CLINICAL STUDY PROTOCOL TITLE PAGE

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Tislelizumab (BGB-A317) Versus Placebo in Combination With Concurrent Chemoradiotherapy in Patients With Localized Esophageal Squamous Cell Carcinoma

Brief Title:

A Study to Investigate Tislelizumab (BGB-A317) Versus Placebo in Combination With Concurrent Chemoradiotherapy in Patients With Localized Esophageal Squamous Cell Carcinoma

Protocol Number:	BGB-A317-311	
Amendment Number:	Amendment 4 Global	
Investigational Medicinal Product:	Tislelizumab	
Regulatory Agency Identification Number(s):	Clinical Drug Trials ID:	CTR20190198
	ClinicalTrials.gov Identifier:	NCT03957590
Sponsor:	BeiGene (Shanghai) Co., Ltd. 4th Floor, Building D 780 Cailun Road China (Shanghai) Pilot-free Trade Zone Shanghai 201203, P.R. China	
Approval Date:	*See electronic signature*	
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FINAL PROTOCOL APPROVAL SHEET

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Tislelizumab (BGB-A317) Versus Placebo in Combination With Concurrent Chemoradiotherapy in Patients With Localized Esophageal Squamous Cell Carcinoma

BeiGene, Ltd., Approval:

See electronic signature	*See electronic signature*
Sponsor Development Core Team Lead	Date

INVESTIGATOR SIGNATURE PAGE

Protocol Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Tislelizumab (BGB-A317) Versus Placebo in Combination With Concurrent Chemoradiotherapy in Patients With Localized Esophageal Squamous Cell Carcinoma

Protocol Identifier: BGB-A317-311

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. 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 Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd., or one of its subsidiaries.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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DOCUMENT HISTORY

Prior versions of the study protocol are listed in the table below.

Amendment Version Number	Approval Date	Type of Protocol Amendment
BGB-A317-311 Amendment 3.0	18 October 2022	Substantial
BGB-A317-311 Amendment 2.0	18 September 2021	Substantial
BGB-A317-311 Amendment 1.0	29 December 2020	Substantial
Original protocol	10 January 2019	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

The primary purpose of amendment 4.0 is to ensure that the PFS final analysis could be performed within feasible time as event accumulation of PFS is significantly slowing down, incorporating the feedback from health authority. The key changes made in this amendment are described in the table below.

A few clarifications, non-substantial updates, editorial and formatting changes have also been made but are not included in this summary.

Protocol Amendment Summary of Changes Table

Section Number and Title	Summary of Change	Brief Rationale for Change
Section 9.6 Sample Size Consideration Section 9.7 Interim Analyses	• Added that the final analysis of PFS and OS will be performed concurrently when approximately 200 PFS events or approximately 191 OS events have been observed, whichever occurs first • Removed one interim analysis of OS and updated the statistical analysis power accordingly	Ensure that the PFS final analysis could be performed within feasible time as event accumulation of PFS is significantly slowing down, incorporating the feedback from health authority
Section 3.4 Safety Follow-up Section 3.6.3 End of Study Appendix 1 Schedule of Assessments	• Added description of a long-term extension study and posttrial continued access program • Updated the language regarding patients who may benefit from tislelizumab being offered the option to continue treatment after study completion • Added a requirement for patients to complete an End-of-Treatment/Safety Follow-up Visit before continuing in a long-term extension study or posttrial continued access program	Clarify available options for patients to continue treatment after study completion

Section Number and Title	Summary of Change	Brief Rationale for Change
Section 5.5.5 Blinding	• Added unblinding after PFS final analysis • Removed some duplicate statements	• Provide guidance on unblinding after the PFS final analysis • Simplify guidance and avoid potential confusion
Section 1.4.2 Toxicology	Updated toxicology results	Updated toxicology information with results from newly conducted studies
Section 13.4 Patient and Data Confidentiality	Updated language regarding patients' privacy and confidentiality	To be compliant with ICH Good Clinical Practice and local regulations
Section 2.1.3 Exploratory Objectives Section 2.2.3 Exploratory Endpoints Section 7.7 Biomarkers	Updated PBMC testing assay statement	To keep consistent with future testing needs
Title Page, DOCUMENT HISTORY (New Section), and PROTOCOL AMENDMENT SUMMARY OF CHANGES (New Section)	Updated	For consistency with new BeiGene protocol template

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

SYNOPSIS

Name of Sponsor/Company: BeiGene (Shanghai) Co., Ltd.
Investigational Product: Tislelizumab (BGB-A317)
Title of Study: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Tislelizumab (BGB-A317) Versus Placebo in Combination With Concurrent Chemoradiotherapy in Patients With Localized Esophageal Squamous Cell Carcinoma
Protocol Identifier: BGB-A317-311
Phase of Development: 3
Number of Patients: Approximately 366 patients
Study Centers: Approximately 30 centers
Study Objectives: **Primary:** • To compare the progression-free survival (PFS) as assessed by the Blinded Independent Review Committee (BIRC) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (v1.1) in the Intent-to-Treat (ITT) Analysis Set between tislelizumab in combination with concurrent chemoradiotherapy (cCRT) and placebo in combination with cCRT. **Secondary:** <u>Key Secondary</u> • To compare the overall survival (OS) in the ITT Analysis Set between tislelizumab and placebo in combination with cCRT. <u>Other Secondary</u> • To compare the patient-reported outcomes of health-related quality of life (HRQoL) between tislelizumab and placebo in combination with cCRT. • To compare the overall response rate (ORR) as assessed by the BIRC per RECIST v1.1 in the ITT Analysis Set between tislelizumab and placebo in combination with cCRT. • To compare the duration of response (DOR) as assessed by the BIRC per RECIST v1.1 in the ITT Analysis Set between tislelizumab and placebo in combination with cCRT. • To evaluate the safety and tolerability of tislelizumab combined with cCRT. **Exploratory:** • To compare the 1-year PFS rate as assessed by the investigator per RECIST v1.1 in the ITT Analysis Set between tislelizumab and placebo in combination with cCRT. • To compare the 2-year PFS rate as assessed by the investigator per RECIST v1.1 in the ITT Analysis Set between tislelizumab and placebo in combination with cCRT. • To explore the potential predictive, prognostic biomarkers including but not limited to: programmed cell death protein ligand-1 (PD-L1) expression; gene expression profiling (GEP); tumor infiltrating lymphocytes (TILs); tumor mutational burden (TMB), gene mutation, and microsatellite instability (MSI); and/or blood-based biomarkers (flow cytometry, immune-phenotyping [panel: A173, A167, A163, and A378], and circulating tumor DNA [ctDNA] alteration; and peripheral blood mononuclear cell [PBMC] immune cell profiling) in archival and/or fresh tumor tissue and blood samples obtained before and/or during study treatment,

and/or at disease progression, and the association with disease status, response to study treatment and mechanism of resistance.

- To assess the pharmacokinetics (PK) of tislelizumab in combination with cCRT.
- To assess host immunogenicity to tislelizumab.

Study Endpoints:

Primary:

- PFS – defined as the time from randomization to the first documented disease progression as determined by BIRC per RECIST v1.1, or death from any cause, whichever occurs first.

Secondary:

Key Secondary

- OS – defined as the time from the date of randomization to the date of death due to any cause.

Other Secondary

- HRQoL assessment defined as patients' reported treatment effects using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Oesophageal Cancer Module (EORTC QLQ-OES18).
- ORR – defined as the proportion of patients who had complete response (CR) or partial response (PR) as assessed by BIRC per RECIST v1.1.
- DOR – defined as the time from the first occurrence of a documented objective response to the time of relapse, as determined by BIRC per RECIST v1.1 or death from any cause, whichever occurs first.
- The 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, 2017).

Exploratory:

- 1-year PFS rate – defined as the Kaplan-Meier estimator of proportion of patients alive and progression free at 1 year from randomization, as determined by investigator per RECIST v1.1.
- 2-year PFS rate – defined as the Kaplan-Meier estimator of proportion of patients alive and progression free at 2 years from randomization, as determined by investigator per RECIST v1.1.
- Status of PD-L1-related, immune-related, esophageal squamous cell carcinoma (ESCC)-related, and other exploratory biomarkers (GEP, TILs, TMB/gene mutation/MSI, and/or blood-based biomarkers [flow cytometry and immune-phenotyping (panel: A173, A167, A163, and A378), ctDNA alteration, and PBMC immune cell profiling]) in archival and/or fresh tumor tissues and blood samples obtained before and/or during study treatment and/or at disease progression, and the association with disease status and/or response to tislelizumab in combination with cCRT and placebo in combination with cCRT.
- Assessments of PK of tislelizumab when given with cCRT.
- Assessments of immunogenicity of tislelizumab by determining the incidence of anti-drug antibodies (ADA).

Study Design:

This is a double-blind, placebo-controlled, randomized, multicenter, Phase 3 study designed to evaluate the efficacy and safety of tislelizumab versus placebo in combination with cCRT in approximately 366 patients with localized ESCC. This study will be conducted in China.

The primary outcome measure of the study is PFS as assessed by the BIRC in the ITT Analysis Set. Patients with pathologically confirmed localized ESCC who are considered suitable for cCRT (inoperable without prior radiotherapy) are eligible.

Eligible patients will be stratified by the following two factors:

- Eastern Cooperative Oncology Group (ECOG) performance status: 0 versus 1
- Clinical stage: II/III vs IVa (AJCC version 8 [Rice et al 2017])

After 1:1 randomization, patients will begin double-blind treatment with one of the following regimens.

- Arm A (study arm): Tislelizumab + chemotherapy + radiotherapy (concurrent)
- Arm B (control arm): Placebo + chemotherapy + radiotherapy (concurrent)
    - Tislelizumab or placebo
        - 200 mg intravenously on Day 1 of every 21-day cycle (every 3 weeks) up to 24 months (about 35 cycles) (refer to Section 3.6.1 for details on treatment duration).
    - Chemotherapy consists of Cisplatin and Paclitaxel
        - Cisplatin 25 mg/m^2 intravenously on Day 1 to 3 of every 21-day cycle (every 3 weeks) for 2 cycles.
        - Paclitaxel 135 mg/m^2 intravenously on Day 1 of every 21-day cycle (every 3 weeks) for 2 cycles.
    - Radiotherapy
        - Radiotherapy will be delivered in both arms with the total dose of 50.4 Gy in 28 fractions and 5 fractions per week. Radiotherapy based on computed tomography (CT) simulation planning system with 5 mm-thick scan slices throughout the entire neck and thorax is required.

The safety of tislelizumab or placebo in combination with cCRT will be assessed by an Independent Data Monitoring Committee (IDMC) in the first 20 patients (approximately 10 patients per each arm) after they have had at least 6 weeks of follow-up after the last dose of radiotherapy and throughout the conduct of the trial. Enrollment will continue during the safety review.

Study Assessments:

PFS and tumor response will be assessed by BIRC and investigators. Tumor imaging (CT with or without contrast or magnetic resonance imaging [MRI]) and esophagography must be performed within 28 days prior to randomization. On-treatment tumor assessments will occur approximately every 9 weeks (± 7 days) for the first 54 weeks, every 12 weeks (± 7 days) during Years 2 and 3, every 24 weeks (± 7 days) during Years 4 and 5, and then according to local standards with a minimum of 1 tumor response assessment annually thereafter, regardless of treatment delays. If a patient discontinues study treatment due to the reasons other than disease progression, tumor assessments will continue to be performed as scheduled until the patient begins a new anticancer therapy, experiences disease progression (confirmed by the investigator or BIRC, whichever is later), lost to follow-up, withdraws consent, death, or until the study terminates, whichever occurs first. At the discretion of the investigator, patients may be treated beyond progression assessed by BIRC per RECIST v1.1 after obtaining agreement from the sponsors medical monitor. After agreement is reached, the treating

investigator 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.

Patient-reported outcomes of HRQoL will be collected using the EORTC QLQ-C30 and EORTC QLQ-OES18 at screening or baseline, prior to dosing of every treatment cycle for the first 6 cycles, then after every other cycle afterwards and at end of treatment.

After initiation of study treatment, all adverse events (AEs) and serious adverse events (SAEs), regardless of relationship to study treatment, will be reported until 30 days after last dose of study treatment (including chemoradiotherapy) or until the initiation of another anticancer therapy, whichever occurs first. Immune-mediated AEs (imAEs) will be recorded up to 90 days after the last dose of tislelizumab, regardless of whether the patient starts a new anticancer therapy. The investigator should report any SAEs that are believed to be related to tislelizumab treatment at any time after treatment discontinuation.

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

Duration of Patient Participation:

Duration of treatment will be up to 24 months for tislelizumab or placebo, including approximately 6 weeks for concurrent administration of chemotherapy and radiotherapy. Each patient's treatment course will include:

- Screening period of up to 28 days
- Treatment until disease progression (or any other reasons for discontinuation before progression)
- Safety Follow-up Visit to occur within 30 days (± 7 days) after the last dose of study treatment of tislelizumab/placebo or chemoradiotherapy (whichever is later)

Survival follow-up information will be collected every 3 months after the Safety Follow-up Visit until death (or withdraw of consent, loss to follow-up, or study completion by the sponsor). 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.

Study Population:

Patients with histologically confirmed localized ESCC suitable for cCRT are eligible.

Key Eligibility Criteria:

Key inclusion criteria

Patients with histologically confirmed diagnosis of ESCC and suitable for cCRT, including:

- Patients with Stage II-IVa inoperable ESCC (medically unsuitable for surgery or refuses surgical intervention) are eligible. Patients who received prior ≤ 3 cycles of chemotherapy without radiotherapy can be enrolled.

Key exclusion criteria

- Except ≤ 3 cycles of chemotherapy, received any other prior antineoplastic therapy(ies) for ESCC (eg, therapies targeting programmed cell death protein-1 (PD-1), PD-L1, programmed cell death protein ligand-2 (PD-L2) or other immune-oncology therapies, radiotherapy, targeted therapies, ablation, or other systemic or local antineoplastic treatment)
- History of fistula due to primary tumor invasion
- Patients with high risk of fistula or sign of perforation

- Evidence of distant metastases (M1 disease)
- Clinically uncontrolled pleural effusion, pericardial effusion, or ascites requiring frequent drainage or medical intervention within 2 weeks prior to randomization
- Indicators of severe malnutrition.

Investigational Product, Dose, and Mode of Administration:

Tislelizumab or placebo will be administered at a dose of 200 mg intravenously on Day 1 of every 21-day cycle. Tislelizumab or placebo will be given concurrently with the chemotherapy doublet and radiotherapy.

Reference Therapy, Dose, and Mode of Administration:

Chemotherapy consists of Cisplatin and Paclitaxel for 2 cycles (approximately 6 weeks):

- Cisplatin 25 mg/m^2 intravenously on Day 1 to 3 of every 21-day cycle (every 3 weeks).
- Paclitaxel 135 mg/m^2 intravenously on Day 1 of every 21-day cycle (every 3 weeks).

Radiotherapy:

- A total dose of 50.4 Gy in 28 fractions (1.8 Gy/fraction and 5 fractions/week)

Statistical Methods:

PFS is the primary endpoint of the study with the one-sided alpha (α) type I error rate controlled under 0.025. The initial α allocated to PFS will be transferred to secondary endpoints once the primary endpoint is statistically significant. The secondary endpoints will be tested sequentially, ie, starting with the key secondary endpoint (OS), and followed by HRQoL. Testing for the secondary endpoints will continue until the first failure of rejection occurs.

Analysis Sets:

- The ITT Analysis Set includes all randomized patients. It will be the primary analysis set for the efficacy analysis
- Safety Analysis Set includes all patients who received at least 1 dose of study treatment. It will be the primary analysis set for safety analysis
- The PK Analysis Set includes all patients who are randomized to the tislelizumab arm, and for whom postdose PK data are available
- The ADA Analysis Set includes all patients who are randomized to the tislelizumab arm and have a baseline and at least 1 postbaseline ADA result

Primary Efficacy Endpoint Analysis:

PFS Assessed by BIRC

PFS assessed by BIRC is defined as the time from randomization to the first documented disease progression as determined by the BIRC according to RECIST v1.1, or death by any cause, whichever occurs first. The actual tumor assessment visit date will be used to calculate PFS. The PFS censoring rule will follow United States (US) Food and Drug Administration (FDA) Guidance for Industry, Clinical Trial Endpoints for Approval of Cancer drugs and Biologics (Food and Drug Administration Center for Drug Evaluation Research and Center for Biologics Evaluation and Research, 2018). Data for patients without disease progression or death at the time of analysis will be censored at the time of the last tumor assessment. Data for patients who are lost to follow-up prior to documented disease progression will be censored at the last tumor assessment date when the patient is known to be progression-free. Data for patients who start to receive new anticancer therapy will be censored at the last tumor assessment date prior to the introduction of new therapy.

