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BeiGene

# STATISTICAL ANALYSIS PLAN

# ADDENDUM

| | |
|---|---|
| **Study Protocol Number:** | BGB-A317-204 |
| **Study Protocol Title:** | A Single-Arm, Multicenter Phase 2 Study of BGB-A317 in Patients with Previously Treated PD-L1+ Locally Advanced or Metastatic Urothelial Bladder Cancer |
| **Date:** | September 26, 2019 |
| **Version:** | Addendum 1.0 |

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## SIGNATURE PAGE

**Author:** [redacted]
**Sr. Principal Statistician**

[redacted]

## Approval

[redacted]
**Vice President, Biometrics**

[redacted]

[redacted]
**Executive Director, Clinical Development I/O**

[redacted]

[redacted]
**Medical Director, Clinical Development**

[redacted]

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## RATIONALE FOR ADDENDUM

This addendum describes the analyses of secondary efficacy endpoints of ORR, DOR, PFS and DCR assessed by investigators per irRECIST, which was not included in the Statistical Analysis Plan (SAP) Version 1.1.

Other notable modifications include:

• Change of the definition of dose modification

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# 1 INTRODUCTION

The original analyses of Protocol BGB-A317-204 "A Single-Arm, Multicenter Phase 2 Study of BGB-A317 in Patients with Previously Treated PD-L1+ Locally Advanced or Metastatic Urothelial Bladder Cancer" were described in the Statistical Analysis Plan Version 1.1 (03/04/2019). The purpose of this addendum is to describe the statistical analysis methods that will be used to analyze ORR, DOR, PFS and DCR assessed by investigators per irRECIST which was not included in the original SAP. This addendum also describes the change of the definition of dose modification.

# 2 ANALYSIS OF ORR, DOR, PFS AND DCR ASSESSED BY INVESTIGATORS PER irRECIST

The analysis methods of IRC-assessed ORR, DOR, PFS and DCR as well as ORR, DOR, PFS and DCR per investigator review according to RECIST version 1.1 were described in the Section 6.4.1 and Section 6.4.2 in the original SAP.

ORR, DOR, PFS and DCR per investigator review according to irRECIST, will be analyzed using the same analysis methods as corresponding IRC-assessed efficacy endpoints.

# 3 CHANGE OF THE DEFINITION OF DOSE MODIFICATION

Dose modification was defined to include dose delay, infusion rate decreased and infusion interruption in the original SAP. This addendum changes the definition of dose modification to include dose delay and infusion interruption.

This change of the definition of dose modification will also change the summaries of patients with any TEAE leading to dose modification as well as patients with any treatment-related TEAE leading to dose modification described in the original SAP.

# 4 REFERENCES

Bohnsack O, Hoos A, and Ludajic K. Adaptation of the immune related response criteria: irRECIST. Annals of Oncology. 2014;25 (suppl_4): iv361-iv372.

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BeiGene

# STATISTICAL ANALYSIS PLAN

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| **Study Protocol Number:** | BGB-A317-204 |
| **Study Protocol Title:** | A Single-Arm, Multicenter Phase 2 Study of BGB-A317 in Patients with Previously Treated PD-L1+ Locally Advanced or Metastatic Urothelial Bladder Cancer |
| **Date:** | Mar 4, 2019 |
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## SIGNATURE PAGE

**Author:** [redacted]
**Sr. Statistician I**

[redacted]
Date: _____

## Approval

[redacted]
**Vice President, Biometrics**

[redacted]
Date: _____

[redacted]
**Chief Medical Officer, I/O**

[redacted]
Date: _____

[redacted]
**Medical Director, Clinical Development**

[redacted]
Date: _____

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## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Term |
|---|---|
| ADA | Anti-drug antibody |
| AE | adverse event |
| BOR | best overall response |
| BP | blood pressure |
| CI | confidence interval |
| CR | complete response |
| CRF | case report form |
| CT | computerized tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| $C_{trough}$ | minimum observed plasma concentration |
| DCR | disease control rate |
| DOR | duration of response |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| GEP | gene expression profiling |
| IC | immune cell |
| IRC | independent review committee |
| irRECIST | Immune-related RECIST |
| KM | Kaplan-Meier |
| MedDRA® | Medical Dictionary for Regulatory Activities |
| NCI-CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| ORR | objective response rate |
| OS | overall survival |
| PD | progressive disease |
| PD-1 | programmed cell death-1 |
| PD-L1+ | Program Death Ligand-1 positive |
| PFS | progression-free survival |
| PK | pharmacokinetics |
| PR | partial response |
| PT | preferred term |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| SAE | serious adverse events |

