STATISTICAL ANALYSIS PLAN

Study Protocol Number:	BGB-A317-207
Study Protocol Title:	A Phase 2, Open-Label Study of tislelizumab in Patients with Relapsed or Refractory Mature T- and NK-cell Neoplasms
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ADI	Actual dose intensity
AE	Adverse event
AITCL	Angioimmunoblastic T-cell lymphoma
ATC	Anatomical Therapeutic Chemical
ALCL	Anaplastic large cell lymphoma
CI	Confidence interval
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Lowest concentration reached before the next dose administered
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EBV	Epstein Barr Virus
EBER	Epstein–Barr virus-encoded small RNA
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30
EQ-5D-5L	5-level EQ-5D version
eCRF	Electronic case report form
irAE	Immune-related adverse event
ISH	In situ hybridization
ISCL/EORTC	International Society for Cutaneous Lymphomas/European Organization of Research and Treatment of Cancer
LYRIC	Lymphoma response to immunomodulatory therapy criteria
MedDRA	Medical Dictionary for Regulatory Activities
MF	Mycosis Fungoides
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
PTCL-NOS	Peripheral T-cell lymphoma - not otherwise specified
RDI	Relative dose intensity
Serious TEAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SS	Sèzary Syndrome
TEAE	Treatment-emergent adverse event
TTR	Time to response
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 the protocol BGB-A317-207 amendment 3.0 dated 1-Mar-2019 titled: *A Phase 2, Open-Label Study of tislelizumabin Patients with Relapsed or Refractory Mature T- and NK-cell Neoplasms*. The focus of this SAP is for the planned primary and final analyses specified in the study protocol.

2 STUDY OVERVIEW

This is a multi-center, prospective, non-randomized, open-label, phase 2 clinical study to evaluate the safety and efficacy of tislelizumab in patients with relapsed or refractory mature T-cell and NK-cell neoplasms. There will be three cohorts of patients: Cohort 1: patients with relapsed or refractory extranodal NK/T cell lymphoma; Cohort 2: patients with other mature T-cell neoplasms, limited to the following histologies; peripheral T-cell lymphoma - not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITCL), and anaplastic large cell lymphoma (ALCL); and Cohort 3: patients with cutaneous T cell lymphomas, limited to Mycosis Fungoides (MF) or Sèzary Syndrome (SS), stage IB or higher. Approximately 70 patients will be enrolled into Cohort 1, 50 patients into Cohort 2, and 10 patients into Cohort 3 for a total sample size of up to 130 patients. Cohort 2 will include up to 20 patients with PTCL-NOS, up to 10 with AITCL, and up to 20 with ALCL. Cohort 3 will be available for accrual only in North America (U.S. and Canada) and in the EU (Italy, France, and Germany). EBV status in Cohorts 1 and 2 will be determined by EBV-encoded RNAs (EBER) in situ hybridization (ISH) from local pathology report or, if not previously performed, testing from archival or fresh tumor tissue. For Cohort 3, EBV status is not mandatory. Patients' EBV status will be recorded if their local pathology report includes available EBV testing. Enrollment will be held for the following:

- Cohort 1: patients with relapsed or refractory extranodal NK/T cell lymphoma (nasal or non-nasal type)
- Cohort 2: patients with other mature T-cell neoplasms, limited to the following histologies: PTCL-NOS, AITCL, ALCL
- Cohort 3: patients with cutaneous T cell lymphomas, limited to MF or SS, stage IB or higher

Tislelizumab will be administered intravenously as a 200-mg infusion every three weeks. The primary efficacy endpoint is overall response rate (ORR) determined by investigator. Disease response for the primary endpoint for Cohorts 1 and 2 will be assessed per the Lugano criteria (Cheson et al 2014) with the Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC) modification for immunomodulatory therapy (Cheson et al 2016). Disease response for Cohort 3 for the primary endpoint will be assessed per International Society for Cutaneous Lymphomas/European Organization of Research and Treatment of Cancer (ISCL/EORTC) guidelines (Olsen et al 2011).