The null hypothesis to be tested is:

H_0: PFS in Arm A ≤ PFS in Arm B

against the alternative:

H_1: PFS in Arm A > PFS in Arm B

This will be the primary analysis once the targeted PFS event number assessed by BIRC is reached. The p-value from the stratified log-rank test will be presented using the stratification factors at randomization (ECOG: 0 versus 1 and stage: II/III versus IVa). The median PFS will be calculated for each treatment arm and presented with 2-sided 95% confidence intervals (CIs). Kaplan-Meier survival probabilities for each arm will be plotted over time. The treatment effect in the form of hazard ratio (HR) and its 95% CI will be estimated using a Cox regression model incorporating the treatment arm as the independent variable and the prespecified stratification factors as the strata. These analyses will be performed in the ITT Analysis Set as the primary analysis.

Secondary Efficacy Endpoint Analyses:

Key Secondary Endpoint - Overall Survival

The OS is defined as the time from the date of randomization to the date of death due to any cause.

The null hypothesis to be tested is:

H_0: OS in Arm A ≤ OS in Arm B

against the alternative:

H_1: OS in Arm A > OS in Arm B

The distribution of OS will be compared between the 2 treatment arms using a stratified log-rank test at one-sided 2.5% level of significance, the p-value from the stratified log-rank test will be presented using the stratification factors at randomization (ECOG: 0 versus 1 and stage: II/III versus IVa). The median OS will be calculated for each treatment arm and presented with 2-sided 95% CIs. Kaplan-Meier survival probabilities for each arm will be plotted over time. The treatment effect in the form of HR and its 95% CI will be estimated using a Cox regression model incorporating the treatment arm as the independent variable and the prespecified stratification factors as the strata. These analyses will be performed in the ITT Analysis Set.

Other Secondary Endpoints

HRQoL

HRQoL is an assessment of a patient's overall health status using the EORTC QLQ-C30 index and the EORTC QLQ-OES18. The postbaseline scores will be compared between the 2 treatment arms, and the changes from the baseline scores will be summarized descriptively.

Objective Response Rate by the BIRC

The ORR is the proportion of patients who had a CR or PR as determined by BIRC per RECIST v1.1 in the ITT Analysis Set. Patients without any postbaseline assessment will be considered nonresponders. The 2-sided 95% CIs for the odds ratio in the ORR will be calculated, as well as Clopper-Pearson 95% CIs of ORR for each treatment arm.

Duration of Response

The DOR assessed by BIRC per RECIST v1.1 will be analyzed only in responders. The statistical methods applied to DOR is similar to the analysis described in the above section for PFS analysis.

Exploratory Efficacy Analyses:

1-Year PFS Rate

The 1-year PFS rate is defined as the Kaplan-Meier estimator of proportion of patients alive and progression free at 1 year after randomization. The 1-year PFS rate and the 2-sided CIs for the 2 arms will be estimated using the Kaplan-Meier estimator.

2-Year PFS Rate

The 2-year PFS rate is defined as the Kaplan-Meier estimator of proportion of patients alive and progression free at 2 years after randomization. The 2-year PFS rate and the 2-sided CIs for the 2 arms will be estimated using the Kaplan-Meier estimator.

Distribution of PD-L1 expression in tumor tissue will be examined in the ITT Analysis Set. The association between PD-L1 expression and tislelizumab treatment effect over the control (PFS, OS, ORR, DOR and disease control rate [DCR]) will be explored.

Status of PD-L1 expression in tumor tissue will be examined in the ITT Analysis Set. The association between PD-L1 expression and study treatment will be explored.

Other immune, ESCC-related and exploratory biomarkers including but not limited to gene expression profiling and tumor mutational profile and their association with disease status and/or response to study treatment will also be explored.

Safety Analyses:

Extent of exposure to each treatment 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), dose intensity, and relative dose intensity.

The verbatim description of AEs will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA) terms and graded per NCI-CTCAE v5.0. All TEAEs will be summarized. A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study treatment up to 30 days following study treatment discontinuation or initiation of new anticancer therapy, whichever occurs first. SAEs, deaths, TEAEs with Grade 3 or above, treatment-related TEAEs, TEAEs that lead to treatment discontinuation, dose reduction, dose interruption or dose delay, and imAE will be summarized.

Clinical laboratory data with values outside of the normal ranges will be identified. Select laboratory data will be summarized by grade. Changes in vital signs will also be summarized by visit.

Pharmacokinetic Analyses:

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, safety endpoints) analyses may be conducted as appropriate and the results of such analysis may be reported separately from the clinical study report (CSR).

Immunogenicity Analysis:

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

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 of PFS in the primary comparisons are based on the following assumptions:

- Median PFS of 14 months in Arm B.
- 1.5-month delayed treatment effect (ie, assuming HR = 1 in the first 1.5 months; and HR = 0.65 thereafter, corresponding to an improvement in median PFS from 14 months to 21.5 months).
- One-sided α of 0.025.
- 1-year drop-out rate of 5% for both treatment arms.
- Randomization ratio of 1:1.

With these assumptions, approximately 200 PFS events are required to occur in the ITT Analysis Set for the PFS final analysis to obtain approximately 80% power. Approximately 366 patients will be enrolled, with enrollment duration of 24.0 months. The interim PFS analysis will be performed at 25.5 months after the first patient was randomized, when 115 PFS events occurred, with error spent from a Lan-DeMets O'Brien-Fleming approximation spending function. The boundaries for PFS interim and final analysis could be found in Table 10.

To demonstrate the OS superiority of Arm A over Arm B in the ITT Analysis Set, the following assumptions are made: (1) median OS of 35 months in Arm B, (2) HR of 0.65, corresponding to an improvement in median OS from 35 months to 53.8 months. Approximately 191 death events will provide approximately 85% power using a 1-sided α of 0.025, with interim analysis for OS at the time of the interim PFS analysis.

The final analysis of PFS and OS will be performed concurrently when approximately 200 PFS events or approximately 191 OS events have been observed, whichever occurs first.

Interim Analysis:

PFS

The PFS interim analysis was planned when 115 target PFS events were reported.

The stopping boundaries (p-values from stratified log-rank test) of the test for PFS at the interim and final analyses are shown in Table 10. The boundaries will be updated according to the actual number of events during analysis, to ensure overall type I error controlled.

OS

The key secondary endpoint of OS will be tested only after the primary endpoint is statistically significant. If the test of PFS is significant, the total α = 0.025 will be allocated to OS interim and final analyses to test for significance. The interim analysis of OS was planned at the time of the PFS interim analysis, with a fixed 1-sided α level of 0.0001 allocated, and the remaining fixed 1-sided α = 0.0249 will be allocated for the final analysis of OS.

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BIRC	Blinded Independent Review Committee
BOR	best overall response
cCRT	concurrent chemoradiotherapy
CI	confidence interval
CR	complete response
CSR	clinical study report
CT	computed tomography
DCR	disease control rate
dCRT	definitive chemoradiation therapy
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EORTC QLQ-OES18	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Oesophageal Cancer Module
ESCC	esophageal squamous cell carcinoma
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FOLFOX	5-fluorouracil, leucovorin, and oxaliplatin
HBV	hepatitis B virus
HR	hazard ratio
HRQoL	Health-related quality of life
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
imAE	immune-mediated adverse event
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
ORR	overall response rate
OS	overall survival
PD-1	programmed cell death protein-1
PD-L1	programmed cell death protein ligand-1
PD-L2	programmed cell death protein ligand-2
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

1. INTRODUCTION

1.1. Background Information on Esophageal Carcinoma

Esophageal cancer is the eighth most common cancer worldwide and the sixth most common cause of death from cancer (GLOBOCAN v1.0 2012). The incidence, prevalence, and histologic type of esophageal cancer varies between geographic regions, particularly between Western countries (United States and Europe) and an area commonly referred to as the "esophageal cancer belt," which is a geographic area stretching across Central-Eastern Asia from the Caspian region to northern China (Arnold et al 2015). Approximately 75% of all cases occur in Asia with China bearing the largest burden, accounting for about 50% of total cases and cancer specific deaths (GLOBOCAN v1.0 2012). In China, esophageal cancer is the third most common cancer and the fourth leading cause of death from cancer, based on an estimation of 477,900 new esophagus cancer cases and 375,000 deaths from this disease expected in 2015 (Chen et al 2016). Esophageal squamous cell carcinoma (ESCC) is the predominant histologic type (90% to 95%) among esophageal cancer (Arnold et al 2015; Wang et al 2014).

Most patients with esophageal cancer are in the mid-advanced disease at their first diagnosis and more than half of them are medically unfit for surgery, hence concurrent chemoradiotherapy (cCRT) is an accepted alternative standard treatment to surgery. Approximately 70% to 80% of resected specimens harbor metastases in the regional lymph nodes. Thus, clinicians are often dealing with an advanced-stage, incurable cancer in newly diagnosed patients. However, prognosis for these patients remains poor and the 5-year overall survival (OS) is approximately 20% (Stahl and Budach 2017; Meng et al 2013; McNamara et al 2012; NCCN Guidelines, v2, 2018).

1.2. Current Treatment of Esophageal Carcinoma and Unmet Clinical Needs

The treatment of esophageal cancer is based on the extent of disease at presentation and tumor histology. International treatment guidelines are consistent in the approach to the treatment of this disease. Therapeutic treatment modalities include endoscopic resection for focal disease or esophagectomy with lymph node resection for larger tumors in patients who are considered medically fit (Lordick et al 2016; NCCN Guidelines, v2, 2018; Stahl et al 2009). Concurrent chemoradiation therapy may be given to those with larger tumors in the neo-adjuvant, adjuvant, locoregional recurrence from surgery or inoperable localized esophageal cancer. Postoperative chemotherapy or chemoradiation is commonly given to patients who have positive lymph nodes after R0 resection, or those with microscopic or macroscopic residual cancer (R1 and R2 resection, respectively) after surgery. Systemic therapy regimens are recommended for advanced esophageal and esophagogastric junction adenocarcinoma. Regimens should be chosen in the context of performance status, comorbidities, and toxicity profile (Lordick et al 2016; NCCN Guidelines, v2, 2018; Japanese Gastric Cancer Association Gastric Cancer, 2017; Stahl et al 2009).

A multimodality approach plays a key role in the treatment of patients with localized ESCC. In 1992, the RTOG 8501 trial established definitive chemoradiotherapy as a standard treatment for localized esophageal cancers. The combination of 5-fluorouracil plus cisplatin (CDDP) is most commonly used, with a median survival time of 16 months. However, the standard regimen

remains controversial as more radiosensitive chemotherapeutic drugs, such as paclitaxel (PTX), have been investigated in esophageal cancer (Herskovic et al 1992; Minsky et al 2002; Cooper et al 1999; Zhu HT et al 2017; NCCN Guidelines, v2, 2018). Definitive chemoradiation therapy (dCRT), using the FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin) regimen, cisplatin plus paclitaxel and docetaxel plus cisplatin regimen, has also been proved effective (Table 1). Anti-epidermal growth factor receptor antibodies have been evaluated in combination with dCRT. However, the SCOPE and RTOG 0436 trials failed to show any survival benefits with the addition of cetuximab to chemoradiotherapy in esophageal cancer, which means this combination does not any additive benefits (Crosby et al 2017; Suntharalingam et al 2017). To date, there has been no demonstration that anti-epidermal growth factor receptor antibodies have any additional benefit in combination with dCRT.

Although long-term survival and cure have been observed in some patients with dCRT, most patients experience local failure or distant metastasis and eventually die from the disease, which represents a large unmet medical need. Several studies have confirmed dCRT in esophageal carcinoma with survival rates of 35% to 40% at 2 years and about 20% at 5 years (Stahl and Budach 2017).

A locoregional recurrence after dCRT occurs in about 50% of patients with inoperable esophageal cancer. In addition, the majority of patients (86%) experience a locoregional recurrence within the radiation field (primary tumor alone in 57%) (Stahl and Budach 2017; Hirano et al 2018).

Table 1: Definitive CRT Treatment and Outcomes for Esophageal Squamous Cell Carcinoma

Reference	Sample Size by Histology (n)	Stage	Regimen	ORR (%)	PFS (median months	OS (median months)
Cisplatin + 5-FU						
Herskovic et al 1992 Cooper et al 1999	ESCC (51)	T1-3N0-1 M0	Cisplatin 75 mg/m^2 intravenously Day 1 5-FU 1000 mg/m^2 intravenously infusion Days 1-4 Q4W RT:50.4 Gy	NA	NA	14.1
Conroy et al 2010	ESCC (38)	II-IVa	Cisplatin 75 mg/m^2 intravenously day 1 5-FU 1000 mg/m^2 intravenously infusion Days 1-4 Q4W RT: 50 Gy	68.3	9.2	15.1
Zhao et al 2012	ESCC (45)	II-IVa	Cisplatin 75 mg/m^2 intravenously Day 1 5-FU 250 mg/m^2 intravenously infusion Days 1-4 Q4W RT:50.4 Gy	53.3	14	22.3
Conroy et al 2014	ESCC (115)	II-IVa	Cisplatin 75 mg/m^2 intravenously Day 1 5-FU 1000 mg/m^2 intravenously infusion Days 1-4 Q4W RT: 50Gy	65	9.4	17.5

Reference	Sample Size by Histology (n)	Stage	Regimen	ORR (%)	PFS (median months	OS (median months)
Zhu Y et al 2017	ESCC (41)	II-IVa	Cisplatin 80 mg/m^2 intravenously Day 1 5-FU 1000 mg/m^2 intravenously infusion Days 1-4 Q3W RT: 60-64 Gy	84.4	NA	NR
FOLFOX						
Conroy et al 2010	ESCC (42)	II-IVa	Oxaliplatin 85 mg/m^2 intravenously Day 1 leucovorin 200 mg/m^2 intravenously Day 1 5-fluorouracil 400 mg/m^2 intravenously followed by 600 mg/m^2 in 22h days 1, 2 Q2W RT:50 Gy	78.7	15.2	22.7
Conroy et al 2014	ESCC (114)	II-IVa	oxaliplatin 85 mg/m^2 intravenously Day 1 leucovorin 200 mg/m^2 intravenously Day 1 5-fluorouracil 400 mg/m^2 intravenously followed by 600 mg/m^2 in 22h days 1, 2 Q2W RT:50 Gy	67	9.7	20.2
Cisplatin + docetaxel						
Zhao et al 2012	ESCC (45)	II-IVa	Cisplatin 75 mg/m^2 intravenously Day 1 docetaxel 75 mg/m^2 intravenously Day 1 Q4W RT:50.4 Gy	73.3	25.3	43.2
Zhu Y et al 2017	ESCC (45)	II-IVa	Cisplatin 80 mg/m^2 intravenously Day 1 docetaxel 60 mg/ m^2 intravenously Day 1 Q3W RT: 60-64 Gy	84.4	NA	NR
5-FU + paclitaxel						
Xia et al 2017	ESCC (50)	II-IVa (62%) Postoperative recurrent	paclitaxel 50 mg/m^2, 5-FU 300 mg/m^2 days 1, 8, 15, 22, 29; paclitaxel 135 mg/ m^2, 5-FU 1800 mg/m^2 days 57, 85 RT: 50.4 Gy/28 fractions or 61.2 Gy/34 fractions	NA	12.4	17.9
Cisplatin + paclitaxel						
Tu et al 2013	ESCC (36)	II-IVa	Cisplatin 75 mg/m^2 intravenously Day 1 Q3W Paclitaxel 135 mg/m^2 intravenously Day 1 Q3W RT: 60 Gy	50	12.0	18.0

Reference	Sample Size by Histology (n)	Stage	Regimen	ORR (%)	PFS (median months	OS (median months)
Tang et al 2016	ESCC (76)	II-IV	Cisplatin 25 mg/m^2 intravenously Day 1-3 Q3W Paclitaxel 175 mg/m^2 intravenously Day 1 Q3W RT: 61.2Gy/34 fractions or 68.4 Gy/44 fractions	NA	14.7	28.5
Zhu HT et al 2017	ESCC (76)	II-IVa	Cisplatin 25 mg/m^2 intravenously Day 1-3 Q4W Paclitaxel 175 mg/m^2 intravenously Day 1 Q4W RT: 61.2 Gy/34 fractions	NA	13.3	23.7

Abbreviations: CRT, chemoradiotherapy; 5-FU, 5-fluorouracil; ESCC, esophageal squamous cell carcinoma; FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; Gy, gray; NA, not available; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Q2W, once every 2 weeks; Q3W, once every 3 weeks; Q4W, once every 4 weeks; RT: radiotherapy.

