CLINICAL STUDY PROTOCOL

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
Protocol Identifier:	BGB-A317-309
Phase:	3
Investigational Product:	Tislelizumab (BGB-A317)
Indication:	Recurrent or Metastatic Nasopharyngeal Cancer
Sponsors:	**BeiGene, Ltd.** c/o BeiGene USA, Inc. 2955 Campus Drive, Suite 200 San Mateo, CA 94403 USA **BeiGene (Shanghai) Co., Ltd.** 4th Floor, Building D 780 Cailun Road China (Shanghai) Pilot Free Trade Zone Shanghai, China 201203
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Original Protocol:	28 November 2018
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Confidentiality Statement

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FINAL PROTOCOL APPROVAL SHEET

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BeiGene, Ltd. Approval:

[redacted]

INVESTIGATOR SIGNATURE PAGE

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Protocol Identifier: BGB-A317-309

This protocol is a confidential communication of BeiGene, Ltd., and its subsidiaries. I confirm that I have read this protocol, I understand it, and I will work according to this protocol and the terms of the clinical study agreement governing the study. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd., or one of its subsidiaries.

Instructions for Investigator: Please SIGN and DATE this signature page prior to implementation of this sponsor-approved protocol. PRINT your name, title, and the name of the center in which the study will be conducted.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

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SYNOPSIS

Name of Sponsor/Company: BeiGene, Ltd.

Investigational Product: Tislelizumab (BGB-A317)

Title of Study: 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

Protocol Identifier: BGB-A317-309

Phase of Development: 3

Number of Patients: Approximately 256

Study Centers: Approximately 42 sites

Study Objectives:

Primary:

- To compare the progression-free survival as assessed by the Independent Review Committee per Response Evaluation Criteria in Solid Tumors (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.

Secondary:

- 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 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-programmed cell death protein-1 (PD1)/programmed cell death protein ligand-1 (PD-L1) agents for patients who are randomized to the 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.

Exploratory:

- 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 as 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.

Study Endpoints:

Primary:

- PFS as assessed by the IRC: the time from randomization to the first objectively documented disease progression, or death from any cause, whichever occurs first, as assessed by the IRC per RECIST v1.1 in an ITT analysis set.

Secondary:

- ORR as assessed by the IRC: the proportion of patients who had complete response (CR) or partial response (PR) as assessed by the IRC per RECIST v1.1 in all randomized patients with measurable disease at baseline.
- DOR as assessed by the IRC: 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 IRC per RECIST v1.1 in all randomized patients with documented objective responses.
- OS: the time from the date of randomization to the date of death due to any cause in an ITT analysis set.
- PFS 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 ITT analysis set.
- PFS2 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.

- HRQoL is measured via patient reported outcomes (PRO) questionnaires using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and its Head and Neck-35 module (EORTC QLQ-H&N35).
- Incidence and severity of treatment-emergent adverse events (TEAEs) graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0.

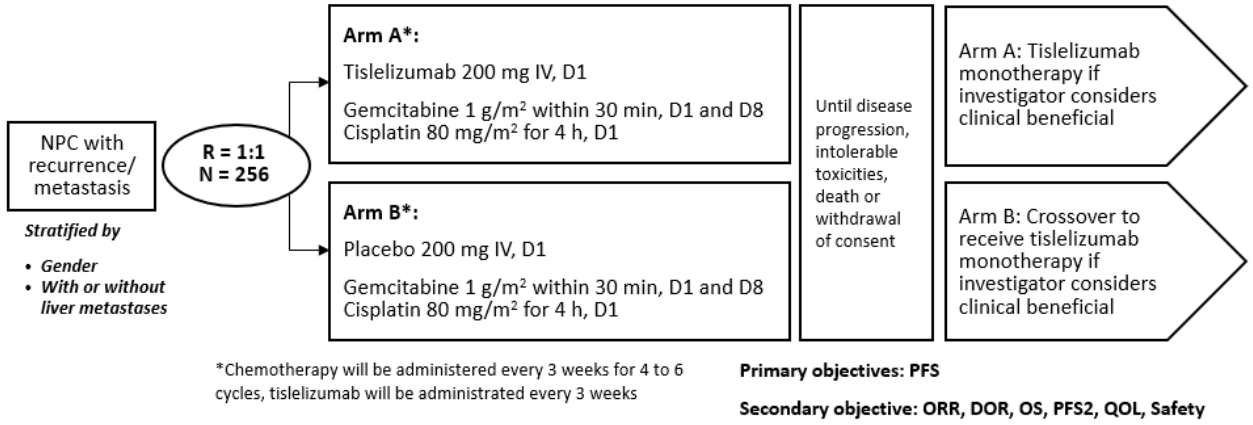
Exploratory:

- ORR as assessed by the investigator: 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.
- DOR 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.
- DCR: the proportion of patients who had CR, PR, or stable disease (SD) 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 cell subpopulation analysis in peripheral blood and tumor tissues, tumor mutation analysis and gene expression profiling.
- Levels of circulating Epstein-Barr virus (EBV) DNA as a potential surrogate biomarker for antitumor efficacy prediction in patients with EBV-positive disease.
- Summary of serum concentrations of tislelizumab.
- Assessment of immunogenicity of tislelizumab by determining the incidence of antidrug antibodies (ADAs).

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 NPC with recurrence or metastasis.

The study schema is presented as below:



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.

The primary endpoint of the study is measured by PFS as assessed by the IRC in an ITT analysis set.

Patients who have histologically or cytologically confirmed NPC with recurrence or metastasis are eligible.

Eligible patients will be stratified by gender and metastatic status (with or without liver metastases), and randomized by 1:1 to receive one of the following treatment regimens:

- Arm A: tislelizumab + gemcitabine + cisplatin
- Arm B: placebo + gemcitabine + cisplatin

Both Arm A and Arm B will be double blinded.

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.

For all patients in Arm A and Arm B, if progression of disease is unconfirmed by the IRC and the patient is clinically stable, it is at the discretion of the investigator to continue treating the patient with the assigned treatment per protocol until progression of disease is confirmed at least 28 days (or at the next scheduled tumor assessment) from the date of the scan suggesting progression of disease. If a patient has confirmed progression of disease by RECIST v1.1 as assessed by the IRC, the patient should not receive further chemotherapy treatment on study, and unblinding will be performed. The following guidance should be followed.

For Arm A (Experimental arm):

Patients whose tumors show progressive disease per RECIST v1.1 during the chemotherapy combination phase or thereafter while receiving tislelizumab monotherapy will be permitted to continue tislelizumab monotherapy provided that they meet all the following additional criteria, and upon discussion and agreement with the medical monitor:

1. Evidence of clinical benefit as assessed by the investigator
2. Absence of symptoms and signs (including clinically significant worsening of laboratory values [eg, new, or worsening hypercalcemia]) indicating unequivocal progression of disease

3. No decline in Eastern Cooperative Oncology Group (ECOG) performance status that can be attributed to disease progression
4. Absence of tumor progression at critical anatomical sites (eg, central nervous system [CNS] disease) that cannot be managed by protocol-allowed medical interventions
5. Patients must provide written consent to acknowledge deferring other treatment options in favor of continuing study treatment at the time of initial progression

The decision to continue tislelizumab beyond investigator-assessed progression must be documented in the study records.

Patients may continue tislelizumab until loss of clinical benefit as assessed by the investigator, withdrawal of consent, study termination by the sponsor, start of a new anticancer therapy, or death, whichever occurs first.

For Arm B (Control arm):

Patients who develop radiographic disease progression per RECIST v1.1 at an initial or, if continued treatment, at the time of repeat computed tomography (CT) scan, will be given the option to cross over to receive tislelizumab monotherapy (Section 7.4), provided that disease progression has been confirmed by the IRC and as long as the following criteria are met:

1. ECOG performance status ≤ 1
2. Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, CNS disease) that cannot be managed by protocol-allowed medical interventions
3. Patient provided written consent to acknowledge that tislelizumab is an experimental treatment used after failure of prior first-line platinum-containing regimen

Crossover is optional and is at the discretion of the investigator and with the sponsor's agreement.

For Both Arms:

Once patients are receiving tislelizumab monotherapy, the investigator may consider continuing tislelizumab monotherapy beyond investigator-assessed progression, provided that patients meet the above outlined criteria, and upon discussion and agreement with the medical monitor.

The decision to continue tislelizumab beyond investigator-assessed progression must be documented in the study records.

Patients may continue tislelizumab until loss of clinical benefit as assessed by the investigator, withdrawal of consent, study termination by the sponsor, start of a new anticancer therapy, or death, whichever occurs first.

A Steering Committee consisting of qualified investigators will be implemented to support the study and structure the scientific input.

Safety monitoring and interim efficacy data review will be performed by an Independent Data Monitoring Committee (IDMC). The first safety monitoring and review will occur after the first 30 patients recruited have been on treatment for ≥ 1 month or completed at least 1 cycle of study treatment. Thereafter, the IDMC will review data approximately every 6 months, or more frequently if indicated or requested by the medical monitor based on ongoing safety monitoring of patients on study. The IDMC may recommend study modification including early termination of the study due to safety concerns, or for evidence of compelling efficacy at a preplanned interim analysis. A formal interim analysis for PFS in an ITT analysis set is planned after approximately 70% of the targeted events in the ITT analysis set have been observed. The early stopping rule for the interim analysis will be set for superiority. The function and membership of the IDMC will be described in the IDMC charter.

The study is a double-blind, placebo-controlled, randomized, and multicenter study.

Study Assessments:

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, or loss of clinical benefit (for tislelizumab-only patients who continue treatment after radiographic disease progression according to RECIST v1.1), or the second radiographic disease progression per RECIST v1.1 (for patients randomized to Arm B who cross over to receive tislelizumab after radiographic disease progression according to RECIST v1.1), withdrawal of consent, study termination by sponsor, start of a new anticancer therapy, or death, whichever occurs first.

Patients who discontinue treatment for reasons other than radiographic disease progression (eg, toxicity) will continue scheduled tumor assessments until radiographic disease progression per RECIST v1.1, withdrawal of consent, loss to follow-up, study termination by sponsor, start of a new anticancer therapy, or death, whichever occurs first.

To determine the pharmacokinetic (PK) properties of tislelizumab and host immunogenic response to tislelizumab, blood samples will be collected at various timepoints as outlined in Appendix 1.

Patients will be evaluated for adverse events (AEs) and immune-mediated adverse events (imAEs) (all grades according to NCI-CTCAE v5.0). Serious adverse events (SAEs) and any AE that lead to treatment discontinuation will be followed and documented until the event resolves, the investigators assess the event as stable, or the patient is lost to follow-up, whichever occurs first.

After initiation of study drug, all AEs and SAEs, regardless of relationship to the study drug, will be reported until either 30 days after last dose of study treatment (including chemotherapy) or initiation of new anticancer therapy, whichever occurs first. All imAEs (serious or nonserious) should be reported up to 90 days after the last dose of tislelizumab (or placebo), regardless of whether 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.

Duration of Patient Participation:

The duration of the study from first enrolled patient to final analysis for PFS is estimated to be approximately 21.5 months.

Study Population:

The study will enroll approximately 256 patients who meet the following inclusion/exclusion criteria, with approximately 128 patients each in Arm A (tislelizumab combined with gemcitabine + cisplatin) and Arm B (placebo + gemcitabine + cisplatin) at a 1:1 randomization ratio.

Key Eligibility Criteria:

The population under study are adult patients (18 to 75 years old on the day the patient voluntarily agrees to participate in the study) with histologically or cytologically confirmed NPC with recurrence or metastasis. Patients must be able to provide fresh or archival tumor tissues (formalin-fixed paraffin-embedded [FFPE] blocks or approximately 10 [≥ 5] freshly cut unstained FFPE slides) with an associated pathological report. In the absence of sufficient archival tumor tissues, a fresh biopsy of a tumor lesion at baseline is mandatory. Patients must have an ECOG performance status of ≤ 1. Patients must have ≥ 1 measurable lesions as defined per RECIST v1.1 and must be treatment-naive for NPC with recurrence or metastasis. Patients who have received prior neoadjuvant, adjuvant chemotherapy, radiotherapy, or chemoradiotherapy with curative intent for nonmetastatic disease must have experienced a treatment-free

interval of ≥ 6 months from the last dose of chemotherapy and/or radiotherapy prior to randomization. Patients who have received prior neoadjuvant chemotherapy regimen for ≥ 4 cycles are excluded. Patients who have received prior treatment with therapies targeting PD-1 or PD-L1 are excluded. Patients must have a life expectancy of ≥ 12 weeks. Patients must have adequate organ function as indicated by the screening laboratory values (obtained within 7 days prior to randomization) described in Section 4.1.

Test Product, Dose, and Mode of Administration:

Tislelizumab will be administered at a dose of 200 mg intravenously (IV) once every 3 weeks (Q3W).

Reference Therapy, Dose, and Mode of Administration:

Cisplatin: 80 mg/m^2, Day 1 of each cycle, administered as an IV infusion for 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 for 4 to 6 cycles.

Gemcitabine: 1 g/m^2, Day 1, Day 8 of each cycle, administered as an IV infusion within 30 minutes, for 4 to 6 cycles.

Statistical Methods:

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.

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.

The PK analysis set includes all patients who receive any dose of tislelizumab per the protocol, for whom any postdose PK data are available.

The Immunogenicity analysis set includes all patients who receive any dose of tislelizumab for whom both baseline ADA and ≥ 1 postbaseline ADA results are available.

Primary Efficacy Endpoint Analysis:

PFS as assessed by the IRC:

PFS per the IRC 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 will be analyzed in the ITT analysis set. Actual tumor assessment visit date will be used to calculate PFS.

PFS per the IRC will be compared between tislelizumab + gemcitabine + cisplatin (Arm A) and placebo + gemcitabine + cisplatin (Arm B) at a 1-sided α of 2.5% using stratified log-rank test methodology. 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) system at randomization. The hazard ratio (HR) for PFS will be estimated using a stratified Cox regression model, respectively. The 95% confidence interval [CI] for the HR will be provided. Unstratified analysis will also be presented. Kaplan-Meier methodology will

be used to estimate median PFS for each treatment arm, and a Kaplan-Meier curve will be constructed to provide a visual description of the difference among arms.

Secondary Efficacy Endpoint Analyses:

Objective response rate per the IRC

ORR (confirmation not required according to RECIST v1.1) is the proportion of patients who had CR or PR per RECIST v1.1 in all randomized patients with measurable disease at baseline. The difference in ORR between arms in the ITT analysis set will be evaluated using the Cochran-Mantel-Haenszel chi-square test with the actual stratification factors as strata. The two-sided 95% CIs for the odds ratio and the difference in ORR will be calculated, as well as Clopper-Pearson 95% CIs for the ORR within each arm.

Duration of response per the IRC

DOR is defined as the time from the first documented objective response to documented disease progression using RECIST v1.1, or death from any cause, whichever occurs first. DOR will be estimated using Kaplan-Meier methodology. Comparison between Arm A and Arm B will be made using the stratified and unstratified log-rank test for descriptive purposes only.

Overall survival

OS is defined as the time from randomization to death from any cause. OS will be analyzed in the ITT analysis set.

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

Progression-free survival per the investigator

PFS per the investigator is defined as the time from randomization to the first objectively documented disease progression, or death from any cause, whichever occurs first, as determined per RECIST v1.1 in an ITT analysis set.

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

Second progression-free survival per the investigator

Analysis of progression-free survival after next line of treatment (PFS2), 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. Descriptive analysis of PFS2 will be performed as needed.

Health-related quality of life

HRQoL is measured via PRO questionnaires using the EORTC QLQ-C30 and EORTC QLQ-H&N35.

Descriptive statistics analysis of time to deterioration (TTD) will be performed and the results will be used for comparisons between Arm A and Arm B on the PRO endpoints.

Safety Analyses:

Safety will be assessed by monitoring and recording all AEs graded by NCI-CTCAE v5.0. Laboratory values (eg, hematology, clinical chemistry, urinalysis), vital signs, electrocardiograms (ECGs), and physical examinations will also be used in determining safety. Descriptive statistics will be used to analyze all safety data in the Safety analysis set.

Sample Size Considerations:

The sample size calculation is based on the number of events required to demonstrate the PFS superiority

of Arm A over 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 are based on the following assumptions:

1. Median PFS of 7 months in Arm B.
2. At a 1-sided α of 0.025, 82% power to detect 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 are 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 the first patient is randomized.

Sample size is calculated by EAST (version 6.0).

Interim Analyses:

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 for each comparison is based on Lan-DeMets O'Brien-Fleming approximation spending function. The interim and final analysis timing, and stopping boundaries are summarized in Section 9.7, Table 7.

LIST OF ABBREVIATIONS AND 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
EBV	Epstein-Barr virus
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
HBV	hepatitis B virus
HCV	hepatitis C virus
HR	hazard ratio
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

Abbreviation	Definition
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
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
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

1.1. Background Information on Nasopharyngeal Cancer

Nasopharyngeal cancer (NPC), while uncommon worldwide with a crude incidence of less than 1 per 100,000 persons year in western countries, is endemic in Southern China, Southeast Asia, and the Middle East/North Africa with an incidence approaching 30 cases per 100 000 people. NPC remains an important cause of death from cancer with a global incidence of mortality of approximately 50,000 cases per year (Chang and Adami 2006; World Health Organization: GLOBOCAN 2012; Tang et al 2016).

Depending on the degree of differentiation NPC is categorized into three pathological subtypes on the basis of WHO criteria. Differentiated tumors with surface keratin are defined as type I, whereas types II and III refer to non-keratinizing differentiated and undifferentiated tumors, respectively. In 1991, types II and III were combined into a single category of non-keratinizing carcinoma. In regions where NPC is endemic, nonkeratinizing subtypes constitute most cases (> 95%) and are invariably associated with Epstein-Barr virus (EBV) infection, whereas type I disease is more common in other parts of the world (Wang et al 2013; Wei and Sham 2005; Nicholls 1997). EBV infection is the most extensively studied etiological factor for NPC. On the basis of *in situ* hybridization techniques for EBV-encoded RNAs, the virus is detected exclusively in all tumor cells but not in normal nasopharyngeal epithelium, suggesting that EBV activation is necessary in the pathogenesis of NPC (Pathmanathan et al 1995; Chan et al 2000).

The incidence and mortality rate of NPC have decreased in several endemic areas, possibly as a result of lifestyle changes, and advances in management, including improvement of radiotherapy technology, broader application of chemotherapy, and more accurate disease staging (Lau et al 2013; Hsu et al 2006). Current therapeutic decisions are based mainly on disease stage (NCCN guidelines 2018; Chan et al 2012): Stage I disease are treated with radiotherapy alone; Stage II disease are treated with radiotherapy with or without concurrent chemotherapy; Stage III to IVb disease are treated with radiotherapy and concurrent chemotherapy. Local and regional control of nearly 90% at 3 years after treatment for stage III-IVb NPC can be achieved (Kam et al 2007; Lee et al 2009; Ng et al 2014; Tham et al 2009; Peng et al 2012; Zhong et al 2017). However, between 17-54% of patients with NPC fail treatment due to distant metastases and approximately one third of patients presented with disseminated disease at Stage IVc primary diagnosis (Liu et al 2003; Lee et al 1992; Chiesa and De Paoli 2001; Ng et al 2014; Sun et al 2014; Lee et al 2015). Most recurrent cases are not amenable to salvage therapy with surgery and/or radiotherapy with or without concurrent chemotherapy. Treatment options for the majority of patients with NPC with recurrence or metastasis are largely limited to palliative systemic therapies (Lee et al 2015). For patients with stage IVc and recurrent disease, the reported progression-free survival (PFS) was 7 months, and overall survival (OS) was 20-29 months, respectively (Boussen et al 1991; Au and Ang 1994; Yeo et al 1998; Taamma et al 1999; Ngan et al 2002; Chua et al 2005; Li et al 2008; Ma et al 2009; Chan 2010).

High plasma EBV DNA levels are a poor prognostic factor (Lin et al 2004) and the dynamic change of plasma EBV DNA after chemotherapy or chemoradiotherapy correlates with treatment efficacy (An et al 2011). In addition, EBV DNA levels are also useful for assessing treatment-response and detecting disease relapse after radiotherapy (Lo et al 1999a; Lo et al 1999b; Lo et al

2000; Chan et al 2002). Novel prognostic markers using genetic signatures and microRNA have also shown promising results (Liu et al 2012; Wang et al 2011).

1.2. Current Treatment of NPC With Recurrence or Metastasis

1.2.1. Chemotherapy

The unique geographic distribution and low overall incidence of this disease has presented challenging obstacles for the development of new agents and treatment options assessment for patients with recurrent or metastatic NPC in Phase 3 randomized clinical trials. Cisplatin and fluorouracil have been the conventional choices achieving response rates of 70-80% while cisplatin-based doublets that include combination with 5-FU, paclitaxel, docetaxel, gemcitabine have been demonstrated as effective regimens (reported response rate range between 60-74%) which are well tolerated as first-line chemotherapy for patients with recurrent or metastatic NPC (Jin et al 2012).

A randomized Phase 3 clinical trial comparing two platinum-based combination chemotherapy regimens in the first-line setting for NPC with recurrence or metastasis reported improved median OS for gemcitabine plus cisplatin (GP) compared to fluorouracil plus cisplatin (FP): 29.1 months versus 20.9 months (hazard ratio [HR]= 0.62 [95% CI: 0.45-0.84]; p = 0.0025]. The reported PFS for GP versus FP is 7 months versus 5.6 months（HR = 0.55 [95% CI: 0.44-0.68]; p < 0.001). Overall, both treatment regimens were well tolerated with predictable toxic profiles and low rates of discontinuation (Zhang et al 2016).

The standard treatment for this patient population is platinum-based doublet chemotherapy (NCCN Guidelines 2018). However, very poor outcomes have been observed, with a median OS of about 20 months (Wei and Sham 2005). Therefore, improvements in clinical outcomes are needed for metastatic patients and for patients unsuitable for radiotherapy (Lee et al 2016; Zhang et al 2016).

Table 1. Chemotherapy for the Treatment of Advanced or Metastatic Nasopharyngeal Cancer

Study	Zhang et al 2016		Chua et al 2005	Leong et al 2008
Patient number	N = 362		N = 19	N = 28
Treatment	Gemcitabine + cisplatin (n = 181)	Fluorouracil + cisplatin (n = 181)	Docetaxel + cisplatin (n = 19)	Gemcitabine + paclitaxel + carboplatin (n = 28)
OS (months)	29.1	20.9	12.4	22
HR (95% CI)	0.62 (0.45-0.84); p = 0.0025		NA	NA
mPFS (months)	7.0 (4.4-10.9)	5.6 (3.0-7.0)	5.6	8
HR (95% CI)	0.55 (0.44-0.68); p < 0·0001		NA	NA
ORR (%)	64	42	62.5	86
p-value	p < 0.001		NA	NA
TEAE ≥ Grade 3 (%)	43	36	NA	NA

Abbreviations: HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TEAE, treatment-emergent adverse event.

1.2.2. Checkpoint Inhibitor

The availability of checkpoint inhibitors (CPIs) bringing promising and effective treatment for melanoma (Wolchok et al 2013), renal cell carcinoma (Motzer et al 2015), lung cancer (Reck et al 2016) has expanded the development of new treatment strategy for NPC. Programmed cell death protein ligand-1 (PD-L1) expression is reported to occur in 89% to 95% of NPC tumors, with greater than 50% of tumor cells staining positive for PD-L1 in the majority of these tumors and a positive correlation of PD-L1 expression with clinical outcomes in NPC patients had been observed (Fang et al 2014; Zhang et al 2015; Chen et al 2013). In a Phase 1b trial that enrolled 27 patients with recurrent NPC harboring tumors with ≥ 1% PD-L1 expression tumors, the patients received pembrolizumab monotherapy. Of the 27 patients, 70.4% had received 3 or more prior therapies. Partial response (PR) and stable disease (SD) were observed in 7 and 14 patients, respectively, for an objective response rate (ORR) of 25.9% (95% CI, 11.1 to 46.3) over a median follow-up of 20 months (Hsu et al 2017); nivolumab also demonstrated ORR of 20.5% with 1-year OS rate of 59% (95% CI, 44.3% to 78.5%) and 1-year PFS rate was 19.3% (95% CI, 10.1% to 37.2%) (Ma et al 2018). Preliminary antitumor activity of camrelizumab (SHR-1210, a programmed cell death-1 [PD-1] inhibitor) in Chinese patients with recurrent or metastatic NPC had been reported in two Phase 1 studies. The first trial tested camrelizumab monotherapy in 93 patients who received at least one previous line of treatment for NPC with recurrence or metastasis, where an ORR of 34% (95% CI, 24% to 44%) was observed and 2 patients had a complete response (CR). The second trial tested camrelizumab in combination with gemcitabine and cisplatin as a first-line treatment in 23 treatment-naive patients, where an ORR of 91% (95% CI, 77% to 97%) was reported and 1 patient had a CR. Both trials showed good safety profiles

with no treatment-related deaths observed. These are the most promising results reported so far for PD-1 inhibitors tested in NPC (Fang et al 2018). Collectively, these preliminary results arising from both tumor antigen-specific and agnostic immunotherapeutic strategies favor the notion of EBV-positive NPC as a highly immune-enriched tumor, and therefore supports extending the consideration of immunotherapy in combination with chemotherapy in treatment-naïve metastatic NPC.

1.3. Background Information on Tislelizumab

1.3.1. Pharmacology

Tislelizumab (also known as BGB-A317) is a humanized, immunoglobulin G4 (IgG4)-variant monoclonal antibody against PD-1 under clinical development for the treatment of several human malignancies.