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| | |
|---|---|
| SAF | Safety analysis set |
| SAP | statistical analysis plan |
| SD | stable disease |
| SOC | system organ class |
| TC | tumor cell |
| TEAE | treatment-emergent adverse event |
| TLG | table listing and graph |
| TMB | tumor mutation burden |
| UBC | urothelial bladder cancer |

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# 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 Protocol BGB-A317-204 "A Single-Arm, Multicenter Phase 2 Study of BGB-A317 in Patients with Previously Treated PD-L1+ Locally Advanced or Metastatic Urothelial Bladder Cancer". The focus of this SAP is for the planned primary, secondary [redacted] analysis specified in the study protocol.

[redacted]

Reference materials for this statistical plan include the protocol BGB-A317-204 (version 4.0, dated 11 July 2018). If the protocol or case report forms are amended or updated then appropriate adjustments to the SAP may be made if they are related to the planned analyses.

The SAP described hereafter is an a priori plan. This is an open label study and the SAP will be finalized and approved before database lock. Statistical programming may occur as study data accumulate in order to have analysis programs ready at the time the study finishes.

# 2 STUDY OVERVIEW

## Study Design

This is a single-arm, multicenter, Phase 2 study to evaluate the efficacy and safety of the anti-PD-1 monoclonal antibody tislelizumab in participants with PD-L1+ locally advanced or metastatic urothelial bladder cancer (UBC) who have progressed during or following a platinum-containing regimen. The study is composed of an initial screening phase (up to 28 days), a treatment phase (until disease progression, intolerable toxicity, or withdrawal for other reasons), safety follow-up phase (around 30 days), and survival follow-up phase.

Approximately 110 patients will be allocated to receive tislelizumab 200 mg intravenously every 3 weeks. Radiological assessment of tumor-response status should be performed every 9 weeks (±1 week). Tumor response will be assessed by independent review committee (IRC) based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and by investigators based on RECIST version 1.1 and immune-related RECIST (irRECIST). Pseudo-progression may occur due to immune cell infiltration and other mechanisms as manifested by apparent increase of existing tumor masses or appearance of new tumor lesions. Thus, for progressive disease (PD) suspected by the investigator as pseudo-progression, treatment may continue until confirmation of PD with repeat imaging at least 4 weeks later or at the next regularly scheduled imaging time point, but not to exceed 12 weeks from the initial documentation of PD. The patient must be re-consented and the following criteria must be met in order to continue the treatment after initial PD: a. Absence of clinical symptoms and signs of disease progression (including worsening laboratory values). b. Stable ECOG performance status. c. Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g. cord compression) that necessitates urgent alternative medical intervention.

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Patients will be evaluated for adverse events (AEs) (all grades, according to National Cancer Institute Common Terminology Criteria for Adverse Event (NCI-CTCAE) version 4.03). All AEs and serious adverse events (SAEs) will be recorded during the trial and for up to 30 days after the last dose of study treatment or until the initiation of another anticancer therapy, whichever occurs first. Immune-related AEs should be reported for 90 days after the last dose of study treatment, regardless of whether or not the patient starts a new anticancer therapy. Patients who have an ongoing study treatment-related AE upon study completion or at discontinuation from the study will be followed until the event has resolved to baseline or ≤ Grade 1, the investigator assesses the event as stable; the patient is lost to follow-up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of AE. If a patient discontinues study treatment due to the reason other than disease progression or death, then tumor assessments should continue to be performed following the scheduled assessment plan until the start of new anti-cancer therapy, disease progression, death, lost to follow-up or withdrawn consent.