1.3. Anti-PD-1 Therapy for Esophageal Squamous Cell Carcinoma

Clinical outcome data are available from early phase studies evaluating tislelizumab, nivolumab, and pembrolizumab in patients with advanced esophageal carcinoma. There are no data with checkpoint inhibitors given in the chemoradiotherapy treatment setting in patients with esophageal carcinoma. Nevertheless, all data described below are supportive of the safety and antitumor activity of anti-PD-1 (programmed cell death protein-1) monoclonal antibodies in esophageal carcinoma.

Tislelizumab

Please refer to Section 1.4.4.2 for details regarding efficacy data of tislelizumab.

Nivolumab

An open-label, single-arm, multicenter Phase 2 study with ESCC patients treated with nivolumab (a PD-1 monoclonal antibody) was conducted (Kudo et al 2017). This study enrolled 65 patients with ESCC even though the study was designed to recruit patients with squamous, adenocarcinoma, or adeno-squamous cell histologies. These patients were considered refractory or intolerant to fluoropyrimidine, platinum, and taxane-based chemotherapies. Patients were treated with nivolumab 3 mg/kg given intravenously once every 2 weeks. Tumor response was assessed every 6 weeks. Median follow-up was 10.8 months (interquartile range: 4.9 to 14.3 months) and patients received a median of 3 nivolumab cycles (range: 1 to 10 cycles). The overall response rate (ORR) was 17.2% (95% confidence interval [CI]: 9.9% to 28.2%) by central radiology assessment and 21.9% (95% CI: 13.5% to 33.4%) by investigator assessment. The disease control rate (DCR), defined as the proportion of patients who achieve complete response (CR), partial response (PR), or stable disease, was 42% (95% CI: 31% to 54%) by central assessment and 53% (95% CI: 41% to 65%) by investigator assessment. The median duration of OS was 10.8 months (95% CI: 7.4 to 13.9 months). The 2-year OS was 17.2%. The median duration of progression-free survival (PFS) was 1.5 months (95% CI: 1.4 to 2.8 months) and 2.3 months (95% CI: 1.5 to 3.0 months) by central and investigator assessment, respectively.

Pembrolizumab

KEYNOTE-028 (NCT02054806), a multicohort, Phase 1b trial, recruited patients with advanced ESCC and adenocarcinoma with disease progression following standard therapy. Patients received pembrolizumab 10 mg/kg once every 2 weeks. Response was assessed every 8 weeks for the first 6 months and every 12 weeks thereafter. Primary endpoint was ORR per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 by investigator review. In this cohort of 23 patients, 87% received ≥ 2 prior therapies for advanced/metastatic disease and 78% (17 patients) had ESCC. With a median follow-up of 7 months (range: 1 to 33 months), ORR was 30% (95% CI: 13-53%), median PFS was 1.8 months, and median OS was 7 months. The median duration of response (DOR) was 15 months (range: 6 to 26 months). ORR was 28% for patients with ESCC (Doi et al 2018).

KEYNOTE-180 (NCT02559687), a phase 2, open-label study, recruited 121 patients with metastatic esophageal cancer and ≥ 2 prior lines of therapy; 53% of these patients had ESCC. In this study, patients received pembrolizumab 200 mg once every 3 weeks for up to 2 years. As of 18 September 2017, median duration of follow-up was 5.8 months (range: 0.2 to 18.3) and ORR (CR+PR) was 10% (95% CI: 5% to 17%). PR and stable disease were observed in 12 (10%) and 25 (21%) patients, respectively. Median DOR was not reached, and median PFS was 2 months (95% CI: 1.9 to 2.1 months) with a 6-month PFS rate of 16% (95% CI: 10% to 23%). Median OS was 5.8 months (95% CI: 4.5 to 7.2 months) with a 12-month OS rate of 28% (95% CI: 20% to 37%). ORR was 14% (95% CI: 7 to 25) in patients with ESCC and 5% (95% CI: 1 to 14) in patients with esophageal adenocarcinoma. ORR was 14% (95% CI: 6 to 25) in patients with programmed cell death protein ligand-1 (PD-L1) positive (+) cancer and 6% (95% CI: 2 to 16) in patients with PD-L1 negative (-) cancer. As of 18 September 2017, 15 (12%) patients had at least 1 treatment-related treatment-emergent adverse event (TEAE) with severity ≥ Grade 3. Five (4%) patients discontinued due to a treatment-related TEAE. There was 1 treatment-related death from pneumonitis (Shah et al 2018).

1.4. Background Information on Tislelizumab

1.4.1. Pharmacology

Tislelizumab (also known as BGB-A317) is a humanized, immunoglobulin G4 (IgG4)-variant monoclonal antibody against PD-1 and is being developed for the treatment of several human malignancies. 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 or complement-dependent cytotoxicity effects in humans (Labrijn et al 2009).

Tislelizumab acts by binding to the extracellular domain of human PD-1 with high specificity as well as high affinity (dissociation constant = 0.15 nM). It competitively blocks binding efforts by both PD-L1 and programmed cell death protein ligand-2 (PD-L2), 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 pre-activated, primary peripheral blood mononuclear cells. In addition, tislelizumab has demonstrated antitumor activity in several allogeneic xenograft models, in which peripheral

blood mononuclear cells were co-injected with human cancer cells (A431 [epidermoid carcinoma]) or tumor fragments (BCCO-028 [colon cancer]) into immunocompromised mice.

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

1.4.2. Toxicology

The toxicity and safety profile of tislelizumab was characterized in single-dose intravenous (IV) toxicology studies in mice and monkeys and in two separate repeated-dose IV toxicology studies in cynomolgus monkeys dosed once every two weeks for 13 weeks. The tissue cross-reactivity was evaluated in the normal frozen tissues from both humans and monkeys. In addition, the potential off-target binding of tislelizumab was screened using the Retrogenix microarray and subsequently verified by Biacore assays. The cytokine release assays were also evaluated using fresh human whole blood cells. 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 monkeys at single doses up to 100 mg/kg. No apparent tislelizumab-related toxicity was noted in the 13-week repeated-dose monkey toxicology studies at doses up to 30 mg/kg. Apparent but likely immunogenicity-related toxicity was noted in individual monkeys given 60 mg/kg in the 13-week repeated-dose study. However, immunogenicity-related changes due to formation of antidrug antibodies (ADAs) and immune complex formation in nonhuman primates are generally considered not translatable to humans (Vahle 2018). The no-observed-adverse-effect level of tislelizumab in the 13-week monkey toxicology studies was considered to be 30 mg/kg, approximately 10-fold higher than the clinical dose (200 mg, once every 3 weeks). The toxicokinetic profile was well characterized in cynomolgus monkeys, with dose-proportional increases in systemic exposure, without apparent accumulation or sex difference.

No tissue cross-reactivity was found in either human or monkey tissues, nor was any effect on cytokine release observed in a human whole blood assay. In addition, the Retrogenix microarray screen of > 6000 human proteins and follow-up verification by Biacore assays revealed no biologically significant off-target binding of tislelizumab.

The safety profile of tislelizumab is considered adequate to support the current Study BGB-A317-311.

Refer to the tislelizumab Investigator's Brochure for more information regarding IV toxicology studies.

1.4.3. 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 using noncompartmental methods, using serum concentrations from patients who received doses of 0.5, 2.0, 5.0, and 10 mg/kg once every 2 weeks, and 2.0 mg/kg, 5.0 mg/kg, and 200 mg once every 3 weeks (Phase 1a Parts 1, 2, and 3, and Phase 1b in BGB-A317_Study_001), and patients who received doses of 200 mg once every 3 weeks 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 (AUC) 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 28 patients who were administered 1 dose of 200 mg once every 3 weeks (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 plasma clearance of tislelizumab of 0.173 L/day, volume of distribution (V_d) in the central and peripheral compartments of 2.89 L 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 clearance of tislelizumab, which supports fixed-dosing across different ethnic groups.

Non-compartmental analysis is available for Studies 001 and 102. Comparison of intensive PK data after a single intravenous infusion of tislelizumab indicated that dose-normalized exposure ($AUC_{0\text{-}14day}$) was consistent between Study 001 with non-Chinese patients (n=91 mostly Caucasian) and Study 102 with Chinese patients (n=20). This shows that the PK of tislelizumab is comparable between Chinese and non-Chinese patients. Additionally, dose-normalized exposure ($AUC_{0\text{-}14day}$) was also consistent across Asian patients (n=27, including 20 Chinese and 7 non-Chinese Asian) and Caucasian patients (n=80). This finding is consistent with the evidence that ethnic differences in PK are not expected for therapeutic monoclonal antibodies (Chiba et al 2014, Matsushima et al 2015, Zhou et al 2012).

Similarly, comparison of trough (predose) and peak (end-of-infusion) concentration data after multiple intravenous infusions of 200 mg Q3W tislelizumab between Chinese (Studies 102 and 203) and non-Chinese (Study 001) patients, and between advanced solid tumors (Studies 001 and 102) and classical Hodgkin lymphoma (Study 203) showed that the levels are generally similar between the 2 ethnic groups and between different tumor types.

1.4.4. Prior Clinical Experience of Tislelizumab

As of 20 May 2020, there are 28 ongoing studies with tislelizumab. Of these, 15 studies have preliminary data available in the Investigator's Brochure version 8, 10 September 2020: 7 monotherapy studies, 2 chemotherapy combination therapy studies; and 6 targeted therapy combination studies.

Please refer to the tislelizumab Investigator's Brochure for more detailed information on tislelizumab efficacy and safety when given as monotherapy or in combination with chemotherapy.

1.4.4.1. Pooled Safety Assessment of Monotherapy Studies and Combination Studies With Chemotherapy

Monotherapy Studies

A pooled analysis of 7 monotherapy studies was conducted to provide a comprehensive safety assessment separately from combination therapy.

Overall, there were 1328 patients in the pooled monotherapy studies: 1181 patients treated in 5 solid tumor studies and 147 patients treated in 2 hematologic malignancies studies.

Of the 1328 patients enrolled, 368 patients (27.7%) remained on study as of 20 May 2020; and 189 patients (14.2%) were still receiving tislelizumab treatment.

Combination Studies With Chemotherapy

A pooled analysis of 2 chemotherapy combination therapy studies was conducted to provide a comprehensive safety assessment separately from other combination therapy studies.

Overall, there were 84 patients in the pooled chemotherapy combination studies. Of the 84 patients enrolled, 13 patients (15.5%) remained on study as of 20 May 2020; and 7 patients (8.3%) were still receiving tislelizumab treatment.

Refer to the tislelizumab Investigator's Brochure for more detailed information on tislelizumab safety data when given as monotherapy or in combination with chemotherapy.

1.4.4.1.1. Pooled Demographics and Baseline Characteristics

Monotherapy Studies

Overall, the 1181 patients in the pooled solid tumor monotherapy analysis had a median treatment exposure duration of 3.68 months (range: 0.13 to 55.26) and median study follow-up duration of 9.89 months (range: 0.07 to 58.91). The pooled solid tumor monotherapy population had a median age of 60 years and was 67.1% male.

Combination Studies With Chemotherapy

Overall, the 84 patients in the pooled chemotherapy combination analysis had a median treatment exposure duration of 7.805 months (range: 0.66 to 30.88) and median study follow-up duration of 21.225 months (range: 0.10 to 31.24). The pooled chemotherapy combination population had a median age of 61 years and was 77.4% male.

1.4.4.1.2. Treatment-Emergent Adverse Events Assessed as Related to Treatment

Monotherapy Studies

Of the 1181 patients in the solid tumor group of the pooled monotherapy studies, 788 (66.7%) experienced at least one treatment-related TEAE. The most commonly occurring TEAEs assessed as related to tislelizumab were aspartate aminotransferase increased (136 patients, 11.5%), alanine aminotransferase increased (125 patients, 10.6%), hypothyroidism (106 patients, 9.0%), rash (97 patients, 8.2%), and fatigue and pruritis (95 patients each, 8.0%).

Of the 1181 patients in the solid tumor group of the pooled monotherapy studies, 167 (14.1%) experienced at least one ≥ Grade 3 TEAE assessed as related to tislelizumab. The only ≥ Grade 3 TEAEs that occurred in ≥ 1% (≥ 12 patients) in the solid tumor group were aspartate aminotransferase increased (21 patients, 1.8%), alanine aminotransferase increased (17 patients, 1.4%), and anaemia (13 patients, 1.1%).

Combination Studies With Chemotherapy

Of the 84 patients in the pooled chemotherapy combination studies, 69 (82.1%) experienced at least one treatment-related TEAE. The most commonly occurring TEAEs assessed as related to tislelizumab were asthenia (17 patients, 20.2%), alanine aminotransferase increased (12 patients, 14.3%), and aspartate aminotransferase increased (11 patients, 13.1%).

Of the 84 patients in the pooled chemotherapy combination studies, 18 (21.4%) experienced at least one ≥ Grade 3 TEAE assessed as related to tislelizumab. The only ≥ Grade 3 TEAEs that

occurred in ≥ 2 patients were aspartate aminotransferase increased and hepatic function abnormal (2 patients each, 2.4 %).

1.4.4.1.3. Treatment-Emergent Serious Adverse Events

Monotherapy Studies

Of the 1181 patients in the solid tumor group of the pooled monotherapy studies, 415 (35.1%) experienced at least one treatment-emergent serious adverse event (SAE). The most commonly occurring treatment-emergent SAEs in the solid tumor group were pneumonia (41 patients, 3.5%), and ascites and pyrexia (15 patients each, 1.3%).

Combination Studies With Chemotherapy

Of the 84 patients in the pooled chemotherapy combination studies, 29 (34.5%) experienced at least one treatment-emergent SAE. The most commonly occurring treatment-emergent SAEs occurring in ≥ 2 patients in the pooled analysis were pneumonitis (4 patients, 4.8%), platelet count decreased and thrombocytopenia (3 patients each, 3.6%), blood bilirubin increased, anaemia, hepatic function abnormal, dysphagia, and fatigue (2 patients each, 2.4%).

1.4.4.1.4. Immune-Mediated Adverse Events

Anti-PD1 therapies are known to cause immune-mediated adverse events (imAEs) in some patients and therefore have been defined as AEs of special interest in tislelizumab clinical studies.

Immune-mediated AEs are consistent with an immune-related mechanism or immune-related component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. Immune-mediated AEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. There is a potential temporal relationship between the initiation of treatment with tislelizumab and onset of an imAE that spans a window of days to several months.

All adjudicated imAEs presented in the tislelizumab Investigator's Brochure were adjudicated by clinical team from the identified potential imAEs based on clinical information in the clinical database and the safety database. Certain imAEs have multiple Medical Dictionary for Regulatory Activities (MedDRA) terms associated with the same category. Special categories have been created to group patients experiencing these events.

Monotherapy Studies

Of the 1113 patients in the adjudicated solid tumor group for the Pooled Monotherapy studies, 233 (20.9%) experienced at least one imAE. The most commonly occurring imAEs were hypothyroidism (69 patients, 6.2%), hyperthyroidism (37 patients, 3.3%), and rash (34 patients, 3.1%). Analysis of the total patients with ≥ 1 imAE that also was ≥ Grade 3 in severity showed that 52 patients (4.7%) experienced such events. The most commonly occurring imAEs ≥ Grade 3 in severity were alanine aminotransferase increased (9 patients, 0.8%),aspartate aminotransferase increased, and pneumonitis (7 patients each, 0.6%).