Tislelizumab acts by binding to the extracellular domain of human PD-1 with high specificity as well as high affinity (dissociation constant [K_D] = 0.15 nM). It competitively blocks binding efforts by both PD-L1 and programmed cell death protein ligand-2, thus inhibiting PD-1-mediated negative signaling in T cells. In in vitro cell-based assays, tislelizumab was observed to consistently and dose-dependently enhance the functional activity of human T cells and preactivated, primary peripheral blood mononuclear cells. In addition, tislelizumab has demonstrated antitumor activity in several allogeneic xenograft models, in which peripheral blood mononuclear cells were coinjected with human cancer cells (A431 [epidermoid carcinoma]) or tumor fragments (BCCO-028 [colon cancer]) into immunocompromised mice.

The IgG4 variant antibody has very low binding affinity to gamma fragment crystallizable region (Fc) receptor IIIA (FcγRIIIA) and complement 1q, a subunit of complement 1, by in vitro assays, suggesting either low or no antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) effects in humans (Labrijn et al 2009).

Please refer to the tislelizumab Investigator's Brochure for additional details regarding nonclinical studies of tislelizumab.

1.3.2. Toxicology

The toxicity and safety profile of tislelizumab was characterized in single-dose toxicology studies in mice and monkeys and in a 13-week repeat dose toxicology study in cynomolgus monkeys. The tissue cross-reactivity was evaluated in the normal frozen tissues from both humans and monkeys. The cytokine release assays were also evaluated using fresh human whole blood cells. The pivotal toxicology studies were conducted following Good Laboratory Practice (GLP) regulations. The single dosing regimens spanned from the intended human doses to 10-fold higher than the maximum of the intended human doses, and the repeat dosing regimens spanned to 3-fold higher than the maximum of the intended human doses. The cynomolgus monkey was the only relevant species based on the target sequence homology and binding activity.

Overall, no apparent toxicity was noted in mice or monkey toxicity studies. No tissue cross-reactivity was found in either human or monkey tissues, nor was any effect on cytokine release observed in human whole-blood assay. The toxicokinetics profile was well characterized with

dose proportional increases in systemic exposure without apparent accumulation or sex difference. Immunogenicity was observed without apparent immunotoxicity or effect on the systemic exposure. The No-Observed-Adverse-Effect-Level of tislelizumab in the 13-week monkey toxicity study was considered to be 30 mg/kg. The safety profile of tislelizumab is considered adequate to support the current study BGB-A317-309.

Please refer to the tislelizumab Investigator's Brochure for more detailed information on the toxicology of tislelizumab.

1.3.3. Clinical Pharmacology

In the Phase 1 BGB-A317_Study_001 and Study BGB-A317-102, interim pharmacokinetics (PK) analysis (data cutoff date 28 August 2017) was conducted by noncompartmental methods, using serum concentrations from patients who received doses of 0.5, 2.0, 5.0, 10 mg/kg once every 2 weeks (Q2W) and 2.0 mg/kg, 5.0 mg/kg, 200 mg once every 3 weeks (Q3W) (Phase 1a Parts 1, 2, and 3, and Phase 1b in BGB-A317_Study_001) and patients who received doses of 200 mg Q3W in Phase 1 of Study BGB-A317-102 (n = 19). The maximum observed plasma concentration (C_{max}) and the area under the plasma or serum concentration-time curve increased in a nearly dose-proportional manner from 0.5 mg/kg to 10 mg/kg, both after single-dose administration at steady state. Preliminary PK data from 27 patients who were administered 1 dose of 200 mg Q3W (Phase 1a, Part 3 and Study BGB-A317-102) showed tislelizumab concentrations between the range of concentrations observed for patients who were administered 2 mg/kg and 5 mg/kg doses.

Preliminary population PK analysis using a 2-compartment model with first order elimination shows a systemic plasm clearance (CL) of tislelizumab of 0.173 L/day, volume of distribution in the central and peripheral compartments of 2.89 and 1.76 L, respectively, and half-life ($t_{1/2}$) of approximately 19 days. Race, gender, and body weight were not significant covariates on the CL of tislelizumab, which supports fixed-dosing across different ethnic groups.

1.3.4. Prior Clinical Experience of Tislelizumab

As of 20 May 2020, there are currently 28 ongoing studies with tislelizumab with over 1917 patients treated. Of these, 15 studies have preliminary data available in the Investigator's Brochure (IB) version 8, dated 10 September 2020: 7 monotherapy studies, 2 chemotherapy combination therapy studies, and 6 targeted therapy combination studies. Of the ongoing monotherapy studies in solid tumors, available data from BGB-A317_Study_001 and BGB-A317-102 are summarized in Section 1.3.4.1 and Section 1.3.4.2 (with a clinical cutoff date of 28 August 2017).

Please refer to the tislelizumab Investigator's Brochure for more detailed information on efficacy and safety of tislelizumab.

1.3.4.1. BGB-A317_Study_001 (Data cutoff 28 August 2017)

Study BGB-A317_Study_001 is a 2-stage study consisting of a Phase 1a dose-escalation and dose-finding component with 3 parts: to establish the maximum tolerated dose, if any; a recommended Phase 2 dose (RP2D) for the Phase 1b; and a flat dose (fixed dose); followed by a

Phase 1b component to investigate efficacy in select tumor types in indication expansion arms and to further evaluate safety and tolerability of tislelizumab.

As of 28 August 2017, in Phase 1a, 116 patients had received tislelizumab at dose regimens including 0.5 mg/kg, 2 mg/kg, 5 mg/kg, or 10 mg/kg Q2W; 2 mg/kg or 5 mg/kg Q3W; and 200 mg Q3W. In Phase 1b, 323 patients had received tislelizumab in Phase 1b across 9 indication-expansion cohorts.

Overall, for the 439 patients in the study, the median age was 60.0 years, 53.8% of the population was male, and 65.6% of patients were white. The median number of prior anticancer therapy regimens was 2 (range: 0 to 12). The median treatment exposure duration was 2.50 months (range: 0 to 23.0) and the median study follow-up duration was 5.56 months (range: 0.0 to 26.9). As of 28 August 2017, there were 210 patients (47.8%) remaining on study in Study BGB-A317_Study_001.

Preliminary Safety

Of the 439 total patients in the Safety Population for BGB-A317_Study_001, 240 (54.7%) experienced at least 1 treatment-emergent adverse event (TEAE) assessed as related to tislelizumab by the Investigator and 34 (7.7%) experienced at least 1 ≥ Grade 3 related TEAE. The most commonly occurring related TEAEs for patients treated with the tislelizumab monotherapy in BGB-A317_Study_001 were fatigue (12.8%), rash (7.7%), nausea (6.8%), diarrhea (6.6%), and hypothyroidism (4.8%). The ≥ Grade 3 related TEAEs occurring in ≥ 2 patients were pneumonitis (6 patients, 1.4%); colitis and alanine aminotransferase (ALT) increased (4 patients each, 0.9%); fatigue, type 1 diabetes mellitus, and aspartate aminotransferase (AST) increased (3 patients each, 0.7%); and diarrhea, gamma-glutamyltransferase (GGT) increased, and diabetic ketoacidosis (2 patients each, 0.5%). All other events occurred in single patients. Lastly, 18 patients (4.1%) experienced an infusion-related reaction; all were mild/moderate in severity.

Preliminary Efficacy

For patients in Phase 1a (n = 116, evaluable), there were 20 patients with a confirmed response and 42 patients with a best overall response (BOR) of SD.

For patients in Phase 1b (n = 286 evaluable), a total of 26 patients had a confirmed response. Additionally, there were 101 patients with a BOR of SD.

1.3.4.2. Study BGB-A317-102 (Data cutoff 28 August 2017)

This Phase 1/2 study was a dose verification of tislelizumab and an indication-expansion study of tislelizumab conducted in Chinese patients with advanced solid tumors.

Overall, for the 123 patients in Study BGB-A317-102, the median age was 54.0 years, 66.7% of the population was male, and 100% of patients were Asian (Chinese). The median number of prior anticancer therapy regimens was 2 (range: 0 to 9). The median treatment exposure duration was 1.78 months (range: 0 to 8.0) and the median study follow-up duration was also 1.78 months (range: 0.0 to 8.0). As of 28 August 2017, there were 113 patients (91.9%) remaining on study in Study BGB-A317-102.

Preliminary Safety

Of the 123 total patients in the Safety Population for Study BGB-A317-102, 69 (56.1%) experienced at least 1 TEAE assessed as related to tislelizumab by the investigator and 10 (8.1%) were ≥ Grade 3 in severity. The most commonly occurring related TEAEs were aspartate aminotransferase (AST) increased (20 patients, 16.3%), alanine aminotransferase (ALT) increased (17 patients, 13.8%), and blood bilirubin increased and anaemia (13 patients each, 10.6%). The ≥ Grade 3 related TEAEs occurring in ≥ 2 patients were AST increased (3 patients, 2.4%) and ALT increased (2 patients, 1.6%). All other events occurred in single patients including a case of retinal detachment (Grade 4).

Preliminary Efficacy in NPC Patients

As of 12 October 2018, 20 patients (including 17 males) were enrolled to the NPC cohort, with median age of 49 years (range: 7-61 years). The median number of prior systemic anticancer therapy regimens was 2.6 (range: 0 to 10). There were 10 patients (50%) remaining on study. Median duration of treatment is 25.5 weeks (range: 9-63). All patients were evaluable for response, 6 with a confirmed response, 2 with an unconfirmed response, and 10 patients with a BOR of SD. All patients had tumors with PD-L1 expression (data on file).

1.3.4.3. Immune-Mediated Reactions

In patients treated with tislelizumab monotherapy, the following immune-mediated adverse events (imAEs) were observed:

- Acute hepatitis and abnormal liver function have been reported, including 1 patient with fatal hepatitis. Additionally, 3.2% of patients experienced treatment-related abnormal liver function tests, and 1.4% of patients experienced immune-mediated hepatitis or hyperbilirubinaemia.
- Pneumonitis has been reported in 2.1% of patients, including 1 patient with fatal pneumonitis.
- Colitis has been reported in 2% of patients treated. Diarrhea has been reported in 6.6% of patients.
- Endocrinopathies have been reported including diabetes mellitus (hyperglycemia and ketoacidosis). In addition, thyroiditis, including thyrotoxicosis and hypothyroidism has been reported. Furthermore, hypophysitis has been reported in < 1% of patients treated.
- Other immune-mediated events (<1% of patients with tislelizumab monotherapy except where noted): skin reactions (20.5%, including rash and pruritus); arthralgia (2.5%); haemolytic anaemia, nephritis, proteinuria (1.8%); encephalitis, neuropathy, arthritis, pancreatitis, stomatitis, uveitis, and dry eye (1.4%).

Beyond patients treated with tislelizumab monotherapy, a case of fatal myocarditis and polymyositis was reported in 1 patient who received a single dose of tislelizumab, in combination with paclitaxel and cisplatin (see tislelizumab Investigator's Brochure). The patient's initial symptoms were dyspnea and tea-colored urine 2 weeks after starting treatment. Elevated urine and serum cardiac and skeletal muscle enzymes were reported. The patient died of multi-organ failure 6 days later.

1.4. Study Rationales

1.4.1. Rationale for Gemcitabine Plus Cisplatin as the Comparator

In 2016, Zhang et al (Zhang et al 2016) reported a phase 3 randomized clinical trial comparing the efficacy and toxicity of GP versus FP as first-line chemotherapy in NPC with recurrence or metastasis, which was the first head-to-head randomized study in this disease in recent era. It is reported that ORR was higher in the GP group (64% versus 42%, relative risk = 1.5 (95% CI, 1.2-1.9), $P < 0.0001$) while DCR was similar for both groups (90% versus 86%). GP prolonged PFS (7.0 versus 5.6 months; hazard ratio = 0.55 (95% CI, 0.44-0.68), $P < 0.0001$). Meta-analysis showed ORR and DCR of GP and FP regimens are similar, while 1-year OS rate of GP regimen is a little lower than taxanes plus platinum regimen but higher than FP regimen. GP regimen prolongs PFS in patients with NPC with recurrence or metastasis (Ma et al 2018). The results establish GP as the standard first-line treatment option for this population.

1.4.2. Rationale for Tislelizumab in the Treatment of NPC With Recurrence or Metastasis

The immune CPI programmed cell death protein-1 (PD-1) and its major ligand PD-L1 are overexpressed in NPC, contributing to immune evasion (Hsu et al 2010; Zhang et al 2015; Lee et al 2016; Zhou et al 2017). Tislelizumab disrupts PD-1-mediated signaling, restoring T-cell antitumor function. Immunotherapy is emerging as a new treatment modality with promising initial data and a robust breadth of ongoing trials. Efficacy with anti-PD-1 observed is yet limited with monotherapy pembrolizumab, nivolumab and JS001 showed efficacy in later line setting (Chiun et al 2017; Ma et al 2017; Wang et al 2017). Preliminary data of tislelizumab in NPC arm of study BGB-A317-102 is encouraging (refer to Section 1.3.4.2 for details).

1.4.3. Rationale for Selection of Tislelizumab Dose in Combination With Chemotherapy

The PK, safety, and efficacy data obtained from the first-in-human study BGB-A317_Study_001, as well as other clinical study data, were analyzed in aggregate to determine the recommended dose for pivotal studies of tislelizumab. The flat dose of 200 mg IV Q3W was selected for further evaluation.

Rates of treatment-related AEs and serious adverse events (SAEs) observed in patients receiving 2 mg/kg and 5 mg/kg Q2W and Q3W were comparable, suggesting no clear dose-dependence across these regimens. Similarly, confirmed ORRs in patients treated with tislelizumab 2 mg/kg and 5 mg/kg Q2W ranged between 10% and 15%, compared to a range of 15% to 38% for patients treated at 2 mg/kg and 5 mg/kg Q3W.

According to PK data from BGB A317_Study_001, Phase 1a, the CL of tislelizumab was found to be independent of body weight, ethnicity, and gender, and the observed serum exposure of a 200-mg dose fell between serum exposure observed after 2 mg/kg and 5 mg/kg doses (dose range with comparable safety and efficacy rates).

Additionally, no unexpected treatment-related AEs occurred in the 200-mg fixed dose cohort (BGB A317_Study_001, Phase 1a, Part 3) when compared to body-weight-based cohorts. Of the evaluable patients treated (n = 13), 3 patients (23%) had a BOR of PR, 4 patients (31%) had a BOR of SD, and 6 patients (46%) had a BOR of progressive disease. Therefore, clinical activity with a manageable and tolerable safety profile is expected to be maintained in patients receiving tislelizumab 200 mg Q3W. This also allows for a convenient integration with common chemotherapeutic regimens.

The doses of all chemotherapy drugs are based on product labelling, literature, and local guidelines. Several Phase 1 and Phase 2 studies showed that the safety profile of anti PD-1 antibodies in combination with carboplatin-based doublet chemotherapy was consistent with that expected in individual agents. There were no known overlapping, significant toxicities or drug–drug interactions between anti-PD-1 antibodies and carboplatin or paclitaxel observed in these studies.

Further, preliminary data from the ongoing Phase 2 BGB-A317-206 study which evaluates the combination of tislelizumab at the fixed dose of 200 mg Q3W with various chemotherapies at the dose of standard of care as treatment for first-line NSCLC (see tislelizumab Investigator's Brochure) supports the dose and schedule.

In conclusion, tislelizumab 200 mg Q3W is the recommended dose for combination with chemotherapy in this Phase 3 global safety study.

1.4.4. Rationale for Matched Placebo in Combination With Chemotherapy as the Comparator

The comparator arm (Arm B) will consist of a chemotherapy doublet in combination with the matched placebo and compared to the same chemotherapy in combination with the study drug tislelizumab. The "matched" placebo will contain the same composition as the solution for the active drug (tislelizumab), except that no active drug will be present in the formulation. The placebo will be used to preserve the scientific integrity of the study and reduce any potential observational or assessment bias. Patients in the placebo arm (Arm B) will still receive the recommended chemotherapy doublet for this patient population, minimizing the risk generally associated with placebo-alone arms in controlled studies.

1.4.5. Rationale for Primary Endpoint of Progression-free Survival as Assessed by the Independent Review Committee

PFS as an endpoint can reflect tumor growth and can be assessed before the determination of a survival benefit; in addition, its determination is generally not confounded by subsequent therapies.

Whether an improvement in PFS represents a direct clinical benefit or a surrogate for clinical benefit depends on the magnitude of the effect and the benefit-risk of the new treatment compared with available therapies (FDA 2007; European Medicines Agency 2012).

New treatment modalities, such as targeted therapies and immunotherapy as monotherapy in patients with highly expressing PD-L1 tumors or in combination with chemotherapy (Langer et al 2016), are emerging as highly effective regimens that are providing improvements in patient outcomes far beyond what has been achieved before (Ellis et al 2014). In particular, immunotherapy has been correlated or associated with durable responses, significant prolongation of PFS, and improvement of quality of life (Langer et al 2016).

The subjectivity in the measurement of PFS assessments is acknowledged with the fact that the assessment depends on frequency, accuracy, reproducibility, and completeness, and may affect the observed magnitude of effect and carry the risk of bias. Therefore, tumor assessment by the IRC per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, scheduled every 6 weeks for the first 6 months, every 9 weeks for the remainder of Year 1, and every 12 weeks from Year 2 onwards, regardless of treatment delay until disease progression, is to be implemented in this study to ensure lack of bias when comparing Arm A versus Arm B.

1.4.6. Rationale for Plasma EBV DNA Measurement

The quantitative real-time polymerase chain reaction method has already been developed to measure the plasma EBV DNA level (Lo et al 2000). A direct relationship between tumor load and plasma EBV DNA concentration is established in NPC patients, therefore it is reasonable to deduce that the change of plasma EBV DNA level would be useful to predict clinical benefit of NPC patients after different therapy (Ma et al 2006). Furthermore, pretreatment plasma EBV DNA was discovered as prognostic biomarker for overall disease-free survival in a previous study (Leung et al 2006). In this study, we will explore the plasma EBV level as a surrogate biomarker for antitumor efficacy prediction, and whether plasma EBV DNA could become a predictive biomarker for PD-1/PD-L1 treatment.

1.4.7. Rationale for Allowing Patients to Continue Tislelizumab Until Loss of Clinical Benefit

Conventional response criteria may not adequately assess the activity of immunotherapeutic agents because progressive disease (determined by initial radiographic evaluation) does not necessarily reflect therapeutic failure. A recent retrospective analysis of the Phase 3 OAK study evaluated 332 NSCLC patients who experienced disease progression per RECIST v1.1 while being treated with atezolizumab (Gandara et al 2017). The results showed that 51% (n = 168) continued treatment with atezolizumab beyond progression. Of those 7% (12/168) achieved subsequent response in target lesions (≥ 30% reduction from new baseline at disease progression) and 49% (83/168) had stable target lesions (best change between +20% and -30%). Median OS was 12.7 months (95% CI: 9.3, 14.9) post progressive disease for patients on atezolizumab treatment beyond progression, with a tolerable safety profile. That is in contrast to median OS of 8.8 months (95% CI: 6.0, 12.1) and 2.2 months (95% CI: 1.9, 3.4) for patients who either received other (n = 94, 28%) or no anticancer treatment (n = 70, 21%), respectively, at the time of progression. These data suggest considerable benefit from continued immunotherapy treatment past disease progression, which may include patients with recurrent or metastatic NPC.

Recent results from Phase 1-2 trials reported manageable safety profiles and favorable antitumor activities (ORR ranged from 20.5% to 43%) of anti-PD-1 drugs, such as pembrolizumab, nivolumab, camrelizumab, toripalimab, and tislelizumab, in patients who have NPC with

recurrence or metastasis and have failure on ≥ 1 line of platinum-based chemotherapies (Hsu et al 2017; Ma et al 2018; Fang et al 2018; Wang et al 2020; Wang et al 2019). These preliminary results arising from both tumor antigen-specific and agnostic immunotherapeutic strategies favor the notion of EBV-positive NPC as a highly immune enriched tumor, which supports extending the consideration of immunotherapy in previously treated patients who have NPC with recurrence or metastasis.

This study will allow patients randomized to the tislelizumab in combination with chemotherapy treatment arm to remain on tislelizumab-containing treatment after apparent radiographic progression, provided the benefit-risk ratio is judged to be favorable. Patients should be discontinued for unacceptable toxicity or symptomatic deterioration attributed to disease progression as assessed by the investigator after an integrated assessment of radiographic data and clinical status (Section 3.3).

This study will allow patients randomized to the placebo in combination with chemotherapy treatment arm to have the opportunity to cross over to receive tislelizumab if they experience radiographic disease progression on chemotherapy; that is, if disease progression per RECIST v1.1 has been confirmed by the IRC and provided the benefit-risk ratio is judged to be favorable and approved by the medical monitor (Section 7.4). Patients should be discontinued for unacceptable toxicity or symptomatic deterioration attributed to disease progression as assessed by the investigator after an integrated assessment of radiographic data and clinical status (Section 3.3).

1.4.8. Rationale for Selection of the Patient-Reported Outcome for Assessments of Health-Related Quality of Life

Patient-reported outcomes (PROs) assessments have been shown to provide the most robust descriptions of the treatment experience, with the incorporation of multiple modes of endpoint measurements in clinical studies, and would supplement the data derived from clinically reported Common Terminology Criteria for Adverse Events (NCI-CTCAE) (Dajczman et al 2008). With growing recognition of the importance of patient-centered care, PROs have also been reported to have positive effects on the well-being of patients with cancer (Basch et al 2016). Evidence of benefits of incorporating PROs in the chemotherapeutic setting, specifically in patients with lung cancer, would further characterize clinical benefit beyond radiographic measures.

Two validated and frequently used PRO instruments have been selected: the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (QLQ-C30) to measure general cancer signs and symptoms, and its head and neck cancer module QLQ-H&N35 to measure nasopharyngeal-specific symptoms.

1.5. Benefit-Risk Assessment

Available data from clinical studies of other anti-PD-1 antibodies, such as nivolumab and pembrolizumab, have demonstrated favorable benefit/risk profiles in patients with advanced NPC (Chiun et al 2017; Ma et al 2017). Preliminary data of tislelizumab in an expansion cohort of patients with NPC in Study BGB-A317-102 is encouraging (refer to Section 1.3.4.2 for details). Preliminary data from the ongoing Phase 2 BGB-A317-206 study, which evaluates the combination of tislelizumab at the fixed dose of 200 mg Q3W with various chemotherapies at

the dose of standard of care as treatment for first-line lung cancer, supports the dose and schedule (Zhao et al 2018).

As of 28 August 2017, 439 patients have been treated with tislelizumab monotherapy at clinically relevant doses (≥ 2 mg/kg) and in combination. Clinical activity with a manageable and tolerable safety profile is expected to be maintained in patients receiving tislelizumab 200 mg Q3W. The safety profile is largely consistent with that of other anti-PD-1 antibodies and included mostly mild/moderate AEs. Very few Grade 3/4 imAEs have been observed and have been generally reversible and manageable with study drug interruption and/or steroid treatment. (For further information on the safety profile of tislelizumab, please refer to the Investigator's Brochure.) Preliminary data from the ongoing Phase 2 BGB-A317-206 study, which evaluates the combination of tislelizumab at the fixed dose of 200 mg Q3W with various chemotherapies at the dose of standard of care as treatment for first-line lung cancer, including tislelizumab in combination with pemetrexed + platinum (n = 16), paclitaxel + platinum (n = 15), gemcitabine + platinum (n = 6), and etoposide + platinum (n = 17), supports the dose and schedule. As of 5 June 2018, the median duration of treatment was 20 weeks; all 54 patients with lung cancer enrolled in the study were evaluated for response, with a total of 35 patients remaining on treatment. Among 54 evaluable NSCLC and small cell lung cancer patients, there were 29 patients with a confirmed response and 17 patients with a BOR of SD. The safety profile of tislelizumab in combination with chemotherapy has been largely consistent with the known tolerability profile of PD-1 inhibitors in combination with chemotherapy (Zhao et al 2018). Therefore, the clinical development of tislelizumab, an anti-PD-1 antibody, in combination with chemotherapy, may improve upon outcomes for Chinese patients with advanced solid tumors, including NPC.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

- 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.

2.1.2. 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.

2.1.3. 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.

2.2. Study Endpoints

2.2.1. Primary Endpoint

- PFS as assessed by the IRC: the time from randomization to the first objectively documented disease progression, or death from any cause, whichever occurs first, as assessed by the IRC per RECIST v1.1 in an ITT analysis set.

2.2.2. Secondary Endpoints

- ORR as assessed by the IRC: the proportion of patients who had CR or PR as assessed by the IRC per RECIST v1.1 in all randomized patients with measurable disease at baseline.
- DOR as assessed by the IRC: 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 IRC per RECIST v1.1 in all randomized patients with documented objective responses.
- OS: the time from the date of randomization to the date of death due to any cause in an ITT analysis set.
- PFS 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 ITT analysis set.
- PFS2 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.
- HRQoL is measured via PRO questionnaires using the EORTC QLQ-C30 and EORTC QLQ-H&N35.
- Incidence and severity of TEAEs graded according to NCI-CTCAE v5.0.

2.2.3. Exploratory Endpoints

- ORR as assessed by the investigator: 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.
- DOR 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.
- DCR: the proportion of patients who had CR, PR, or SD 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 as potential surrogate biomarker for antitumor efficacy prediction with EBV-positive disease.
- Summary of serum concentrations of tislelizumab.
- Assessments of immunogenicity of tislelizumab by determining the incidence of antidrug antibodies.