# 3 STUDY OBJECTIVES

## 3.1 PRIMARY OBJECTIVES

- To determine the efficacy of tislelizumab in patients with previously treated, PD-L1+, locally advanced or metastatic UBC, as measured by the Objective Response Rate (ORR) according to RECIST Version 1.1 assessed by IRC

## 3.2 SECONDARY OBJECTIVES

- To evaluate the efficacy of tislelizumab as measured by duration of response (DOR), progression-free survival (PFS), and disease control rate (DCR) according to RECIST version 1.1 assessed by IRC
- To evaluate the efficacy of tislelizumab as measured by overall survival (OS)
- To evaluate the efficacy of tislelizumab as measured by ORR, DOR, PFS and DCR according to RECIST version 1.1 and irRECIST assessed by investigators
- To evaluate the safety and tolerability of tislelizumab as determined by the frequency and severity of AEs according to NCI-CTCAE version 4.03, and the rate of discontinuation of treatment due to AEs

## 3.3 EXPLORATORY OBJECTIVES

# 4 STUDY ENDPOINTS

## 4.1 PRIMARY ENDPOINTS

- ORR defined as the proportion of patients who achieved confirmed best overall response (BOR) of complete response (CR) or partial response (PR) assessed by IRC using RECIST version 1.1

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### 4.2 SECONDARY ENDPOINTS

*Efficacy:*

- DOR– defined as the time from the first determination of a confirmed objective response by IRC according to RECIST version 1.1 until the first documentation of progression or death, whichever comes first.
- PFS– defined as the time from date of first dose of study drug to date of first documentation of disease progression assessed by IRC or death, whichever occurs first using RECIST version 1.1
- DCR– defined as the proportion of patients who achieved a confirmed BOR of CR, PR, or SD assessed by IRC using RECIST version 1.1
- OS – defined as the time from the date of first dose of study drug until date of death from any cause.
- ORR, DOR, PFS and DCR assessed by investigator per RECIST version 1.1 are defined similarly as ORR, DOR, PFS and DCR by IRC

*Safety:*

To evaluate the safety and tolerability of tislelizumab, as defined by:

- The incidence and severity of AEs according to NCI-CTCAE version 4.03
- Changes in vital signs, physical findings, and clinical laboratory results

### 4.3 EXPLORATORY ENDPOINTS

## 5 SAMPLE SIZE CONSIDERATIONS

The sample size calculation was based on the power of the comparison between estimated ORR in the study and the historical rate. It is assumed an ORR of 25% in the study as compared to 10% in the historical control. Using a binomial exact text, the power is 0.986 with 110 patients to demonstrate statistical significance at a 1-sided alpha of 0.025.

## 6 STATISTICAL METHODS

### 6.1 ANALYSIS SETS

Safety analysis set (SAF) includes all patients who received any dose of tislelizumab. The SAF analysis set will be used for all safety summaries.

Efficacy Evaluable analysis set (EE) includes all patients who have received any dose of tislelizumab and had measurable disease per IRC according to RECIST version 1.1 at baseline. This will be the primary analysis set population for the efficacy analyses.

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Per-Protocol analysis set (PP) includes patients in the Efficacy Evaluable analysis set who had no important protocol deviations. Important 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 15% patients who had important protocol deviations.

The PK analysis set (PK) includes all patients who receive at least 1 dose of tislelizumab per the protocol, for whom any post dose tislelizumab PK data are available.

ADA analysis set includes all patients who have non-missing baseline ADA and at least one non-missing post-baseline ADA results.

## 6.2 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, minimum (Min), maximum (Max) and n. Categorical variables will be summarized as number (percentage) of patients.

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

### 6.2.1 Definitions and Computations

Study day: Study day will be calculated in reference to the date of the first dose of study drug. For assessments conducted on or after the date of the first dose of study drug, study day will be calculated as (assessment date – date of first dose of study drug + 1). For assessments conducted before the date of the first dose of study drug, study day is calculated as (assessment date – date of first dose of study drug). There is no study day 0.

Treatment duration (day): The treatment duration will be calculated as (date of the last dose of study drug – date of first dose of study drug + 21 days).

Baseline: Baseline is defined as the last non-missing value collected before or at the time of first dose date.

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 and unscheduled data.

### 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

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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'.

#### 6.2.3 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 concomitant medications.

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.

#### 6.2.4 Adjustment for Covariates

No adjustments for covariates are planned for primary, secondary and exploratory analyses in the study.

#### 6.2.5 Multiplicity Adjustment

No multiplicity adjustments will be made in this trial.