Combination Studies With Chemotherapy

ImAEs were adjudicated and collected for Study BGB-A317-206 only. Of the 54 patients treated in this study, 17 (31.5%) experienced at least one imAE. The most commonly occurring imAEs of any grade were hypothyroidism (7 patients, 13.0%), pneumonitis (4 patients, 7.4%), and hyperthyroidism (3 patients, 5.6%). Analysis of the total patients with ≥ 1 imAE that also was ≥ Grade 3 in severity showed that 3 patients (5.6%) experienced such events (immune-mediated pneumonitis, bilirubin conjugated increased, hepatic function abnormal, immune-mediated hepatitis myocarditis, and rhabdomyolysis).

1.4.4.1.5. Infusion-Related Reactions

Infusion-related reactions, including high-grade hypersensitivity reactions, following administration of tislelizumab are uncommon.

Monotherapy Studies

Of the 1181 patients in the solid tumor group within the pooled monotherapy studies, 45 (3.8%) experienced ≥ 1 infusion-related reaction. The most commonly occurring infusion-related reactions that occurred in the solid tumor group were infusion-related reaction (28 patients, 2.4%), pyrexia (10 patients, 0.8%), and nausea (4 patients, 0.3%). Two patients experienced ≥ Grade 3 infusion-related reactions in the solid tumor group of the pooled monotherapy studies and all other ≥ Grade 3 events occurred in single instances.

Combination Studies With Chemotherapy

Of the 84 patients in the pooled chemotherapy combination studies, 3 (3.6%) experienced ≥ 1 infusion-related reaction. The infusion-related reactions that occurred in single instances included pruritis, rash, chills, palpitations, pyrexia, and flushing (all < Grade 3). No severe infusion-related reactions were observed in this study.

1.4.4.1.6. Fatal Adverse Events

Monotherapy Studies

A total of 104 patients (8.8%) in the solid tumor studies died ≤ 30 days from the last study drug dose as of 20 May 2020. Of these 104 patients, there were 18 patients (1.5%) who had an AE with a fatal outcome ≤ 30 days from the last study drug dose. Of 683 patients (57.8%) who died > 30 days after the last study drug dose, 8 patients (0.7%) died as a result of an AE (refer to the Investigator's Brochure Edition 8, Section 5.2.1.10).

Combination Studies With Chemotherapy

One patient (1.2%) died ≤ 30 days from the last study drug dose due to an AE in the Pooled Chemotherapy Combination Studies as of 20 May 2020. Of 35 patients (41.7%) who died > 30 days after the last study drug dose, 1 patient (1.2%) died as a result of an AE, 26 patients (31.0%) died as a result of progressive disease, and 8 patients (9.5%) died as a result of "other" causes of death (refer to the Investigator's Brochure Edition 8, Section 5.2.2.9).

1.4.4.2. Efficacy Assessment of Tislelizumab

Efficacy data are available from 3 of the ongoing studies in solid tumors, BGB A317_Study_001, BGB-A317-102, and BGB-A317-205, which are summarized below.

1.4.4.2.1. Study BGB-A317_001 (Data Cutoff 27 October 2018)

This is a 2-stage study. Phase 1a consists of a dose-escalation and dose-finding component, and Phase 1b investigates efficacy and safety in select tumor types.

There were 451 patients treated in the study. Of the 53 esophageal carcinoma patients included in the Efficacy Evaluable Analysis Set, there were 6 patients (11.3%) with a confirmed response and 14 patients (26.4%) with a best overall response (BOR) of stable disease.

1.4.4.2.2. Study BGB-A317-102 (Data Cutoff 01 December 2018)

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.

There were 300 patients treated in the study. Of the 17 esophageal carcinoma patients included in the Efficacy Evaluable Analysis Set, there was 1 patient (5.9%) with a confirmed response and 7 patients (41.2%) with a BOR of stable disease.

1.4.4.2.3. Study BGB-A317_205 (Data Cutoff 31 Mar 2019)

This is a multicohort, Phase 2 study of tislelizumab in combination with standard chemotherapy as first-line treatment in Chinese patients. An ESCC cohort and a gastric and gastroesophageal junction adenocarcinoma (GAC/GEJ adenocarcinoma) cohort have been enrolled concurrently. In the ESCC cohort, patients are treated with tislelizumab 200 mg intravenously on Day 1, cisplatin 80 mg/m² IV on Day 1, and 5-fluorouracil (5-FU) 800 mg/m²/day intravenously using continuous pumping system on Days 1 through 5 during each 21-day cycle.

There were 30 patients treated in the study and 26 patients were included in the Efficacy Evaluable Analysis Set. Of the 13 patients in the ESCC cohort, there were 7 patients (53.8%) with a confirmed response and 5 patients (38.5%) with a BOR of stable disease.

1.5. Study Rationales

1.5.1. Rationale for Tislelizumab in the Treatment of Esophageal Carcinoma

High levels of FcγR-expressing myeloid derived cells (eg, M2 macrophage, myeloid-derived suppressor cell) in tumor tissues predict a poor survival of tumor-bearing animals after anti-PD-1 monoclonal antibody treatment; this is possibly due to Fc-FcγR-mediated antibody-dependent cellular cytotoxicity or antibody-dependent cellular phagocytosis (ADCP) depletion of effector T-cells (Gül and Egmond 2015; Prieto et al 2015; Makarova-Rusher et al 2015; Beers et al 2016; Dahan et al 2015). As a non or low-FcγR-binding agent (thus causing minimal antibody-dependent cellular cytotoxicity/ADCP effect), tislelizumab may show superior efficacy and lower toxicity in esophageal carcinoma. Available data from a clinical trial with other anti-PD-1 monoclonal antibodies, nivolumab and pembrolizumab, has shown that the drugs have both manageable safety profiles and promising antitumor activity in patients with esophageal carcinoma (Section 1.3).

Finally, according to the latest data collected from the Phase 1 BGB-A317_Study_001, tislelizumab monotherapy has established a manageable safety profile, with the most common side effects consistent with known class effects of other anti-PD-1 antibodies, as well as evidence for anti-tumor activity (Section 1.3).

1.5.2. Rationale for Selection of Tislelizumab Dose

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 intravenously once every 3 weeks was selected for further evaluation.

Rates of treatment-related AEs and SAEs observed in patients receiving 2 mg/kg and 5 mg/kg once every 2 weeks and once every 3 weeks 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 once every 2 weeks ranged between 10% and 15%, compared to a range of 15% to 38% for patients treated at 2 mg/kg and 5 mg/kg once every 3 weeks.

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 stable disease, 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 once every 3 weeks.

In conclusion, tislelizumab 200 mg once every 3 weeks is the recommended dose for pivotal studies.

1.5.3. Rationale for Tislelizumab in Combination With Chemoradiotherapy

Radiotherapy is an important nonsurgical treatment in management of esophageal cancer. Concurrent chemoradiotherapy has become the standard of care for the treatment of localized ESCC. As shown by the RTOG 8501 study, cCRT significantly improved OS compared to radiotherapy alone. But there was no substantial improvement subsequently with cCRT alone despite exploration of different treatment options such as dose escalation of radiation, induction chemotherapy, and various chemotherapy of cCRT (Stahl and Budach 2017; Hirano and Boku 2018).

There is strong evidence that not only can there be synergy of checkpoint inhibitors with chemotherapy; this can occur with cCRT as well. It is now known that both chemotherapy and radiotherapy can up-regulate the expression of PD-L1 (Zhang et al 2008; Deng et al 2014) due to the release of cytokines and other inflammatory molecules, which could make such tumors sensitive to a PD-1/PD-L1 directed therapy. In this setting, chemotherapy and radiotherapy act as priming agents for immunotherapy; elimination of cancer cells by chemotherapy and/or radiotherapy triggers release of antigens, which can turn poorly immunogenic or

immunosuppressive tumors into an immunogenic environment (Vanneman and Dranoff 2012). In addition, radiotherapy has an impact on the immune system by engaging both the innate and the adaptive arms, eliciting tumor-specific T-cells and establishing an immune memory against the tumor. This prolongs the effect of radiation, improving locoregional control, decreasing metastatic spread, and increasing OS (Formenti and Demaria 2013).

The results from a preclinical model of ESCC showed that anti-PD1 treatment works synergistically with chemoradiation to increase tumor control and increase tumor-infiltrating lymphocytes while decreasing the number of anergic tumor-infiltrating lymphocytes. This may prove an effective strategy to improve combination therapy in localized ESCC (Oh et al 2016).

The utility of combined immunotherapy and radiotherapy has been demonstrated in the clinical setting. A Phase 3 trial (PACIFIC trial) was conducted to compare durvalumab with placebo as consolidation therapy after platinum-based dCRT in patients with stage III non–small cell lung cancer (Antonia et al 2017). The PFS was significantly longer in the durvalumab group as compared with the placebo group (median PFS: 16.8 months versus 5.6 months; hazard ratio [HR]: 0.52, $P < 0.001$). No significant difference was observed in the incidence of Grade 3/4 pneumonitis or radiation pneumonitis. This trial demonstrated the efficacy and manageable toxicity of durvalumab as consolidation therapy after dCRT. A secondary analysis of the KEYNOTE-001 trial revealed that previous radiotherapy might improve PFS and OS in patients with advanced non-small cell lung cancer (Shaverdian et al 2017). The PFS was significantly longer in patients who received any radiotherapy compared with patients who received no radiotherapy (median PFS: 4.4 months versus 2.1 months; HR: 0.56, $P = 0.019$). The OS was also significantly improved in patients who received any radiotherapy compared with patients who did not receive any radiotherapy (median OS: 10.7 months versus 5.3 months; HR: 0.58, $P = 0.026$). As with non-small cell lung cancer, a combination of immunotherapy and chemoradiotherapy may be beneficial in patients with unresectable localized ESCC. The interim safety analysis of a Phase 1b study (LA-SCCHN), analyzing pembrolizumab in combination with chemoradiotherapy in patients with locally advanced squamous cell carcinoma of the head and neck, supported that pembrolizumab can be safely delivered with weekly cisplatin and radiotherapy with no new toxicity signals observed (Powell et al 2017). To address any potential toxicities of administering anti-PD-1 treatment particularly when given simultaneously with cCRT, a rigorous safety assessment will be implemented with Independent Data Monitoring Committee (IDMC) reviewing early safety signals.

1.5.4. Rationale for Cisplatin and Paclitaxel Chemotherapy

Although Study RTOG 8501 showed a better OS in the cCRT group with the cisplatin/5-fluorouracil (PF) regimen, the results revealed that the PF regimen was not an optimal regimen with only 30% patients surviving over 3 years and 44% and 20% patients developing severe and life-threatening side effects, respectively. In 1994, paclitaxel (PTX) was proved to be one of the effective agents in the treatment of esophageal carcinoma, with the response rate of 28% in squamous cell carcinoma (Ajani et al 1994; Ilson et al 2007). Thereafter, many institutions have conducted numerous studies using PTX combined with other agents, among which PTX plus cisplatin were the most common combinations used in the treatment of advanced esophageal carcinoma, with a response rate of 39% to 60% (van de Gaast et al 1997; Kelsen et al 1997; Polee et al 2002; Huang et al 2004). In 2008, the Radiation Therapy Oncology

Group reported a phase 2 randomized control study called RTOG 0113, which compared 2 PTX-based regimens used in induction chemotherapy followed by cCRT to determine which regimen could achieve a better 1-year OS and surpass the historical result of Study RTOG 9405 (Ajani et al 2008; Minsky et al 2002). The results of RTOG 0113 demonstrate that such intense therapies are associated with considerable morbidity and neither of the two treatments proved to be sufficiently superior to the historical control of RTOG 9405 (Ajani et al 2008). A retrospective study of comparison of taxane and fluorouracil-based chemoradiotherapy in patients with inoperable ESCC showed that chemoradiation with taxane-based regimens was well tolerated with potentially promising efficacy which could become a good alternative treatment in these patients (Sun et al 2016). A phase 2 study of cCRT with cisplatin and paclitaxel for inoperable ESCC showed that cCRT with cisplatin 25 mg/m^2 day 1 to 3 once every 3 weeks and paclitaxel 175 mg/m^2 day 1 once every 3 weeks resulted in an encouraging overall survival rate (Tang et al 2016).

1.5.5. Rationale for Radiotherapy Dose

RTOG 8501 trial established cCRT as a standard treatment for localized esophageal carcinoma with a total radiotherapy dose of 50.4 Gy. However, the incidence of locoregional recurrence is over 50% (Cooper et al 1999). The recommended dose of radiotherapy remains controversial. A meta-analysis showed that a total dose of ≥ 60 Gy might improve patients' OS, especially those in Asia (Chen et al 2017). But further attempts to improve outcomes were unsuccessful. INT-0123 trial, the only randomized controlled trial that compared different radiation doses (64.8 Gy versus the standard 50.4 Gy) in combination with chemotherapy for nonsurgical esophageal carcinoma patients, showed that a 14.4 Gy dose escalation did not result in either OS or locoregional control benefit. For curative purposes, 50.4 Gy is the optimal radiation dose while minimizing toxicities such as acute radiation esophagitis and pneumonitis as much as possible.

1.5.6. Rationale for Placebo as the Comparator

In this blinded, Phase 3 study, the comparator arm will consist of a matched placebo in combination with chemoradiotherapy doublet. In this study, a matched placebo will be used, which will contain the same composition as the solution for the active drug (tislelizumab), except that no active drug will be present in the formulation. A placebo is being used to preserve the scientific integrity of the study and reduce any potential observational or assessment bias. Patients in the placebo arm will still receive the recommended chemoradiotherapy doublet for this patient population, minimizing the risk generally associated with placebo-alone arms in controlled studies.

1.6. Benefit-Risk Assessment

Patients with localized ESCC suitable for chemoradiotherapy represent a population with a great unmet medical need.

As discussed in Section 1.3, checkpoint inhibition with tislelizumab has been shown to have antitumor activity in esophageal carcinoma patients, with an ORR of 11% (95% CI: 4.3% to 23.0%) and a DCR of 38% (95% CI: 24.8% to 52.1%). A Phase 2 study, BGB-A317-205, as discussed in Section 1.4.4.2.3, which enrolled 15 patients treated with tislelizumab in combination with chemotherapy in the ESCC cohort (13 of them were included in the Efficacy

Evaluable Analysis Set), demonstrated that tislelizumab in combination with chemotherapy has a manageable safety profile. Among the 15 patients, 1 patient experienced a Grade 5 hepatic dysfunction (possibly from progressive disease and underlying hepatitis) which was possibly related to study treatment according to the investigator. Four patients discontinued study treatment due to adverse events (AEs) (Grade 3 tracheal fistula, Grade 3 lung infection, Grade 2 pneumonitis, and Grade 3 increase in aspartate aminotransferase) (Xu et al 2019).

More than 1300 patients have been treated with tislelizumab monotherapy at clinically relevant doses (2 to 5 mg/kg) or in combination. The safety profile is consistent with known class effects of anti-PD-1 antibodies and includes mostly mild/moderate AEs. Grade 3/4 imAEs have been observed and have been generally reversible and manageable with study drug interruption and/or steroid treatment. Fatal imAEs are rare. For further discussion on safety profile of tislelizumab, please refer to the Investigator's Brochure.

Given the unmet medical need and limited treatment options in this indication, the benefit/risk assessment, based on available tislelizumab Phase 1 data combined with the published data from both nivolumab and pembrolizumab clinical trials, is considered favorable. To assess the potential benefit and safety of tislelizumab in combination with chemoradiotherapy over chemoradiotherapy alone, a randomized, blinded trial comparing tislelizumab to placebo will be conducted.

An IDMC will be established to assess the preliminary safety for the first 20 patients, given that there is no direct safety data on this combination, and to regularly monitor the safety of tislelizumab when compared with placebo. An interim analysis for PFS superiority test was planned in the study (Section 9.7).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

- To compare the progression-free survival (PFS) as assessed by the Blinded Independent Review Committee (BIRC) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 in the Intent-to-Treat (ITT) Analysis Set between tislelizumab in combination with concurrent chemoradiotherapy (cCRT) and placebo in combination with cCRT.

2.1.2. Secondary Objectives

Key Secondary Objective

- To compare the overall survival (OS) in the ITT Analysis Set between tislelizumab and placebo in combination with cCRT.