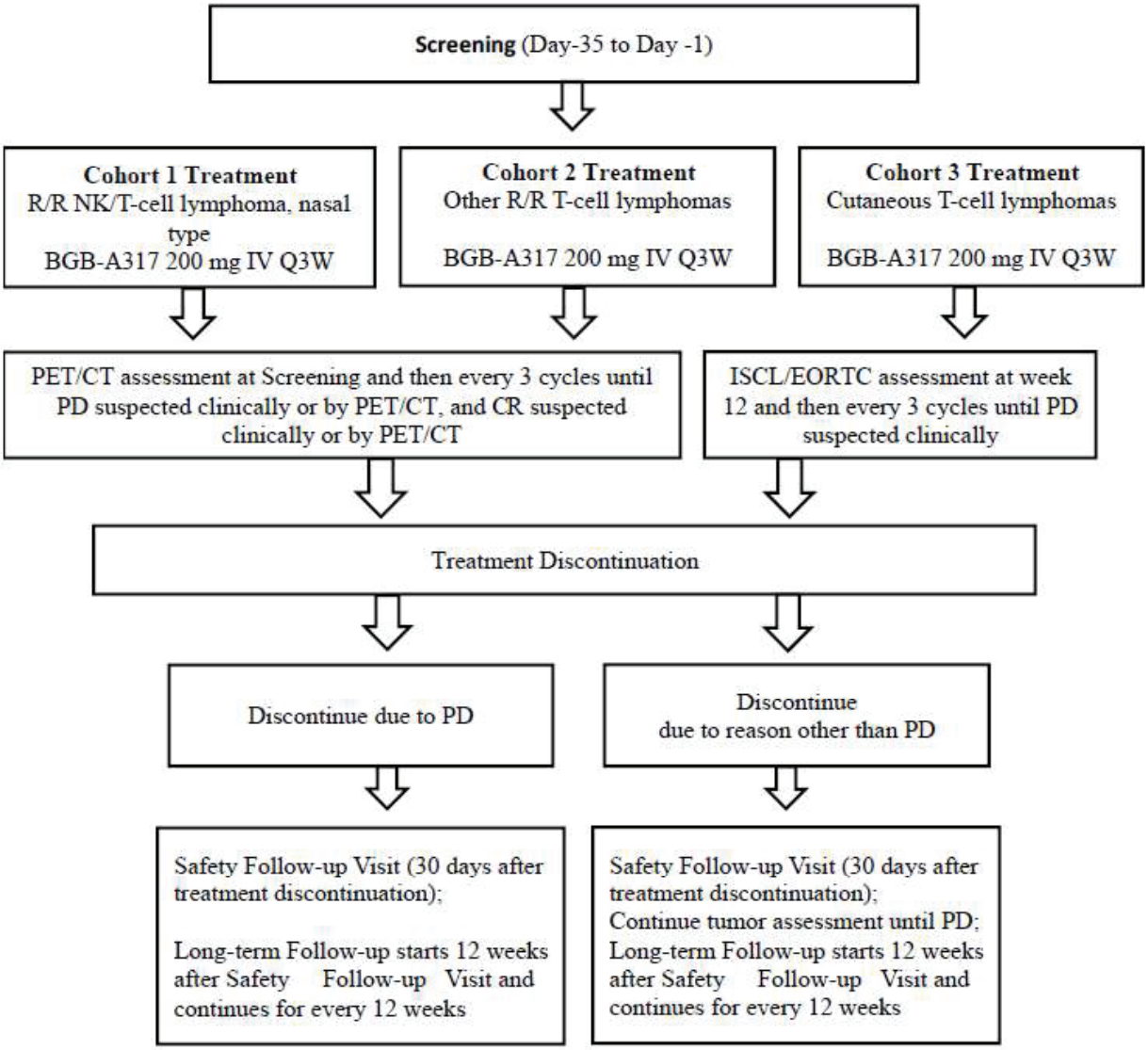
The study procedures will occur over a screening phase (up to 35 days); treatment phase (until disease progression, intolerable toxicity, or withdrawal of informed consent, whichever occurs first); safety follow-up phase (up to 90 days following last study treatment for all AEs and

Serious TEAEs; and a survival follow-up phase (duration varying by patient).

Study treatment must commence within 5 days after screening assessments have been completed and study eligibility has been determined.

Each cycle consists of 21 days.

