Feeding tube | HNFE | 1 | 2 | 63 |
| Weight loss | HNWL | 1 | 2 | 64 |
| Weight gain | HNWG | 1 | 2 | 65 |