3. STUDY DESIGN

3.1. Summary of 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 NPC with recurrence or metastasis.

The primary endpoint of the study is measured by PFS as assessed by the IRC in the ITT analysis set.

Patients who have histologically or cytologically confirmed NPC with recurrence or metastasis are eligible.

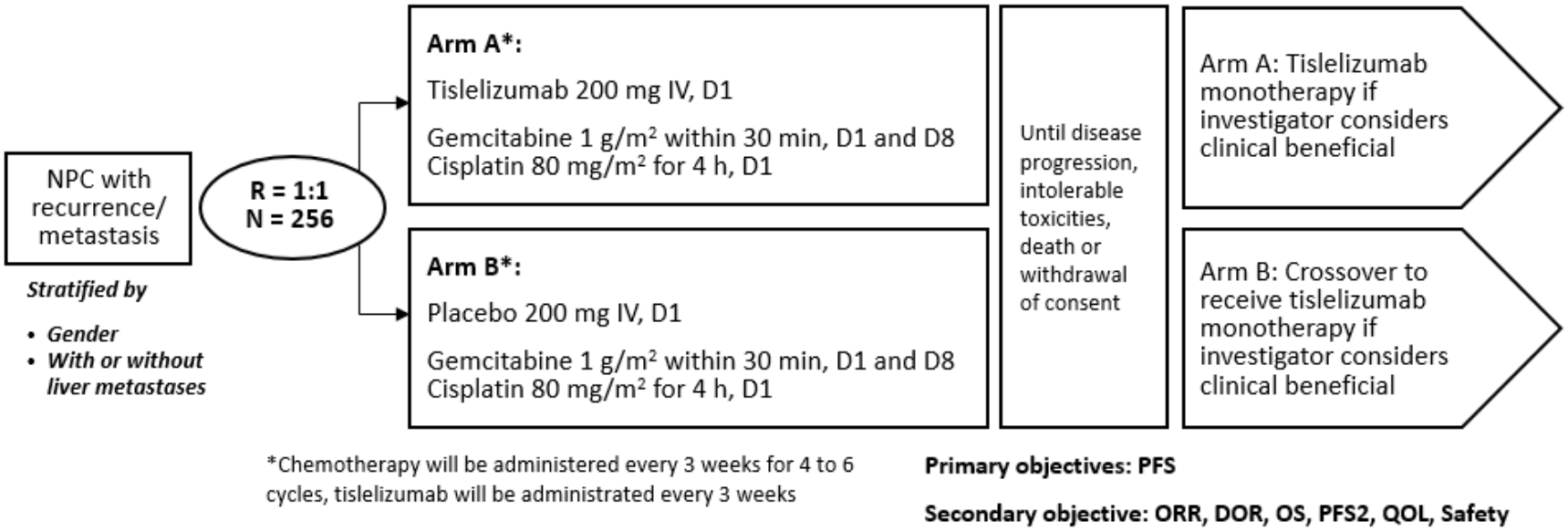
Eligible patients will be stratified by gender and metastatic status (with or without liver metastases), and randomized by a 1:1 ratio to receive one of the following treatment regimens:

- Arm A: tislelizumab + gemcitabine + cisplatin
- Arm B: placebo + gemcitabine + cisplatin

Both Arm A and Arm B will be double blinded.

The study schema is presented in Figure 1.

Figure 1. Study Schema



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, administered as an IV infusion for 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.

For all study procedures see Appendix 1.

3.2. Screening Period

Screening evaluations will be performed within 28 days prior to randomization. Patients who agree to participate in this study will sign the informed consent form (ICF) prior to undergoing any screening procedure. Patients who are suspected to have serious respiratory concurrent illness or exhibit significant respiratory symptoms unrelated to underlying cancer will also take a pulmonary function test (refer to Section 7.1.5 and Appendix 1 for details). Screening evaluations may be repeated as needed within the screening period; the investigator will assess preliminary patient eligibility according to the latest screening assessment results.

3.3. Treatment Period

Patients must be able to provide fresh or archival tumor tissues (formalin-fixed paraffin-embedded [FFPE] blocks or approximately 10 [≥ 5] freshly cut unstained FFPE slides) with an associated pathological report. In the absence of sufficient archival tumor tissues, a fresh biopsy of a tumor lesion at baseline is mandatory (Section 7.8).

Treatment Period

After completing all screening activities, patients confirmed to be eligible by the sponsor will be randomized.

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.

For all patients in Arm A and Arm B, if progression of disease is unconfirmed by the IRC and the patient is clinically stable, it is at the investigator's discretion to continue treating the patient with the assigned treatment per protocol until progression of disease is confirmed at least 28 days (or at the next scheduled tumor assessment) from the date of the scan suggesting progression of disease. If a patient has confirmed progression of disease by RECIST v1.1, as assessed by the IRC, the patient should not receive further chemotherapy treatment on study, and unblinding will be performed. The following guidance should be followed.

For Arm A (Experimental arm):

Patients whose tumors show progressive disease per RECIST v1.1 during chemotherapy combination phase or thereafter while receiving tislelizumab monotherapy will be permitted to continue tislelizumab monotherapy provided that they meet all the following additional criteria, and upon discussion and agreement with the medical monitor:

1. Evidence of clinical benefit as assessed by the investigator;
2. Absence of symptoms and signs (including clinically significant worsening of laboratory values [eg, new, or worsening hypercalcemia]) indicating unequivocal progression of disease;
3. No decline in ECOG performance status that can be attributed to disease progression;
4. Absence of tumor progression at critical anatomical sites (eg, central nervous system [CNS] disease) that cannot be managed by protocol-allowed medical interventions;

5. Patients must provide written consent to acknowledge deferring other treatment options in favor of continuing study treatment at the time of initial progression.

The decision to continue tislelizumab beyond investigator-assessed progression must be documented in the study records.

Patients may continue tislelizumab until loss of clinical benefit as assessed by the investigator, withdrawal of consent, study termination by the sponsor, start of a new anticancer therapy, or death, whichever occurs first.

For Arm B (Control arm):

Patients who develop radiographic disease progression per RECIST v1.1 at an initial or, if continued treatment, at the time of repeat computed tomography (CT) scan, will be given the option to cross over to receive tislelizumab monotherapy (Section 7.4), provided that disease progression has been confirmed by the IRC and as long as the following criteria are met:

1. ECOG performance status ≤ 1;
2. Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, CNS disease) that cannot be managed by protocol-allowed medical interventions;
3. Patient provided written consent to acknowledge that tislelizumab is an experimental treatment used after failure of prior first-line platinum-containing regimen.

Crossover is optional and is at the discretion of the investigator and with the sponsor's agreement.

For Both Arms:

Once patients are receiving tislelizumab monotherapy, the investigator may consider continuing tislelizumab monotherapy beyond investigator-assessed progression, provided that patients meet the above outlined criteria, and upon discussion and agreement with the medical monitor.

The decision to continue tislelizumab beyond investigator-assessed progression must be documented in the study records.

Patients may continue tislelizumab until loss of clinical benefit as assessed by the investigator, withdrawal of consent, study termination by the sponsor, start of a new anticancer therapy, or death, whichever occurs first.

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 of a new anticancer therapy, or death, whichever occurs first.

For patients randomized to Arm B (placebo + gemcitabine + cisplatin arm) who cross over to subsequent tislelizumab monotherapy after initial progression of disease, tumor assessments are to be continued until the subsequent radiographic disease progression as assessed by the

investigator per RECIST v1.1, loss of clinical benefit, withdrawal of consent, study termination by sponsor, start of a new anticancer therapy, or death, whichever occurs first.

To determine the PK properties of tislelizumab and host immunogenic response to tislelizumab, blood samples will be collected at various timepoints as outlined in Appendix 1.

Safety will be assessed throughout the study by monitoring AEs/SAEs (toxicity grades assigned per NCI-CTCAE v5.0), and laboratory results. Vital signs, physical examinations, ECOG performance status change, electrocardiogram (ECG) results, and other examinations will also be used for safety assessment. Safety assessments are further detailed in Section 7.5 and the Schedule of Assessments (Appendix 1).

The End of Treatment Visit is conducted when the investigator determines that tislelizumab or chemotherapy will no longer be used. If routine laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the End of Treatment Visit, these tests need not to be repeated. Tumor assessment is not required at the End of Treatment Visit provided that fewer than 6 weeks have passed since the last assessment.

3.4. Safety Follow-up

Patients who discontinue treatment for any reason will be asked to return to the clinic for the Safety Follow-up Visit (to occur within 30 days [± 7 days] after the last dose of study drug (including chemotherapy-only) or before the initiation of a new anticancer treatment, whichever occurs first. 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 days, and 90 days (± 14 days) after the last dose of study treatment, regardless of whether the patient starts a new anticancer therapy. If patients report a suspected imAE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated.

All AE, including SAEs, will be collected as described in Section 8.6.

The End of Treatment (EOT) Visit at which a response assessment showed progressive disease, resulting in patient discontinuation, may be used as the Safety Follow-up Visit, if it occurred 30 days or more after the last study treatment. Patients who discontinue study treatment prior to disease progression will have their tumors assessed as outlined in Section 7.6.

See Appendix 1 for assessments to be performed at the Safety Follow-up Visit.

3.5. Survival Follow-up

Patients who discontinue study drug for reasons other than disease progression (eg, toxicity) will continue to undergo tumor assessments according to Section 7.6 and the Schedule of Assessments (Appendix 1), until the patient experiences disease progression, withdraws consent, loss to follow-up, death, or until the study completes, whichever occurs first.

Patients will be followed for survival and further anticancer therapy information after discontinuation of study treatment via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (± 14 days) after the Safety Follow-up Visit or as directed by the sponsor until death, loss to follow-up, withdrawal of consent, or study completion by the sponsor.

3.6. Discontinuation From the Study Treatment or From the Study

3.6.1. Discontinuation From Study Treatment

Patients have the right to discontinue study treatment at any time for any reason. In addition, the investigator has the right to discontinue a patient from the study treatment at any time. Patients who discontinue study treatment for reasons other than disease progression, should be followed for assessments of antitumor activity (Section 7.6), safety (Section 7.5) and survival (Section 3.5), if possible.

The primary reason for discontinuation from the study treatment should be documented on the appropriate electronic case report form (eCRF). Patients may discontinue from the study treatment for reasons that include, but are not limited to, the following:

- Radiographic disease progression per RECIST v1.1
- Patient withdrawal of consent
- Pregnancy
- Any medical condition that the investigator determines may jeopardize the patient's safety, if he or she were to continue the study treatment
- Use of any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents [including Chinese herbal medicine and Chinese patent medicines] for the treatment of cancer) (Section 6.2.2).
- Patient noncompliance

3.6.2. Patient Discontinuation from Study (End of Study for an Individual Patient)

Patients may discontinue study for reasons which include, but are not limited to, the following:

- Patient withdrawal of consent
- Death
- Lost to follow-up

  Note: If attempts to contact the patient by telephone are unsuccessful, additional attempts should be made to obtain protocol-required follow-up information. It may be possible to obtain the information from other contacts such as referring physicians or relatives. Attempts of contact should be documented in the patient's source documents. If a patient cannot be contacted despite all attempts, the patient will be considered lost to follow-up, and death information should be obtained through a public record search if local agencies permit.
- Patients have completed all study assessments

3.7. End of Study

The end of study is defined as the timepoint when the final data for a clinical study were collected, which is after the last study patient has made the final visit to the study location.

The sponsor has the right to terminate this study at any time. Reasons for terminating the study early may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients
- Overall patient enrollment is unsatisfactory

The sponsor will notify each investigator if a decision is made to terminate the study. Should this be necessary, prematurely discontinued patients should be seen as soon as possible for an EOT Visit and Safety Follow-up Visit.

The investigators may be informed of additional procedures to be followed to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing Institutional Review Board (IRBs)/Independent Ethics Committees (IECs) of the early termination of the study.

The sponsor has the right to close a site at any time. The decision will be communicated to the site in advance. Reasons for closing a site may include but are not limited to the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Noncompliance with Good Clinical Practice (GCP), applicable laws and regulations
- Study activity is completed (ie, all patients have completed and all obligations have been fulfilled)

4. STUDY POPULATION

The specific eligibility criteria for selection of patients are provided in Section 4.1 and Section 4.2. The sponsor will not grant any eligibility waivers.

4.1. Inclusion Criteria

Each patient eligible to participate in this study must meet all the following criteria:

1. Able to provide written informed consent and can understand and agree to comply with the requirements of the study and the schedule of assessments
2. Aged between 18 to 75 years on the day of signing the informed consent form (or the legal age of consent in the jurisdiction in which the study is taking place)
3. Histologically or cytologically confirmed NPC with recurrence or metastasis
4. Patients must be able to provide fresh or archival tumor tissues (FFPE blocks or approximately 10 [≥ 5] freshly cut unstained FFPE slides) with an associated pathological report. In the absence of sufficient archival tumor tissues, a fresh biopsy of a tumor lesion at baseline is mandatory
5. ECOG performance status ≤ 1
6. Patients must have ≥ 1 measurable lesions as defined per RECIST v1.1
7. Must be treatment-naive for recurrent or metastatic NPC
8. Patients who have received prior neoadjuvant, adjuvant chemotherapy, radiotherapy, or chemoradiotherapy with curative intent for nonmetastatic disease must have experienced a treatment-free interval of ≥ 6 months from the last dose of chemotherapy and/or radiotherapy prior to randomization
9. Patients who have received prior neoadjuvant chemotherapy regimen for < 4 cycles
10. Life expectancy ≥ 12 weeks
11. Adequate organ function as indicated by the following laboratory values (obtained within 7 days prior to randomization):
    a. Patients must not have required a blood transfusion or growth factor support ≤ 14 days before sample collection at screening for any of the following:
        i. Absolute neutrophil count ≥ 1.5 x 10^9/L
        ii. Platelets ≥ 100 x 10^9/L
        iii. Hemoglobin ≥ 90 g/L
        iv. International normalized ratio or prothrombin time ≤ 1.5 x upper limit of normal (ULN)
        v. Activated partial thromboplastin time or partial thromboplastin time ≤ 1.5 x ULN
    b. Serum creatinine ≤ 1.5 x ULN or estimated glomerular filtration rate (GFR) ≥ 60 mL/min/1.73 m^2

c. Serum total bilirubin ≤ 1.5 x ULN (total bilirubin must be < 3 x ULN for patients with Gilbert's syndrome)

d. AST and ALT ≤ 2.5 x ULN or AST and ALT ≤ 5 x ULN for patients with liver metastases

12. Females of childbearing potential must be willing to use a highly effective method of birth control for the duration of the study, and ≥120 days after the last dose of tislelizumab or placebo, and have a negative urine or serum pregnancy test ≤ 7 days before randomization
13. Nonsterile males must be willing to use a highly effective method of birth control for the duration of the study and for ≥120 days after the last dose of tislelizumab or placebo

4.2. Exclusion Criteria

Patients who meet any of the following criteria must be excluded from this study:

1. Patients with locally recurrence suitable for curative surgery or radiotherapy
2. Received any approved systemic anticancer therapy, including hormonal therapy, within 28 days prior to initiation of study treatment. The following exception is allowed:
   - Palliative radiotherapy for bone metastases or soft tissue lesions should be completed > 7 days prior to baseline imaging.
3. Has received any immunotherapy (including but not limited to interferons, interleukin-2, tumor necrosis factor interleukin, and thymoxin) or any investigational therapies within 14 days or 5 half-lives (whichever is longer) of randomization
4. Received prior therapies targeting PD-1 or PD-L1
5. Active leptomeningeal disease or uncontrolled, untreated brain metastasis
   - Patients with a history of treated and, at the time of screening, asymptomatic CNS metastases are eligible, provided they meet all the following:
     - Brain imaging at screening shows no evidence of interim progression
     - Have measurable disease outside the CNS
     - No ongoing requirement for corticosteroids as therapy for CNS disease; anticonvulsants at a stable dose allowed
     - No stereotactic radiation or whole-brain radiation within 14 days prior to randomization
   - Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases.
     - Following treatment, these patients may then be eligible, provided all other criteria, including those for patients with a history of brain metastases, are met.
6. Active autoimmune diseases or history of autoimmune diseases that may relapse

Note: Patients with the following diseases are not excluded and may proceed to further screening:

a. Controlled Type I diabetes
b. Hypothyroidism (provided it is managed with hormone replacement therapy only)
c. Controlled celiac disease
d. Skin diseases not requiring systemic treatment (eg, vitiligo, psoriasis, alopecia)
e. Any other disease that is not expected to recur in the absence of external triggering factors

7. Any active malignancy ≤ 2 years before randomization except for the specific cancer under investigation in this study and any locally recurring cancer that has been treated curatively (eg, resected basal or squamous cell skin cancer, superficial bladder cancer, carcinoma *in situ* of the cervix or breast)
8. Any condition that required systemic treatment with either corticosteroids (> 10 mg daily of prednisone or equivalent) or other immunosuppressive medication ≤ 14 days before randomization

   Note: Patients who are currently or have previously been on any of the following steroid regimens are not excluded:

   a. Adrenal replacement steroid (dose ≤ 10 mg daily of prednisone or equivalent)
   b. Topical, ocular, intra-articular, intranasal, or inhaled corticosteroid with minimal systemic absorption
   c. Short course (≤ 7 days) of corticosteroid prescribed prophylactically (eg, for contrast dye allergy) or for the treatment of a non-autoimmune condition (eg, delayed-type hypersensitivity reaction caused by contact allergen)
9. With uncontrolled diabetes or > Grade 1 laboratory test abnormalities in potassium, sodium, or corrected calcium despite standard medical management or ≥ Grade 3 hypoalbuminemia ≤ 14 days before randomization
10. With history of interstitial lung disease, non-infectious pneumonitis or uncontrolled diseases including pulmonary fibrosis, acute lung diseases, hypertension, etc
11. With severe chronic or active infections (including tuberculosis infection, etc) requiring systemic antibacterial, antifungal or antiviral therapy within 14 days prior to randomization or first dose of study drugs
12. A known history of HIV infection
13. Patients with untreated chronic hepatitis B or chronic hepatitis B virus (HBV) carriers whose HBV DNA is ≥ 500 IU/mL or patients with active hepatitis C virus (HCV) should be excluded. Note: Inactive hepatitis B surface antigen (HBsAg) carriers, treated and stable hepatitis B (HBV DNA < 500 IU/mL), and cured hepatitis C patients can be enrolled.
14. Any major surgical procedure requiring general anesthesia ≤ 28 days before randomization
15. Prior allogeneic stem cell transplantation or organ transplantation

16. Any of the following cardiovascular risk factors:
    a. Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living ≤ 28 days before randomization
    b. Symptomatic pulmonary embolism ≤ 28 days before randomization
    c. Any history of acute myocardial infarction ≤ 6 months before randomization
    d. Any history of heart failure meeting New York Heart Association Classification III or IV (Appendix 6) ≤ 6 months before randomization
    e. Any event of ventricular arrhythmia ≥ Grade 2 in severity ≤ 6 months before randomization or first dose of study drug
    f. Any history of cerebrovascular accident ≤ 6 months before randomization or first dose of study drug
17. A history of severe hypersensitivity reactions to other monoclonal antibodies
18. Patients with toxicities (as a result of prior anticancer therapy) which have not recovered to baseline or stabilized, except for AEs not considered a likely safety risk (eg, alopecia, neuropathy and specific laboratory abnormalities)
19. History of allergic reactions to cisplatin, or other platinum-containing compounds
20. ≥ Grade 2 peripheral neuropathy, as defined by NCI-CTCAE v5.0 criteria
21. Was administered a live vaccine ≤ 4 weeks before randomization

Note: Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines, and are not allowed

22. Underlying medical conditions (including laboratory abnormalities) or alcohol or drug abuse or dependence that, will be unfavorable for the administration of study drug or affect the explanation of drug toxicity or AEs or result in insufficient or might impair compliance with study conduct
23. Concurrent participation in another therapeutic clinical study

5. STUDY TREATMENT

5.1. Formulation, Packaging, and Handling

5.1.1. Tislelizumab

Tislelizumab is a monoclonal antibody formulated for IV injection in a single-use vial (20R glass, United States Pharmacopeia type I), containing a total of 100 mg of antibody in 10 mL of isotonic solution. Tislelizumab has been aseptically filled in single-use vials with a Flurotec-coated butyl rubber stopper and an aluminum cap. Each vial is packaged into a single carton box.

The contents of the label will be in accordance with all applicable local regulatory requirements.

The study drug must be kept at the temperature condition as specified on the label.

Refer to the Pharmacy Manual for details regarding IV administration, accountability, and disposal. Please also refer to the tislelizumab Investigator's Brochure for other details regarding tislelizumab.

5.1.2. Matched Placebo

Matched placebo will be provided in a single-use vial (20R glass, United States Pharmacopeia type I), containing 10 mL of isotonic solution. These single-use vials contain a Flurotec-coated butyl rubber stopper and an aluminum cap. Each vial is packaged into a single carton box.

The contents of the label will be in accordance with all applicable local regulatory requirements.

The vials must be kept at the temperature condition as specified on the label.

Refer to the Pharmacy Manual for details regarding IV administration, accountability, and disposal.

5.1.3. Chemotherapy Agents

Management (ie, labelling, handling, storage, administration, and disposal) of these products will be in accordance with the relevant local guidelines and/or prescribing information.

For further details, see the manufacturer's prescribing information for the respective chemotherapy agents.

5.2. Dosage, Administration, and Compliance

Dosing schedules for all study arms, broken out by individual arm, are provided in Table 2. The first dose of study drug is to be administered within 2 business days of randomization. All patients will be monitored continuously for AEs. Treatment modifications (eg, dose delay, reduction, interruption or discontinuation) will be based on specific laboratory and AE criteria, as described in Section 5.5.

For each cycle, tislelizumab or placebo will be administered before chemotherapy drugs. The order of chemotherapy drug administration will be conducted in accordance with the relevant local guidance and/or clinical practice.

Patients should receive antiemetics and IV hydration for cisplatin-based doublet treatments according to the local standard of care and manufacturer's instruction. Due to their immunomodulatory effects, premedication with steroids should be limited when clinically feasible. Dexamethasone is recommended to be administrated 7.5 mg once daily for 3 days as premedication. In addition, in the event of chemotherapeutic agent-related skin rash, topical steroid use is recommended as front-line treatment whenever it is clinically feasible.

In special situations (eg, when the administration is delayed due to management of adverse events or in the case of an infusion-related reaction), administration of the subsequent study drugs might be delayed to the second day of each cycle.

Table 2. Selection and Timing of Dose for Each Patient

Study drug	Dose	Frequency of administration	Route of administration	Duration of treatment
Tislelizumab or placebo	200 mg	Day 1 of each cycle	Intravenous	See Section 3.3
Gemcitabine	1 g/m^2	Day 1, Day 8 of each cycle	Intravenous	
Cisplatin	80 mg/m^2	Day 1 of each cycle	Intravenous	

Chemotherapy will be administered on a 3-week cycle.

The number of treatment cycles (4 to 6) will be at the discretion of the investigator.

5.2.1. Tislelizumab

Tislelizumab 200 mg will be administered on Day 1 of each 21-day cycle (once every 3 weeks).

Tislelizumab will be administered by IV infusion through an IV line containing a sterile, non-pyrogenic, low-protein-binding 0.2 or 0.22 micron in-line or add-on filter. Specific instructions for product preparation and administration are provided in the Pharmacy Manual.

As a routine precaution, after infusion of tislelizumab on Day 1 of Cycle 1 and Cycle 2, patients must be monitored for at least 60 minutes afterward in an area with resuscitation equipment and emergency agents before chemotherapy. From Cycle 3 onward, a ≥ 30-minute monitoring period is required in an area with resuscitation equipment and emergency agents before chemotherapy.

The initial infusion (Cycle 1, Day 1) will be delivered for over 60 minutes; if this is well tolerated, then the subsequent infusions may be administered for over 30 minutes, which is the shortest time period permissible for infusion. Tislelizumab must not be concurrently administered with any other drug (refer to Section 6).

Guidelines for dose modification, treatment interruption, or discontinuation and for the management for imAEs and infusion-related reactions are provided in details in Section 5.5, Section 8.7 and Appendix 7.

Refer to the Pharmacy Manual for detailed instructions on drug preparation, storage, and administration.

5.2.2. Matched Placebo

Patients will be randomized to receive tislelizumab or matched placebo in a double-blind fashion in Arm A and Arm B such that neither the investigator nor the patient, medical or ancillary

medical staff, or blinded sponsor staff and designees will know which drug is being administered in addition to chemotherapy. Administration of the matched placebo will follow the guidance given for tislelizumab, as described in Section 5.2.1.

Refer to the Pharmacy Manual for detailed instructions on drug preparation, storage, and administration.

5.2.3. Chemotherapy

Cisplatin will be administered after completion of gemcitabine.

Gemcitabine l g/m^2 will be administered as an IV infusion within 30 minutes on Day 1 and Day 8 of each cycle, for 4 to 6 cycles. In addition, all patients should receive the appropriate premedications as per the local approved label. Additional premedications should be administered as per standard practice.

Cisplatin 80 mg/m^2 is suggested to be administered as an IV infusion for 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 on Day 1 of each cycles for 4 to 6 cycles. All patients should receive adequate hydration (including pre-treatment hydration) and diuretics. Urinary output > 2000 mL must be maintained in the following 24 hours of the infusion.

Patients will be monitored continuously for AEs and will be instructed to notify their physician immediately for any AEs. Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of chemotherapy therapy. Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.5.