### 6.3 PATIENT CHARACTERISTICS

#### 6.3.1 Patient Disposition

The number and percentage of patients treated, permanently discontinued from study treatment, remained in treatment, discontinued from study, and remained in study will be summarized in the SAF. 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.

#### 6.3.2 Protocol Deviations

Important protocol deviation criteria will be established and patients with important protocol deviations will be identified and documented before the database lock.

Important protocol deviations will be summarized by category in the SAF. Important protocol deviations will be listed.

#### 6.3.3 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized in the SAF using descriptive statistics.

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Continuous demographic and baseline variables include age, BMI (in $kg/m^2$) and body weight (in kg) ; categorical variables include gender, age group (<65 years, ≥65 years), country, ECOG performance status at baseline, smoking status, and PD-L1 expression.

#### 6.3.4 Disease History

UBC history characteristics will be summarized in the SAF. Categorical disease characteristics variables include site of primary tumor, histology/cytology, histology grade, tumor staging, and known metastasis. Continuous disease history variables include time from initial UBC diagnosis.

#### 6.3.5 Prior Anti-Cancer Drug Therapies, Radiotherapy and Surgeries

The number and percentage of patients with prior anti-cancer drug therapies, with any prior platinum-containing treatment regimen, number of prior regimen, time from end of last therapy to study entry and intent of therapy for last therapy will be summarized in the SAF.

The number and percentage of patients with any prior anti-cancer radiotherapy, anatomical site, time from end of last radiotherapy to study entry will be summarized in the SAF.

The number and percentage of patients with any prior anti-cancer surgeries, surgery and location, and time from last surgery to study entry will be summarized in the SAF.

#### 6.3.6 Prior and Concomitant Medications

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 SAF. Prior medications are defined as medications that stopped before the first dose of study drug. Concomitant medications are 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.

#### 6.3.7 Medical History

Medical history will be coded using MedDRA version currently in effect at BeiGene at the time of database lock. The number and percentage of patients reporting a history of any relevant medical condition (including surgical and allergy history) will be summarized by System Organ Class (SOC) and PT in the SAF.

### 6.4 EFFICACY ANALYSIS

Efficacy analyses will be based on the EE analysis set with the exception that OS will be analyzed in the SAF.

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### 6.4.1 Primary Efficacy Endpoints

The primary efficacy endpoint is ORR as determined by IRC using the RECIST version 1.1. ORR is defined as the proportion of patients achieved confirmed BOR of CR or PR. Patients with no post-baseline response assessment (due to any reason) will be considered non-responders for ORR analysis.

The ORR in this study is estimated as 25%, which is deemed a clinical meaningful improvement from historical control of 10%. Hence, the null and alternative hypotheses are set as follows:

$$H_0: ORR=10\%$$

$$H_a: ORR \geq 25\%$$

The primary efficacy analysis will be conducted no later than 6 months after the first dose of the last patient, and will be based on EE analysis set. The number and percentage of ORR as determined by IRC using the RECIST version 1.1 will be summarized. Clopper-Pearson 95% confidence interval (CI) of ORR will be provided to assess the precision of estimation.

For hypothesis testing, one-sided p-value from the binomial exact test will be provided. If the obtained one-sided p-value is $\leq 0.025$, it will be concluded that the single agent tislelizumab statistically significantly increases ORR compared with historical control. Therefore, the superiority of single agent tislelizumab as measured by ORR will be demonstrated.

In addition, the number and percentage of patients for each of the BOR categories will be presented. Time to confirmed response will also be summarized.

A waterfall plot of best percent change in sum of target lesion diameters from baseline will be provided. The patients will be ordered by the percentage, patients with the largest percentage will be presented on the right.

### 6.4.2 Secondary Efficacy Endpoints

IRC-assessed DCR is defined as the proportion of patients achieved BOR of CR, PR or SD by IRC in accordance with RECIST version 1.1 criteria. DCR as assessed by IRC per RECIST version 1.1 and Clopper-Pearson 95% CI will be provided.