Figure 1 Schema for Study BGB-A317-207



3 STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVES

- To evaluate efficacy, as measured by ORR and determined by investigator

3.2 SECONDARY OBJECTIVES

- To evaluate efficacy, as measured by the following and determined by investigator:
  - Duration of response (DOR) for all cohorts
  - Progression-free survival (PFS) for all cohorts
  - Overall survival (OS) for Cohorts 1 and 2
  - Rate of complete response (CR) or complete metabolic response for all cohorts
  - Time to response (TTR) for all cohorts
  - Patient-reported outcomes (EQ-5D-5L and EORTC QLQ-C30) for all cohorts
- To evaluate the safety and tolerability of tislelizumab for all cohorts

3.3 EXPLORATORY OBJECTIVES

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4 STUDY ENDPOINTS

4.1 PRIMARY ENDPOINTS

The primary endpoint is ORR. ORR is defined as the proportion of patients achieving a best overall response of either complete response (CR) or partial response (PR). Best overall response is defined as the best response recorded from the start of tislelizumab to the end of the best response determination period. Patients with no post-baseline response assessment will be considered non-responders. Efficacy will be assessed every 12 weeks for 96 weeks, then every 24 weeks for an additional 96 weeks, and then yearly until disease progression.

- For Cohorts 1 and 2, ORR will be measured using the Lugano criteria (Cheson et al 2014) with LYRIC modification for immunomodulatory drugs (Cheson et al 2016) and determined by investigator
- For Cohort 3, ORR will be measured using the ISCL/EORTC guidelines (Olsen et al 2011) and determined by investigator

4.2 SECONDARY ENDPOINTS

For Cohorts 1 and 2, efficacy measures will be determined using the Lugano criteria (Cheson et al 2014) with LYRIC modification for immunomodulatory drugs (Cheson et al 2016). For Cohort 3, efficacy measures will be determined using the ISCL/EORTC guidelines (Olsen et al 2011). All measures will be assessed by investigator.

- DOR defined as the time from the first determination of an objective response until disease progression or death, whichever occurs first, for all cohorts
- PFS defined as the time from first study drug administration to the date of disease progression or death, whichever occurs first, for all cohorts
- OS, defined as the time from first study drug administration to the date of death due to any reason, for Cohorts 1 and 2
- Rate of CR or complete metabolic response defined as the proportion of patients who achieve CR or complete metabolic response as best overall response, for all cohorts
- TTR defined as the time from first study drug administration to the time the response criteria (CR or PR) are first met, for all cohorts
- Patient-reported outcomes measured by EORTC QLQ-C30 and EQ-5D-5L questionnaires for all cohorts
- Safety parameters, including AEs, Serious TEAEs, clinical laboratory tests, physical exams, electrocardiograms, ophthalmologic examination, and vital signs for all cohorts

4.3 EXPLORATORY ENDPOINTS

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5 SAMPLE SIZE CONSIDERATIONS

The sample size is based on the precision of the estimates of the ORR. With 10, 20, 50 and 70 subjects in one cohort/subtype, if the observed ORR is 30%, the corresponding Clopper-Pearson 95% CIs are as follows: 10 subjects (6.67%, 65.25%); 20 subjects (11.89%, 54.28%); 50 subjects (17.86%, 44.61%); and 70 subjects (19.62%, 42.13%).

A more detailed list of tables with ORR and corresponding Clopper-Pearson 95% CIs for several potential outcomes under assumed cohort/subtype sample sizes are provided below.

Sample Size	Observed Responses	ORR	95% CI	
10	2	20%	2.52%	55.61%
10	3	30%	6.67%	65.25%
10	4	40%	12.16%	73.76%
10	5	50%	18.71%	81.29%
10	6	60%	26.24%	87.84%

Sample Size	Observed Responses	ORR	95% CI	
20	4	20%	5.73%	43.66%
20	6	30%	11.89%	54.28%
20	8	40%	19.12%	63.95%
20	10	50%	27.20%	72.80%
20	12	60%	36.05%	80.88%

Sample Size	Observed Responses	ORR	95% CI	
50	10	20%	10.03%	33.72%
50	15	30%	17.86%	44.61%
50	20	40%	26.41%	54.82%
50	25	50%	35.53%	64.47%
50	30	60%	45.18%	73.59%

Sample Size	Observed Responses	ORR	95% CI	
70	14	20%	11.39%	31.27%
70	21	30%	19.62%	42.13%
70	28	40%	28.47%	52.41%
70	35	50%	37.80%	62.20%
70	42	60%	47.59%	71.53%

6 STATISTICAL METHODS

6.1 DATA ANALYSIS GENERAL CONSIDERATIONS

All analyses except for efficacy analyses will be performed by cohort and combined.

Efficacy analyses will be performed by cohort and further by subtype in Cohorts 2 and 3 if data permit.