5.3. Overdose

Any overdose (defined as ≥ 600 mg of tislelizumab or placebo in a 24-hour period) or incorrect administration of study drug should be noted in the patient's chart and on the appropriate eCRF. AEs associated with an overdose or incorrect administration of study drug will be recorded on the AE eCRF. Any SAEs associated with an overdose or incorrect administration are required to be reported within 24 hours of awareness via SAE reporting process as described Section 8.6. Supportive care measures should be administered as appropriate.

5.4. Investigational Medicinal Product Accountability

The investigational medicinal products (IMPs) required for completion of this study (tislelizumab or placebo, gemcitabine, and cisplatin) will be provided by the sponsor, as required by local or country-specific guidance. The investigational site will acknowledge receipt of IMPs. Any damaged shipments will be replaced.

Accurate records of all IMP received, dispensed, returned, and disposed should be recorded on the site's Drug Inventory Log. Refer to the Pharmacy Manual for details of IMP management.

5.5. Dose Delay, Interruption and Modification

Dose delay is defined as interruption of the treatment regimen (ie, the drug is withheld beyond visit window). Dose interruption is defined as an interruption of infusion.

Every effort should be made to administer tislelizumab or placebo and chemotherapies on the same day according to the planned dose and schedule (see Appendix 1), and as the patient's condition allows. In the event of significant toxicities, dosing may be delayed and/or reduced based on the guidelines provided below. Reasons for dose modifications or delays, the supportive measures taken, and the outcome will be documented in the patient's chart and recorded in the eCRF.

The tumor assessment schedule (see Appendix 1) will not be altered if chemotherapy or tislelizumab or placebo are delayed or discontinued.

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (eg, elective surgery, unrelated medical events, patient vacation, and/or holidays). Patients should continue study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the sponsor.

5.5.1. General Guidance Regarding Dose Modifications

The severity of adverse events will be graded according to the NCI-CTCAE v5.0 grading system.

- Dose modifications for chemotherapy should be performed per prescribing information and per local practice according to the treating physician's clinical judgment (please see Section 5.5.3).
- Tislelizumab or placebo might be delayed as defined in Section 5.5.2.
- For any adverse events already apparent at baseline, the dose modifications will apply according to the corresponding shift in toxicity grade, if the investigator feels it is appropriate. For example, if a patient has Grade 1 asthenia at baseline that increases to Grade 2 during treatment, this will be considered a shift of 1 grade and treated as Grade 1 toxicity for dose-modification purposes.
- When several toxicities with different grades of severity occur at the same time, the dose modifications should be according to the highest grade observed.
    - If one component of the chemotherapy regimen is held due to AE, the other component will also be held until AE resolution permits continuation of both components of the chemotherapy regimen. Tislelizumab or placebo may continue as indicated.
    - If both components of the chemotherapy are withheld because of toxicity for more than 2 cycles, chemotherapy should be discontinued; tislelizumab or placebo may be continued if the toxicity resulting in chemotherapy discontinuation is not considered by the investigator to be related to tislelizumab. Exceptions based on clinical benefit require the prior approval of the medical monitor.
    - If tislelizumab or placebo is discontinued permanently during the 4 to 6 cycles of chemotherapy treatment, the patient may continue the chemotherapy.
- Administration of chemotherapy should ideally remain synchronized with pre-defined cycles and tislelizumab or placebo infusions (Section 5.2.1, Section 5.2.2).

- If chemotherapy related toxicities warrant dose delays, chemotherapy administration should be restarted to ideally coincide with the next treatment cycle or may be given during an unscheduled visit and resynchronized at later cycle, if possible. For example, if chemotherapy related toxicity resolves on Day 7, chemotherapy may be administered that day and resynchronized as permissible at next or subsequent cycle; if chemotherapy related toxicity resolves on Day 14, chemotherapy may be administered on Day 1 of the next planned cycle.

- Following either completion of, or discontinuation from chemotherapy, tislelizumab or placebo should be continued as scheduled, if clinically appropriate (Section 3.3).
- Dose modification guidelines for chemotherapy, described below (Section 5.5.3), depend on the severity of toxicity and an assessment of the risk versus benefit for the patient, with the goal of maximizing the patient's compliance and access to supportive care.

5.5.2. Dose Interruption or Delay for Tislelizumab

There will be no dose reduction for tislelizumab or placebo in this study.

Patients may temporarily suspend study treatment if they experience toxicity that is considered related to tislelizumab or placebo and requires a dose to be withheld. The patients should resume tislelizumab or placebo treatment as soon as possible after the AEs recover to baseline or Grade 1 (whichever is more severe) and within 12 weeks after last dose of tislelizumab or placebo. If the patient is unable to resume tislelizumab or placebo within 12 weeks after the last dose of tislelizumab or placebo, then the patient should be discontinued from treatment.

If a patient is benefiting from the study treatment while meeting the discontinuation criteria, resumption of study treatment may occur upon discussion and agreement with the medical monitor.

Dose modification related to imAEs and infusion-related reactions are described in Appendix 7 and Section 8.7.1, respectively.

If a dose is delayed for tislelizumab or placebo for ≤ 10 days for a planned dosing cycle (eg, Cycle 3 Day 1), tislelizumab or placebo should be administered. If the delay is > 10 days, the patient should skip the tislelizumab or placebo dose, and tislelizumab or placebo will be administered on Day 1 of the next planned cycle (ie, Cycle 4 Day 1).

5.5.3. Dose Modifications of Chemotherapy Treatment

Dose modifications for chemotherapy should be performed per prescribing information and per local practice according to the treating physician's clinical judgment.

- Baseline body weight is used to calculate the required chemotherapy doses. Dose modifications are required if the patient's body weight changes by > 10% from baseline (or the new reference body weight). Chemotherapy doses should not be modified for any body weight change of less than 10%.

- Study-drug-related toxicities are highly recommended to be resolved to baseline or Grade 0-1 prior to administering the next dose, except for alopecia or Grade 2 fatigue. A maximum of 2 dose reductions for each chemotherapeutic agent is allowed. Once the dose has been decreased, it should remain reduced for all subsequent administrations or further reduced if necessary. There will be no dose escalations in this study. If additional reductions are required, that chemotherapeutic agent must be discontinued.
- Chemotherapy treatment may be delayed up to 21 days, if the reason for the delay is toxicity/AE. All subsequent chemotherapy doses must be rescheduled according to the last chemotherapy dose administration date.

Dose modification of gemcitabine and cisplatin: restart at 75% of the initial or previous dose for patients who had Grade 3 or 4 hematological and non-hematological AE that resolved to NCI-CTCAE < Grade 2. For patients with neutropenia, Day 8 gemcitabine could be given at a reduced dose or postponed for up to 5 days to allow for recovery, otherwise it should be skipped.

SELECTED PRECAUTIONS:

- Neutropenia: Fever or other evidence of infection must be assessed promptly and treated aggressively following the local clinical practice and/or the guidelines.
  - Renal toxicity: nephrotoxicity is common with cisplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside antibiotics.
  - Hemolytic uremic syndrome can occur in patients treated with gemcitabine. Hemolytic uremic syndrome was reported in 0.25% of patients. Most fatal cases of renal failure were due to hemolytic uremic syndrome.
- Ototoxicity and sensory neural damage should be assessed prior to each cycle. Cisplatin is contraindicated in patients with a pre-existing hearing deficit.
- Prolongation of the infusion time of gemcitabine beyond 60 minutes resulted in an increased incidence of clinically significant hypotension, severe flu-like syndromes etc. It is recommended that gemcitabine infusion time is limited to 30 minutes.
- Pulmonary toxicity has been reported in patients who were treated with gemcitabine. In some cases, these events can lead to fatal respiratory failure.
- Capillary leak syndrome with severe consequences has been reported in patients treated with gemcitabine.
- Posterior reversible encephalopathy syndrome has been reported in patients receiving gemcitabine. Posterior reversible encephalopathy syndrome can present with unspecific neurological symptoms.
- For toxicities not listed above, dose modifications are permitted per local standards.
- For cisplatin, dose modification should be based on the prechemotherapy creatinine clearance rate (CCR) in every cycle, calculated with the Cockcroft-Gault formula.
  - If CCR is higher than or equal to 60 mL/min, cisplatin should be given at full dose.

  - If CCR is between 41 mL/min and 59 mL/min, an equal dose to the CCR value (mg/m²) should be applied.
  - If CCR is less than 41 mL/min, cisplatin should be stopped in the current cycle and the dose of cisplatin should be evaluated in the next cycle.
- Recommended premedication for cisplatin is dexamethasone 7.5 mg once daily for three days.

Guidance regarding dose modifications for certain toxicities is presented in detail in Appendix 10.

5.6. Criteria for Discontinuing Chemotherapy Regimens

Except where specified above, both chemotherapy drugs in the cisplatin-based doublet regimen should be discontinued for any of the following:

- Any Grade 3 peripheral neuropathy.
- Persistent Grade 3 paraesthesia.
- Grade 3 or 4 drug-related thrombocytopenia associated with clinically significant bleeding
- Any drug-related liver function test abnormality value that meets any of the following criteria requires discontinuation:
  - AST or ALT > 5 to 10 x ULN for > 2 weeks
  - AST or ALT > 10 x ULN or
  - Total bilirubin > 5 x ULN or
  - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Any cisplatin-related decrease in creatinine clearance to <30 mL/min (using the Cockroft-Gault formula) requires discontinuation of cisplatin.
- Any drug-related AE that recurs after 2 prior dose reductions for the same drug-related AE requires discontinuation of the drug(s).
- Any Grade 3 or 4 drug-related hypersensitivity reaction or infusion reaction requires discontinuation of the drug(s) assessed to be causing the reaction. If the drug is assessed as not related to the hypersensitivity reaction or infusion reaction, it may be continued.
- Any Grade 4 AE that the investigator considers related to study drug and inappropriate to be managed by dose reduction(s) requires discontinuation of drug(s). If the drug is not assessed to be related to the event it may be continued.
- If any toxicity does not resolve within 21 days, that component will be discontinued.

For toxicities not listed above, the investigator's medical judgment would determine whether chemotherapy regimen should be discontinued, in accordance with patient's well-being and local standards.

Refer to Section 3.4 regarding safety follow-up procedures.

5.7. Blinding

This is a randomized, double-blind, placebo-controlled Phase 3 study.

Patients will be randomized to receive tislelizumab or matched placebo in a double-blind fashion in Arm A and Arm B such that neither the investigator, nor the patient, nor medical or ancillary medical staff, nor the blinded sponsor staff or its designees, will know which drug is being administered in addition to chemotherapy.

Emergency unblinding

Emergency unblinding for AEs may be performed through an Interactive Web Response System.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Sponsor medical monitor prior to unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient. If a patient's treatment assignment is unblinded, the sponsor must be notified immediately.

Inadvertent unblinding

Every effort will be made to blind both the patient and the investigator to the identity of tislelizumab or placebo, but the inadvertent unblinding of a patient may occur. If an investigator, site personnel performing assessments, or patient is unblinded, the unblinding will not be sufficient cause (in and of itself) for that patient to be discontinued from study therapy or excluded from any safety or efficacy analyses.

Additionally, there may be ethical reasons to have the patient remain on the study treatment. For patients to continue on study treatment in the event of unblinding, the investigator must obtain specific approval from the Sponsor medical monitor for the patient to continue in the study.

6. PRIOR AND CONCOMITANT THERAPY

6.1. Prior Therapy

The exclusion criteria (Section 4.2) specify that patients will not have received prior systemic therapies targeting PD-1 or PD-L1.

6.2. Concomitant Therapy

6.2.1. Permitted Concomitant Medications

Most concomitant medications and therapies deemed necessary and in keeping with local standards of medical care at the discretion of the investigator for the supportive care (eg, anti-emetics, antidiarrheals) and in a patient's interest are allowed. Patients should receive full supportive care, including epoetin and other hematopoietic growth factors, transfusions of blood and blood products, antibiotics, antiemetics, and/or other applicable medications, as needed.

Systemic corticosteroids given for the control of imAEs must be tapered gradually (Appendix 7) and be at nonimmunosuppressive doses (≤ 10 mg/day of prednisone or equivalent) before the next tislelizumab or placebo administration. The short-term use of steroids as prophylactic treatments (eg, patients with contrast allergies to diagnostic imaging contrast dyes) is permitted.

Bisphosphonates and Receptor activator of nuclear factor kappa-B ligand inhibitors are allowed for bone metastases if initiated prior to enrollment and at a stable dose. Bisphosphonates are permitted during the study for a nonmalignant indication.

Whole-brain radiation therapy and stereotactic radiosurgery are permitted for patients with disease progression limited to the CNS. Palliative (limited-field) radiation therapy is permitted, but only for pain control or prophylaxis of bone fracture to sites of bone disease present at baseline provided the following criteria are met:

- Repeat imaging demonstrates no new sites of bone metastases
- The lesion being considered for palliative radiation is not a target lesion for RECIST v1.1.
- The case is discussed with the medical monitor, and the medical monitor agrees that the conditions required to receive palliative radiation are met.

Additionally, palliative radiation or other focally ablative therapy for other non-target sites of the disease is permitted if clinically indicated per investigators' discretion and after consultation with the medical monitor. Whenever possible, these patients should have a tumor assessment of the lesion(s) before receiving the radiotherapy in order to rule out progression of disease.

6.2.2. Prohibited Concomitant Medications/Procedures

The following medications are prohibited during the study:

- Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents [including Chinese (or other Country) herbal medicines and Chinese patent medicines] for the treatment of cancer is not allowed.

- Live vaccines within 28 days before randomization and 60 days following the last dose of study drug(s).
- Herbal remedies with immune-stimulating properties (ie, mistletoe extract) or that are known to potentially interfere with liver or other major organ functions (ie, hypericin). Patients must notify the investigator of all herbal remedies used during the study.

6.2.3. Restricted Concomitant Medications/Procedures

The following medications are restricted during the study:

- Immunosuppressive agents (except to treat a drug-related AE).
- Systemic corticosteroids > 10 mg daily (prednisone or equivalent), except to treat or control a drug-related AE (per protocol) or for short-term use as prophylactic treatment.
- Patients should avoid alcohol completely and should avoid other addictive drugs during the study.
- Use of potentially hepatotoxic drugs in patients with impaired hepatic function should be carefully monitored.
- Radiation therapy is not allowed, except for palliative radiation therapy described in Section 6.2.1.

Opiates and other medication required for palliative management of patients are allowed. Patients must notify the investigator of all concurrent medications used during the study.

6.3. Potential Interactions Between the Study Drugs and Concomitant Medications

The potential for drug-drug interaction between the study drugs (tislelizumab) and small-molecule drug products is very low, given that tislelizumab is a therapeutic monoclonal antibody. Because tislelizumab is expected to be degraded into amino acids and recycled into other proteins, it is unlikely to influence drug metabolizing enzymes or transporters.

The major route of elimination of cisplatin is renal excretion. Cisplatin produces cumulative nephrotoxicity which is potentiated by aminoglycoside antibiotics. The serum creatinine, blood urea nitrogen, creatinine clearance, and magnesium, sodium, potassium, and calcium levels should be measured prior to initiating therapy, and prior to each subsequent course.

Plasma levels of anticonvulsant agents may become subtherapeutic during cisplatin therapy. In a randomized trial in advanced ovarian cancer, response duration was adversely affected when pyridoxine was used in combination with altretamine (hexamethylmelamine) and cisplatin.

7. STUDY ASSESSMENTS AND PROCEDURES

A table of scheduled study assessments is provided in Appendix 1. Patients will be closely monitored for safety and tolerability throughout the study. All assessments must be performed and documented in the medical record for each patient.

Dosing will occur only if the clinical assessment and local laboratory test values (that must be available before any dosing) have been reviewed and found to be acceptable per protocol guidelines.

7.1. Screening

Screening evaluations will be performed within 28 days prior to randomization. Patients who agree to participate will sign the ICF prior to undergoing any screening procedure. The screening period begins on the first day a screening procedure is conducted. Patients who are suspected or known to have serious respiratory concurrent illness or exhibit significant respiratory symptoms unrelated to underlying cancer should take a pulmonary function test (refer to Appendix 1 for details). Screening evaluations may be repeated as needed within the screening period; the investigator will assess patient eligibility according to the latest screening assessment results.

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 unless otherwise indicated.

Procedures conducted during the Screening Visit only are described in this section. For the description of other assessments that are conducted during screening, as well as throughout the study, refer to Safety Assessments (Section 7.5), Tumor and Response Evaluations (Section 7.6), and Biomarkers (Section 7.8).

Rescreening under limited conditions may be allowed after consultation with BeiGene: eg, when a patient narrowly misses a laboratory criterion and it is correctable and not due to rapidly deteriorating condition or disease progression. Rescreening is allowed only once.

7.1.1. Demographic Data and Medical History

Demographic data will include year of birth (or age), gender, and self-reported race/ethnicity.

Medical history includes any history of clinically significant disease, surgery, or cancer history; reproductive status (ie, of childbearing potential or no childbearing potential); history of alcohol consumption and tobacco (ie, former or current or never); and all medications (eg, prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 30 days before randomization.

Cancer history will include an assessment of prior surgery, prior radiotherapy, and prior drug therapy including start and stop dates, best response, and reason for discontinuation. Radiographic studies performed prior to study entry may be collected for review by the investigator.

7.1.2. Females of Childbearing Potential and Contraception

Childbearing potential is defined as being physiologically capable of becoming pregnant. Refer to Appendix 9 for contraception guidelines and definitions of "Women of Childbearing Potential" and "No Childbearing Potential."

7.1.3. Informed Consent and Screening Log

Voluntary, written, informed consent for participation in the study must be obtained before performing any study-specific procedures. The ICFs for enrolled patients and for patients who are screened but not enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

7.1.4. Patient Numbering

After obtaining informed consent, study site personnel will access the Interactive Response Technology (IRT) system to assign a unique patient number to a potential study participant.

7.1.5. Pulmonary Function Tests

Patients who are suspected or known to have serious/severe respiratory conditions or exhibit significant respiratory symptoms unrelated to the underlying cancer will undergo pulmonary function testing (Pellegrino et al 2005) which may include, but is not limited to: spirometry and assessment of diffusion of oxygenation (at a minimum pulse oximetry at rest and with exercise), or alternatively, assessment of diffusion capacity, during the Screening period to assist the determination of suitability on the study.

Tests may be repeated as clinically indicated while on study (refer to Appendix 1 for details).

7.2. Enrollment

7.2.1. Confirmation of Eligibility

The investigator will assess, and the sponsor will confirm, the eligibility of each patient. All screening procedure results and relevant medical history must be available before eligibility can be determined. All inclusion criteria must be met and none of the exclusion criteria may apply. No eligibility waivers will be granted.

After a patient is screened and the investigator determines the patient is eligible for randomization (or enrollment), study site personnel will complete an Eligibility Authorization Packet and send it to the medical monitor or designee to approve the enrollment. Study site personnel should ensure that a medical monitor's confirmation has been received before randomization.

7.2.2. Randomization

Site personnel will access the IRT system to randomize the patient to treatment assignment and assign study drugs. Study treatment must commence within 2 business days after randomization/treatment assignment.

7.3. Tislelizumab, Placebo and Chemotherapy Dispensation

Tislelizumab or placebo and chemotherapy treatments will be dispensed and administered as described in Section 5.2.

7.4. Crossover

7.4.1. Crossover for Patients in Chemotherapy in Arm B With Documented and IRC Confirmed Disease Progression

For patients who experience disease progression, unblinding is indicated. Patients who are randomized into the chemotherapy arm (Arm B) will have the opportunity to cross over to receive tislelizumab if they experience radiographic disease progression on chemotherapy; that is, if disease progression per RECIST v1.1 has been confirmed by the IRC and approval by the medical monitor has been obtained. Patients who permanently discontinue chemotherapy due to an AE, withdrawal of consent, or for any reason other than progressive disease will not be eligible for crossover. Crossover patients should not initiate treatment with tislelizumab prior to resolution of treatment-related toxicities to ≤ Grade 1 (NCI-CTCAE) or baseline, with the exception of select chemotherapy-related toxicities such as hair loss, but should be initiated within 42 days (if applicable), and upon consultation with the medical monitor.

Patients who develop radiographic disease progression per RECIST v1.1 will be allowed to cross over to start tislelizumab provided that patients meet all the following criteria:

1. ECOG performance status ≤ 1
2. Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, CNS disease) that cannot be managed by protocol-allowed medical interventions
3. Patient provided written consent to acknowledge that tislelizumab is an experimental treatment used after failure of prior first-line platinum-containing regimen

Crossover is optional and is at the discretion of the investigator with the sponsor's agreement.

7.4.2. Crossover Assessments and Procedures

If a patient experiences radiographic disease progression per RECIST v1.1 while on chemotherapy (Arm B) the investigator should discuss treatment options with the patient, including the option to continue chemotherapy until confirmation of progression (Section 3.3), and determine whether there is desire and the patient meets criteria to cross over to tislelizumab monotherapy. If that is the case, the patient's informed consent needs to be obtained. Note that radiographic imaging scans must be the most recent at time of progressive disease and, if not already transmitted, at minimum at time of baseline and sum of the longest diameter nadir.

Procedures and assessments obtained at the time of assessing progressive disease may be used as appropriate for the start of the crossover phase of the study.

The tumor imaging used to determine progressive disease can be used as the new baseline imaging for the crossover phase if:

1. it occurred within 28 days prior to receiving the first dose of tislelizumab monotherapy, and
2. no study treatment was administered between the imaging and the first dose of tislelizumab monotherapy,

Otherwise a new baseline imaging must be performed prior to tislelizumab monotherapy treatment.

All the visits and safety assessments for patients who cross over to tislelizumab monotherapy should follow the schedule upon previously original Cycle 1 Day 1 before crossover; data for biomarkers other than EBV-DNA, as well as PK and ADA, will be nevertheless not required to be collected.

Patients who permanently discontinue the crossover phase will follow the same Safety Follow-up and Survival Follow-up periods.

7.5. Safety Assessments

7.5.1. Vital Signs

Vital signs will include measurements of body temperature (˚C), pulse rate, and blood pressure (systolic and diastolic) while the patient is in a seated position after resting for 10 minutes.

Height (baseline only) and weight should be measured and recorded in the eCRF.

For the first 2 infusions of tislelizumab or placebo, the patient's vital signs should be determined within 60 minutes before starting the infusion, at least once during the infusion, and 30 minutes following completion of the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before infusion and, if clinically indicated, during and 30 minutes after the infusion. Patients will be informed about the possibility of delayed postinfusion symptoms and instructed to contact their study physician if they develop such symptoms. Refer to Section 5.2.1 regarding precautionary monitoring of patients postinfusion of tislelizumab or placebo.

7.5.2. Physical Examinations

During the Screening Visit, a complete physical examination will be conducted including evaluation of 1) head, eyes, ears, nose, throat; 2) cardiovascular; 3) dermatological; 4) musculoskeletal; 5) respiratory, 6) gastrointestinal; and 7) neurological systems. Any abnormality identified during screening will be graded according to NCI-CTCAE v5.0 and recorded on the Medical History eCRF with appropriate disease/condition terms.

In addition, investigators should solicit patients regarding changes in vision, visual disturbance, or ocular inflammation at each scheduled study visit during study treatment. For any change in vision, referral to an appropriate specialist will be made for further management guidance (Appendix 7).

At subsequent visits (and as clinically indicated), limited, symptom-directed physical examinations will be performed. Changes from baseline will be recorded. New or worsened

clinically significant abnormalities are to be recorded as AEs on the eCRF. Refer to Section 8.3 regarding AE definitions and reporting and follow-up requirements.

7.5.3. Eastern Cooperative Oncology Group Performance Status

ECOG performance status (Appendix 3) will be assessed during the study.

7.5.4. Laboratory Safety Tests

Laboratory assessments of serum chemistry, hematology, coagulation, cardiac enzymes, and urinalysis will be conducted, of which certain elements will be collected as specified in Appendix 2.

If laboratory tests for serum chemistry, hematology, coagulation, cardiac enzymes, and urinalysis at screening are not performed within 7 days prior to the administration of study drug(s) on Cycle 1 of Day 1, these tests should be repeated and reviewed before study drug(s) administration. Hematology and serum chemistry (including liver function tests) as specified in Appendix 2 should be performed and reviewed prior to dosing of each treatment cycle, as clinically indicated during the treatment cycle, and upon discontinuation of chemotherapy. After Cycle 1, results are to be reviewed within 48 hours before study drug administration, and a minimum laboratory test to support dosing decision must include hematology and serum chemistry parameters.

Details about sample collection and shipment will be provided in a separate instruction manual. Investigators may use results from local laboratories for assessing eligibility, safety monitoring and dosing decision.

Total creatinine kinase and creatinine kinase cardiac isoenzyme will be assessed for all patients (including patients who will be receiving tislelizumab after crossover) at screening and, at scheduled visits during treatment cycles and at the end of treatment and safety follow up visits. ECG, serum troponins, and other investigations as clinically indicated and as appropriate, if significant abnormalities are detected.

7.5.5. Electrocardiograms

The ECG recordings will be obtained during screening, the Safety Follow-up Visit, and as clinically indicated.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper or electronic copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

When coinciding with blood draws at the same timepoint, ECG assessment should be performed prior to blood draws. Patients should rest in semi-recumbent supine position for at least 10 minutes prior to ECG collection.

7.5.6. Adverse Events

AEs will be graded and recorded throughout the study according to NCI-CTCAE Version 5.0. Characterization of toxicities will include severity, duration, and time to onset.

All AEs, including SAEs, will be collected as described in Section 8.6.