Other Secondary Objectives

- To compare the patient reported outcomes of health-related quality of life (HRQoL) between tislelizumab and placebo in combination with cCRT.
- To compare the overall response rate (ORR) as assessed by the BIRC per RECIST v1.1 in the ITT Analysis Set between tislelizumab and placebo in combination with cCRT.
- To compare the duration of response (DOR) as assessed by the BIRC per RECIST v1.1 in the ITT Analysis Set between tislelizumab and placebo in combination with cCRT.
- To evaluate the safety and tolerability of tislelizumab in combination with cCRT.

2.1.3. Exploratory Objectives

- To compare the 1-year PFS rate as assessed by the investigator per RECIST v1.1 in the ITT Analysis Set between tislelizumab and placebo in combination with cCRT.
- To compare the 2-year PFS rate as assessed by the investigator per RECIST v1.1 in the ITT Analysis Set between tislelizumab and placebo in combination with cCRT.
- To explore the potential predictive, prognostic biomarkers including but not limited to programmed cell death protein ligand-1 (PD-L1) expression; gene expression profiling (GEP); tumor infiltrating lymphocytes (TIL); tumor mutational burden (TMB), gene mutation, and microsatellite instability (MSI); and/or blood-based biomarkers (flow cytometry and immune-phenotyping [panel: A173, A167, A163, and A378], and circulating tumor DNA [ctDNA] alteration and peripheral blood mononuclear cell [PBMC]immune cell profiling) in archival and/or fresh tumor tissue and blood samples obtained before and/or during the study treatment and/or at disease progression, and the association with disease status, response to study treatment and mechanisms of resistance.
- To assess the pharmacokinetics (PK) of tislelizumab in combination with cCRT.
- To assess host immunogenicity to tislelizumab.

2.2. Study Endpoints

2.2.1. Primary Endpoint

- PFS – defined as the time from randomization to the first documented disease progression, as determined by BIRC per RECIST v1.1, or death from any cause, whichever occurs first.

2.2.2. Secondary Endpoints

Key Secondary Endpoint

- OS – defined as the time from the date of randomization to the date of death due to any cause.

Other Secondary Endpoints

- HRQoL assessment defined as patients' reported treatment effects using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Oesophageal Cancer Module (EORTC QLQ-OES18).
- ORR – defined as the proportion of patients who had complete response (CR) or partial response (PR) as assessed by BIRC per RECIST v1.1.
- DOR – defined as the time from the first occurrence of a documented objective response to the time of relapse, as determined by the BIRC per RECIST v1.1, or death from any cause, whichever occurs first.
- The incidence and severity of TEAEs graded according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE, v5.0, 2017).

2.2.3. Exploratory Endpoints

- 1-year PFS rate – defined as the Kaplan-Meier estimator of proportion of patients alive and progression free at 1 year from randomization, as determined by investigator per RECIST v1.1.
- 2-year PFS rate – defined as the Kaplan-Meier estimator of proportion of patients alive and progression free at 2 years from randomization, as determined by investigator per RECIST v1.1.
- Status of PD-L1-related, immune-related, esophageal squamous cell carcinoma (ESCC)-related, and other exploratory biomarkers (GEP, TILs, TMB/gene mutation/MSI, and/or blood based biomarkers [flow cytometry and immune-phenotyping (panel: A173, A167, A163, and A378), ctDNA alteration, and PBMC immune cell profiling]) in archival and/or fresh tumor tissues and blood samples obtained before and/or during study treatment and/or at disease progression, and the association with disease status and/or response to tislelizumab in combination with cCRT and placebo in combination with cCRT.

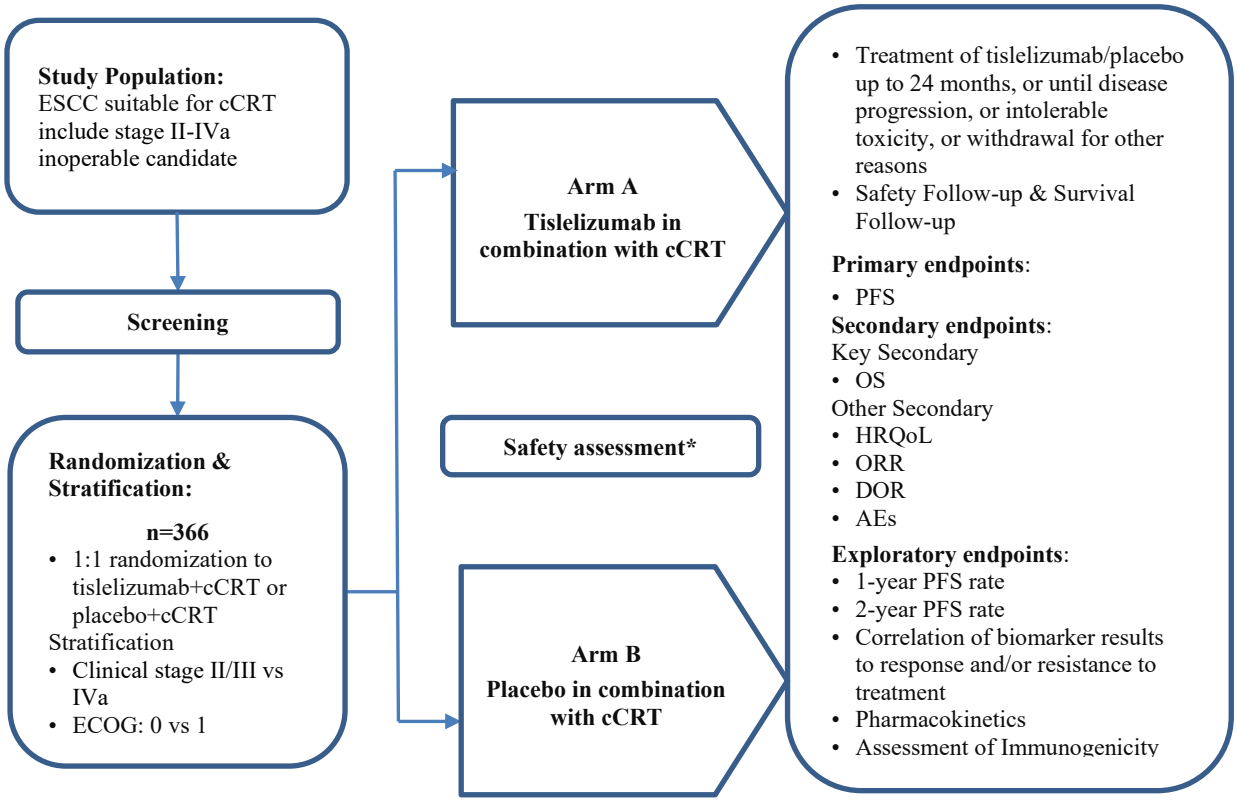
- Assessments of PK of tislelizumab when given with cCRT.
- Assessments of immunogenicity of tislelizumab by determining the incidence of anti-drug antibodies (ADAs).

3. STUDY DESIGN

3.1. Summary of Study Design

The study design schematic is presented in Figure 1.

Figure 1: Study Schema



Abbreviations: AE, adverse event; cCRT, concurrent chemoradiotherapy; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; ESCC, esophageal squamous cell carcinoma; HRQoL, health-related quality of life; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; vs, versus.
*Safety of tislelizumab or placebo in combination with cCRT will be assessed by an Independent Data Monitoring Committee in the first 20 patients (approximately 10 patients per each arm) after they have had at least 6 weeks of follow-up after the last dose of radiotherapy. Enrollment will continue during the safety review.

For all study procedures, see Section 7 and 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. All patients will take a pulmonary function test (refer to Section 7.1.4 and Appendix 1 for details). Screening evaluations may be repeated as needed within the screening period; the investigator is to assess preliminary patient eligibility according to the latest screening assessment results.

Archival tumor tissue will be collected for the purpose of biomarker analysis. If no archival samples are available, a fresh tumor biopsy at baseline is strongly recommended if feasible. Refer to Section 7.7 for details.

3.3. Treatment Period

After completing all screening activities, eligible patients will be randomized in a 1:1 ratio to receive either tislelizumab or placebo in combination with cCRT up to approximately 6 weeks followed by tislelizumab or placebo for a total of up to 24 months (refer to Section 3.6.1 for details on treatment duration). Randomization will be stratified according to Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1) and clinical staging (II/III versus IVa). Crossover between treatment arms will not be allowed.

Patients will receive blinded treatment with one of the following:

- Arm A: Tislelizumab 200 mg intravenously once every 3 weeks in combination with cCRT up to approximately 6 weeks followed by tislelizumab for a total of up to 24 months (about 35 cycles), or until disease progression per RECIST v1.1, unacceptable toxicity, withdrawal of consent, or another treatment discontinuation criterion is met, whichever occurs first
- Arm B: Placebo 200 mg intravenously once every 3 weeks in combination with cCRT up to approximately 6 weeks followed by placebo for a total of up to 24 months (about 35 cycles), or until disease progression per RECIST v1.1, unacceptable toxicity, withdrawal of consent, or another treatment discontinuation criterion is met, whichever occurs first

Administration of tislelizumab or placebo will continue for a total of up to 24 months, or until progressive disease as assessed by the investigator per RECIST v1.1, unacceptable toxicity, or death, or until another discontinuation criterion is met. Once disease progression is assessed by the investigator, the BIRC is required to complete central image review and convey the results to the investigator as soon as possible. If the investigator-assessed disease progression is not confirmed by the BIRC, the medical monitor will discuss the findings with the investigator and the study treatment is recommended to continue as long as it is considered to be in the best interest of the patient. In the situation where the investigator believes the patient must urgently begin subsequent systemic therapy without waiting for confirmation of disease progression based on central imaging review, the investigator must contact the medical monitor to inform them of the plan to urgently discontinue study treatment.

In both arms, treatment beyond the initial BIRC-assessed, RECIST v1.1-defined disease progression is permitted provided that the patient: a) has investigator-assessed clinical benefit (clinically stable, no progression requiring urgent intervention and willing to sign informed consent) and b) is tolerating study drug. Specific requirements for postprogression continuation of patients treated with tislelizumab/placebo and chemoradiotherapy are described in Section 7.5.

Radiological evaluation of tumor status should be performed every 9 weeks (± 7 days) for the first 54 weeks, every 12 weeks (± 7 days) during Years 2 and 3, every 24 weeks (± 7 days) during Years 4 and 5, and then according to local standards with a minimum of 1 tumor response

assessment annually thereafter, regardless of treatment delays. Tumor response will be assessed by the BIRC and by investigators. Details are provided in Section 7.5.

Safety will be assessed throughout the study by monitoring AEs/SAEs (toxicity grades assigned per NCI-CTCAE v5.0), and laboratory results. The safety of tislelizumab/placebo in combination with cCRT will be assessed by IDMC in the first 20 patients (approximately 10 patients per each arm) after they have had at least 6 weeks of follow-up after the last dose of radiotherapy and will provide recommendations on the continuation of the study based on the safety and tolerability. During these assessments, the enrollment may continue. 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 7.4 and the Schedule of Assessments (Appendix 1).

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 study treatment of tislelizumab/placebo or chemoradiotherapy [whichever occurs later], before the initiation of a new anticancer treatment, or before administration of the first dose in a long-term extension study or posttrial continued access program, whichever occurs first). In addition, telephone contacts with patients should be conducted to assess all AEs 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 imAE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated.

All AEs, 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 (± 7 days) after the last study treatment. Patients who discontinue study treatment prior to disease progression will have their tumors assessed as outlined in Section 7.5.

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

3.5. Survival Follow-up

Patients who discontinue study treatment for reasons other than disease progression (eg, toxicity) will continue to undergo tumor assessments according to Section 7.5 and the Schedule of Assessments (Appendix 1), until the patient begins a subsequent anticancer treatment, experiences disease progression (confirmed by the investigator or BIRC, whichever is later), withdraws consent, lost to follow-up, death, or until the study terminates, 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 termination by the sponsor. If applicable, the survival follow-up schedule may be adjusted within the allowed time window to perform the planned survival follow-up between 2 scheduled tumor response assessments for patients who enter the survival follow-up period but still need to continue tumor

response assessment per protocol requirement, especially after the completion of the 3-year tumor response assessment (eg, a survival follow-up may be arranged approximately 3 months after the last tumor response assessment, when a 6-month interval is required between 2 tumor assessments). In these survival follow-ups, potential symptoms or signs indicating disease progression should be followed actively. If any suspected symptoms or signs are reported, the investigator should arrange an unscheduled, on-site visit for further assessment. Tumor assessments will be at the discretion of the investigator, per local standards of care, at the time of symptoms or signs of disease progression.

3.6. Discontinuation From the Study Treatment or From the Study

3.6.1. Patient 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 7.5), safety (Section 7.4.1), 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 study treatment for reasons which 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 or sponsor determines may jeopardize the patient's safety, if he or she were to continue the study treatment
- Use of any other concurrent antineoplastic therapy (eg, chemotherapy, hormonal therapy, immunotherapy, or investigational agents)
- Patient noncompliance

When a patient reaches 24-month treatment duration of tislelizumab or placebo, patients may continue study therapy beyond 24-month treatment if the investigator considers this to be in the best interest of the patient based on an assessment of clinical benefit and potential risks. Continuation of study therapy beyond 24-month treatment must be explicitly approved by the sponsor medical monitor. The study assessment and procedure schedule may remain the same.

Patients with durable response (CR or PR) or durable SD may stop treatment after 24-month treatment, the decision should be based on the investigator's evaluation, with the patient's clinical benefit and risk taken into consideration. Prior to stopping the treatment, the investigator should notify the sponsor with the decision of discontinuation from treatment. In these cases, the tumor assessments will remain the same.

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
- Loss to follow-up
- Patients have completed all study assessments

3.6.3. 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
- Long-term extension study or posttrial continued access program becomes available

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.

At the end of the study, any patient who, in the opinion of the investigator, continues to benefit from tislelizumab, will be offered the option to continue treatment in a company-sponsored long-term extension study or posttrial continued access program until tislelizumab is commercially available in the country of the patient's residence.

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 Boards (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 notified 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, applicable laws and regulations
- Study activity is completed (ie, all patients have completed study 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 of the following criteria:

1. Able to provide written informed consent by the patient or by the patient's legally acceptable representative and can understand and agree to comply with the requirements of the study
2. 18 to 75 years on the day of signing the informed consent form
3. Histologically confirmed diagnosis of localized ESCC and is suitable for cCRT, including:
   - Patients with Stage II-IVa (AJCC version 8 [Rice et al 2017]) inoperable ESCC (medically unsuitable for surgery or refuses surgical intervention) are eligible. Patients who received prior chemotherapy without radiotherapy can be enrolled.

     Note: treatment-naive patients are preferred, and prior chemotherapy should be ≤ 3 cycles
4. Measurable and/or nonmeasurable disease defined per RECIST v1.1
5. ECOG Performance Status ≤ 1 assessed by the investigator within 7 days before randomization
6. Adequate organ function as indicated by the following laboratory values (obtained within 14 days prior to randomization):
   a. Patients must not have required a blood transfusion ,growth factor support or other supportive drugs with definite effects on neutrophil count, platelets or hemoglobin ≤ 14 days before sample collection at screening for the following
      i. Absolute neutrophil count ≥ 1.5 x 10^9/L
      ii. Platelets ≥ 100 x 109/L
      iii. Hemoglobin ≥ 90 g/L
   b. Estimated glomerular filtration rate ≥ 60 mL/min/1.73 m2 by Chronic Kidney Disease Epidemiology Collaboration Equation (Appendix 9)
   c. Serum total bilirubin ≤ 1.5 x ULN (total bilirubin must be ≤ 3 x ULN for patients with Gilberts syndrome).
   d. Aspartate transaminase and ALT < 3 x ULN
7. Patients with inactive/asymptomatic carrier, chronic or active HBV must have HBV deoxyribonucleic acid (DNA) < 500 IU/mL (or 2500 copies/mL) at screening.

Note: Patients with detectable hepatitis B surface antigen or detectable HBV DNA should be managed per treatment guidelines. Patients receiving antivirals at screening should have been treated for > 2 weeks prior to enrollment.