IRC-assessed PFS is defined as the time from the date of first study dose of study drug to the date of first documentation of disease progression assessed by IRC using RECIST version 1.1 or death (whichever occurs first). Kaplan-Meier method will be used to estimate median and other quartiles of PFS along with its 95% confidence interval (constructed using Brookmeyer and Crowley method). Kaplan-Meier curves will be constructed to provide a visual description of the PFS change over time. Event free rate at selected timepoints will be estimated with 95% confidence interval using Greenwood formula. Follow-up time will be estimated by the reverse Kaplan-Meier method.

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OS is defined as the date of first dose of study drug until date of death from any cause. Patients who remained alive before data cutoff or discontinuation of the study (discontinued study due to reasons other than 'Death') will be censored at the time of data cutoff or the last date the patient was known to be alive. OS will be analyzed similarly as PFS.

DOR for responders (IRC-assessed CR or PR) is defined as the time from the first determination of a confirmed objective response by IRC according to RECIST version 1.1 until the first documentation of progression or death, whichever comes first. Only patients in EE who have achieved an objective response will be included in the analysis of DOR. Censoring rule for DOR will follow PFS censoring rule. DOR will be analyzed similarly as PFS.

A swimmer plot of duration of treatment, with indicators for the start and end of each disease response episode assessed by IRC, will also be provided. The patients will be ordered by the duration of exposure. Patients with the longest duration will be presented at the top of the plot.

ORR, DOR, PFS and DCR per investigator review according to RECIST version 1.1, will be analyzed using the same analysis methods as corresponding IRC-assessed efficacy endpoints above.

#### 6.4.3 Subgroup Analyses

Primary endpoint will be summarized based on following baseline characteristics and prognostic subgroups including age group <65 years vs. ≥65 years; country (China vs Korea); smoking status (never vs current vs former); ECOG performance status 0 vs. 1; PD-L1(TC <50% and IC<50% vs. TC≥50% or IC≥50%); lymph node only (Yes vs. No);visceral metastasis (Yes vs. No); Liver metastasis (Yes vs. No); most recent prior anti-cancer therapy received, if deemed necessary and when there is sufficient number of patients in the subgroup, otherwise relevant subgroups may be combined.

Within each selected subgroup, ORR and corresponding 95% CI will be displayed using forest plot.

#### 6.4.4 Exploratory Efficacy Endpoints

Not applicable.

### 6.5 SAFETY ANALYSES

All safety analyses will be based on SAF. The incidence of treatment-emergent adverse events (TEAEs, Section 6.5.2) and SAEs will be summarized. Laboratory test results, vital signs, ECG, ECOG and their changes from baseline will be summarized using descriptive statistics. Abnormal values will be flagged.

#### 6.5.1 Extent of Exposure

The tislelizumab dose information of each patient will be assessed by the following variables:

- Number of treatment cycles equals to the count of cycles with tislelizumab

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- Duration of exposure (weeks) is defined as:

(date of last dose of tislelizumab + 21 days – date of first dose of tislelizumab)/7

- Cumulative dose (mg): the sum of all actual doses of tislelizumab, given from first to last administration

- Actual dose intensity (ADI) in mg/cycle is defined as:

Cumulative dose (mg) / Duration of exposure (cycle)

- 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 equals to 200 mg/cycle.

Number of treatment cycles by patient as a quantitative variable and by category (ie, number (%) of patient receiving at least 1 cycle, at least 2 cycles etc), duration of exposure, cumulative dose, ADI and RDI will be summarized by descriptive statistics.

The following analyses will be performed to describe tislelizumab dose delay/infusion change, where infusion change includes infusion rate decrease, infusion interrupted, and infusion discontinued. The number (percentage) of patients requiring dose delay/ infusion change will be summarized. The cycle in which the first dose delay/ infusion change occurred will be summarized using descriptive statistics. Frequency of dose delay/ infusion change will be summarized by categories.

### 6.5.2 Adverse Events

AEs will be graded by the investigators using CTCAE version 4.03 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 following the last dose of study drug. The TEAE classification also applies to immune related AEs (irAE) that are recorded up to 90 days after the last dose of tislelizumab, regardless of whether or not the patient starts a new anticancer therapy. Only those AEs that are treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in patient data listings.