7.5.7. Hepatitis B and C Testing

Testing will be performed by a central laboratory and/or the local laboratory at screening and will include HBV/HCV serology (HBsAg, hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb), and HCV antibody) and viral load assessment (HBV DNA and HCV RNA). Hepatitis B and C testing will be monitoring during study conduct as clinically needed.

7.6. Tumor and Response Evaluations

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.

Screening assessments and each subsequent assessment must include contrast-enhanced magnetic resonance imaging (MRI) of the nasopharynx and neck, and CT scans (with oral/IV contrast, unless contraindicated) or MRI of the chest, abdomen, and pelvis. Other known or suspected sites of disease must be included in the imaging assessments (brain, etc).

All measurable and evaluable lesions should be assessed and documented at the Screening Visit and reassessed at each subsequent tumor evaluation. The same radiographic procedure used to assess disease sites at Screening are required to be used throughout the study (eg, the same contrast protocol for MRI and CT scans). All known sites of disease must be documented at screening and reassessed at each subsequent tumor evaluation.

- Imaging of the brain (MRI or CT) at baseline (≤ 28 days of informed consent) is required for all screened patients.
- For a patient with known and previously treated brain metastases the MRI scan should be within 14 days of planned Cycle 1, Day 1.
- If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the study, a non-contrast CT of the chest plus a contrast-enhanced MRI (if possible) of abdomen and pelvis should be performed.
- If a CT scan for tumor assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan.
- Bone scans (Technetium-99m [TC-99m]) or PET should be performed at screening if clinically indicated. If bone metastases are present at screening and cannot be seen on CT or MRI scans afterwards, or clinically indicated, TC-99m or PET bone scans should be repeated when a CR is suspected in target lesion or when progression in bone is suspected.
- CT scans of the extremities should also be performed if clinically indicated and followed throughout the study, if there is evidence of metastatic disease in these regions at screening. At the investigator's discretion, other methods of assessment of target lesion and nontarget lesions per RECIST v1.1 may be used.

Response will be assessed by the IRC and the investigator using RECIST v1.1 (see Appendix 4). The same evaluator should perform assessments, if possible, to ensure internal consistency across visits.

After first documentation of response (CR or PR), confirmation of tumor response should occur at 4 weeks or later after the first response or at the next scheduled assessment time point.

For immune therapies such as tislelizumab, pseudoprogression may occur due to immune-cell infiltration and other mechanisms leading to apparent increase of existing tumor masses or appearance of new tumor lesions. Thus, if radiographic progressive disease is suspected by the investigator to reflect pseudoprogression, patients may continue treatment with tislelizumab until progressive disease is confirmed by repeated imaging ≥ 4 weeks later (but not exceeding 6 to 8 weeks from the date of initial documentation of progressive disease). The following criteria must be met in order to treat patients with suspected pseudoprogression:

- Absence of clinical symptoms and signs of disease progression (including clinically significantly worsening of laboratory values)
- Stable ECOG performance status ≤ 1
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, cord compression) that requires urgent alternative medical intervention
- Investigators must obtain written informed consent for treatment beyond radiologic disease progression and inform patients that this practice is not considered standard in the treatment of cancer.

The decision to continue study drug(s) beyond initial investigator-assessed progression must be agreed with the sponsor medical monitor and documented in the study records.

Patients who discontinue study treatment early for reasons other than disease progression (eg, toxicity) will continue to undergo tumor assessments following the original plan until the patient begins a subsequent anticancer treatment, experiences disease progression, withdraws consent, is lost to follow up, or dies, or until the study terminates, whichever occurs first.

Tumor assessments are required to be performed on schedule regardless of whether study treatment has been administered or held.

7.7. Pharmacokinetic and Antidrug Antibody Testing

Tislelizumab may elicit an immune response. Patients with signs of any potential immune response to tislelizumab will be closely monitored. Validated screening and confirmatory assays will be employed to detect antidrug antibodies (ADAs) at multiple timepoints throughout the study (Appendix 1). The immunogenicity evaluation will utilize a risk-based immunogenicity strategy (Koren et al 2008; Worobec and Rosenberg 2004a; Worobec and Rosenberg 2004b) to characterize ADA responses to tislelizumab in support of the clinical development program. This tiered strategy will include an assessment of whether ADA responses correlate with relevant clinical endpoints. Implementation of ADA characterization assays will depend on the safety profile and clinical immunogenicity data.

The following assessments will be performed at a bioanalysis laboratory:

- ADA assays: serum samples will be tested for the presence of ADAs to tislelizumab using a validated immunoassay
- PK assay: serum samples will be assayed for tislelizumab concentration with use of a validated immunoassay

PK and ADA samples collected from patients randomized to receive placebo will not be analyzed.

Shipping, storage, and handling of samples for the assessment of tislelizumab PK and ADA assays will be managed through a central laboratory. Instruction manuals and supply kits will be provided for all central laboratory assessments.

7.8. Biomarkers

Shipping, storage, and handling of blood, archival tumor, fresh tumor, and leftover tumor tissue for the assessment of biomarkers will be managed through a central laboratory. Refer to the laboratory manual for details of sample handling.

Patients must be able to provide fresh or archival tumor tissues (FFPE blocks or approximately 10 [≥ 5] freshly cut unstained FFPE slides) with an associated pathological report. In the absence of sufficient archival tumor tissues, a fresh biopsy of a tumor lesion at baseline is mandatory. However, fresh biopsy should not be collected from the target lesion only unless there are other sites of measurable disease. For fresh biopsy specimens, acceptable samples include core needle biopsies for deep tumor tissue or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. Tumor tissue should be of good quality based on total and viable tumor content. Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable.

Tumor tissues are to be sent to central laboratory for assessment of PD-L1status. In addition, other biomarkers, including but not limited to tumor-infiltrating lymphocyte, tumor mutation analysis and immune-mediated gene expression profiling, that are related to response or the clinical benefit of tislelizumab may also be evaluated.

Optional biopsies will also be taken for the patients who have confirmed disease progression during the study from accessible tumor sites to obtain samples to explore resistance mechanism. If feasible, any follow-up biopsy should be ideally taken from the same tumor lesion as the baseline biopsy. Written patient consent is required for fresh tumor biopsies.

Blood samples will be collected at specified time points as described in the Schedule of Assessments (Appendix 1) to be used for the evaluation of biomarkers, including blood based germline genomic analysis and plasma EBV DNA level as a surrogate biomarker for antitumor efficacy measurement.

Optional blood samples will be collected for biomarker analysis such as cytokine and soluble protein analysis at specified times as described in the schedule of assessment (Appendix 1).

7.9. Patient-Reported Outcomes

Patients will be asked to complete the EORTC QLQ-C30 and EORTC QLQ-H&N35 modules questionnaires before any clinical activities are performed during on-study clinic visits according to the schedule in Appendix 1. The questionnaires will be provided in the patient's preferred language.

7.10. Visit Windows

All visits must occur within ± 3 days from the scheduled date, unless otherwise noted (Appendix 1). All assessments will be performed on the day of the specified visit unless an acceptable time window is specified. Assessments scheduled on the day of study treatment administration (Day 1) of each cycle should be performed prior to study treatment infusion/dose unless otherwise noted. Laboratory results are required to be reviewed prior to dosing.

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other events, the visit should be scheduled on the nearest feasible date (the visit window is provided in Appendix 1), with subsequent visits conducted according to the planned schedule every 3 weeks from Cycle 1 of Day1.

7.11. Unscheduled Visits

Unscheduled visits may be performed at any time at the patient's or the investigator's request and may include vital signs/focused physical examination, ECOG performance status, AE review, concomitant medications and procedures review, radiographic assessments, physical examination of liver, spleen, and lymph nodes; disease-related constitutional symptoms, and hematology and chemistry laboratory assessments. The date and reason for the unscheduled visit must be recorded in the source documentation.

If an unscheduled visit is necessary to assess toxicity or for suspected disease progression, then diagnostic tests may be performed based on the investigator assessment as appropriate, and the results of these tests should be entered on the unscheduled visit eCRF.

8. SAFETY MONITORING AND REPORTING

The investigator is responsible for the monitoring and documentation of events that meet the criteria and definition of an AE or SAE as provided in this protocol.

8.1. Risks Associated With Study Drugs

8.1.1. Risks Associated With Tislelizumab

Tislelizumab is an investigational agent that is currently in clinical development. Limited safety data are available in patients, and the full safety profile has not been characterized. The following recommendation is based on results from nonclinical and clinical studies with tislelizumab and published data on other molecules within the same biologic class.

The PD-L1/PD-1 pathway is involved in peripheral immune tolerance; therefore, such therapy may increase the risk of imAEs, specifically the induction or enhancement of autoimmune conditions. AEs observed with anti-PD-1 therapy are presented in Section 8.7.3.

Although most imAEs observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Suggested workup procedures for suspected imAEs are provided in Appendix 7.

8.1.2. Risks Associated With Cisplatin in Combination With Gemcitabine

For NPC patients who were treated with cisplatin in a first-line setting, frequent (> 5%) Grade 3 or 4 drug-related toxicities were neutropenia, anemia, nausea, vomiting, and fatigue (Scagliotti et al 2008). Although not life-threatening, these AEs can severely impact the physical, psychological, and social well-being of patients receiving chemotherapy and can lead to dose reductions and discontinuations.

Please refer to Table 3 below for the reported toxicity of the respective chemotherapeutic agents. The investigator should refer to the respective prescribing information for additional details.

Table 3. Commonly and Specifically Reported Toxicity of the Chemotherapeutic Agents

Agents	Common toxicity	Specific toxicity
Cisplatin	Myelosuppression with leukopenia, thrombocytopenia and anemia; infectious	Nephrotoxicity; ototoxicity and peripheral neuropathies

Gemcitabine	complications; nausea/vomiting and other gastrointestinal toxicity; hepatic impairment; fatigue; anorexia; constipation	Pulmonary toxicity; rash; peripheral edema; nephrotoxicity; hemolytic uremic syndrome; exacerbation of radiation therapy toxicity; capillary leak syndrome; posterior reversible encephalopathy syndrome

8.2. General Plan to Manage Safety Concerns

8.2.1. Eligibility Criteria

Eligibility criteria were selected to guard the safety of patients in this study. Results from the nonclinical toxicology studies and clinical data with tislelizumab, as well as the nonclinical/clinical data from other PD-L1/PD-1 inhibitors, were considered. Specifically, patients at risk for study-emergent active autoimmune diseases, or with a history of autoimmune diseases that may relapse, patients who have undergone allogenic stem cell or organ transplantation and patients who have received a live viral vaccine within 28 days before randomization are excluded from the study. Patients with contraindications for chemotherapy treatment are also excluded from the study. Refer to Section 4.2 for the full list of exclusion criteria.

8.2.2. Safety Monitoring Plan

Safety will be evaluated in this study through the monitoring of all AEs, defined and graded according to NCI-CTCAE v5.0. Patients will be assessed for safety (including laboratory values) according to the schedule in Appendix 1. Clinical laboratory results must be reviewed prior to the start of each cycle.

In this study, all enrolled patients will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of AEs, physical examinations, laboratory measurements (hematology, chemistry, etc.) and other assessments. In addition, patients will be closely monitored for the development of any signs or symptoms of autoimmune conditions and infection.

Serum samples will be drawn for determination of ADAs to tislelizumab in all randomized patients but will only be tested for patients randomized to the tislelizumab arm. Administration of tislelizumab will be performed in a setting where emergency medical equipment and staff who are trained to respond to medical emergencies are available (see Section 5.2.1).

Investigators are instructed to report all AEs (including pregnancy-related AEs).

The potential safety issues anticipated in this study, as well as measures intended to avoid or minimize such toxicities, are outlined in the following sections.

8.3. Adverse Events

8.3.1. Definitions and Reporting

An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study drug, whether considered related to study drug or not.

Examples of AEs include:

- Worsening of a chronic or intermittent pre-existing condition, including an increase in severity, frequency, duration, and/or has an association with a significantly worse outcome
- New conditions detected or diagnosed after study drug administration even though it may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concurrent medication (overdose per se should not be reported as an AE or SAE)

When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory results, and diagnostics reports) relative to the AE or SAE. The investigator will then record all relevant information regarding an AE or SAE in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by the sponsor. In this instance, all patient identifiers will be blinded on the copies of the medical records prior to submission to the sponsor.

8.3.2. Assessment of Severity

The investigator will assess the severity for each AE and SAE reported during the study. AEs and SAEs should be assessed and graded based upon the NCI-CTCAE v5.0.

Toxicities that are not specified in the NCI-CTCAE will be defined as follow:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

Note: The terms “severe” and “serious” are not synonymous. Severity is a measure of intensity (for example, grade of a specific AE, mild [Grade 1], moderate [Grade 2], severe [Grade 3], or life-threatening [Grade 4]), whereas seriousness is classified by the criteria based on the

regulatory definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the sponsor to applicable regulatory authorities as described in Section 8.6.2.3.

8.3.3. Assessment of Causality

The investigator is obligated to assess the relationship between the study drug and the occurrence of each AE or SAE, using best clinical judgment. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the AE or SAE to the study drug should be considered and investigated. The investigator should consult the tislelizumab Investigator's Brochure in the determination of his/her assessment.

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always makes an assessment of causality for every SAE prior to transmission of the SAE report to the sponsor, since the causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator may change his/her opinion of causality considering follow-up information, amending the SAE report accordingly.

The causality of each AE should be assessed and classified by the investigator as "related" or "not related." An AE is considered related if there is "a reasonable possibility" that the AE may have been caused by the study drug (ie, there are facts, evidence, or arguments to suggest possible causation). A number of factors should be considered in making this assessment, including:

- Temporal relationship of the AE to the administration of study treatment/study procedure
- Whether an alternative etiology has been identified
- Mechanism of action of the study drug
- Biological plausibility

An AE should be considered "related" to study drug if any of the following criteria are met, otherwise the event should be assessed as not related:

- There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out
- There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
- There is some evidence to suggest a causal relationship (eg, the AE occurred within a reasonable time after administration of the study drug). However, the influence of other factors may have contributed to the AE (eg, the patient's clinical condition or other concomitant AEs).

8.3.4. Following Adverse Events

After the initial AE or SAE report, the investigator is required to proactively follow each patient and provide further information to the sponsor on the patient's condition.

All AEs and SAEs documented at a previous visit/contact and designated as ongoing will be reviewed at subsequent visits/contacts.

All AEs and SAEs will be followed until resolution, the condition stabilizes or is considered chronic, the AE or SAE is otherwise explained, the patient is lost to follow-up, or the patient withdraws consent. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, radiographic imaging, or consultation with other health care professionals.

The sponsor may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obligated to assist. If a patient dies during participation in the study or during a recognized follow-up period, the sponsor will be provided with a copy of any post-mortem findings, including histopathology.

New or updated information should be reported to the sponsor according to the SAE instructions provided by the sponsor within the time frames outlined in Section 8.6.2.

8.3.5. Laboratory Test Abnormalities

Abnormal laboratory findings (eg, clinical chemistry, complete blood count, coagulation, or urinalysis) or other abnormal assessments (eg, ECGs, vital signs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs. This includes clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen during the study. The definition of clinically significant is left to the judgment of the investigator. In general, these are the laboratory test abnormalities or other abnormal assessments that:

- are associated with clinical signs or symptoms, or
- require active medical intervention, or
- lead to dose interruption or discontinuation, or
- require close observation, more frequent follow-up assessments, or further diagnostic investigation.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (eg, alkaline phosphatase and bilirubin 5 x ULN associated with cholestasis), only the diagnosis (ie, cholestasis) should be recorded on the Adverse Event eCRF.

If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as “hyperkalemia.”

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

8.4. Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening

  Note: The term "life-threatening" in the definition of "serious" refers to an AE in which the patient was at risk of death at the time of the AE. It does not refer to an AE, which hypothetically might have caused death, if it were more severe.
- Requires hospitalization or prolongation of existing hospitalization

  Note: In general, hospitalization signifies that the patient was admitted (usually involving at least an overnight stay) to the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.
- Results in disability/incapacity

  Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
- Is considered a significant medical AE by the investigator based on medical judgement (eg, may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The following are NOT considered SAEs:

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline
- Hospitalization for social/convenience considerations
- Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience

8.5. Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is a serious adverse reaction that is both unexpected (ie, not present in the product's Reference Safety Information [RSI]) and meets the definition of a serious adverse drug reaction (ADR), the specificity or severity of which is not consistent with those noted in the tislelizumab Investigator's Brochure.

8.6. Timing, Frequency, and Method of Capturing Adverse Events and Serious Adverse Events

8.6.1. Adverse Event Reporting Period

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.

8.6.2. Reporting Serious Adverse Events

8.6.2.1. Prompt Reporting of Serious Adverse Events

As soon as the investigator determines that an AE meets the protocol definition of an SAE, the event must be reported promptly (within 24 hours) to the sponsor or designee as described in Table 4.

Table 4. Timeframes and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

	Timeframe for Making Initial Report	Documentation Method	Timeframe for Making Follow-up Report	Documentation Method	Reporting Method
All SAEs	Within 24 hours of first knowledge of the SAE	SAE Report	As expeditiously as possible	SAE Report	Email or fax SAE form or Pregnancy form

Abbreviations: SAE, serious adverse event.

8.6.2.2. Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a patient, he/she is to report the information to the sponsor within 24 hours as outlined above in Section 8.6.2.1. The SAE Report will always be completed as thoroughly as possible with all available details of the event and forwarded to the sponsor or designee within the designated time frames.

If the investigator does not have all information regarding an SAE, he/she is not to wait to receive additional information before notifying the sponsor or designee of the SAE and completing the form. The form will be updated when additional information is received.

The investigator must always provide an assessment of causality for each SAE as described in Section 8.3.3.

The sponsor will provide contact information for SAE receipt.

8.6.2.3. Regulatory Reporting Requirements for Serious Adverse Events

The investigator will promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 8.6.2.1. The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the IRB/IEC.

All SUSARs (as defined in Section 8.5), will be submitted to all applicable regulatory authorities and investigators for tislelizumab studies.

When a study center receives an initial or follow-up safety report or other safety information (eg, revised Investigator's Brochure) from the sponsor, the investigator or designated responsible person is required to promptly notify his/her IRB or IEC. The investigator should place copies of Safety Reports from the sponsor in the Investigator Site File.

8.6.3. Eliciting Adverse Events

The investigator or designee will ask about AEs by asking the following standard questions:

- How are you feeling?
- Have you had any medical problems since your last visit?
- Have you taken any new medicines since your last visit?

8.6.4. Disease Progression

Disease progression (including fatal disease progression), which is expected in this study population and measured as an efficacy endpoint, should not be reported as an AE term. Instead, the symptoms, signs or clinical sequelae that result from disease progression should be reported as the AE term(s).

For instance, a patient presents with pleural effusion resulting from disease progression of metastasis to lungs. The event term should be reported as "pleural effusion" instead of disease progression. If a patient experienced a fatal multi-organ failure due to disease progression, the term "multi-organ failure" should be reported as the SAE with death as outcome instead of reporting "fatal disease progression" or "death due to disease progression."

8.6.5. Deaths

Death is an outcome and not usually considered an event. If the only information available is death and the cause of death is unknown, then the death is reported as an event, eg, "death," "death of unknown cause," or "death unexplained."

8.6.6. Recording Pregnancies

If a female patient or the partner of a male patient becomes pregnant while receiving investigational therapy or within 120 days after the last dose of tislelizumab or within the 30 days after the last dose of chemotherapy, a pregnancy report form is required to be completed

and expeditiously submitted to the sponsor to facilitate outcome follow-up. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE.

An abortion, whether accidental, therapeutic, or spontaneous should be always reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a patient exposed to the study drug should be recorded and reported as an SAE.

8.6.7. Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Independent Ethics Committees

The sponsor will promptly assess all SAEs against cumulative study drug experience to identify and expeditiously communicate new safety findings to regulatory authorities, investigators, IRBs, and IECs based on applicable legislation.

To determine the reporting requirements for individual SAEs, the sponsor will assess the expectedness of the SAEs using the following reference safety information (RSI) documents:

- Tislelizumab Investigator's Brochure
- Cisplatin label
- Gemcitabine label

8.6.8. Assessing and Recording Immune-Mediated Adverse Events

Since treatment with anti-PD-1 therapy can cause autoimmune disorders, AEs considered by the investigator to be immune-mediated (Section 8.7.3) should be classified as imAEs and identified as such in the eCRF AE page until 90 days after treatment discontinuation.

Investigators should consult the guidance on diagnostic evaluation and management of imAEs, which are commonly seen with immune CPIs, in Appendix 7.

An extensive list of potential imAEs appears in Section 8.7.3, Table 6. All conditions similar to those listed should be evaluated to determine whether they are imAEs, based on a similar diagnostic process to those reactions that are presented in more detail in Appendix 7.

8.7. Management of Adverse Events of Special Interest

As a routine precaution, after infusion of tislelizumab on Day 1 of Cycle 1 and Cycle 2, patients must be monitored for ≥ 1 hour afterwards in an area with resuscitation equipment and emergency agents before chemotherapy. From Cycle 3 onward, a minimum of a 30-minute monitoring period is required in an area with resuscitation equipment and emergency agents before chemotherapy.

The management of infusion-related reactions, severe hypersensitivity reactions, and imAEs according to the NCI-CTCAE criteria are outlined below.

8.7.1. Infusion-Related Reactions

The symptoms of infusion-related reactions include fever, chills/rigor, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness, or hypertension. Severe reactions may include acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. Patients should be closely monitored for such reactions. Immediate access to an intensive care unit (ICU) or equivalent environment and appropriate medical therapy (including epinephrine, corticosteroids, IV antihistamines, bronchodilators, and oxygen) must be available to treat infusion-related reactions.

Treatment modification for symptoms of infusion-related reactions due to study drug(s) is provided in Table 5.

Table 5. Treatment Modification for Symptoms of Infusion-Related Reactions Due to Study Drug(s)

NCI-CTCAE Grade	Treatment Modification for Tislelizumab
Grade 1 - mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease infusion rate by 50%. Any worsening is closely monitored. Medical management as needed. Subsequent infusions should be given after premedication and at the reduced infusion rate.
Grade 2 - moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h.	Stop infusion. Infusion may be resumed at 50% of previous rate once infusion-related reactions has resolved or decreased to Grade 1 in severity. Any worsening is closely monitored. Proper medical management should be instituted as described below. Subsequent infusions should be given after premedication and at the reduced infusion rate.
Grade 3 - severe Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae.	Immediately stop the infusion. Proper medical management should be instituted as described below. The patient should be withdrawn from study drug(s) treatment.
Grade 4 - life threatening Life-threatening consequences; urgent intervention indicated.	Immediately stop the infusion. Proper medical management should be instituted as described below. The patient should be withdrawn from study drug(s) treatment. Hospitalization is recommended.

Abbreviations: h, hours; IV, intravenous; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NSAIDs, nonsteroidal anti-inflammatory drugs.

Once the tislelizumab infusion rate has been decreased by 50% or suspended due to an infusion-related reaction, it must remain decreased for all subsequent infusions with premedication. If the patient has a second infusion-related reaction (≥ Grade 2) on the slower infusion rate, infusion should be discontinued, and the patient should be withdrawn from tislelizumab treatment.

NCI-CTCAE Grade 1 or 2 infusion reaction: Proper medical management should be instituted, as indicated per type of the reaction. This includes but is not limited to an

antihistamine (eg, diphenhydramine or equivalent), antipyretic (eg, paracetamol or equivalent), and if considered indicated oral or IV glucocorticoids, epinephrine, bronchodilators, and oxygen. In the next cycle, patients should receive oral premedication with an antihistamine (eg, diphenhydramine or equivalent) and an antipyretic (eg, paracetamol or equivalent), and they should be closely monitored for clinical signs and symptoms of an infusion reaction.

NCI-CTCAE Grade 3 or 4 infusion reaction: Proper medical management should be instituted immediately, as indicated per type and severity of the reaction. This includes but is not limited to oral or IV antihistamine, antipyretic, glucocorticoids, epinephrine, bronchodilators, and oxygen.

8.7.2. Severe Hypersensitivity Reactions and Flu-Like Symptoms

If hypersensitivity reaction occurs, the patient must be treated according to the best available medical practice as described in the complete guideline for emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (UK) (Soar et al 2008). Patients should be instructed to report any delayed reactions to the investigator immediately.

In the event of a systemic anaphylactic/anaphylactoid reaction (typically manifested within minutes following administration of the drug/antigen, and characterized by: respiratory distress; laryngeal edema; and/or intense bronchospasm; and often followed by vascular collapse or shock without antecedent respiratory difficulty; cutaneous manifestations such as pruritus and urticaria with/without edema; and gastrointestinal manifestations such as nausea, vomiting, crampy abdominal pain, and diarrhea), the infusion must be immediately stopped and the patient discontinued from the study.

The patients will be administered epinephrine injection and dexamethasone infusion if hypersensitivity reaction is observed and then the patient should be placed on monitor immediately and ICU should be alerted for possible transfer if needed.

For prophylaxis of flu-like symptoms, a dose of 25 mg indomethacin or a comparable dose of nonsteroidal anti-inflammatory drugs (ie, 600 mg ibuprofen, 500 mg naproxen sodium) may be administered 2 hours before and 8 hours after the start of each dose of study drugs(s) infusion. Alternative treatments for fever (ie, paracetamol) may be given to patients at the discretion of the investigator.

8.7.3. Immune-Mediated Adverse Events

Immune-mediated AEs are of special interest in this study. If the events listed below or similar events occur, the investigator should exclude alternative explanations (eg, combination drugs, infectious disease, metabolic, toxin, disease progression or other neoplastic causes) with appropriate diagnostic tests, which may include but are not limited to serologic, immunologic, and histologic (biopsy) data. If alternative causes have been ruled out; the AE required the use of systemic steroids, other immunosuppressants, or endocrine therapy and is consistent with an immune-mediated mechanism of action, the imAE indicator in the eCRF AE page should be checked.