8. Females of childbearing potential must be willing to use a highly effective method of birth control for the duration of the study, ≥ 120 days after the last dose of tislelizumab or placebo, ≥ 180 days after the last dose of chemotherapy and radiotherapy, and have a negative urine or serum pregnancy test ≤ 7 days of randomization
9. Non-sterile 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 and ≥ 180 days after the last dose of chemotherapy and radiotherapy

4.2. Exclusion Criteria

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

1. History of fistula due to primary tumor invasion
2. Patients with high risk of fistula or sign of perforation
3. Evidence of distant metastases (M1 disease AJCC version 8 [Rice et al 2017])
4. History of surgery for esophageal cancer
5. Indicators of severe malnutrition
6. Clinically uncontrolled pleural effusion, pericardial effusion, or ascites requiring frequent drainage or medical intervention within 2 weeks prior to randomization
7. Known to be intolerable or resistant to treatment with the protocol-specified chemotherapy
8. Except ≤ 3 cycles of chemotherapy, received any other prior antineoplastic therapy(ies) for ESCC (eg, therapies targeting PD-1, PD-L1, PD-L2 or other immune-oncology therapies, radiotherapy, targeted therapies, ablation, or other systemic or local antineoplastic treatment)
9. 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
10. 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)
11. 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 inhalational 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)

12. With uncontrolled diabetes or > Grade 1 laboratory test abnormality in potassium, or sodium despite standard medical management or ≥ Grade 3 hypoalbuminemia ≤ 14 days before randomization
13. With history of interstitial lung disease, non-infectious pneumonitis or uncontrolled systemic diseases, including pulmonary fibrosis, acute lung diseases, etc.
14. With severe chronic or active infections (including tuberculosis infection, etc) requiring systemic antibacterial, antifungal or antiviral therapy within 14 days prior to randomization.

    Note: antiviral therapy is permitted for patients with chronic HBV or hepatitis C virus infection.

15. A known history of HIV infection
16. Any major surgical procedure ≤ 28 days before randomization

Note: Minimally invasive procedure (eg, introduction of peripherally inserted central catheter [PICC]) is not a major surgical procedure.

17. Prior allogeneic stem cell transplantation or organ transplantation
18. 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 7) ≤ 6 months before randomization
    e. Any event of ventricular arrhythmia ≥ Grade 2 in severity ≤ 6 months before randomization
    f. Any history of cerebrovascular accident ≤ 6 months before randomization
    g. Uncontrolled hypertension: systolic pressure ≥ 160 mmHg or diastolic pressure ≥ 100 mmHg despite anti-hypertension medications ≤ 28 days before randomization
    h. Any episode of syncope or seizure ≤ 28 days before randomization

19. History of severe hypersensitivity reactions to other monoclonal antibodies or cisplatin or paclitaxel

20. Has received any chemotherapy, immunotherapy (eg, interleukin, interferon, thymosin, etc) or any investigational therapies within 14 days or 5 half-lives (whichever is longer) of the first study drug administration
21. Has received any herbal medicine used to control cancer within 14 days of the first study drug administration
22. 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)
23. Was administered a live vaccine ≤ 28 days before randomization

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

24. 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.
25. Concurrent participation in another therapeutic clinical trial

5. STUDY TREATMENT

5.1. Formulation, Packaging, and Handling

5.1.1. Tislelizumab

Tislelizumab is a monoclonal antibody formulated for intravenous 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 intravenous administration, accountability, and disposal. Please also refer to the Investigator's Brochure for other details regarding tislelizumab.

5.1.2. Placebo

Placebo is a sterile, preservative-free solution for infusion formulated in the same buffer as tislelizumab. All excipients used for the manufacture of placebo are of pharmacopeial grade. No animal-derived components are used in the manufacture of placebo. Each vial is packaged into a single carton box.

As with tislelizumab, the contents of the label on placebo 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 intravenous administration, accountability, and disposal.

5.1.3. Chemotherapy Agents

Management (ie, labeling, 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 both arms, broken out by individual arm, are provided in Table 2. The first dose of study drug is to be administered within 3 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 and radiotherapy will be conducted in accordance with the relevant local guidance and/or clinical practice.

Patients should receive antiemetics and intravenous hydration for chemotherapy according to the standard of care and manufacturer's instruction. Due to their immunomodulatory effects, premedication with steroids should be limited when clinically feasible. In addition, in the event of chemotherapeutic agent-related skin rash, topical steroid use is recommended as treatment whenever it is clinically feasible.

In special situations (eg, when the administration is delayed due to management of AEs 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 every 3 weeks	Intravenous	Up to 24 months, until disease progression, unacceptable toxicity, or voluntary withdrawal of consent per patient decision
Paclitaxel	135 mg/m^2	Day 1 of every 3 weeks	Intravenous	Treatment will be administered until one of the following occurs (whichever occurs first): completed administration of 2 cycles; unacceptable toxicity; or documented disease progression.
Cisplatin	25 mg/m^2	Day 1 to 3 of every 3 weeks	Intravenous	

5.2.1. Tislelizumab

Tislelizumab 200 mg will be administered on Day 1 of each 21-day cycle (once every 3 weeks) for up to 24 months (about 35 cycles).

Tislelizumab will be administered by intravenous infusion through an intravenous 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. From Cycle 3 onward, a ≥ 30-minute monitoring period is required in an area with resuscitation equipment and emergency agents.

The initial infusion (Cycle 1, Day 1) will be delivered over 60 minutes; if this is well tolerated, then the subsequent infusions may be administered 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 of imAEs and infusion-related reactions are provided in detail in Section 8.7 and Appendix 8.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

5.2.2. Matched Placebo

All personnel at the study sites and all patients and the sponsor will be blinded to study treatment. Administration of 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

Patients in both arms will receive treatment with paclitaxel and cisplatin.

Paclitaxel 135 mg/m^2 will be administered as an intravenous infusion over 3 hours on Day 1 of every 21-day cycle (every 3 weeks) for 2 cycles. In addition, all patients should receive the appropriate premedications as per the local approved label. The premedication regimen should be determined by the investigator and administered as close to treatment as possible. Premedication may consist of an oral steroid (such as dexamethasone 8 to 20 mg or equivalent administered 6 to 12 hours orally or 30 to 60 minutes intravenously before paclitaxel), an antihistamine (H1 antagonist [such as diphenhydramine hydrochloride 50 mg intravenously or equivalent] or H2 antagonist [such as cimetidine 300 mg intravenously or equivalent]), and an antiemetic (such as ondansetron 8 mg/kg intravenously or equivalent administered 30 to 120 minutes before paclitaxel).

Cisplatin 25 mg/m^2 will be administered as an intravenous infusion over 60 minutes on Day 1 to 3 of every 21-day cycle (every 3 weeks) for 2 cycles. Additional premedications should be administered as per standard practice. The premedication regimen should be determined by the investigator and administered as close to treatment as possible. Premedication may consist of hydration with 1 to 2 liters of fluid prior to and after dosing. The use of diuretics for fluid maintenance is allowable.

All medications will be documented on the CRF.

There is a 3-day window for all treatments in the second cycle. If dosing is delayed due to administrative or other reasons (holidays, intercurrent illnesses, etc), the subsequent visit should be scheduled as clinically appropriate.

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

The chemotherapy should generally be delivered prior to the radiation therapy on the day of treatment. Chemotherapy doses that are missed during a 3-week schedule concurrent with radiotherapy are not to be administered to make up for missed individual doses, but these should be documented.

5.2.4. Radiotherapy

Prior to inclusion of any patient on this study, the radiation oncologist will evaluate the thoracic computed tomography (CT) scan or magnetic resonance imaging (MRI) to ensure that the treatment volumes are unlikely to significantly exceed the specified normal tissue constraints and it is feasible to administer the radiotherapy dose at 50.4 Gy for the patients.

All patients will receive radiotherapy using either a standardized intensity modulated radiotherapy (IMRT), or volumetric modulated arc therapy (VMAT) on a linear accelerator delivering a beam energy of ≥ 6 MV. The total dose of radiotherapy will be 50.4 Gy, administered in 28 once-daily fractions of 1.8 Gy and 5 fractions per week.

Every effort should be made to continue the radiotherapy during the concurrent phase in an uninterrupted manner. Should a patient develop severe esophagitis necessitating interruption of chemotherapy, the radiotherapy may continue, provided that the investigator believes supportive care will enable the patient to complete this part of the therapy without excess risk.

Strictly refer to the radiotherapy manual for detailed instructions.

5.2.5. Supportive Care

Patients should receive full supportive care, including epoetin and other hematopoietic growth factors (eg, colony-stimulating factors), transfusions of blood and blood products, antibiotics, antiemetics, other applicable medications, as needed according to local standard of care guidelines or practices.

All patients are strongly suggested to accept nutrition support if there is any indication including (not limited to): Medium-severe dysphagia; Weight loss > 5% in 1 month; BMI < 18.5 kg/m^2; Scored patient-generated subjective global assessment ≥ 4 score; Food intake is < 60% required for > 3 days.

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 in Section 8.7. 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 and placebo) 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 IMPs 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 and Modification

Every effort should be made to administer the study drug(s) according to the planned dose and schedule. 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.

5.5.1. General Guidance Regarding Dose Modifications

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

The chemotherapy-related toxicities should be managed according to the prescribing information for the approved product or institutional standard practices. The details in this section are for reference of this study:

- 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 newly referred body weight). Chemotherapy doses should not be modified for any body weight change of <10%, unless there is an ongoing toxicity requiring dose modification. When several toxicities with different grades of severity occur at the same time, the dose modifications should be made according to the highest grade observed.
- In case of chemotherapy-related toxicity, chemotherapy should be delayed until it is resolved to baseline or ≤ Grade 1 prior to administering the next dose of chemotherapy, with the exception of alopecia, Grade 2 fatigue, or other AEs, which, in the opinion of the investigator, would not affect the safety evaluation of the study drugs. Tislelizumab or placebo and radiotherapy should continue as scheduled. If the AE is resolved to baseline or ≤ Grade 1 within 21 days from Cycle 1 Day 1 (C1D1), chemotherapy will be administrated on Cycle 2 Day 1 (C2D1) as scheduled. If the AE is not resolved within 21 days from C1D1, chemotherapy will be delayed until the AE is resolved. If the AE is not resolved within 21 days from planned C2D1, chemotherapy should be discontinued.
- In case of tislelizumab or placebo related toxicity, tislelizumab or placebo will be delayed until the toxicity resolves to baseline or ≤ Grade 1 prior to administering the next dose of tislelizumab or placebo, with the exception of alopecia, Grade 2 fatigue, or other AEs, which, in the opinion of the investigator, would not affect the safety evaluation of the study drugs. Chemotherapy and radiotherapy should continue as scheduled. If the AE is resolved to baseline or ≤ Grade 1 within 10 days from the scheduled date of dose administration, tislelizumab or placebo will be administrated. If the AE is not resolved within 10 days from the scheduled date of dose administration, tislelizumab or placebo will be held until the next cycle. If AE is resolved to baseline or ≤ Grade 1 within 21 days from the scheduled date of dose administration, tislelizumab or placebo will be administered on Day 1 of the next planned cycle.

- The tumor assessment schedule will not be altered if chemotherapy and/or tislelizumab or placebo are delayed or discontinued.
- Every effort should be made to continue treatments in combination when patient's condition allows, also taking into consideration patient's convenience for the treatment schedule.
- Following either completion of or discontinuation from chemotherapy and radiotherapy, tislelizumab or placebo should be continued as scheduled, if clinically appropriate.
- If 1 component of chemotherapy is discontinued permanently during the initial 6 weeks of treatment for reasons other than progressive disease, the other component of chemotherapy could be continued per the study protocol or local practice. The patient may continue the radiotherapy and tislelizumab or placebo per the study protocol.
- If tislelizumab or placebo is discontinued permanently during the initial 6 weeks of treatment for reasons other than progressive disease, the patient may continue the chemotherapy and radiotherapy per the study protocol.
- If radiotherapy is discontinued permanently during the initial 6 weeks of treatment for reasons other than progressive disease, the patient may continue the chemotherapy and tislelizumab or placebo per the study protocol.

Dose modification guidelines for chemotherapy are described in Section 5.5.3 depending on the severity of toxicity and an assessment of the risk versus benefit for the patient, with the goal of maximizing patient compliance and access to supportive care.

5.5.2. Dose Delay or Modification for Tislelizumab or placebo

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 if AE recovers within 10 days of AE onset. If AE is ongoing more than 10 days, the patients should hold tislelizumab or placebo until the next cycle. The patients should resume tislelizumab or placebo treatment as soon as possible after 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 modifications related to imAEs and infusion-related reactions are described in Appendix 8 and Section 8.7.1, respectively.

5.5.3. Dose Delay or Modifications for Chemotherapy

Chemotherapy related toxicities must be resolved to baseline or Grade 0-1 prior to administering the next dose, with the exception of alopecia or Grade 2 fatigue, or other AEs which, in the opinion of the investigator, would not affect the safety evaluation of the study drugs. A maximum dose reduction of 2 levels is permitted for cisplatin and paclitaxel. Dose reduction of one chemotherapeutic agent does not require the same dose reduction of the other chemotherapeutic agent within the combination, unless the toxicities can reasonably be attributed to both agents. There will be no dose escalations in this study. If any chemotherapy agent is held for more than 3 weeks from the anticipated treatment date, or the dose is not tolerated, chemotherapy should be permanently discontinued. The possibility of immune-mediated toxicity should also be considered when managing patients (see Appendix 8).

Dose modification guidelines for chemotherapy are described as below depending on the severity of toxicity and an assessment of the risk versus benefit for the patient, and dose modifications are permitted per local standards or at investigator's discretion.

5.5.3.1. Dose Reduction Level and Dose Modification for Hematologic Toxicity

Dose adjustments are based on nadir blood counts since the first dose chemotherapy administration. Dose reduction levels for cisplatin and paclitaxel are provided in Table 3. Recommended dose modifications in next cycle for hematologic toxicity are provided in Table 4.

Table 3: Dose Reduction Level of Cisplatin and Paclitaxel

Drug Dose	**Standard Level** (Every 3 weeks as a cycle)	**1st Level**	**2nd Level**
Cisplatin	25 mg/m^2 (Day 1-3)	20 mg/m^2 (Day 1-3)	15 mg/m^2 (Day 1-3)
Paclitaxel	135 mg/m^2 (Day 1)	100 mg/m^2(Day 1)	50 mg/m^2(Day 1)

Table 4: Dose Modification based on Hematologic Nadir Values Prior to the Next Dose

ANC x 10^9/L		**PLT x 10^9/L**	**Dose for Cisplatin or paclitaxel**
≥ 1	and	≥ 75	Full dose
0.5-1	or	50-75	1st dose level
< 0.5	or	< 50	2nd dose level

Abbreviations: ANC, absolute neutrophil count; PLT, platelets.

Prior to treatment, the absolute neutrophil count must be ≥ 1.5 x 10^9/L and platelets must be ≥ 100 x 10^9/L. For any grade toxicity, if the hematologic toxicity does not recover to Grade 1 or baseline despite the G-CSF support in 3 weeks, chemotherapy must be discontinued.

5.5.3.2. Dose Modifications for Renal and Hepatic Impairment

Dose adjustments are based on renal or hepatic function since the first dose chemotherapy administration. Recommended dose modifications in next cycle for renal or hepatic toxicity are provided in Table 5 and Table 6.

Dose Modifications for Renal Impairment

Table 5: Dose Modifications of Cisplatin for Renal Impairment

eGFR mL/min	Dose for Cisplatin
> 50 mL/min	Full dose
41-50 mL/min	1st dose level
≤ 41 mL/min	Discontinue Cisplatin

Dose Modification for Hepatic Impairment

Table 6: Treatment Modification of Paclitaxel for Hepatic Impairment

Degree of Hepatic Impairment			Treatment
Transaminase levels		Bilirubin Levels	
< 10 x ULN	And	≤ 1.25 x ULN	Full dose
< 10 x ULN	And	1.26 - 2.0 x ULN	1st dose level
< 10 x ULN	And	2.01 - 5.0 x ULN	2nd dose level
≥ 10 x ULN	OR	> 5.0 x ULN	Discontinue Paclitaxel

Abbreviation: ULN, upper limit of normal.

If the liver function test abnormalities do not recover to Grade1 in 3 weeks, paclitaxel must be discontinued.

Does Modification for Allergic Reaction/Hypersensitivity

For moderate symptoms, paclitaxel infusion must be stopped; and diphenhydramine 25 to 50 mg, dexamethasone 10 mg, or other appropriate therapy as per institutional guidelines must be administered. Paclitaxel infusion may be gradually resumed after recovery of symptoms. Paclitaxel may be dosed over 3 hours. If symptoms recur with reinstitution of the paclitaxel infusion, the infusion must be stopped.