6.1.1 Definitions and Computations

Study drug: the study drug in this study is tislelizumab.

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: The treatment duration will be calculated as (date of the last dose of study drug – date of first dose of study drug + 1).

Baseline: Unless otherwise specified, a baseline value is defined as the last non-missing value collected on/before the first dose date of study drug.

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.

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

6.1.2 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 decimal place.
- 1 month = 30.4375 days. Number of months is calculated as (days/30.4375) rounded up to 1 decimal place.
- 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'.
- Missing efficacy or safety data will not be imputed unless otherwise specified.
- Time-to-event or duration of event endpoints will be based on the actual date the radiograph was obtained rather than the associated visit date.
- 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).

6.1.3 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 prior/concomitant medications/procedures, subsequent anti-cancer therapies, adverse events, and deaths as detailed in Appendix A.

By-visit summary of variables with missing data will use only non-missing data, not imputed one, unless otherwise specified.

6.1.4 Adjustment for Covariates

Not applicable.

6.1.5 Multiplicity Adjustment

Not applicable.

6.1.6 Data Integrity

Before any pre-specified statistical analysis begins, the integrity of the data should be reviewed to ensure that the data is accurate and complete up to a pre-specified cutoff date. Consistency checks and appropriate source data verification should be complete.

6.2 ANALYSIS SETS

The Safety analysis set includes all patients who received at least one dose of tislelizumab. It will be the primary analysis set for both efficacy and safety analyses.

The PK analysis set includes all treated patients for whom at least one PK sample is collected according to the protocol and laboratory manual.

6.3 PATIENT CHARACTERISTICS

6.3.1 Patient Disposition

The number (percentage) of patients enrolled, treated, discontinued from study drug and those with important protocol deviations will be counted. The primary reason for study drug discontinued will be summarized according to the categories in the eCRF.

The end of study status (alive, deceased, withdrew consent or lost to follow-up) at the data cutoff date will be summarized using the data from the eCRF.

Survival status (alive, deceased or lost to follow-up) at the data cutoff date will be summarized using the data from the survival follow-ups.

Study follow-up time will be defined as the time from first dose date to the death date or end of study date (whichever occurs earlier) for patients discontinued from study, or the database cutoff date for ongoing patients. Study follow-up time will be summarized descriptively.

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 for all patients in the Safety analysis set. They will also be listed by category.

6.3.3 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized in Safety analysis set using descriptive statistics. Continuous variables include age, weight, height, and BMI; Categorical variables include sex, age group (< 65, ≥ 65), race, country, and ECOG performance status. A listing of demographic will be provided.

6.3.4 Disease History and Characteristics

The number (percentage) of patients reporting a history of disease and characteristic, as recorded on the CRF, will be summarized in Safety analysis set. Disease characteristics include time from first diagnosis of underlying disease to study entry (in months), disease subtype, disease status (relapse, refractory), disease stage at study entry, mSWAT score for cohort 3 at study entry, EBV by EBER-ISH status, bone marrow involvement at study entry, B-symptom at study entry, LDH at study entry, and lymphocytes count at study entry. The number (percentage) of patients with prior radiotherapy, the time from end of last therapy to study entry (in months) and the number (percentage) of patients with prior autologous stem cell transplant will be summarized. A listing of disease history will be provided.

6.3.5 Prior Anti-Cancer Therapies

The number (percentage) of patients with prior systemic therapy, the number of prior regimen, the reason why the last regimen ended, time from the end of last regimen to study entry (in months), duration of last regimen (in months), best overall response to last regimen, time from end of last progressive disease to study entry (in months), and prior L-asparagine usage will be summarized. The therapies with the same regimen are counted as one prior therapy. Summary of prior non-systemic therapy for cohort 3 may be conducted. A listing of prior anti-cancer therapies will be provided.

6.3.6 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO DD) drug codes 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 (percentage) of patients reporting prior and concomitant medications will be summarized by ATC medication class and WHO DD preferred name in the Safety analysis set. Prior medications are defined as medications that started before the first dose date. 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.

6.3.7 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 (SOC) and preferred term (PT) in the Safety analysis set.

6.4 EFFICACY ANALYSIS

All efficacy analyses will be based on the Safety analysis set.