A list of potential imAEs is shown below in Table 6. All conditions similar to those listed should be evaluated in patients receiving tislelizumab to determine whether they are immune mediated.

Recommendation for diagnostic evaluation and management of imAEs is based on European Society for Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) guidelines (Haanen et al 2017; Brahmer et al 2018), and common immune-mediated toxicities are detailed in Appendix 7. For any AEs not included in Appendix 7, please refer to the ASCO Clinical Practice Guideline (Brahmer et al 2018) for further guidance on diagnostic evaluation and management of immune-mediated toxicities.

Table 6. Immune-Mediated Adverse Events

Body System Affected	Events
Skin (mild-common)	pruritus or maculopapular rash; vitiligo
Skin (moderate)	follicular or urticarial dermatitis; erythematous/lichenoid rash; Sweet's syndrome
Skin (severe-rare)	full-thickness necrolysis/Stevens-Johnson syndrome
Gastrointestinal	colitis (includes diarrhea with abdominal pain or endoscopic/radiographic evidence of inflammation); pancreatitis; hepatitis; aminotransferase (ALT/AST) elevation; bowel perforation
Endocrine	thyroiditis, hypothyroidism, hyperthyroidism; hypophysitis with features of hypopituitarism, eg, fatigue, weakness, weight gain; insulin-dependent diabetes mellitus; diabetic ketoacidosis; adrenal insufficiency
Respiratory	pneumonitis/diffuse alveolitis
Eye	episcleritis; conjunctivitis; iritis/uveitis
Neuromuscular	arthritis; arthralgia; myalgia; neuropathy; Guillain-Barre syndrome; aseptic meningitis; myasthenic syndrome/myasthenia gravis, meningoencephalitis; myositis
Blood	anemia; leukopenia; thrombocytopenia
Renal	interstitial nephritis; glomerulonephritis; acute renal failure
Cardiac	pericarditis; myocarditis; heart failure

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Recommendations for managing imAEs are detailed in Appendix 7.

If a toxicity does not resolve to ≤ Grade 1 within 12 weeks, study drug(s) should be discontinued after consultation with the sponsor. Patients who experience a recurrence of any event at the same or higher severity grade with rechallenge should permanently discontinue treatment.

9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

The statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released. Details of the statistical analyses will be included in a separate Statistical Analysis Plan.

9.1. Statistical Analysis

9.1.1. Randomization Methods

As discussed in Section 7.2.2, patients will be randomized using the IRT system for this study by permuted block stratified randomization with gender and metastatic status (with or without liver metastases).

9.1.2. 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.

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.

The PK analysis set includes all patients who receive any dose of tislelizumab per the protocol, for whom any postdose PK data are available.

The Immunogenicity analysis set includes all patients who receive any dose of tislelizumab for whom both baseline ADA and ≥ 1 postbaseline ADA results are available.

9.1.3. Patient Disposition

The number of patients randomized, treated, and discontinued from study drug and/or study and those with major protocol deviations will be counted. The primary reason for study drug and/or study discontinuation will be summarized according to the categories in the eCRF. The end-of-study status (alive, dead, withdrew consent or lost to follow-up) at the data cutoff date will be summarized using the data from the eCRF.

Major protocol deviations will be summarized and listed by each category.

9.1.4. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics of the ITT analysis set will be summarized using descriptive statistics. Continuous variables include age, weight, vital signs, time since initial cancer diagnosis, and time since metastatic/recurrent disease diagnosis, EBV DNA viral load. Categorical variables include histology, prior neoadjuvant or adjuvant therapy, stage of disease, PD-L1 expression in TC, gender, ECOG performance status, race, smoking status, prior systemic therapies, and metastatic site.

9.1.5. Prior and Concomitant Medications

Concomitant medications will be coded using the WHO Drug Dictionary drug codes. Concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical (ATC) code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class in the clinical study report (CSR) for this protocol. Prior medications will be defined as medications that 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 days, and 90 days (± 14 days) after the last dose of study treatment, regardless of whether or not the patient starts a new anticancer therapy. If patients report a suspected immune-mediated AE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated.

9.2. Efficacy Analyses

9.2.1. Primary Efficacy Analysis

PFS per the IRC in ITT Analysis Set:

PFS per the IRC 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. The actual tumor assessment visit date will be used to calculate PFS. Data for patients without disease progression or death at the time of analysis will be censored at the time of the last valid tumor assessment. Data for patients without postbaseline tumor assessment will be censored at the time of randomization. Data for patients who start to receive new anticancer therapy or are lost to follow-up will be censored at the last valid tumor assessment date prior to the introduction of new therapy or loss to follow-up.

PFS per the IRC will be compared between tislelizumab + gemcitabine + cisplatin (Arm A) and placebo + gemcitabine + cisplatin (Arm B) at a 1-sided α of 2.5% using stratified log-rank test methodology. 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) system at randomization. The median PFS will be calculated for each treatment arm and presented with two-sided 95% CIs. Kaplan-Meier survival probabilities for each arm will be plotted over time. The HR for PFS will be estimated using a stratified Cox regression model, with treatment arm as a factor and stratified by the actual value of the stratification factors as recorded in eCRF. The 95% CI for the HR will be provided. Unstratified analysis will also be presented for descriptive purposes.

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 (former versus current versus never), etc.

9.2.2. Secondary Efficacy Analyses

Objective Response Rate per the IRC

ORR (confirmation not required according to RECIST v1.1) is the proportion of patients who had a CR or PR as assessed by the IRC per RECIST v1.1 in all randomized patients with measurable disease at baseline. Patients without any postbaseline assessment will be considered nonresponders. The difference in ORR between Arm A and Arm B in the ITT analysis set will be evaluated using the Cochran-Mantel-Haenszel chi-square test with the actual stratification factors as strata. The two-sided 95% CIs for the odds ratio and the difference in ORR will be calculated, as well as Clopper-Pearson 95% CIs for the ORR within each arm.

Duration of Response per the IRC

DOR per the IRC is defined as the time from the first documented objective response to documented disease progression as assessed by the IRC using RECIST v1.1, or death from any cause, whichever occurs first. Data for patients who are alive and who have not experienced disease progression at the time of analysis will be censored at the date of the last tumor assessment. If no tumor assessments were performed after the date of the first occurrence of the objective response (CR or PR), DOR will be censored at the date of the first occurrence of the objective response. DOR will be estimated using Kaplan-Meier methodology. Comparison between Arm A and Arm B will be made using the stratified and unstratified log-rank test for descriptive purposes only.

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.

Progression-Free Survival per the Investigator

PFS per the investigator is defined as the time from randomization to the first objectively documented disease progression, or death from any cause, whichever occurs first, as determined per RECIST v1.1 in an ITT analysis set. Similar methodology used to evaluate PFS per the IRC will be applied to analysis of PFS per the investigator.

Second Progression-free Survival per the Investigator

Analysis of PFS2, 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. Descriptive analysis of PFS2 will be performed as needed.

Health-Related Quality of Life

HRQoL is measured via PRO questionnaires using the EORTC QLQ-C30 and EORTC QLQ-H&N35.

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.

Time to deterioration (TTD) is defined as the time from randomization to first onset time at which deterioration is clinically meaningful (≥ 10 points in the direction of worsening) in the score of QLQ-C30's GHS and the QLQ-H&N35's index score for 2 executive assessments or 1 assessment followed by death from any cause within 3 weeks. TTD will be calculated using Kaplan-Meier estimates and presented with 2-sided 95% CIs.

9.2.3. Exploratory Efficacy Analyses

Objective Response Rate per the Investigator

ORR (confirmation not required according to RECIST v1.1) 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 as 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

DOR per the investigator is defined as the time from the first documented objective response to documented disease progression as assessed by the investigator using RECIST v1.1, or death from any cause, whichever occurs first. Data for patients who are alive and who have not experienced disease progression at the time of analysis will be censored at the date of the last tumor assessment. If no tumor assessments were performed after the date of the first occurrence of the objective response (CR or PR), DOR will be censored at the date of the first occurrence of the objective response. 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 the same as those for ORR per the investigator.

Time to Response per the Investigator

Time to response (TTR) per the investigator is defined for patients with an objective response by the investigator as the time from randomization to the first occurrence of a CR or PR as assessed by the investigator using RECIST v1.1. TTR will be summarized for descriptive purposes. The mean, standard error, median, and range of TTR will be provided.

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.

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.

9.3. Safety Analyses

Safety will be assessed by monitoring and recording of all AEs graded by NCI-CTCAE v5.0. Laboratory values (eg, hematology, clinical chemistry, urinalysis), vital signs, ECGs, and physical examinations will also be used in determining safety. Descriptive statistics will be used to analyze all safety data in the Safety analysis set.

9.3.1. Extent of Exposure

Extent of exposure to each study drug will be summarized descriptively as the number of cycles received (number and percentage of patients), duration of exposure (days), cumulative total dose received per patient (mg), and relative dose intensity.

The number (percentage) of patients requiring dose reduction, interruption, dose delay, and drug discontinuation due to AEs will be summarized for each study drug. Frequency of the above dose adjustments and discontinuation will be summarized by category.

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

9.3.2. Adverse Events

The AE verbatim descriptions (the investigator's description from the eCRF) will be coded using Medical Dictionary for Regulatory Activities (MedDRA). AEs will be coded to MedDRA (Version 20.0 or higher) by lowest level term, preferred term, and primary system organ class (SOC).

A 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 (Safety Follow-up Visit) or initiation of new anticancer therapy, whichever occurs first. For the tislelizumab arm, the TEAE classification also applies to imAEs that are recorded up to 90 days after discontinuation from 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.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by SOC and preferred term. A patient will be counted only once by the highest severity grade per NCI-CTCAE v5.0 within an SOC and preferred term, even if the patient experienced > 1 TEAE within a specific SOC and preferred term. The number (percentage) of patients with TEAEs will also be summarized by relationship to the study drug. Treatment-related AEs include those events considered by the investigator to be related to study treatment or with missing assessment

of the causal relationship. SAEs, deaths, TEAE with ≥ Grade 3 severity, imAE, treatment-related TEAEs and TEAEs that led to treatment discontinuation, dose interruption, dose reduction, or dose delay will be summarized.

9.3.3. Laboratory Analyses

Clinical laboratory (eg, hematology, serum chemistry) values will be evaluated for each laboratory parameter as appropriate. 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 CSR for this protocol. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) for laboratory parameters and their changes from baseline will be calculated. Laboratory values will be summarized by visit and by worst postbaseline visit.

Laboratory parameters that are graded in NCI-CTCAE v5.0 will be summarized by NCI-CTCAE Grade. In the summary of laboratory parameters by NCI-CTCAE Grade, parameters with NCI-CTCAE grading in both high and low directions (eg, glucose, potassium, sodium) will be summarized separately.

9.3.4. 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.

9.4. Pharmacokinetic Analysis

Pharmacokinetic samples will be collected in this study as outlined in Appendix 1.

Tislelizumab postdose and trough serum concentration (C_{trough}) data will be tabulated and summarized by visit/cycle at which these concentrations are collected. Descriptive statistics will include means, medians, ranges, and standard deviations, as appropriate.

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

9.5. Immunogenicity Analysis

Samples to assess anti-tislelizumab antibodies will be collected in all randomized patients and in sites that are able to adequately perform sampling, handling and processing procedures outlined in the laboratory manual. ADA test will be performed for the patients randomized to receive tislelizumab.

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.

9.6. Sample Size Consideration

The sample size calculation is based on the number of PFS events required to demonstrate the PFS superiority of Arm A over 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 Arm B.
2. At a 1-sided α of 0.025, 82% power to detect 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 are 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).

9.7. Interim Analyses

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 for each comparison is based on Lan-DeMets O'Brien-Fleming approximation spending function. The interim and final analysis timing, and stopping boundaries are summarized in Table 7 below.

Table 7. Analysis Timing and Stopping Boundaries for PFS in Each of the Primary Tests at a 1-sided α = 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

10. STUDY COMMITTEES AND COMMUNICATION

10.1. Blinded Independent Central Review

A Blinded Independent Central Review (BICR) committee will be established to perform an independent review of all radiological images for the efficacy analysis and to determine all instances of response and disease progression based on RECIST v1.1 criteria, in addition to the local investigator review of radiographs. The results from the investigator's review of radiographic images will be used to determine whether patients should be enrolled or should continue study treatment. The tumor assessment by the BICR will be used for the reporting of the study results.

All decisions made during the performance of the study will be based on the local investigator's assessment of radiographic images, clinical status, and relevant examination of the patients. Sites will submit specific radiographic image files to the centralized data review facility during the study on an ongoing basis or at the sponsor's request. Detailed rules and guidelines for radiographic imaging and tumor assessments by the BICR are outlined separately in the Imaging Manual and the BICR Charter.

10.2. Independent Data Monitoring Committee

Safety monitoring and interim efficacy data review will be performed by an Independent Data Monitoring Committee (IDMC). The first IDMC safety monitoring and review will occur after the first 30 patients recruited have been on treatment for ≥ 1 month or completed at least 1 cycle of study treatment. Thereafter, IDMC will review data approximately every 6 months, or more frequently if indicated or requested by the medical monitor based on ongoing safety monitoring of patients on study. The IDMC may recommend study modification including early termination of the study due to safety concerns, or for evidence of compelling efficacy at a preplanned interim analysis. The function and membership of the IDMC will be described in the IDMC charter.

In addition to the planned IDMC review(s), ad hoc reviews may take place based on new information.

Following IDMC review and discussion, the sponsor will make all final decisions regarding any change in study conduct. Please see the details in the IDMC charter.

11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

The investigator must maintain adequate and accurate records to ensure that the conduct of the study may be fully documented. Such records include but are not limited to the protocol, protocol amendments, ICFs, and documentation of IRB/IEC and governmental approvals. In addition, at the end of the study, the investigator will receive patient data, which will include an audit trail containing a complete record of all changes to such data.

11.1. Access to Information for Monitoring

In accordance with International Council for Harmonisation (ICH) GCP guidelines, the study monitor must have direct access to the investigator's source documentation to verify the data recorded in the eCRFs for consistency.

The monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any patient records needed to verify the entries on the eCRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected while these monitoring visits are resolved.

11.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of BeiGene may conduct inspections or audits any time during or after completion of this clinical study. If the investigator is notified of an inspection by a regulatory authority, the investigator agrees to notify the sponsor or its designee immediately. The investigator agrees to provide to representatives of a regulatory agency or BeiGene access to records, facilities, and personnel for the effective conduct of any inspection or audit.

12. QUALITY ASSURANCE AND QUALITY CONTROL

12.1. Regulatory Authority Approval

The sponsor will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements or file the protocol to the appropriate regulatory agency before the study is initiated at a study center in that country/region.

12.2. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, the sponsor may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her personnel to the auditor/inspector to discuss findings and any relevant issues.

12.3. Study Site Inspections

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures, working practice documents, and applicable regulations and guidelines. Site audits may be made periodically by the sponsor's or the contract research organization's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

Site visits will be conducted by the sponsor or an authorized representative to inspect study data, patients' medical records, and eCRFs. The investigator is to permit national and local health authorities; sponsor study monitors, representatives, and collaborators; and IRB/IEC members to inspect all facilities and records relevant to this study.

12.4. Drug Accountability

The investigator or designee (ie, pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient drug dispensation records, and returned or destroyed study product. Dispensation records will document quantities received from BeiGene's designated depot or its designee and quantities dispensed to patients, including batch/lot number, date dispensed, patient identifier number, patient initials (if allowed), and the initials of the person dispensing the medication.

At study initiation, the monitor will evaluate the site's standard operating procedure for study drug disposal/destruction to ensure that it complies with BeiGene requirements specified in the Pharmacy Manual. At the end of the study, or at appropriate times during the conduct of the study, following drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures. If the site cannot meet BeiGene's requirements specified in the Pharmacy Manual for disposal, arrangements will be made between the site and BeiGene or its representative for destruction or return of unused study drug supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

13. ETHICS/PROTECTION OF HUMAN PATIENTS

13.1. Ethical Standard

This study will be conducted by the principal investigator and the study center in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

13.2. Institutional Review Board/Independent Ethics Committee

This protocol, the ICFs, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/IEC by the principal investigator and reviewed and approved by the IRB/IEC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/IEC.

The principal investigator is responsible for providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC. Investigators are also responsible for promptly informing the IRB/IEC of any protocol amendments. In addition to the requirements for reporting all AEs to the sponsor, investigators must comply with requirements for reporting SAEs to the local health authority and IRB/IEC. Investigators may receive written investigational new drug safety reports or other safety-related communications from the sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/IEC and archived in the site's study file.

13.2.1. Protocol Amendments

Any protocol amendments will be prepared by the sponsor. All protocol modifications must be submitted to competent authorities according to local requirements and to the IRB/IEC together with, if applicable, a revised model ICF in accordance with local requirements. Written documentation from competent authorities (according to local requirements) and from the IRB/IEC and required site approval must be obtained by the sponsor before changes can be implemented, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (eg, change in medical monitor or contact information).

Information on any change in risk and/or change in scope must be provided to patients already actively participating in the study, and they must read, understand, and sign each revised ICF confirming willingness to remain in the study.

13.3. Informed Consent

The sponsor's sample ICF will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The final IRB/IEC-approved ICFs must be provided to the sponsor for health authority submission purposes according to local requirements.

The ICFs must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The ICFs will be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB-/IEC-approved consent forms must be provided to the sponsor for health authority submission purposes.

Patients must be reconsented to the most current version of the ICFs (or to a significant new information/findings addendum in accordance with applicable laws and IRB/IEC policy) during their participation in the study. For any updated or revised ICFs, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised ICFs for continued participation in the study.

A copy of each signed ICF must be provided to the patient or the patient's legally authorized representative. All signed and dated ICFs must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

13.4. Patient and Data Confidentiality

The sponsor will maintain confidentiality and privacy standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This approach ensures that patients' names are not included in any data set transmitted to any sponsor location.

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the signed ICF (or a separate authorization for the use and disclosure of personal health information that has been signed by the patient), unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated during this study must be available for inspection upon request by representatives of the US Food and Drug Administration, China Health Authority, and all other national and local health authorities; by sponsor monitors, representatives, and collaborators; and by the IRBs/IECs for each study site, as appropriate.

The investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. The investigator agrees that all information received from the sponsor, including but not limited to the Investigator's Brochure, this protocol, eCRFs, the investigational new drug, and any other study information, remains the sole and exclusive property of sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study, or as required by law) without prior written consent from the sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

13.5. Financial Disclosure

Investigators are required to provide the sponsor with sufficient accurate financial information in accordance with regulations to allow the sponsor to submit complete disclosure or certification to the absence of certain financial interest of the clinical investigators and/or disclose those financial interests, as required to the appropriate health authorities. This is intended to ensure financial interests and arrangements of the clinical investigators with BeiGene that could affect reliability of data submitted to health authorities are identified and disclosed by the sponsor. Investigators are responsible for providing information about their financial interests before participation in the study, and to update this information if any relevant changes occur during the study and for 1 year after completion of the study (ie, last patient, last visit).

14. DATA HANDLING AND RECORD KEEPING

14.1. Data Collection and Management Responsibilities

14.1.1. Data Collection

Data required by the protocol will be entered into an EDC system.

Data collection in the eCRF should follow the instructions described in the eCRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered in the eCRF. The investigator must provide e-signature in the EDC system to attest to its accuracy, authenticity, and completeness.

Data contained in the eCRFs are the sole property of BeiGene and should not be made available in any form to third parties without written permission from BeiGene, except for authorized representatives of BeiGene or appropriate regulatory authorities.

14.2. Data Management/Coding

All final patient data, both eCRF and external data (eg, laboratory data), collected according to the protocol, will be stored at BeiGene at the end of the study.

Standard procedures (including following data review guidelines, computerized validation to produce queries, and maintenance of an audit file which includes all database modifications) will be followed to support accurate data collection. Data will be reviewed for outliers, logic, data inconsistencies, and completeness.

During the study, a study monitor (clinical research associate) will make site visits to review protocol compliance, compare eCRFs against individual patient's medical records, and ensure that the study is being conducted according to pertinent regulatory requirements.

The eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained. Checking the eCRFs for completeness, clarity, and cross-checking with source documents is required to monitor the progress of the study. Direct access to source data is also required for inspections and audits and will be carried out with due consideration given to data protection and medical confidentiality.

AEs will be coded using the MedDRA Version 20.0 or higher. Concomitant medications will be coded using the World Health Organization Drug Dictionary. Concomitant diseases/medical history will be coded using the MedDRA Version 20.0 or higher.

14.3. Data Integrity and In-house Blinding

In this double-blind, placebo-controlled, randomized study, all patients and personnel involved in the conduct and interpretation of the study, including the investigators, BeiGene study team, and site personnel, will be blinded. Randomization data will be kept strictly confidential; filed securely by the appropriate groups for BeiGene, the IRT and the IDMC; and will be accessible only to authorized personnel per SOPs until the time of unblinding.

14.4. Study Records Retention

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories: 1) the investigator's study file and 2) the patient clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRF and query forms, IRB/IEC, and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Patient clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the eCRFs) would include documents such as (although not be limited to) the following: patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, electroencephalogram, X-ray, pathology and special assessment reports, consultant letters, screening and enrollment log, etc.

Following closure of the study, the investigator must maintain all study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (eg, audit or inspection) and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and personnel. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (eg, microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible, are a true and accurate copy of the original, and meet accessibility and retrieval standards, including regenerating a hard copy, if required. Furthermore, the investigator must ensure that there is an acceptable backup of these reproductions and that an acceptable quality-control process exists for making these reproductions.

The sponsor will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that study center for the study, as dictated by any institutional requirements or local laws or regulations, or the sponsor's standards/procedures; otherwise, the retention period will default to 5 years.

The investigator must notify the sponsor of any changes in the archival arrangements, including but not limited to archival at an off-site facility or transfer of ownership of or responsibility for the records in the event the investigator leaves the study center.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and BeiGene to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the site.

14.5. Protocol Deviations

The investigator is responsible for ensuring that the study is conducted in accordance with the procedures and evaluations described in this protocol. Investigators assert that they will apply due diligence to avoid protocol deviations.

The investigator is to document and explain any deviations from the approved protocol. The investigator must promptly report any major deviations that might impact patient safety and/or data integrity to the sponsor and to the IRB/IEC, in accordance with established IRB/IEC policies and procedures.

14.6. Publication and Data-Sharing Policy

CSRs will be prepared and provided to the regulatory agency(ies). BeiGene will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

The results of this study will be published or presented at scientific meetings in a timely, objective, and clinically meaningful manner that is consistent with good science, industry, and regulatory guidance, and the need to protect the intellectual property of BeiGene (sponsor), regardless of the outcome of the study. The data generated in this clinical study are the exclusive property of the sponsor and are confidential. As this is a multicenter study, the first publication or disclosure of study results shall be a complete, joint, multicenter publication or disclosure coordinated by the sponsor. Thereafter, any secondary publications will reference the original publication(s). Authorship will be determined by mutual agreement and all authors must meet the criteria for authorship established by the International Committee of Medical Journal Editors Uniform Requirements for Manuscripts or stricter local criteria (International Committee of Medical Journal Editors 2016).

Each investigator agrees to submit all manuscripts, abstracts, posters, publications, and presentations (both oral and written) to the sponsor prior to submission or presentation in accordance with the clinical study agreement. This allows the sponsors to protect proprietary information, provide comments based on information from other studies that may not yet be available to the investigator, and ensure scientific and clinical accuracy. The process of reviewing manuscripts and presentations that are based on the data from this study is detailed in the investigator's clinical study agreement. Each investigator agrees that, in accordance with the terms of the clinical study agreement, a further delay of the publication/presentation may be requested by the sponsor to allow for patent filings in advance of the publication/presentation.

14.7. Study and Study Center Closure

Upon completion of the study, the monitor will conduct the following activities in conjunction with the investigator or study center personnel, as appropriate:

- Return of all study data to the sponsor
- Resolution and closure of all data queries
- Accountability, reconciliation, and arrangements for unused study drug(s)
- Review of study records for completeness
- Return of treatment codes to the sponsor
- Shipment of PK samples to assay laboratories

In addition, the sponsor reserves the right to suspend the enrollment or prematurely discontinue this study either at a single study center or at all study centers at any time for reasons including,

but not limited to, safety or ethical issues or severe noncompliance. If the sponsor determines such action is needed, the sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. When feasible, the sponsor will provide advance notification to the investigator of the impending action prior to it taking effect.

The sponsor will promptly inform all other investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must be returned to the sponsor. In addition, arrangements will be made for the return of all unused study drug(s) in accordance with the applicable sponsor procedures for the study.

Financial compensation to the investigators and/or institutions will be in accordance with the agreement established between the investigator and the sponsor.

14.8. Information Disclosure and Inventions

All rights, title, and interests in any inventions, know-how, or other intellectual or industrial property rights which are conceived or reduced to practice by the study center personnel during the course of or as a result of the study are the sole property of the sponsor and are hereby assigned to the sponsor.

If a written contract for the conduct of the study which includes ownership provisions inconsistent with this statement is executed between the sponsor and the study center, that contract's ownership provisions shall apply rather than this statement.

All information provided by the sponsor and all data and information generated by the study center as part of the study (other than a patient's medical records) are the sole property of the sponsor and will be kept confidential by the investigator and other study center personnel.