Patients who experience severe or life-threatening symptoms of hypersensitivity despite standard pretreatment medications must discontinue paclitaxel permanently.

5.5.3.3. Chemotherapy Delay or Dose Modification for Other Toxicities

For other non-hematologic toxicities such as Grade 3 nausea, vomiting, diarrhea or stomatitis that occur despite supportive care, chemotherapy will be held at the first occurrence and resume at the first dose level once the toxicity has recovered to Grade 0-1 in severity within 3 weeks. In the event of skin reactions, paronychia, alopecia, fatigue, nausea/vomiting or other AEs which, in the opinion of the investigator, would not affect the safety evaluation of the study drugs, chemotherapy can resume when the toxicity has recovered to ≤ Grade 2.

Some radiotherapy related AE may require delay or discontinuation of chemotherapy and/or tislelizumab/placebo. Refer to the radiotherapy manual for detailed instructions.

If considered in the best interest of the patient and consistent with local practice, investigators may decide to use supportive measures or treatment and/or secondary prophylaxis for the next dose.

5.5.4. Dose Delay or Modifications for Radiotherapy

Strictly refer to the radiotherapy manual for detailed instructions.

5.5.5. Blinding

This is a randomized, double-blind, Phase 3 study. Patients will be randomized to receive either tislelizumab or matching placebo in a double-blind fashion that neither the investigator, nor the patient, nor medical or ancillary medical staff, nor the blinded sponsor or its designees, will know which drug is being administered in addition to cCRT.

- Emergency unblinding

  Emergency unblinding for AEs may be performed through the Interactive Response Technology (IRT).

  In case of an emergency, such as when a patient has an AE suspected to be related to the investigational drug product and for which management of the AE with one or more drug products with substantial toxicity or invasive procedures is being considered, unblinding can occur. 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.

  Unblinded patients may remain on study treatment at the discretion of the investigator in consultation with the medical monitor and only as permissible per definitions in this study protocol.

- Non-Emergency unblinding

  Non-emergency unblinding to tislelizumab versus placebo administration may occur on an individual patient basis and only after consultation with and approval from the medical monitor at the time of 1) disease progression confirmed by BIRC and the patient has discontinued all study treatments, or 2) when the patient has discontinued all study treatments for toxicity and a new anticancer treatment is going to be started.

- Inadvertent unblinding

  Every effort should 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 a sufficient cause (in and of itself) for that patient to be discontinued from the study therapy or excluded from any safety or efficacy analyses.

- Unblinding after PFS final analysis

Investigators, site personnel, and patients will be unblinded to the treatment arms after the PFS final analysis. Placebo administration will be discontinued after the unblinding for patients in Arm B who are still on study treatment. Crossover between the treatment arms will not be allowed.

Bioanalysis laboratory may not be blinded as long as there are no means for the investigators or blinded sponsor team to know which samples will be analyzed or not.

6. PRIOR AND CONCOMITANT THERAPY

6.1. Prior Therapy

The exclusion criteria (Section 4.2) specify that patients must have not received any prior therapies targeting PD-1, PD-L1 or PD-L2 or other immune-oncology therapies. Prior radiotherapy is not allowed. All prior cancer treatments, treatments for underlying active medical conditions, 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 must be recorded on the appropriate CRF.

6.2. Concomitant Therapy

6.2.1. Permitted Concomitant Medications

Most concomitant medications and therapies deemed necessary and in keeping with the local standards of medical care at the discretion of the investigator for the supportive care (eg, antiemetics, antidiarrheals, pain medications, and nutritional support) and in a patient's well-being are allowed. All concomitant medications will be recorded on the eCRF including all prescriptions, over-the-counter drugs, herbal supplements, and intravenous medications and fluids. If changes (dose, stop, or start) in concomitant medication occur during the study, documentation of drug dosage, frequency, route, date, and reason for use will be recorded on the eCRF.

All concomitant medications received within 30 days before the first dose of study drug and 30 days after the last infusion or dose of study treatment should be recorded.

Nutritional support for patients with a history of weight loss is strongly recommended as a routine standard-of-care therapy, and such support should be recorded as a concomitant medication.

Systemic corticosteroids given for the control of imAEs must be tapered gradually (see Appendix 8) and be at non-immunosuppressive 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. Patients may continue to receive hormone replacement or supportive care if initiated prior to enrollment. Premedication with steroids for chemotherapy is acceptable.

Bisphosphonates are permitted during the study for a non-malignant indication.

Patients with active hepatitis B, defined as HBV DNA ≥ 500 IU/mL at screening, must initiate antiviral treatment 2 weeks prior to randomization and continue until 6 months after the last dose. Patients should continue effective antiviral treatment during the study to decrease potential viral reactivation risk. Tenofovir, and entecavir are recommended in the American Association for the Study of Liver Disease (AASLD) guideline because they lack resistance with long-term use (Terrault et al 2016). The investigator might use other antiviral agents, if appropriate, following local guidelines. However, interferon-based therapy for hepatitis B is not permitted on study.

Management of prophylactic antiviral therapy for patients with inactive, treated, and stable hepatitis B (HBV DNA < 500 IU/mL) is at the discretion of the investigator, as aligned with local guidance. Such medications must be documented in the patient's chart and recorded in the eCRF. Patients receiving antivirals at screening should be treated for > 2 weeks before enrollment and continue treatment during the study and for 6 months after study drug treatment discontinuation.

Patients with detectable hepatitis C virus RNA and who are receiving treatment at screening should remain on continuous, effective antiviral therapy during the study. The investigator can consider treatment with sofosbuvir alone or in combination with other antivirals following the AASLD guideline or the local guidelines as appropriate. However, interferon-based therapy for either HBV or hepatitis C virus is not permitted on study. Patients who are given antiviral therapy must initiate treatment > 2 weeks prior to randomization.

6.2.2. Prohibited Concomitant Medications

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 medicine] 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.

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 have an effect on drug metabolizing enzymes or transporters.

During cisplatin use, concurrent therapy with drugs having a potential ototoxic or nephrotoxic effect (eg, aminoglycosides, cefalotin, furosemide, amphotericin B) should be avoided or adequately monitored since this may lead to increased or exacerbated toxicity due to platin-induced changes in renal clearance of these substances.

The metabolism of paclitaxel is catalyzed, in part, by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Therefore, in the absence of a PK drug-drug interaction study, caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit either CYP2C8 or CYP3A4 (eg, ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir), because the toxicity of paclitaxel may be increased due to higher paclitaxel exposure. Administering paclitaxel concomitantly with medicines known to induce either CYP2C8 or CYP3A4 (eg, rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) is not recommended because efficacy may be compromised because of lower paclitaxel exposures.

Refer to the approved product labeling for chemotherapy complete information regarding drug-drug interactions.

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. All patients will take a pulmonary function test (refer to Appendix 1 for details). Screening evaluations may be repeated as needed within the screening period; the investigator is to 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 7.4), tumor and response evaluations (Section 7.5) and biomarkers (Section 7.7) sections. The PK sampling schedule is shown in Appendix 1.

Rescreening under limited conditions may be allowed after consultation with sponsor, 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).

Cancer history will include pathologic diagnosis, stage at screening, tumor location and an assessment of 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 10 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. Informed consent forms 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. Pulmonary Function Tests

Pulmonary function testing including spirometry and assessment of oxygenation, at a minimum, pulse oximetry at rest and with exercise, or alternatively, assessment of diffusion capacity, are to be performed for all patients during the screening period to assist in determining the suitability for the study. Respective test results must be submitted to the sponsor.

For test results indicative of significantly impaired pulmonary function, eg, resting pulse oximetry < 90% on room air and further desaturation upon exercise, forced expiratory volume (FEV1) < 60% or diffusing capacity of the lungs for carbon monoxide (DLCO) (if performed) < 60% of age and sex adjusted predicted performance levels (Pellegrino et al 2005), the medical monitor must be consulted to confirm eligibility.

Tests may be repeated as clinically indicated while on study.

7.2. Enrollment

7.2.1. Confirmation of Eligibility

The investigator will assess and 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, study site personnel will complete a treatment authorization form 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. Patient Numbering

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

7.2.3. Enrollment/Randomization

Site personnel will access the IRT system to randomize to treatment assignment and to assign study drugs. Study treatment must commence within 3 days after randomization.

7.3. Tislelizumab or Placebo Drug Dispensation

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

7.4. Safety Assessments

7.4.1. Vital Signs

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

7.4.2. Physical Examinations

During the screening visit, a complete physical examination will be conducted including evaluations 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 eCRF with appropriate disease/condition terms.

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 eCRF. Refer to Section 8.3 regarding AE definitions and reporting and follow-up requirements.

7.4.3. Eastern Cooperative Oncology Group Performance Status

ECOG Performance Status (Appendix 4) will be assessed during the study.

7.4.4. Laboratory Safety Tests

Local laboratory assessments on serum chemistry, hematology, coagulation, and urinalysis will be conducted, of which certain elements will be collected as specified in Appendix 3.

If laboratory tests at screening are not performed within 7 days prior to the administration of study drug(s) on Cycle 1 Day 1, these tests should be repeated and reviewed before study drug(s) administration. Hematology and serum chemistry (including C reactive protein) as specified in Appendix 3 should be performed weekly and reviewed 72 hours before study drug(s) administration for the cCRT duration and at the beginning of subsequent tislelizumab/placebo cycles. After Cycle 1 of tislelizumab/placebo, results are to be reviewed within 72 hours before study drug administration.

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.

7.4.5. Electrocardiograms

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.

Patients should rest in semi-recumbent supine position for at least 10 minutes prior to ECG collection.

7.4.6. Adverse Events

AEs will be graded and recorded throughout the study according to NCI-CTCAE v5.0. 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. 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 9 weeks (± 7 days) for the first 54 weeks, every 12 weeks (± 7 days) during Years 2 and 3, every 24 weeks (± 7 days) during Years 4 and 5, and then according to local standards with a minimum of 1 tumor response assessment annually thereafter, regardless of treatment delays. All tumor responses will be assessed by the BIRC and investigators using RECIST v1.1 criteria.

Screening assessments must include CT scans (with oral/intravenous contrast, unless contraindicated) or MRI of the neck, chest, and abdomen, ultrasound of cervical and supraclavicular lymph nodes, and esophagography. If feasible, esophagoscopy, including esophagoendoscopic ultrasonography should be included as well. Other known or suspected sites of disease must be included in the imaging assessments (bone, brain, etc).

Tumor assessments must include CT scans (with oral/intravenous contrast, unless contraindicated) or MRI, with preference for CT, of the neck, chest, and abdomen, and esophagography. Esophagoscopy and biopsy (if disease progression is suspected) could be included. 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 CT scans). All known sites of disease must be documented at screening and reassessed at each subsequent tumor evaluation.

- 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 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.

Response will be assessed by BIRC and the investigator using RECIST v1.1 (see Appendix 5). 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 disease progression per RECIST v1.1 assessed by the BIRC is suspected by the investigator to reflect pseudoprogression, patients may continue treatment with tislelizumab or placebo 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 BIRC-assessed progression must be agreed with the sponsor medical monitor and documented in the study records.

Tumor assessment will continue until disease progression has been confirmed by the investigators or BIRC (whichever is later). 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 (confirmed by the investigator or BIRC, whichever is later), withdraws consent, lost to follow-up, death, 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.

7.6. Pharmacokinetic and Anti-Drug 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 ADAs at multiple time points throughout the study (see 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 central 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.

7.7. 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 and Schedule of Assessments (Appendix 1 and Appendix 2).

Archival tumor tissues (formalin-fixed paraffin-embedded block or approximately 15 [≥ 6] unstained slides), if feasible, are required for PD-L1 assessment and exploratory biomarker analysis at a central laboratory or sponsor designed laboratory. In addition to PD-L1 expression, other exploratory predictive biomarkers, such as TMB/gene mutation/MSI, GEP, and TILs that are related to response or clinical benefit of tislelizumab may also be evaluated. If no archival samples are available, a fresh tumor biopsy at baseline is strongly recommended if feasible. The baseline tissue sample can be collected at any stage of study after local regulation approval.

Optional biopsies will also be taken from patients who have disease progression during the study from accessible tumor sites 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.

Tumor tissue should be of good quality based on total and viable tumor content. 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. Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable.

Blood for ctDNA (10 mL each timepoint) will be requested at baseline (predose at Day 1 of Cycle 1), and optional at C3D1 (predose at Day 1 of Cycle 3), and from patients who have disease progression. Blood for flow cytometry (9 mL each timepoint; panel: A173, A167, A163, and A378) and PBMC isolation for immune cell profiling (10 mL each timepoint) will be collected at baseline (predose at Day 1 of Cycle 1), C3D1 (predose at Day 1 of Cycle 3), and from patients who had disease progression to explore the potential resistance mechanism. Blood collection and testing for flow cytometry will be terminated after 50 paired samples (C1D1 and C3D1) are collected. Written patient consent is required for blood sample collections.

7.8. Patient-Reported Outcomes

Patients will be asked to complete the EORTC QLQ-C30 and EORTC QLQ-OES18 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.

7.9. Visit Windows

All visits must occur within ± 3 days from the scheduled date, unless otherwise noted (see 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 Day 1.

7.10. 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 investigator assessment as appropriate, and the results of these tests should be entered on the unscheduled visit eCRF.

8. SAFETY MONITORING AND REPORTING

8.1. Risks Associated With Study Treatment

8.1.1. Risks Associated With Tislelizumab

Tislelizumab is an investigational agent that is currently in clinical development. 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 8.

8.1.2. Risks Associated With Concurrent Chemotherapy

Cisplatin

Cisplatin produces cumulative nephrotoxicity which is potentiated by aminoglycoside antibiotics. The serum creatinine, blood urea nitrogen, creatinine clearance, magnesium, sodium, potassium, and calcium levels should be measured prior to initiating therapy, and prior to each subsequent course. Elderly patients may be more susceptible to nephrotoxicity. A urine output of 100 mL/hour or greater will tend to minimize cisplatin nephrotoxicity. This can be accomplished by increased hydration before and after treatment.

There are reports of severe neuropathies in patients in whom regimens are employed using higher doses of cisplatin or greater dose frequencies than those recommended. These neuropathies may be irreversible and are seen as paresthesias in a stocking-glove distribution, areflexia, and loss of proprioception and vibratory sensation. Elderly patients may be more susceptible to peripheral neuropathy.

Loss of motor function has also been reported.

Anaphylactic-like reactions to cisplatin have been reported. These reactions have occurred within minutes of administration to patients with prior exposure to cisplatin, and have been alleviated by administration of epinephrine, corticosteroids, and antihistamines.

Toxicity has been observed in patients treated with a single dose of cisplatin. Hearing loss can be unilateral or bilateral and tends to become more frequent and severe with repeated doses; however, deafness after initial dose of cisplatin has been reported rarely. It is unclear whether cisplatin-induced ototoxicity is reversible. Careful monitoring by audiometry should be performed prior to initiation of therapy and prior to subsequent doses of cisplatin.

Cisplatin can cause fetal harm when administered to a pregnant woman. Cisplatin is mutagenic in bacteria and produces chromosome aberrations in animal cells in tissue culture. In mice, cisplatin is teratogenic and embryotoxic. If this drug is used during pregnancy or the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Patients should be advised to avoid becoming pregnant.

The development of acute leukemia coincident with the use of cisplatin has been reported. In these reports, cisplatin was generally given in combination with other leukemogenic agents.

Injection site reactions may occur during the administration of cisplatin. Given the possibility of extravasation, it is recommended to closely monitor the infusion site for possible infiltration during drug administration. A specific treatment for extravasation reactions is unknown at this time.

Paclitaxel

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2% to 4% of patients receiving paclitaxel in clinical trials. Fatal reactions have occurred in patients despite premedication. All patients should be pretreated with corticosteroids, diphenhydramine, and H2 antagonists. Patients who experience severe hypersensitivity reactions to paclitaxel should not be re-challenged with the drug.

Bone marrow suppression (primarily neutropenia) is dose-dependent and is the dose-limiting toxicity. Neutrophil nadirs occurred at a median of 11 days. Paclitaxel should not be administered to patients with baseline neutrophil counts of $< 1.5 \times 10^9$/L or before platelets recover to a level $> 100 \times 10^9$/L.