6.4.1 Primary Efficacy Endpoint

ORR by Investigator (All cohorts)

The primary efficacy endpoint is ORR determined by investigator using the Lugano criteria (Cheson et al 2014) with LYRIC modification for immunomodulatory drugs (Cheson et al 2016) for Cohorts 1 and 2 and using the ISCL/EORTC guidelines (Olsen et al 2011) for Cohort 3.

The point estimates of ORR and corresponding Clopper-Pearson 95% CIs will be presented.

The proportion for each response category (CR, PR, SD, and progressive disease (PD)) of the best overall response will be presented.

The primary efficacy analysis for each cohort will be conducted when mature response rate data have been observed, estimated as no later than 12 months after the last patient in each cohort received the first dose of study drug.

6.4.2 Secondary Efficacy Endpoints

PFS by Investigator (All cohorts)

PFS is defined as the time (in weeks) from the date of first study dose to disease progression or death of any cause, whichever occurs first:

PFS=(The earlier of disease progression or death date – the date of first study dose +1)/7.

PFS will be right-censored based on rules provided in Table 1 below. These conventions are modified based on the 2018 FDA Guidance for Industry: "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" (FDA Guidance for Industry 2018).

Kaplan-Meier methodology will be used to estimate the median and other quantiles of PFS. Kaplan-Meier curves will be constructed to provide a visual description of the PFS change with time. Two-sided 95% CIs of median and other quantiles, if estimable, will be constructed with a generalized Brookmeyer and Crowley method (Brookmeyer 1982; Klein 1997) with log-log transformation. PFS rates at selected landmark time points (e.g. 6-month) will be provided with corresponding 95% confidence intervals calculated based on the Greenwood's formula (Kalbfleisch and Prentice 1980) with log-log transformation.

The duration of the follow-up for PFS will be determined by reverse Kaplan-Meier method (Schemper 1996).

Note that the frequency of disease assessments is every 12 weeks in the first 96 weeks and every 24 weeks for additional 96 weeks, and then yearly until disease progression. Therefore, missing

more than one disease assessment will be interpreted as gaps longer than 24 weeks in the first 96 weeks or gaps longer than 48 weeks thereafter for censoring purposes of PFS.

Table 1. Censoring Rules for Analysis of Progression-Free Survival

No.	Situation	Date of Progression or Censoring	Outcome
1	No baseline and/or post-baseline disease assessments	Date of the first dose	Censored
2	Death or PD between planned disease assessments	Date of death or first disease assessment showing PD, whichever occurs first	Progressed
3	Alive without documented disease progression at the time of data cut-off or withdrawal from study (including lost-to-follow-up without disease progression)	Date of last disease assessment	Censored
4	New anticancer treatment started before documented disease progression or death	Date of last disease assessment prior to date of new anticancer treatment	Censored
5	Death before first disease assessment	Date of death	Progressed
6	Death or progression after more than one missed scheduled disease assessment	Date of last disease assessment without documented disease progression before missed tumor assessments	Censored

DOR by Investigator (All cohorts)

DOR for responders (CR or PR) is defined as the time (in weeks) from the date when the response criteria were first met (PR or better) to the date that disease progression is objectively documented or death, whichever occurs first. Censoring rule for DOR will follow PFS censoring rule. DOR will be analyzed using the same method as described for PFS if data allows. Only responders will be included in this analysis.

OS (Cohorts 1 and 2)

OS is defined as the time (in weeks) from the date of first study dose to death due to 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 using the same method as described for PFS, except the censoring criteria.

CR/Complete Metabolic Response by Investigator (All cohorts)

CR rate and complete metabolic response rate will be calculated as the proportion of patients whose best overall response is CR or complete metabolic response, respectively. CR/complete metabolic response rate will be analyzed using same method applied on ORR.

TTR by Investigator (All cohorts)

TTR for responders (CR or PR) is defined as the time from the first dose to the date of the earliest qualifying response (PR or better). TTR will be summarized by sample statistics such as mean, median and standard deviation for responders only.

Patient-Reported Outcomes

The scoring of European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) and 5-level EQ-5D version (EQ-5D-5L) will follow their corresponding manuals (Fayers et al. 2001; EuroQol Group 1990; EuroQol Group 2015; Herdman et al 2011).

- EORTC QLQ-C30 (version 3.0)

The EORTC QLQ-C30 is a questionnaire developed to assess the quality of life of cancer patients which includes 30 separate questions (items) resulting in 1 Global Health Status/QoL scale, 5 functional scales (Physical Functioning, Role Functioning, Emotional Functioning, Cognitive Functioning, and Social Functioning), 3 symptom scales (Fatigue, Nausea and Vomiting, and Pain), and 6 single items (Dyspnea, Insomnia, Appetite Loss, Constipation, Diarrhea, and Financial Difficulties).