This information and data will not be used by the investigator or other study center personnel for any purpose other than conducting the study without the prior written consent of the sponsor.

These restrictions do not apply to:

- Information which becomes publicly available through no fault of the investigator or study center personnel
- Information which is necessary to disclose in confidence to an IEC/IRB solely for the evaluation of the study
- Information which is necessary to disclose to provide appropriate medical care to a patient
- Study results which may be published as described in Section 14.6

If a written contract for the conduct of the study which includes provisions inconsistent with this statement is executed, that contract's provisions shall apply rather than this statement.

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APPENDIX 1. SCHEDULE OF ASSESSMENTS

Assessment	Screening[1]	Treatment Cycles					Safety Follow-up[3]	Survival Follow-up[4]
		Cycles 1 to 6 (every 21 days)			Cycle 7 and subsequent cycles (every 21 days)	End of Treatment Visit[2]		
Days (Window)	**-28 to -1**	**1 (± 3)**	**8 (± 2)[26]**	**15 (± 2)[26]**	**1 (± 3)**	**0 to 7 Days**	**30 ± 7 Days After Last Dose**	**Every 3 Months**
Informed consent	X							
Inclusion/exclusion criteria	X							
Randomization	X[5]							
Demographics/medical history/prior medications[6]	X							
Vital signs/ height and weight[7]	X	X			X	X	X	
Physical examination[8]	X	X			X	X	X	
ECOG Performance Status	X	X			X	X	X	
12-lead ECG[9]	X						X	
Adverse events[10]	X	X	X	X	X	X	X	X
Concomitant medications[10]	X	X	X	X	X	X	X	
Hematology[11]	X	X			X	X[2]	X	
Serum chemistry[11]	X	X			X	X[2]	X	
Coagulation parameters[11,12]	X	X			X	X[2]	X	
Total CK and CK-MB[11]	X	X			X	X[2]	X	
Urinalysis[11]	X	As clinically indicated						
Pregnancy test[13]	X	X			X			

Assessment	Screening[1]	Treatment Cycles					Safety Follow-up[3]	Survival Follow-up[4]
		Cycles 1 to 6 (every 21 days)			Cycle 7 and subsequent cycles (every 21 days)	End of Treatment Visit[2]		
Days (Window)	**-28 to -1**	**1 (± 3)**	**8 (± 2)[26]**	**15 (± 2)[26]**	**1 (± 3)**	**0 to 7 Days**	**30 ± 7 Days After Last Dose**	**Every 3 Months**
Thyroid function (every 3 cycles)[14]	X	X[14]			X[14]		X	
HBV/HCV tests[15]	X	As clinically indicated						
Pulmonary function tests[16]	X							
Pharmacokinetics[17]		X			X		X	
Anti-tislelizumab antibodies[18]		X			X		X	
Tumor assessment[19]	X	X			X	X[2]		
Archival/fresh tumor tissue[20]	X					X (optional)		
Mandatory blood sample for biomarker analysis[21]	X	X						
Tislelizumab/Placebo administration[22]		X			X			
Cisplatin administration[23]		X						
Gemcitabine administration[23]		X	X					
EORTC QLQ-C30[24]	X	X			X	X		
EORTC QLQ-H&N35[24]	X	X			X	X		
Optional blood sample for biomarker analysis[25]		X[25]				X[25]		
Survival status								X

Abbreviations: ADA, antidrug antibody; AE, adverse event; AUC, area under the plasma or serum concentration-time curve; CK, Creatinine kinase; CK-MB, creatinine kinase cardiac isoenzyme; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; 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; FFPE, formalin-fixed paraffin-embedded; HBcAb, hepatitis B core antibody; HBsAg, hepatitis B

surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HBsAb, hepatitis B surface antibody; IEC, Independent Ethics Committee; imAE, immune-mediated adverse event; IRB, Institutional Review Board; IRC, Independent Review Committee; IRT, interactive response technology; IV, intravenous; MRI, magnetic resonance imaging; PET, position emission tomography; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PK, pharmacokinetic; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; TSH, thyroid stimulating hormone; v, version.

1. Written informed consent is required prior to performing any study-specific tests or procedures. Results of standard of care tests or examinations performed prior to obtaining informed consent and within 28 days prior to randomization may be used for screening assessments rather than repeating such tests.
2. The End of Treatment Visit is conducted when the Investigator determines that tislelizumab or placebo and/or chemotherapy will no longer be used. If routine laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the End of Treatment Visit, tests need not be repeated. Tumor assessment is not required at the End of Treatment Visit provided that fewer than 6 weeks have passed since the last assessment.
3. The Safety Follow-up Visit is required to be conducted 30 days (± 7 days) after the last dose of tislelizumab or placebo and/or chemotherapy, or before the initiation of a new anticancer treatment, whichever occurs first. The End of Treatment (EOT) Visit at which a response assessment showed progressive disease, resulting in patient discontinuation, may be used as the Safety Follow-up Visit, if it occurred 30 days or more after the last study treatment.
4. Survival Follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months after the Safety Follow-up Visit until death, loss to follow-up, withdrawal of consent, or study termination by sponsor. All patients will be followed for survival and subsequent anticancer therapy information unless a patient requests to be withdrawn from follow-up.
5. Patients will be randomized into either Arm A or Arm B via IRT. All patients are required to receive study treatment within 2 business days of randomization.
6. Includes age or year of birth, gender, and self-reported race/ethnicity; history of treatment for the primary diagnosis, including prior medication, loco-regional treatment(s), and surgical treatment(s). Information on radiographic studies performed prior to study entry may be collected for review by the Investigator.
7. Vital signs collected on study include temperature, pulse rate, and blood pressure. For the first 2 infusions of tislelizumab or placebo, the patient's vital signs are required to be recorded within 60 minutes before starting the infusion, at least once during the infusion, and 30 minutes following the completion of the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before infusion and if clinically indicated, during and 30 minutes after the infusion. Height should only be measured and recorded during screening.
8. During the Screening Visit, a complete physical examination will be conducted. At subsequent visits (and as clinically indicated), limited, symptom-directed physical examinations will be performed.
9. The ECG recordings will be obtained during screening, the Safety Follow-up Visit, and as clinically indicated at other timepoints. When coinciding with blood draws, ECG assessment should be performed prior to blood draws. Patients should be resting in semi-recumbent supine position for ≥ 10 minutes prior to each ECG measurement.
10. The AEs and laboratory abnormalities will be graded per NCI-CTCAE v5.0. All AEs will also be evaluated for seriousness. After the informed consent form has been signed, but prior to the administration of study drug, only SAEs should be reported. After the first dose of study drug, all AEs and SAEs, regardless of their assessed relationship to study drug, are to be reported until either 30 days after the last dose of study treatment (including chemotherapy) or the initiation of new anticancer therapy, whichever occurs first. Weekly review of AEs and concomitant medications, may be conducted by telephone on non-infusion days, ie, Day 15. In addition, telephone contacts with patients should be conducted to assess immune-mediated AEs and concomitant medications (if appropriate, ie, associated with an immune-mediated AE or is a new anticancer therapy) at 60 days, and 90 days (± 14 days) after the last dose of study treatment, regardless of whether the patient starts a new anticancer therapy. Immune-mediated AEs (serious or nonserious) will be reported until 90 days after the last dose of tislelizumab (or placebo), regardless of whether the patient starts a new anticancer therapy.
11. Laboratory assessments on serum chemistry, hematology, coagulation, total CK and CK-MB, and urinalysis will be conducted, of which certain elements will be collected as specified in Section 7.5.4. These laboratory assessments preferentially should be performed at the clinical trial site. However,

recognizing that this might pose a hardship on patients traveling from afar, BeiGene agrees that visits on non-infusion days, if indicated, may be done at an alternate site upon agreement with study principal investigator, and the medical monitor needs to be informed. In the event that CK-MB fractionation is not available, please assess troponin I and/or troponin T instead. If laboratory tests for serum chemistry, hematology, coagulation, cardiac enzymes, and urinalysis at screening are not performed within 7 days prior to the administration of study drug(s) on Cycle 1 of Day 1, these tests should be repeated and reviewed before study drug(s) administration. Hematology and serum chemistry (including liver function tests) will be performed and reviewed prior to dosing of each treatment cycle, as clinically indicated, and upon discontinuation of chemotherapy. Total CK and CK-MB will be assessed for all patients (including the patients who will be receiving tislelizumab after crossover) at screening, at scheduled visits during treatment cycles and at the end of treatment and safety follow-up visits (data collected as specified in Section 7.5.4). After Cycle 1, results are to be reviewed within 48 hours before study drug administration, and a minimum laboratory test to support dosing decision must include hematology and serum chemistry parameters. Urinalysis is to be conducted during the treatment period only if clinically warranted. Refer to Section 8.3.5 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.

12. Includes international normalized ratio, prothrombin time, and activated partial thromboplastin time or partial thromboplastin time.
13. Urine or serum pregnancy (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 7 days prior to randomization. Urine pregnancy tests will be performed at each visit prior to dosing of each cycle. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.
14. Analysis of free T3, free T4, and TSH will be performed by a central laboratory or the local study site laboratory. Thyroid function tests will be performed at screening and every 3 cycles (ie, Cycles 4, 7, 10, etc.), and at the Safety Follow-up Visit.
15. Testing will be performed by a central laboratory and/or the local laboratory at screening and will include HBV/HCV serology (HBsAg, HBsAb, HBcAb, and HCV antibody) and viral load assessment (HBV DNA and HCV RNA).
16. Patients who are suspected or known to have serious/severe respiratory conditions or exhibit significant respiratory symptoms unrelated to the underlying cancer will undergo pulmonary function testing which may include, but is not limited to, spirometry and assessment of diffusion of oxygenation, at a minimum pulse oximetry at rest and with exercise, or alternatively, assessment of diffusion capacity done during the Screening period to assist the determination of suitability on the study.
17. PK samples will be collected for all randomized patients and in sites that are able to adequately perform PK sampling and handling. For tislelizumab, predose (within 60 minutes before starting infusion) samples are required to be collected at Day 1 of Cycles 1, 2, 5, 9, and 17; a postdose (within 30 minutes after completing tislelizumab or placebo infusion) sample is required to be collected at Day 1 of Cycles 1 and 5. An additional PK sample is required to be collected at the mandatory Safety Follow-up. Should a patient present with any ≥ Grade 3 imAE, an additional blood PK sample may be taken to determine the serum concentration of tislelizumab. These tests are required for patients randomized to receive tislelizumab when it is allowed by local regulations/IRBs/IECs.
18. ADA samples will be collected for all randomized patients and in sites that are able to adequately perform ADA sampling and handling. Blood used to test for anti-tislelizumab antibodies should be collected within 60 minutes before beginning the Day 1 infusion of Cycles 1, 2, 5, 9 and 17, and at the mandatory Safety Follow-up Visit. All samples should be drawn at the same time as blood collection for predose PK analysis. These tests are required for patients randomized to receive tislelizumab when it is allowed by local regulations/IRBs/IECs.
19. Radiologic images captured as standard of care prior to obtaining written informed consent and within 28 days of randomization may be used rather than repeating tests, provided they meet the protocol specifications. All measurable and evaluable lesions are required to be assessed and documented at the Screening Visit and reassessed at each subsequent tumor evaluation. An MRI (or CT scan if MRI is contraindicated or not readily available) of the head is required at screening; bone scan or PET is required if clinically indicated. The same radiographic procedure must be used throughout the study for each patient.
    The Investigator must review radiograph results before dosing at the next cycle. Patients will undergo tumor assessments approximately 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 assessment). The Investigator may perform additional scans or more frequent assessments if clinically indicated. See Section 7.6 for more information. Patients who discontinue study treatment early for reasons other than disease progression (eg, toxicity) will continue to undergo tumor assessments following the original plan until the patient experiences disease progression, withdraws consent, dies, or until the study terminates, whichever occurs first.

20. Patients are to provide archival tumor tissues (FFPE blocks or approximately 10 [≥ 5] unstained slides) for biomarker analysis. Fresh biopsy: In the absence of sufficient archival tumor tissues, a fresh biopsy of a tumor lesion at baseline is mandatory (written informed consent is required prior to fresh tumor biopsies). However, fresh biopsy should not be collected from the target lesion only unless there are other sites of measurable disease. See Section 7.8 for more information. Patients who have progressive disease will be asked to provide optional biopsy samples for the assessment of mechanism of resistance (written informed consent is required prior to fresh tumor biopsy).
21. Mandatory blood sample will be collected for biomarker analysis including plasma EBV DNA measurement and germline genomic analysis. Blood samples for plasma EBV analysis will be taken at baseline (both screening and predose on Cycle 1 Day 1); after Cycle 1 Day 1, the following samples will be collected within the visit window and coincide with tumor assessment. On the day of tumor assessment, the blood sample for plasma EBV DNA analysis need to be collected before MRI or CT scan. If a dose has been planned, the blood sample would be recommended to be taken prior to dosing. Blood sample for germline genomic analysis will be collected at screening.
22. Tislelizumab will be given IV Q3W for patients in Arm A. The initial infusion (Cycle 1, Day 1) will be delivered for over 60 minutes, and then can be administered for over 30 minutes for subsequent infusions if well tolerated. Patients must be monitored for ≥ 1 hour after infusion of tislelizumab on Day 1 of Cycle 1 and Cycle 2; from Cycle 3 onward, a monitoring period of ≥ 30 minutes is required. Treatment could continue beyond progression if clinical benefit is seen and treatment is tolerated per the investigator's discretion. Patients should sign an informed consent form for continued treatment beyond RECIST v1.1. Patients in Arm B who will be receiving tislelizumab following crossover after IRC confirmed radiographic disease progression on chemotherapy should not initiate treatment with tislelizumab prior to resolution of treatment-related toxicities to ≤ Grade 1 or baseline, with the exception of select chemotherapy-related toxicities such as hair loss, but should be initiated within 42 days (if applicable), and upon consultation with the medical monitor. Patients in Arm B should follow the same schedule of assessments. Refer to Section 7.4 for further specifications regarding crossover.
23. Chemotherapy will be given as IV infusions for all patients for 4 to 6 cycles. Cisplatin: 80 mg, Day 1 of each cycle; gemcitabine 1 g/m^2, Day 1, Day 8 of each cycle. Refer to Section 5.2 for detail dose and schedule.
24. To be completed prior to any clinical activities during on-study site visits. EORTC QLQ-C30 and EORTC QLQ-H&N35 will be completed at screening, at every other cycle through Cycle 12, then every 4 cycles thereafter, and at the end of treatment.
25. Optional blood sample will be collected for biomarker analysis such as cytokine and soluble protein analysis. The blood sample will be collected at Cycle 1 Day 1 (predose), Cycle 2 Day 1 (predose) and Cycle 3 Day 1 (predose) (written informed consent is required prior to blood collection), and at time of confirmed PD as assessed by the investigator.
26. Day 8 and Day 15 of the first 6 cycles after crossover are not required.

APPENDIX 2. CLINICAL LABORATORY ASSESSMENTS

Serum Chemistry	Hematology	Coagulation
Alanine aminotransferase Aspartate aminotransferase Total bilirubin Direct bilirubin Blood urea nitrogen or urea Creatinine Glucose Alkaline phosphatase Lactate dehydrogenase Magnesium Potassium Sodium Chloride Corrected calcium Total protein Albumin Creatinine Kinase[a] CK-MB[a]	CBC including RBC Hematocrit Hemoglobin Platelet counts WBC count with differential	Prothrombin time Partial thromboplastin time or activated partial thromboplastin time International normalized ratio
Urinalysis[b]	**Pregnancy Test**	**Thyroid Function**
Specific gravity pH Glucose Protein Ketones RBC WBC	Urine or serum pregnancy test	TSH Free T3 Free T4

Abbreviations: CBC, complete blood count; CK-MB, creatine kinase cardiac isoenzyme; pH, negative of the logarithm to base 10 of the activity of the (solvated) hydronium ion; RBC, red blood cell; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone; WBC, white blood cells.

a. In the event that CK-MB fractionation is not available, please assess troponin I and/or troponin T instead.

b. On routine urinalysis, if urine protein is ≥ 2+ by dipstick, then obtain a 24-hour urine sample for total protein and a random urine sample for total protein and creatinine to determine a protein to creatinine ratio.

APPENDIX 3. ECOG PERFORMANCE STATUS

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about > 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair > 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

As published by Oken MM, Creech RH, Tormey DC, et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-55.

APPENDIX 4. THE RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) GUIDELINES, VERSION 1.1

The text below was obtained from the following reference:

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

DEFINITIONS

Response and progression will be evaluated in this trial using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (v1.1). Changes in only the largest diameter (uni-dimensional measurement) of the tumor lesions are used in the RECIST criteria.

Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

Measurable Disease

Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan and MRI (no less than double the slice thickness and a minimum of 10 mm)
- 10 mm caliper measurement by clinical exam (when superficial)
- 20 mm by chest X-ray (if clearly defined and surrounded by aerated lung)

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Nonmeasurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter ≥ 10 to < 15 mm with conventional techniques or < 10 mm using spiral CT scan), are considered nonmeasurable disease. Leptomeningeal disease, ascites, pleural, or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques are all non-measurable.

Bone lesions:

- Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or

MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above

- Blastic bone lesions are nonmeasurable

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Trial protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organ, but in addition should be those that lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan, this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but < 15 mm) should be considered nontarget lesions. Nodes that have a short axis < 10 mm are considered nonpathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Nontarget Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present", "absent", or in rare cases "unequivocal progression" (more details to follow). In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (eg, "multiple enlarged pelvic lymph node" or "multiple liver metastases").

GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are accessible by clinical examination.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and P10 mm diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the trial.

- Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scans).
- Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

- Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.
- Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in CR. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and prostate-specific antigen response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.
- Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or SD in order to differentiate between response (or SD) and progressive disease.

RESPONSE CRITERIA

Evaluation of Target Lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study
- Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report recorded in a separate section where, in order to qualify

for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

- Target lesions that become "too small to measure". While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure".
  When this occurs, it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.
- Lesions that split or coalesce on treatment: When non-nodal lesions "fragment", the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion".

Evaluation of Nontarget Lesions

While some nontarget lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- CR: Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (<10 mm short axis).
- PD: Unequivocal progression (as detailed below) of existing nontarget lesions. (Note: the appearance of one or more new lesions is also considered progression.)
- Non-CR/Non-PD: Persistence of one or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits
- When the patient also has measurable disease: In this setting, to achieve "unequivocal progression" on the basis of the nontarget disease, there must be an overall level of substantial worsening in nontarget disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit

discontinuation of therapy. A modest "increase" in the size of one or more nontarget lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in nontarget disease in the face of SD or PR of target disease will therefore be extremely rare.

- When the patient has only non-measurable disease: This circumstance arises in some phase 3 trials when it is not a criterion of trial entry to have measurable disease. The same general concept applies here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase diameter in a measurable lesion).
- Examples include an increase in a pleural effusion from "trace" to "large", an increase in lymphangitic disease from localized to widespread, or may be described in protocols as "sufficient to require a change in therapy". If "unequivocal progression" is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified on a follow-up trial in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on trial has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While fluorodeoxyglucose (FDG)-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible "new" disease). New lesions on the basis of

FDG-PET imaging can be identified according to the following algorithm:
Negative FDG-PET at baseline, with a positive FDG-PET at follow-up, is a sign of PD based on a new lesion.

- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Evaluation of Best Overall Response

The BOR is the best response recorded from the start of the study drug treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of BOR. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's BOR assignment will depend on the findings of both target and nontarget disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the trial and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "best overall response".

The BOR is determined once all the data for the patient is known. Best response determination in trials where confirmation of CR or PR IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a BOR of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero."

In trials where confirmation of response is required, repeated "NE" time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping trial therapy.

Conditions that define "early progression, early death, and inevaluability" are trial specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of CR. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/ sensitivity.

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes, or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at

the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

Confirmation

In nonrandomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, ie, in randomized trials (phase 2 or 3) or trials where SD or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in trials which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after trial entry at a minimum interval (in general not less than 6 weeks).

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease

SD is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of SD varies in different studies and diseases. If the proportion of patients achieving SD for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between 2 measurements for determination of SD.

Note: The duration of response and SD as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity, and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

APPENDIX 5. PRE-EXISTING IMMUNE DEFICIENCIES OR AUTOIMMUNE DISEASES

Prospective patients should be carefully questioned to determine whether they have any history of an acquired or congenital immune deficiency or autoimmune disease.

Please contact the medical monitor regarding any uncertainty about immune deficiency/autoimmune disease exclusions.

Acute disseminated encephalomyelitis	Addison's disease
Ankylosing spondylitis	Antiphospholipid antibody syndrome
Aplastic anemia	Autoimmune hemolytic anemia
Autoimmune hepatitis	Autoimmune hypoparathyroidism
Autoimmune hypophysitis	Autoimmune myocarditis
Autoimmune oophoritis	Autoimmune orchitis
Autoimmune thrombocytopenic purpura	Behcet's disease
Bullous pemphigoid	Chronic inflammatory demyelinating polyneuropathy
Chung-Strauss syndrome	Crohn's disease
Dermatomyositis	Dysautonomia
Epidermolysis bullosa acquisita	Gestational pemphigoid
Giant cell arteritis	Goodpasture's syndrome
Granulomatosis with polyangiitis	Graves' disease
Guillain-Barré syndrome	Hashimoto's disease
Immunoglobulin A (IgA) neuropathy	Inflammatory bowel disease
Interstitial cystitis	Kawasaki's disease
Lambert-Eaton myasthenia syndrome	Lupus erythematosus
Lyme disease (chronic)	Mooren's ulcer
Morphea	Multiple sclerosis
Myasthenia gravis	Neuromyotonia
Opsoclonus myoclonus syndrome	Optic neuritis
Ord's thyroiditis	Pemphigus
Pernicious anemia	Polyarteritis nodusa
Polyarthritis	Polyglandular autoimmune syndrome
Primary biliary cirrhosis	Psoriasis
Reiter's syndrome	Rheumatoid arthritis
Sarcoidosis	Sjögren's syndrome
Stiff person syndrome	Takayasu's arteritis
Ulcerative colitis	Vogt-Kovangai-Harada disease

APPENDIX 6. NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

Class	Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Adapted from Dolgin M, Association NYH, Fox AC, Gorlin R, Levin RI, New York Heart Association. Criteria Committee. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, MA: Lippincott Williams and Wilkins; March 1, 1994.
Original source: Criteria Committee, New York Heart Association, Inc. Diseases of the Heart and Blood Vessels. Nomenclature and Criteria for diagnosis, 6th edition Boston, Little, Brown and Co. 1964, p 114.

APPENDIX 7. IMMUNE-MEDIATED ADVERSE EVENT EVALUATION AND MANAGEMENT

The recommendations below for the diagnosis and management of any immune-mediated AE (imAE) are intended as a guidance. This document should be used in conjunction with expert clinical judgement (by specialist physicians experienced in the treatment of cancer using immunological agents), and individual institutional guidelines or policies.

Criteria used to diagnose imAEs include blood tests, diagnostic imaging, histopathology, and microbiology assessments to exclude alternative causes such as infection, disease progression, and adverse effects of concomitant drugs. In addition to the results of these tests, the following factors should be considered when making an imAE diagnosis:

- What was the temporal relationship between initiation of tislelizumab and the adverse event?
- How did the patient respond to withdrawal tislelizumab?
- Did the event recur when tislelizumab was reintroduced?
- Was there a clinical response to corticosteroids?
- Is the event an autoimmune endocrinopathy?
- Is disease progression or an alternative diagnosis a more likely explanation?

When alternative explanations to autoimmune toxicity have been excluded, the imAE field associated with the AE in the eCRF should be checked.

Recommended Diagnostic Tests in the Management of Possible Immune-Mediated Adverse Events

Immune-Mediated Toxicity	Diagnostic Evaluation Guideline
Thyroid Disorders	Scheduled and repeat thyroid function tests (TSH and T4).
Hypophysitis	Check visual fields and consider pituitary endocrine axis blood profile. Perform pituitary and whole brain MRI in patients with headache, visual disturbance, unexplained fatigue, asthenia, weight loss and unexplained constitutional symptoms. Consider consultation with an endocrinologist if an abnormality is detected.
Pneumonitis	All patients presenting with new or worsened pulmonary symptoms or signs, such as an upper respiratory infection, new cough, shortness of breath or hypoxia should be assessed by high-resolution CT. Consider pulmonary function test including *D*LCO. Radiographic appearance is often nonspecific. Depending on the location of the abnormality, bronchoscopy and bronchoalveolar lavage or lung biopsy may be considered. Consult with a respiratory medicine physician for cases of uncertain cause.