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

- patients with any TEAE

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- patients with any TEAE with grade 3 or higher
- patients with any serious TEAEs
- patients with any TEAE leading to death
- patient with any TEAE leading to treatment discontinuation
- patients with any TEAE leading to dose modification, including dose delay, infusion rate decreased and infusion interruption
- patients with any treatment-related TEAE
- patients with any treatment-related TEAE with grade 3 or higher
- patients with any treatment-related serious TEAEs
- patients with any treatment-related TEAE leading to death
- patient with any treatment-related TEAE leading to treatment discontinuation
- patients with any treatment-related TEAE leading to dose modification, including dose delay, infusion rate decreased and infusion interruption
- patients with any irTEAE
- patients with any infusion-related TEAE

Treatment-related TEAEs include those events considered by the investigator to be definitely, possibly or probably related or possibly unrelated to study treatment 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 v4.03 will be used.

If the grade is missing for one of the treatment-emergent occurrences of an adverse event, the maximal severity 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 severity on all TEAE with the same preferred term; If the severity 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 order of the frequency of the SOC first and then by decreasing order of the frequency of the PT within the SOC:

- TEAE (any grade)
- TEAE by maximum severity
- TEAE leading to treatment discontinuation
- TEAE leading to dose modification
- TEAE leading to death

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- TEAE with grade 3 or higher
- Treatment-related TEAE
- Serious TEAE
- Treatment-related Serious TEAE
- Infusion related 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.

### 6.5.3 Laboratory Values

Laboratory results will be summarized for selected parameters described in Table 1.

For all parameters listed in Table 1 the actual value and the change from baseline will be summarized by visit using descriptive statistics.

Laboratory parameters that are graded according to CTCAE v4.03 will be summarized by shifts from baseline CTCAE grades to the worst post-baseline grades. In the summary of laboratory parameters by CTCAE grade, parameters with CTCAE grading in both high and low directions will be summarized separately.

**Table 1 Clinical Laboratory Tests**

| Serum Chemistry | Hematology | Urinalysis | Thyroid Function |
|---|---|---|---|
| Alkaline phosphatase (ALP) | Red blood cell (RBC) count | Specific gravity | Free Triiodothyronine (FT3) |
| Alanine aminotransferase (ALT) | Hemoglobin<br>Hematocrit | pH | Free Thyroxine (FT4)<br>Thyroid Stimulating Hormone (TSH) |
| Aspartate aminotransferase (AST) | White blood cell (WBC) count | | |
| Albumin | Neutrophil (Absolute) | | |
| Amylase | Lymphocyte (Absolute) | RBC | |
| bilirubin | Monocyte (Absolute) | WBC | |
| Blood Urea Nitrogen | Basophil (Absolute) | | |
| Urea | Eosinophil (Absolute) | | |
| | Platelet count | | |
| Creatinine | | | |
| Calcium | | | |

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| | | | |
|---|---|---|---|
| Phosphate | | | |
| Glucose | | | |
| Lactate dehydrogenase | | | |
| Total Protein | | | |
| Potassium | | | |
| Sodium | | | |
| Magnesium | | | |
| Chloride | | | |
| CK | | | |
| CK-MB | | | |
| Troponin T | | | |
| Troponin I | | | |

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferases, WBC = white blood cell

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### 6.5.4 Vital Signs

Descriptive statistics for vital signs parameters (i.e., diastolic and systolic BP, heart rate, pulse rate, temperature) and changes from baseline will be summarized by visit.

### 6.5.5 Electrocardiograms (ECG)

ECG will be performed during screening, safety follow-up and as clinically indicated at other timepoints. ECG abnormality by visit will be summarized.

### 6.5.6 ECOG

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

## 6.6 PHARMACOKINETIC ANALYSES

Tislelizumab trough serum concentration ($C_{trough}$) will be tabulated and summarized for each cycle at which PK is to be measured. Descriptive statistics will include means, medians, ranges, standard deviation, coefficient of variation (CV%), Geometric mean and geometric CV%, as appropriate.

Additional PK analyses may be conducted as appropriate.

## 6.7 IMMUNOGENIC ANALYSES

Immunogenic response to tislelizumab will be summarized descriptively.

# 7 INTERIM ANALYSIS

No interim analysis for anti-tumor activity or efficacy is planned.

# 8 CHANGES IN THE PLANNED ANALYSIS

ORR, DOR, PFS and DCR assessed per irRECIST will not be analyzed. Besides, predictive biomarkers, including TMB and GEP will not be analyzed.

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