The scores at each assessment timepoint and changes from baseline in Global Health Status/QoL scale, 5 functional scales, and 9 symptom scales/items will be summarized descriptively (e.g., mean, standard deviation, median, Q1, Q3, minimum, maximum).

- EQ-5D-5L

The EQ-5D-5L comprises a descriptive system for use as a measure of health outcome with following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and an EQ Visual Analogue scale (EQ VAS). Each dimension has five levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ VAS records the respondent's self-rated health on a 0 to 100 scale, with 100 labelled 'the best health you can imagine' and 0 'the worst health you can imagine'.

The number (percentage) of each level of all five dimensions at each assessment timepoint will be summarized. The VAS score at each assessment timepoint and changes from baseline will be summarized descriptively (e.g., mean, standard deviation, median, Q1, Q3, minimum, maximum).

6.4.3 Subgroup Analyses

Primary and selected secondary endpoints will be summarized descriptively in the specified subgroups, as appropriate (i.e. when there is sufficient number of patients in the subgroup, otherwise relevant subgroups may be combined): sex, age group (< 65, ≥ 65), race,

country/region (APAC vs. non-APAC), and ECOG-performance status (0 vs. ≥ 1). Within group values (ORR, medians for PFS with their 95% CIs) will be presented in forest plots. The subgroup variables and the cutoff values are subject to change if warranted to better represent the data.

6.4.4 Exploratory Efficacy Endpoints

[redacted]

6.5 PHARMACOKINETIC ANALYSES

All PK analyses will be performed based on the PK analysis set. Tislelizumab post-dose and trough serum concentration data (C_{trough}) will be tabulated and summarized by visit/cycle at which these concentrations are collected. Descriptive statistics will include n, mean, coefficient of variation, standard deviation, median, min, max, geometric mean, and geometric coefficient of variation.

Additional PK analyses, including population PK analyses and exposure-response (efficacy, safety endpoints) analyses may be conducted as appropriate and the results of such analysis may be reported separately from the Clinical Study Report.

6.6 SAFETY ANALYSES

All safety analyses will be performed based on the Safety analysis set.

The incidence of treatment-emergent adverse events (TEAEs) and serious treatment-emergent adverse events (Serious TEAEs) will be summarized. Laboratory test results, vital signs and their changes from baseline will be summarized using descriptive statistics (e.g., n, mean, standard deviation, median, Q1, Q3, minimum, maximum for continuous variables; n [%] for categorical variables). Abnormal values will be flagged.

6.6.1 Extent of Exposure

The tislelizumab dose information of each patient will be described as follows:

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

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

- Cumulative dose (in g): the sum of all actual doses of tislelizumab, given from first to last administration
- Actual dose intensity (ADI) (in mg/week) is defined as:

  Cumulative dose (in mg) / Duration of exposure (in weeks)
- Relative dose intensity (RDI) (%) is defined as:

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

  where Planned dose intensity equals to (200/3) mg/week.

All above extent to exposure variables will be summarized descriptively.

The following analyses will be performed to describe tislelizumab dose modifications:

- The number (percentage) of patients with dose interruption/dose delay and the primary reason (e.g., due to AEs) will be summarized
- Frequency of dose interruptions/dose delay per patient will be summarized descriptively
- The cycle in which the first dose interruption/dose delay occurred will be summarized

Patient data listings will be provided for all dosing records, and for the above calculated summary statistics.

6.6.2 Adverse Events

AEs will be graded by the investigators using Common Terminology Criteria for Adverse Events (CTCAE) v4.03. The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized PT and SOC using the Medical Dictionary for Regulatory Activities (MedDRA).

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 study drug discontinuation or initiation of a new anticancer therapy. TEAEs also include all irAEs and drug-related serious AEs recorded up to 90 days after the last dose of study drug, regardless of whether or not 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.

Treatment-related AEs include those events considered by the investigator to be “related” or with missing assessment of the causal relationship.