Recommended Diagnostic Tests in the Management of Possible Immune-Mediated Adverse Events

Immune-Mediated Toxicity	Diagnostic Evaluation Guideline
Neurological Toxicity	Perform a comprehensive neurological examination and brain MRI for all CNS symptoms; review alcohol history and other medications. Conduct a diabetic screen, and assess blood B12/folate, HIV status, TFTs, and consider autoimmune serology. Consider the need for brain/spine MRI/MRA and nerve conduction study for peripheral neuropathy. Consult with a neurologist if there are abnormal findings.
Colitis	Review dietary intake and exclude steatorrhea. Consider comprehensive testing, including the following: CBC, UEC, LFTs, CRP, TFTs, stool microscopy and culture, viral PCR, Clostridium difficile toxin, cryptosporidia (drug-resistant organism). In case of abdominal discomfort, consider imaging, eg, X-ray, CT scan. If a patient experiences bleeding, pain or distension, consider colonoscopy with biopsy and surgical intervention, as appropriate.
Eye Disorders	If a patient experiences acute, new onset, or worsening of eye inflammation, blurred vision, or other visual disturbances, refer the patient urgently to an ophthalmologist for evaluation and management.
Hepatitis	Check ALT/AST/total bilirubin, INR/albumin; the frequency will depend on severity of the AE (eg, daily if Grade 3-4; every 2-3 days if Grade 2, until recovering). Review medications (eg, statins, antibiotics) and alcohol history. Perform liver screen including Hepatitis A/B/C serology, Hepatitis E PCR and assess anti-ANA/SMA/LKM/SLA/LP/LCI, iron studies. Consider imaging, eg, ultrasound scan for metastases or thromboembolism. Consult with a hepatologist and consider liver biopsy.
Renal toxicity	Review hydration status and medication history. Test and culture urine. Consider renal ultrasound scan, protein assessment (dipstick/24-hour urine collection), or phase-contrast microscopy. Refer to nephrology for further management assistance.
Dermatology	Consider other causes by conducting a physical examination, consider dermatology referral for skin biopsy.
Joint or muscle inflammation	Conduct musculoskeletal history and perform complete musculoskeletal examination. Consider joint X-ray and other imaging as required to exclude metastatic disease. Perform autoimmune serology and refer to rheumatology for further management assistance. For suspected myositis/rhabdomyolysis/myasthenia include: CK, ESR, CRP, troponin and consider a muscle biopsy.
Myocarditis	Perform ECG, echocardiogram, CK/CK-MB, troponin (I and/or T), and refer to a cardiologist.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; CK, creatinine kinase; CK-MB, creatinine kinase cardiac isoenzyme; CNS, central nervous system; CRP, C-reactive protein; CT, computed tomography; *D*LCO, diffusing capacity for carbon monoxide; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; CBC, complete blood count; HIV, human immunodeficiency virus; INR, international normalized ratio; LCI, liver cytosolic antigen; LFT, liver function test; LKM, liver kidney microsomal antibody; LP, liver pancreas antigen; MRA, magnetic resonance angiogram; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; SLA, soluble liver antigen; SMA, smooth muscle antibody; T4, thyroxine; TFT, thyroid function tests; TSH, thyroid-stimulating hormone; UEC, urea electrolytes and creatinine.

Treatment of Immune-Mediated Adverse Events

- Immune-mediated AEs can escalate quickly; study treatment interruption, close monitoring, timely diagnostic work-up and treatment intervention, as appropriate, with patients is required
- Immune-mediated AEs should improve promptly after introduction of immunosuppressive therapy. If this does not occur, review the diagnosis, seek further specialist advice and contact the study medical monitor
- For some Grade 3 toxicities that resolve quickly, rechallenge with study drug may be considered if there is evidence of a clinical response to study treatment, after consultation with the study medical monitor
- Steroid dosages in the table below are for oral or intravenous (methyl)prednisolone. Equivalent dosages of other corticosteroids can be substituted. For steroid-refractory imAEs, consider use of steroid-sparing agents (eg, mycophenolate mofetil [MMF])
- Consider prophylactic antibiotics for opportunistic infections if the patient is receiving long-term immunosuppressive therapy

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Thyroid Disorders	**1-2** Asymptomatic TFT abnormality or mild symptoms	Replace thyroxine if hypothyroid, until TSH/T4 levels return to normal range. Thyrotoxic patients should be referred to an endocrinologist. In cases with systemic symptoms: withhold study treatment, treat with a beta blocker and consider oral prednisolone 0.5 mg/kg/day for thyroid pain. Taper corticosteroids over 2-4 weeks. Monitor thyroid function regarding the need for hormone replacement.	Continue study treatment or withhold treatment in cases with systemic symptoms.
	3-4 Severe symptoms, hospitalization required	Refer patient to an endocrinologist. If hypothyroid, replace with thyroxine 0.5-1.6 µg/kg/day (for the elderly or those with co-morbidities, the suggested starting dose is 0.5 µg/kg/day). Add oral prednisolone 0.5 mg/kg/day for thyroid pain. Thyrotoxic patients require treatment with a beta blocker and may require carbimazole until thyroiditis resolves.	Hold study treatment; resume when resolved/improved to Grade 0-1.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Hypophysitis	**1-2** Mild-moderate symptoms	Refer patient to an endocrinologist for hormone replacement. Add oral prednisolone 0.5-1 mg/kg/day for patients with pituitary inflammation. Taper corticosteroids over at least 1 month. If there is no improvement in 48 hours, treat as Grade 3-4. Taper corticosteroids over at least 1 month.	Continue study treatment.
	3-4 Severe or life-threatening symptoms	Refer patient to an endocrinologist for assessment and treatment. Initiate pulse IV methylprednisolone 1 mg/kg for patients with headache/visual disturbance due to pituitary inflammation. Convert to oral prednisolone and taper over at least 1 month. Maintain hormone replacement according to endocrinology advice. Maintain hormone replacement according to endocrinology advice.	Hold study treatment for patients with headache/visual disturbance due to pituitary inflammation until resolved/improved to Grade 2 or less. Discontinuation is usually not necessary.
Pneumonitis	**1** Radiographic changes only	Monitor symptoms every 2-3 days. If appearance worsens, treat as Grade 2.	Consider holding study treatment until appearance improves and cause is determined.
	2 Symptomatic: exertional breathlessness	Commence antibiotics if infection suspected. Add oral prednisolone 1 mg/kg/day if symptoms/appearance persist for 48 hours or worsen. Consider Pneumocystis infection prophylaxis. Taper corticosteroids over at least 6 weeks. Consider prophylaxis for adverse steroid effects: eg, blood glucose monitoring, vitamin D/calcium supplement.	Hold study treatment. Retreatment is acceptable if symptoms resolve completely or are controlled on prednisolone ≤ 10 mg/day. Discontinue study treatment if symptoms persist with corticosteroid treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3-4 Severe or life-threatening symptoms Breathless at rest	Admit to a hospital and initiate treatment with IV methylprednisolone 2-4 mg/kg/day. If there is no improvement, or worsening after 48 hours, add infliximab 5 mg/kg (if no hepatic involvement). Convert to oral prednisolone and taper over at least 2 months. Cover with empiric antibiotics and consider prophylaxis for Pneumocystis infection and other adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement.	Discontinue study treatment.
Neurological Toxicity	**1** Mild symptoms	–	Continue study treatment.
	2 Moderate symptoms	Treat with oral prednisolone 0.5-1 mg/kg/day. Taper over at least 4 weeks. Obtain neurology consultation.	Hold study treatment; resume when resolved/improved to Grade 0-1.
	3-4 Severe/life-threatening	Initiate treatment with oral prednisolone or IV methylprednisolone 1-2 mg/kg/day, depending on symptoms. Taper corticosteroids over at least 4 weeks. Consider azathioprine, MMF, cyclosporine if no response within 72-96 hours.	Discontinue study treatment.
Colitis/Diarrhea	**1** Mild symptoms: < 3 liquid stools per day over baseline and feeling well	Symptomatic management: fluids, loperamide, avoid high fiber/lactose diet. If Grade 1 persists for > 14 days manage as a Grade 2 event.	Continue study treatment.
	2 Moderate symptoms: 4-6 liquid stools per day over baseline, or abdominal pain, or blood in stool, or nausea, or nocturnal episodes	Oral prednisolone 0.5 mg/kg/day (non-enteric coated). Do not wait for any diagnostic tests to start treatment. Taper steroids over 2-4 weeks, consider endoscopy if symptoms are recurring.	Hold study treatment; resume when resolved/improved to baseline grade.
	3 Severe symptoms: > 6 liquid stools per day over baseline, or if episodic within 1 hour of eating	Initiate IV methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Consider prophylaxis for adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement.	Hold study treatment; retreatment may be considered when resolved/improved to baseline grade and after discussion with the study medical monitor.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	4 Life-threatening symptoms	If no improvement in 72 hours or symptoms worsen, consider infliximab 5 mg/kg if no perforation, sepsis, TB, hepatitis, NYHA grade III/IV CHF or other immunosuppressive treatment: MMF or tacrolimus. Consult gastroenterologist to conduct colonoscopy/ sigmoidoscopy.	Discontinue study treatment.
Skin reactions	**1** Skin rash, with or without symptoms, < 10% BSA	Avoid skin irritants and sun exposure; topical emollients recommended.	Continue study treatment.
	2 Rash covers 10%-30% of BSA	Avoid skin irritants and sun exposure; topical emollients recommended. Topical steroids (moderate strength cream once a day or potent cream twice a day) ± oral or topical antihistamines for itch. Consider a short course of oral steroids.	Continue study treatment.
	3 Rash covers > 30% BSA or Grade 2 with substantial symptoms	Avoid skin irritants and sun exposure; topical emollients recommended. Initiate steroids as follows based on clinical judgement: For moderate symptoms: oral prednisolone 0.5-1 mg/kg/day for 3 days then taper over 2-4 weeks. For severe symptoms: IV methylprednisolone 0.5-1 mg/kg/day; convert to oral prednisolone and taper over at least 4 weeks.	Hold study treatment. Re-treat when AE is resolved or improved to mild rash (Grade 1-2) after discussion with the study medical monitor.
	4 Skin sloughing > 30% BSA with associated symptoms (eg, erythema, purpura, epidermal detachment)	Initiate IV methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Admit to a hospital and seek urgent dermatology consultation.	Discontinue study treatment.
Hepatitis	**1** ALT or AST > ULN to 3X ULN	Check LFTs within 1 week and before the next dose check LFTs to verify that there has been no worsening. If LFTs are worsening, recheck every 48-72 hours until improvement is seen.	Continue study treatment if LFTs are unchanged or improving. Hold study treatment if LFTs are worsening until improvement is seen.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	2 ALT or AST 3-5X ULN	Recheck LFTs every 48-72 hours: For persistent ALT/AST elevation: consider oral prednisolone 0.5-1 mg/kg/day for 3 days then taper over 2-4 weeks. For rising ALT/AST: start oral prednisolone 1 mg/kg/day and taper over 2-4 weeks; re-escalate dose if LFTs worsen, depending on clinical judgement.	Hold study treatment; treatment may be resumed when resolved/improved to baseline Grade and prednisolone tapered to ≤ 10 mg.
	3 ALT or AST 5-20X ULN	ALT/AST < 400 IU/L and normal bilirubin/INR/albumin: Initiate oral prednisolone 1 mg/kg and taper over at least 4 weeks. ALT/AST > 400 IU/L or raised bilirubin/INR/low albumin: Initiate IV (methyl)prednisolone 2 mg/kg/day. When LFTs improve to Grade 2 or lower, convert to oral prednisolone and taper over at least 4 weeks.	Hold study treatment until improved to baseline Grade; reintroduce only after discussion with the study medical monitor.
	4 ALT or AST > 20X ULN	Initiate IV methylprednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 6 weeks.	Discontinue study treatment.
	Worsening LFTs despite steroids: • If on oral prednisolone, change to pulsed IV methylprednisolone • If on IV, add mycophenolate mofetil (MMF) 500-1000 mg twice a day • If worsens on MMF, consider addition of tacrolimus Duration and dose of steroid required will depend on severity of event		
Nephritis	**1** Creatinine 1.5X baseline or > ULN to 1.5X ULN	Repeat creatinine weekly. If symptoms worsen, manage as per criteria below.	Continue study treatment.
	2 Creatinine > 1.5X-3X baseline or > 1.5X-3X ULN	Ensure hydration and review creatinine in 48-72 hours; if not improving, consider creatinine clearance measurement by 24-hour urine collection. Discuss with nephrologist the need for kidney biopsy. If attributed to study drug, initiate oral prednisolone 0.5-1 mg/kg and taper over at least 2 weeks. Repeat creatinine/U&E every 48-72 hours.	Hold study treatment. If not attributed to drug toxicity, restart treatment. If attributed to study drug and resolved/improved to baseline grade: Restart study drug if tapered to < 10 mg prednisolone.
	3 Creatinine > 3X baseline	Hospitalize patient for monitoring and fluid balance; repeat creatinine	Hold study treatment until the cause is

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	or > 3X-6X ULN	every 24 hours; refer to a nephrologist and discuss need for biopsy. If worsening, initiate IV (methyl)prednisolone 1-2 mg/kg. Taper corticosteroids over at least 4 weeks.	investigated. If study drug suspected: Discontinue study treatment.
	4 Creatinine > 6X ULN	As per Grade 3, patient should be managed in a hospital where renal replacement therapy is available.	Discontinue study treatment.
Diabetes/ Hyperglycemia	**1** Fasting glucose value ULN to 160 mg/dL; ULN to 8.9 mmol/L	Monitor closely and treat according to local guideline. Check for C-peptide and antibodies against glutamic acid decarboxylase and islet cells are recommended	Continue study treatment.
	2 Fasting glucose value 160-250 mg/dL; 8.9-13.9 mmol/L	Obtain a repeat blood glucose level at least every week. Manage according to local guideline.	Continue study treatment or hold treatment if hyperglycemia is worsening. Resume treatment when blood glucose is stabilized at baseline or Grade 0-1.
	3 Fasting glucose value 250-500 mg/dL; 13.9-27.8 mmol/L	Admit patient to hospital and refer to a diabetologist for hyperglycemia management. Corticosteroids may exacerbate hyperglycemia and should be avoided.	Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1.
	4 Fasting glucose value > 500 mg/dL; > 27.8 mmol/L	Admit patient to hospital and institute local emergency diabetes management. Refer the patient to a diabetologist for insulin maintenance and monitoring.	
Ocular Toxicity	**1** Asymptomatic eye exam/test abnormality	Consider alternative causes and prescribe topical treatment as required.	Continue study treatment.
	2 Anterior uveitis or mild symptoms	Refer patient to an ophthalmologist for assessment and topical corticosteroid treatment. Consider a course of oral steroids.	Continue study treatment or hold treatment if symptoms worsen or if there are symptoms of visual disturbance.
	3 Posterior uveitis/ panuveitis or significant symptoms	Refer patient urgently to an ophthalmologist. Initiate oral prednisolone 1-2 mg/kg and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1; reintroduce only after discussion with the study medical monitor.
	4	Initiate IV (methyl)prednisolone 2 mg/kg/day. Convert to oral	Discontinue study

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	Blindness (at least 20/200) in the affected eyes	prednisolone and taper over at least 4 weeks.	treatment.
Pancreatitis	**2** Asymptomatic, blood test abnormalities	Monitor pancreatic enzymes.	Continue study treatment.
	3 Abdominal pain, nausea and vomiting	Admit to hospital for urgent management. Initiate IV (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when amylase/lipase improved to Grade 2, and taper over at least 4 weeks.	Hold study treatment; reintroduce only after discussion with the study medical monitor.
	4 Acute abdominal pain, surgical emergency	Admit to hospital for emergency management and appropriate referral.	Discontinue study treatment.
Arthritis	**1** Mild pain with inflammation, swelling	Management per local guideline.	Continue study treatment.
	2 Moderate pain with inflammation, swelling, limited instrumental (fine motor) activities	Management as per local guideline. Consider referring patient to a rheumatologist. If symptoms worsen on treatment manage as a Grade 3 event.	Continue treatment or, if symptoms continue worsens, hold study treatment until symptoms improve to baseline or Grade 0-1.
	3 Severe pain with inflammation or permanent joint damage, daily living activity limited	Refer patient urgently to a rheumatologist for assessment and management. Initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks.	Hold study treatment unless improved to Grade 0-1; reintroduce only after discussion with the study medical monitor.
Mucositis/ stomatitis	**1** Test findings only or minimal symptoms	Consider topical treatment or analgesia as per local guideline.	Continue study treatment.
	2 Moderate pain, reduced oral intake, limited instrumental activities	As per local guidelines, treat with analgesics, topical treatments and oral hygiene care. Ensure adequate hydration. If symptoms worsen or there is sepsis or bleeding, manage as a Grade 3 event.	Continue study treatment.
	3 Severe pain, limited food and fluid intake, daily living activity limited	Admit to hospital for appropriate management. Initiate IV (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when symptoms improved to Grade 2 and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1.
	4 Life-threatening	Admit to hospital for emergency care. Consider IV corticosteroids if	Discontinue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	complications or dehydration	not contraindicated by infection.	
Myositis/ Rhabdomyolysis	**1** Mild weakness with/without pain	Prescribe analgesics. If CK is significantly elevated and patient has symptoms, consider oral steroids and treat as Grade 2	Continue study treatment.
	2 Moderate weakness with/without pain	If CK is 3X ULN or worse, initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks	Hold study treatment until improved to Grade 0-1
	3-4 Severe weakness, limiting self-care	Admit to hospital and initiate oral prednisolone 1 mg/kg. Consider bolus IV (methyl)prednisolone and 1-2 mg/kg/day maintenance for severe activity restriction or dysphagia. If symptoms do not improve add immunosuppressant therapy. Taper oral steroids over at least 4 weeks	Hold study treatment until improved to Grade 0-1. Discontinue if any evidence of myocardial involvement
Myocarditis	**< 2** Asymptomatic but significantly increased CK-MB or increased troponin OR clinically significant intraventricular conduction delay	Initiate cardiac evaluation under close monitoring with repeat serum testing; consider referral to a cardiologist. If diagnosis of myocarditis is confirmed, treat as Grade 2	Hold study treatment. If a diagnosis of myocarditis is confirmed, permanently discontinue study treatment in patients with moderate or severe symptoms. Patients with no symptoms or mild symptoms may not restart tislelizumab unless cardiac parameters have returned to baseline and after discussion with the study medical monitor.
	2 Symptoms on mild-moderate exertion	Admit to hospital and initiate oral prednisolone or IV (methyl)prednisolone at 1-2 mg/kg/day. Consult with a cardiologist and manage symptoms of cardiac failure according to local guidelines. If no immediate response change to pulsed doses of (methyl)prednisolone 1g/day and add MMF, infliximab or anti-thymocyte globulin	
	3 Severe symptoms with mild exertion		
	4 Life-threatening		

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; CHF, congestive heart failure; CK, creatinine kinase; CK-MB, creatinine kinase cardiac isoenzyme; INR, international normalized ratio; IV, intravenous; LFT, liver function test; MMF, mycophenolate mofetil; NYHA, New York Heart Association; T4, thyroxine; TB, tuberculosis; TFT, thyroid function test; TSH, thyroid-stimulating hormone; U&E, urea and electrolytes; ULN, upper limit of normal.

APPENDIX 8. COCKCROFT-GAULT FORMULA AND CALVERT FORMULA

FOR SERUM CREATININE CONCENTRATION (SCr) IN MG/DL[a]

Cl_{cr} for males (mL/min) $= \frac{(140\text{-age})(\text{weight}^{b})}{(72)(\text{SCr})}$

CL_{cr} for females (mL/min) $= \frac{(0.85)(140\text{-age})(\text{weight}^{b})}{(72)(\text{SCr})}$

FOR SERUM CREATININE CONCENTRATION (SCr) IN µMOL/L[a]

Cl_{cr} for males (mL/min) $= \frac{(140\text{-age})(\text{weight}^{b})}{(0.81)(\text{SCr})}$

CL_{cr} for females (mL/min) $= \frac{(0.85)(140\text{-age})(\text{weight}^{b})}{(0.81)(\text{SCr})}$

a Age in years and weight in kilograms.

b If the subject is obese (>30% over ideal body weight), use ideal body weight in calculation of estimated CL_{cr}.

Abbreviation: CL_{cr}, creatinine clearance; SCr, serum creatinine concentration.

CALVERT FORMULA:

(GFR*+25) x AUC= dose in mg.

* glomerular filtration rate (GFR) calculation formula is same as Cl_{Cr} formula as shown above.

APPENDIX 9. CONTRACEPTION GUIDELINES AND DEFINITIONS OF "WOMEN OF CHILDBEARING POTENTIAL," "NO CHILDBEARING POTENTIAL"

Contraception Guidelines

The Clinical Trials Facilitation Group's recommendations related to contraception and pregnancy testing in clinical trials include the use of highly effective forms of birth control. These methods include the following:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with the inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with the inhibition of ovulation (oral, injectable, or implantable)
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized male partner, provided that the vasectomized partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of surgical success.
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of exposure associated with the study treatment).
  - NOTE: Total sexual abstinence should only be used as a contraceptive method if it is in line with the patient's usual and preferred lifestyle. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable methods of contraception.

Of note, barrier contraception (including male and female condoms with or without spermicide) is not considered a highly effective method of contraception and if used, this method must be combined with a highly effective form of birth control, listed above.

Definitions of "Women of Childbearing Potential," "Women of No Childbearing Potential"

As defined in this protocol, "women of childbearing potential" are female patients who are physiologically capable of becoming pregnant.

Conversely, "women of no childbearing potential" are defined as female patients meeting any of the following criteria:

- Surgically sterile (ie, through bilateral salpingectomy, bilateral oophorectomy, or hysterectomy)
- Postmenopausal, defined as:
  - ≥ 55 years of age with no spontaneous menses for ≥ 12 months OR

- < 55 years of age with no spontaneous menses for ≥ 12 months AND with postmenopausal follicle-stimulating hormone concentration > 30 IU/mL and all alternative medical causes for the lack of spontaneous menses for ≥ 12 months have been ruled out, such as polycystic ovarian syndrome, hyperprolactinemia, etc.

If an FSH measurement is required to confirm postmenopausal state, concomitant use of hormonal contraception or hormonal replacement therapy should be excluded.

Adapted from Clinical Trials Facilitation Group (CTFG). Recommendations related to contraception and pregnancy testing in clinical trials. September 15, 2014. http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

APPENDIX 10. DOSE MODIFICATION GUIDELINES FOR CHEMOTHERAPY

For the purposes of this protocol, the sponsor defines a chemotherapy cycle as the administration of at least one chemotherapy component (ie, cisplatin or gemcitabine). Cycles in which no chemotherapy component is given do not count toward the total number of chemotherapy cycles.

If only tislelizumab but no chemotherapeutic partner has been administered during a cycle, the cycle does not count toward the total number of chemotherapy cycles. For example, if 4 cycles of chemotherapy were planned, but no component of chemotherapy could be administered during Cycle 4, Cycle 5 counts as the fourth cycle of chemotherapy. Because of the complex nature and possible permutations of such dosage interruptions and reintroductions, site personnel should contact the monitor, and the monitor will instruct the site on how to open the appropriate visits and electronic Case Report Form (eCRF) so that the site can then record the interruption and reintroduction accordingly on the eCRF.

Dose modification should be made in accordance to prescribing information and as per institutional guidelines.

- If considered in the best interest of the patient and consistent with local practice, investigators may decide to use supportive measures/treatment, and/or secondary prophylaxis instead of dose reductions for the next cycle.
- These provided triggers for dose modifications are recommendations only.
- Dose adjustments are based on nadir blood counts since the preceding chemotherapy administration. Dose level adjustments are relative to that of the preceding administration.
- All dose modifications should be made based on the worst grade toxicity.

Table 8. Chemotherapy Dose Modification for Hematological Toxicity for Gemcitabine and Cisplatin

Adverse Event		Treatment
Febrile neutropenia; documented infection		1) The first episode of febrile neutropenia or documented infection will result in antibiotic treatment and reduction by 25% of both drugs doses 2) If there is a second episode despite dose reduction, the patient must receive prophylactic antibiotics during the subsequent cycles 3) If there is a third episode, the chemotherapy will be discontinued.
Neutropenia	Grade 3 (0.5-0.99 x 10^9/L)	Chemotherapy delay until ≤ Grade 1 (≥ 1.5 x 10^9/L); restart with the full dose
	Grade 4 (< 0.5 x 10^9/L)	Chemotherapy delay until recovered to ≤ Grade 1; dose reduction of all further doses by 25%

Adverse Event		Treatment
Thrombocytopenia	Grade 1	Chemotherapy delay until recovered to normal; restart with the full dose
	≥ Grade 2	Chemotherapy delay until recovered to normal; dose reduction of all further doses by 25%

Note: If considered in the best interest of the patient and consistent with local practice, investigators may decide to use supportive measures/treatment and/or secondary prophylaxis instead of dose reductions for the next cycle. The provided triggers for dose modifications are recommendations only.

Recommended Dose Modifications for Non-hematologic Toxicities

The dose adjustments of chemotherapy for non-hematologic toxicity are described in the following table. All dose modifications should be made based on the worst grade toxicity.

Table 9. Chemotherapy Dose Modifications for Non-Hematological Toxicity for Gemcitabine and Cisplatin

Toxicity	Grade	Treatment
Renal toxicity	≥ Grade 1	Delay chemotherapy until recovered to Grade 0 or baseline, dose reduction by 25% for other drug; if recur, stop chemotherapy
Ototoxicity	Grade 2	dose reduction of all further doses of cisplatin by 25%
	Grade 3-4	Delay chemotherapy until recovered to ≤ Grade 2
Sensory neuropathy	Grade 2	Dose reduction for all further doses of cisplatin by 25%
	Grade 3	Stop cisplatin, stop gemcitabine
	Grade 4	Stop cisplatin, and/or gemcitabine
Other organ toxicity	Grade 2	Delay chemotherapy until ≤ Grade 1 or baseline*.
	Grade 3-4	Delay chemotherapy until recovered to ≤ Grade 1 or baseline*, dose reduction of all further dose by 25%

Note: If considered in the best interest of the patient and consistent with local practice, investigators may decide to use supportive measures/treatment, and/or secondary prophylaxis instead of dose reductions for the next cycle. The provided triggers for dose modifications are recommendations only.
*Skin reactions, paronychia, alopecia, fatigue, nausea/vomiting which may have resolved to Grade 2 or baseline.

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