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

- Patients with at least 1 TEAE
- Patients with at least 1 TEAE with grade 3 or higher

- Patients with at least 1 Serious TEAE
- Patients with at least 1 TEAE leading to death
- Patients with at least 1 TEAE leading to treatment discontinuation
- Patients with at least 1 TEAE leading to dose modification, including dose interruption and dose delay
- Patients with at least 1 treatment-related TEAE
- Patients with at least 1 treatment-related TEAE with grade 3 or higher
- Patients with at least 1 treatment-related Serious TEAE
- Patients with at least 1 treatment-related TEAE leading to death
- Patients with at least 1 treatment-related TEAE leading to treatment discontinuation
- Patients with at least 1 treatment-related TEAE leading to dose modification, including dose interruption and dose delay
- Patients with at least 1 irTEAE

The incidence of following TEAEs and Serious TEAEs will be reported by SOC and PT (and by worst grade if specified), sorted by decreasing frequency of SOC and PT (a patient with multiple occurrences of the same event within a SOC and PT will be counted only once by the worst grade according to CTCAE v4.03):

- TEAE (any grade) by SOC/PT and by SOC/PT/worst grade
- TEAE with grade 3 or higher by SOC/PT/worst grade
- TEAE leading to treatment discontinuation by SOC/PT/worst grade
- TEAE leading to treatment modification (interruption or delay) by SOC/PT/worst grade
- TEAE leading to death by SOC/PT
- Serious TEAE by SOC/PT and by SOC/PT/worst grade
- Treatment-related TEAE by SOC/ PT/worst grade
- Treatment-related Serious TEAE by SOC/PT/worst grade
- Treatment-related grade 3 or higher by SOC/PT/worst grade
- Treatment-related TEAE leading to treatment discontinuation by SOC/PT/worst grade
- Treatment-related TEAE leading to treatment modification (interruption or delay) by SOC/PT/worst grade
- Treatment-related TEAE leading to death by SOC/PT

The incidence of following TEAEs will be reported by PT, in descending order:

- TEAE (any grade)

- Serious TEAE
- TEAE leading to treatment discontinuation
- TEAE leading to dose modification
- TEAE leading to death
- irTEAE

Other specific summary of AE will be conducted:

- irTEAE by PT and time interval.
- irTEAE by category/PT
- Grade 3 or higher irTEAE by category/PT
- irTEAE leading to discontinuation by category/PT
- irTEAE leading to dose modification by category/PT
- irTEAE leading to death by category/PT
- irTEAE leading to steroid treatment by category/PT
- irTEAE leading to hormone replacement treatment by category/PT
- Infusion related reaction by SOC/PT/worst grade

All deaths and deaths within/beyond 90 days of last dose date and the causes 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.

Listings of all AEs, treatment-related AE, grade 3 or above AEs, Serious AEs, AEs leading to treatment discontinuation, AE leading to dose modification, AEs leading to death, and irTEAE will be provided.

6.6.3 Laboratory Values

CBC and serum chemistry values will be evaluated for each laboratory parameter by cohort and combined. Abnormal laboratory values will be flagged and identified as those outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be included in the Clinical Study Report.

Descriptive summary statistics (n, mean, standard deviation, median, Q1, Q3, minimum, maximum for continuous variables; n [%] for categorical variables) for selected laboratory parameters by visit/cycle and changes from baseline will be provided.

Laboratory parameters that are graded in National Cancer Institute (NCI) CTCAE (v.4.03) will be summarized by CTCAE grade. Shifts tables will be used to assess the change of each laboratory parameter from baseline toxicity grade to the worst post-baseline toxicity grade. In the summary of laboratory parameters by CTCAE grade, parameters with CTCAE grading in both high and low directions will be summarized separately.

A summary of patients with an increase of 2 or more toxicity grade compared to baseline and patients with postbaseline toxicity grade of 3 or more will be provided for laboratory parameters of interest. Listings of selected laboratory parameters with grade 3 or higher will be provided.

6.6.4 Vital Signs

Descriptive statistics for vital sign parameters (e.g., systolic and diastolic BP, heart rate, temperature) and changes from baseline will be presented by visit. Vital signs will be listed by patient and visit.

6.6.5 Electrocardiogram (ECG)

A 12-lead electrocardiogram (ECG) will be performed locally in triplicate at screening for all patients and as clinically indicated at other timepoints. Descriptive statistics for ECG parameters by visit and change from baseline (if post-baseline ECG parameters are measured) will be presented.

6.6.6 ECOG

ECOG performance status will be summarized as the number (percentage) of patients with each ECOG grade at the screening visit, each visit during study treatment, and at the Safety follow-up visit. Shift tables assessing the ECOG performance status at baseline versus worst post-baseline performance status on study will be presented.

6.7 OTHER ANALYSES

6.7.1 Immunogenicity Analyses

Samples to assess anti-tislelizumab antibodies will be collected.

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

7 INTERIM ANALYSIS

No formal interim analysis is planned. Enrollment will be held if no confirmed tumor responses are seen in the first 10 evaluable patients for Cohort 1 and in the first 10 evaluable patients for Cohort 2 subtypes of PTCL-NOS and ALCL, respectively, until the study Steering Committee can meet with the sponsor to discuss the risk/benefit ratio and make a joint decision to determine whether enrollment will be permanently discontinued in Cohort 1 or subtype(s), based on the overall available data. If there is only one single confirmed tumor response among the first 10 evaluable patients for Cohort 1 or Cohort 2 subtypes of PTCL-NOS and ALCL, respectively, the Study Steering Committee and sponsor may also meet to discuss the risk/benefit ratio and determine whether it is appropriate to resume enrollment. If more than one confirmed tumor response is seen in the first 10 patients enrolled in Cohort 1 or subtype(s), then enrollment of patients may resume.

8 CHANGES IN THE PLANNED ANALYSIS

Not applicable.

9 REFERENCES

1. Brookmeyer, B et al. (1982), A confidence interval for the median survival time, Biometrics 38(1), p29-41.
2. Cheson B, Fisher R, Barrington S, et al. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. J Clin Oncol. 2014;32(27):3059-67.
3. Cheson BD, Ansell S, Schwartz L, et al. Refinement of the Lugano Classification lymphoma response criteria in the era of immunomodulatory therapy. Blood. 2016;128(21):2489-2496.
4. Common Toxicity Criteria Version 4.03. (2010) Cancer Therapy Evaluation Program. 14 June 2010.
5. EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. Health Policy. 1990;16(3):199-208.
6. EuroQol Group. EQ-5D-5L User Guide: basic information on how to use the EQ-5D-5L instrument. 2015. https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf.
7. Fayers P., Aaronson, NK, Bjordal K., Groenvold M., et al. 2001. EORTC QLQ-C30 Scoring Manual (3rd edition). (3rd ed.) Brussels: European Organization for Research and Treatment of Cancer.
8. Food and Drug Administration Center for Drug Evaluation Research CDER and Center for Biologics Evaluation and Research (2018). FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics.
9. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of Life Research. 2011;20(10):1727-36.
10. Kalbfleisch, J. D. and Prentice, R. L. (1980), The Statistical Analysis of Failure Time Data, New York: John Wiley & Sons.
11. Klein, J. P. and Moeschberger, M. L. (1997), Survival Analysis: Techniques for Censored and Truncated Data, New York: Springer-Verlag.
12. Schemper M., and Smith T.L., (1996), A note on quantifying follow-up in studies of failure time, Controlled Clinical Trials, 17: 343-346.

10 APPENDIX

Appendix A: Missing Data Imputation Rule

In general, missing or partial dates will not be imputed as data level. The following rules will apply for the specific analysis and summary purposes mentioned below only.

A.1 Prior/Concomitant Medications/therapies/procedures

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

If start date of a medication/therapy/procedure 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 end date of a medication/therapy/procedure 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
- For prior anticancer therapy, the imputed end date should be the first dose date – 14 at the latest after imputation.

If start date or end date of a medication/therapy/procedure is completely missing, do not impute.

A.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. The following rules will be applied to impute partial dates for adverse events:

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 as long as adverse event end date is not before 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, then set to treatment start date as long as adverse event end date is not before treatment start date
- If day is missing and month and year ≠ month and year of treatment start date, then set to

first day of the month

- If start date is completely missing, set to treatment start date as long as adverse event end date is not before treatment start date

If 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 end date is completely missing, do not impute.

If the imputed AE end date > last known alive date or end of study date, then set to the last known alive date or end of study date, whichever occurs first.

A.3 Deaths

In case only the day of a death date is missing, the death will be assumed to be on the 1st date of the month if the last date of subject known to be alive is earlier that the 1st date of the month, otherwise the death date will be assumed to be on 1 day after the last date of subject known to be alive.

A.4 Subsequent Anti-cancer Therapies

If the start date of a subsequent anti-cancer therapy is missing, the start date will be assumed to be on the 1st date of the month.