Severe conduction abnormalities have been documented in < 1% of patients during paclitaxel therapy and in some cases requiring pacemaker placement. If patients develop significant conduction abnormalities during paclitaxel infusion, appropriate therapy should be administered, and continuous cardiac monitoring should be performed during subsequent therapy with paclitaxel.

8.1.3. Risks Associated With Radiotherapy

Adverse effects related to radiation therapy include nausea/vomiting, diarrhea, weight loss, fatigue, myelosuppression, skin erythema, subcutaneous fibrosis, esophagitis, esophageal stricture, esophageal fistula, carditis, myelitis, acute radiation pneumonitis, and late pulmonary fibrosis.

Refer to the radiotherapy manual for details.

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 trial. 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, and patients who have received a live viral vaccine within 28 days before randomization are excluded from the study. Patients with contraindications for cisplatin or paclitaxel or radiation treatment are also excluded from the study (see 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.

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 treatment, whether considered related to study treatment 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 follows:

- 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 treatment 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 assess the 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 in light of 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 treatment (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 postmortem 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, X-rays, or 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.

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 (SADR), the specificity or severity of which is not consistent with those noted in the 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 treatments (including chemoradiotherapy) or initiation of new anticancer therapy, whichever occurs first. Immune-mediated AEs (serious or non-serious) 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 must 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 7.

Table 7: 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 AE	SAE Report	As expeditiously as possible	SAE Report	Email or fax SAE form or Pregnancy form

Abbreviations: AE, adverse event; 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 at the time of the initial report 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. Recording Disease Progression

Disease progression (including fatal disease progression) is expected in this study population and measured as an efficacy endpoint and therefore; should not be recorded as an AE term. Similarly, nonserious AEs that are clearly consistent with the pattern of progression of the underlying disease and are considered unequivocally due to disease progression should not be recorded as an AE term. However, if there is any uncertainty as to whether a nonserious AE is due to disease progression, it should be recorded as an AE. All SAEs and deaths regardless of relatedness to disease progression should be recorded and reported (see Section 8.6.2).

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. 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 placebo, or within 180 days after the last dose of chemotherapy or radiotherapy, 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 prescribing information
- Paclitaxel prescribing information

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 (see Section 8.7.3) should be classified as imAEs and identified as such in the eCRF AE page until Day 90, after treatment discontinuation.

Investigators should consult the guidance on diagnostic evaluation and management of imAEs, which are commonly seen with immune checkpoint inhibitors, in Appendix 8.

An extensive list of potential imAEs appears in Table 9. 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 8.

8.7. Management of AE of Special Interest

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

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, intravenous 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 8.

Table 8: Treatment Modification for Symptoms of Infusion-Related Reactions Due to Study Drug(s)

NCI-CTCAE Grade	Treatment Modification for Tislelizumab/Placebo
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, intravenous fluids); prophylactic medications indicated for ≤ 24 h	Stop infusion. Infusion may be resumed at 50% of previous rate once infusion-related reactions have 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 Event; NSAIDs, nonsteroidal anti-inflammatory drugs.

Once the tislelizumab/placebo 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/placebo treatment.

NCI-CTCAE Grade 1 or 2 infusion reaction: Proper medical management should be instituted, as indicated per the type of 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 intravenous 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.

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 intravenous 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 adverse events 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 9. All conditions similar to those listed should be evaluated in patients receiving tislelizumab or placebo to determine whether they are immune-mediated.

Recommendation for diagnostic evaluation and management of imAEs is based on European Society for Medical Oncology 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 8. For any AEs not included in Appendix 8, 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 9: 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 8.

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 stated in Section 7.2.3, patients will be randomized using the IRT system for this study. Permuted block stratified randomization with stratification factors of ECOG performance status (0 versus 1) and clinical stage (II/III versus IVa as per AJCC version 8 [Rice et al 2017]) will be used.

9.1.2. Analysis Sets

The ITT Analysis Set includes all randomized patients. It will be the primary analysis set for the efficacy analysis.

The Safety Analysis Set includes all patients who received at least 1 dose of study treatment. It will be the primary analysis set for safety analysis.

The PK Analysis Set includes all patients who are randomized to the tislelizumab arm, and for whom postdose PK data are available.

The ADA Analysis Set includes all patients who are randomized to the tislelizumab arm and have a baseline and at least 1 postbaseline ADA result.

9.1.3. Patient Disposition

The number of patients randomized, treated, and discontinued from study treatment and/or study and those with major protocol deviations will be counted. The primary reason for study treatment 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 will be summarized in the ITT Analysis Set using descriptive statistics. Continuous variables include age, weight, vital signs, time since initial cancer diagnosis; categorical variables include gender, ECOG, race, smoking status, and alcohol use, clinical staging (AJCC version 8 [Rice et al 2017]), prior chemotherapy.

9.1.5. Prior and Concomitant Medications

Concomitant medications will be coded using the World Health Organization 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 treatment. Concomitant medications will be defined as medications that 1) started before the first dose of study treatment and were continuing at the time of the first dose of study treatment, or 2) started on or after the date of the first dose of study treatment up to 30 days after the patient's last dose (as of Safety Follow-up Visit). In addition, telephone contacts with patients should be conducted to assess imAEs and concomitant medications (if appropriate, ie, associated with an imAE or is a new anticancer therapy) at 60 and 90 days (± 14 days) after the last dose of study treatments regardless of whether the patient starts a new anticancer therapy.

9.2. Efficacy Analyses

PFS is the primary endpoint of the study with the one-sided alpha (α) type I error rate controlled under 0.025. The initial α allocated to PFS will be transferred to secondary endpoints once the primary endpoint is statistically significant. The secondary endpoints will be tested sequentially, ie, starting with the key secondary endpoint (OS), and followed by HRQoL. Testing for the secondary endpoints will continue until the first failure of rejection occurs.

9.2.1. Primary Efficacy Analysis

9.2.1.1. PFS Assessed by BIRC

PFS assessed by BIRC is defined as the time from randomization to the first documented disease progression as determined by the BIRC according to RECIST v1.1, or death by any cause, whichever occurs first. The actual tumor assessment visit date will be used to calculate PFS. The PFS censoring rule will follow the United States (US) Food and Drug Administration (FDA) Guidance for Industry, Clinical Trial Endpoints for the Approval of Cancer drugs and Biologics (US FDA Center for Drug Evaluation Research and Center for Biologics Evaluation and Research, 2018). Data for patients without disease progression or death at the time of analysis will be censored at the time of the last tumor assessment. Data for patients who are lost to follow-up prior to documented disease progression will be censored at the last tumor assessment date when the patient is known to be progression-free. Data for patients who start to receive new anticancer therapy will be censored at the last tumor assessment date prior to the introduction of new therapy.

The null hypothesis to be tested is:

H_0: PFS in Arm A ≤ PFS in Arm B

against the alternative:

H_1: PFS in Arm A > PFS in Arm B

This will be the primary analysis once the targeted PFS event number assessed by BIRC is reached. The p-value from the stratified log-rank test will be presented using the stratification factor at randomization (ECOG performance status: 0 versus 1 and stage: II/III versus IVa).

The median PFS will be calculated for each treatment arm and presented with 2-sided 95% CIs. Kaplan-Meier survival probabilities for each arm will be plotted over time. The treatment effect in the form of HR and its 95% CI will be estimated using a Cox regression model incorporating the treatment arm as the independent variable and the prespecified stratification factors as the strata. These analyses will be performed in the ITT Analysis Set as the primary analysis.

Detailed plan of sensitivity/supportive analyses and subgroup analyses of PFS will be provided in the statistical analysis plan.

9.2.2. Secondary Efficacy Analyses

9.2.2.1. Key Secondary Endpoint - Overall Survival

The OS is defined as the time from the date of randomization to the date of death due to any cause.

The null hypothesis to be tested is:

H_0: OS in Arm A $\leq$ OS in Arm B

against the alternative:

H_1: OS in Arm A > OS in Arm B

The distribution of OS will be compared between the 2 treatment arms using a stratified log-rank test at one-sided 2.5% level of significance, the p-value from the stratified log-rank test will be presented using the stratification factors at randomization (ECOG: 0 versus 1 and stage: II/III versus IVa). The median OS will be calculated for each treatment arm and presented with 2-sided 95% CIs. Kaplan-Meier survival probabilities for each arm will be plotted over time. The treatment effect in the form of HR and its 95% CI will be estimated using a Cox regression model incorporating the treatment arm as the independent variable and the prespecified stratification factors as the strata. These analyses will be performed in the ITT Analysis Set.

9.2.2.2. HRQoL

HRQoL is an assessment of a patient's overall health status using the EORTC QLQ-C30 and EORTC QLQ-OES18. The postbaseline scores will be compared between the 2 treatment arms, and the changes from the baseline scores will be summarized descriptively.

9.2.2.3. Objective Response Rate by the BIRC

The ORR is the proportion of patients who had a CR or PR as determined by BIRC per RECIST v1.1 in the ITT Analysis Set. Patients without any postbaseline assessment will be considered nonresponders. The 2-sided 95% CIs for the odds ratio in the ORR will be calculated, as well as Clopper-Pearson 95% CIs of ORR for each treatment arm.

9.2.2.4. Duration of Response

The DOR assessed by BIRC per RECIST v1.1 will be analyzed only in responders. The statistical methods applied to DOR is similar to the analysis described in Section 9.2.1.1.

9.2.3. Exploratory Efficacy Analyses

9.2.3.1. 1-Year PFS rate

The 1-year PFS rate is defined as the Kaplan-Meier estimator of proportion of patients alive and progression free at 1 year after randomization. The 1-year PFS rate and the 2-sided CIs for the 2 arms will be estimated using the Kaplan-Meier estimator.

9.2.3.2. 2-Year PFS rate

The 2-year PFS rate is defined as the Kaplan-Meier estimator of proportion of patients alive and progression free at 2 years after randomization. The 2-year PFS rate and the 2-sided CIs for the 2 arms will be estimated using the Kaplan-Meier estimator.

Distribution of PD-L1 expression in tumor tissue will be examined in the ITT Analysis Set. The association between PD-L1 expression and tislelizumab treatment effect over the control (PFS, OS, ORR, DOR and DCR) will be explored.

Status of PD-L1 expression in tumor tissue will be examined in the ITT Analysis Set. The association between PD-L1 expression and study treatment will be explored.

Other immune, ESCC-related, and exploratory biomarkers including but not limited to gene expression profiling and tumor mutational profile and their association with disease status and/or response to study treatment will also 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), 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 treatment 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 (milligrams), dose intensity, and relative dose intensity.

The number (percentage) of patients requiring dose reduction, interruption, dose delay, and treatment discontinuation due to AEs will be summarized for each study treatment. 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 (investigator's description from the eCRF) will be coded using MedDRA. The AEs will be coded to MedDRA (Version 20.1 or higher) lower level term, preferred term and primary system organ class.

A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study treatment and up to 30 days following study treatment discontinuation or initiation of new anticancer therapy, whichever occurs first. Only those AEs that were treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in patient data listings.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by system organ class and preferred term. A patient will be counted only once by the highest severity grade per NCI-CTCAE v5.0 within a system organ class and preferred term, even if the patient experienced more than 1 TEAE within a specific system organ class and preferred term. The number (percentage) of patients with TEAEs will also be summarized by relationship to the study treatment. 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, imAEs, treatment-related TEAEs and TEAEs that lead 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, pulse rate, heart rate, respiratory rate, temperature, and 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

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, safety endpoints) analyses may be conducted as appropriate and the results of such analysis may be reported separately from the CSR.

9.5. Immunogenicity Analyses

Samples to assess anti-tislelizumab antibodies will be collected in all randomized patients and at sites that are able to adequately perform the sampling, handling, and processing procedures outlined in the laboratory manual, but will be tested only for 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 ADAs and neutralizing ADAs 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 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 of PFS in the primary comparisons are based on the following assumptions:

- Median PFS of 14 months in Arm B.
- 1.5-month delayed treatment effect (ie, assuming HR = 1 in the first 1.5 months; and HR = 0.65 thereafter, corresponding to an improvement in median PFS from 14 months to 21.5 months).
- One-sided α of 0.025.
- 1-year drop-out rate of 5% for both treatment arms.
- Randomization ratio of 1:1.

With these assumptions, approximately 200 PFS events are required to occur in the ITT Analysis Set for the PFS final analysis to obtain approximately 80% power. Approximately 366 patients will be enrolled, with enrollment duration of 24.0 months. The interim PFS analysis will be performed at 25.5 months after the first patient was randomized, when 115 PFS events occurred, with error spent from a Lan-DeMets O'Brien-Fleming approximation spending function. The boundaries for PFS interim and final analysis could be found in Table 10.

To demonstrate the OS superiority of Arm A over Arm B in the ITT Analysis Set, the following assumptions are made: (1) median OS of 35 months in Arm B; (2) HR of 0.65, corresponding to an improvement in median OS from 35 months to 53.8 months. Approximately 191 death events will provide approximately 85% power using a 1-sided α of 0.025, with interim analysis for OS at the time of the interim PFS analysis.

The final analysis of PFS and OS will be performed concurrently when approximately 200 PFS events or approximately 191 OS events have been observed, whichever occurs first.

9.7. Interim Analyses

PFS

One PFS interim analysis was planned when 115 PFS events were reported.

The efficacy boundary is estimated based on the Lan-DeMets O'Brien-Fleming approximation spending function. The stopping boundaries (p-values) of the stratified log-rank test for PFS at the interim and final analysis are shown in Table 10. The boundaries will be updated according to the actual number of events during analysis, to ensure overall type I error controlled.

OS

The key secondary endpoint of OS will be tested only after the primary endpoint is statistically significant. If the test of PFS is significant, the total $\alpha = 0.025$ will be allocated to OS interim and final analyses to test for significance.

The interim analysis of OS was planned at the time of the PFS interim analysis, with a fixed 1-sided α level of 0.0001 allocated; the remaining fixed 1-sided $\alpha = 0.0249$ will be allocated for final analysis of OS.

Table 10: The Analysis Timing and Efficacy Boundary for PFS in the Interim Analysis and Final Analysis

	Estimated Timing (Months)	Estimated # of Events Observed	p-value [a] for Efficacy	Approximate HR Threshold
Interim Analysis	25.5	115	< 0.0062	< 0.627
Final Analysis [b]	45.1	200	< 0.0224	< 0.753

Abbreviations: HR, hazard ratio; PFS, progression-free survival.
[a] One-sided.
[b] If target number of PFS events have not been observed when there have been approximately 191 OS events, the PFS final analysis will be performed at that time, regardless of the number of PFS events observed.

An IDMC will be responsible for making the recommendation regarding stopping the study early for compelling efficacy results. More details will be given in the IDMC charter.

10. STUDY COMMITTEES AND COMMUNICATION

10.1. Blinded Independent Review Committee

A BIRC 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 on the basis of the 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 the patient should be enrolled or continue on study treatment. The tumor assessment by the BIRC 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 BIRC are outlined separately in the imaging manual and BIRC charter.

10.2. Independent Data Monitoring Committee

Regular safety monitoring (at least every 6 months), and efficacy monitoring will be performed by an IDMC. The first IDMC safety review will occur when the first 20 patients (ie, approximately 10 patients per treatment arm) have had at least 6 weeks of follow-up after the last dose of radiotherapy in order to determine if the proposed regimen of tislelizumab/placebo concurrent with cCRT is safe to continue. The IDMC will also be responsible for reviewing the results from pre-defined analyses, including interim analysis of PFS and making the recommendations for stopping the study for compelling efficacy results. 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 be performed based on new information.

Following the IDMC review and discussion, the sponsor will make all final decisions regarding any changes 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) good clinical practice guidelines, the study monitor must have direct access to the investigator's source documentation in order 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 during 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 with the investigational drug from the China regulatory agency in accordance with applicable regulatory requirements in China before the study is initiated at a study center.

12.2. Quality Assurance

To ensure compliance with good clinical practice 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 performed 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, 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's requirements specified in the pharmacy manual. At appropriate times during the conduct of the study or at the end of the study, the study site will dispose of and/or destroy all unused study drug supplies following drug inventory reconciliation by the monitor. These 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 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 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 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 the 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 sponsor 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 their 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 before 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 reconsent 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

Patient Confidentiality and Data Protection

The investigator, institution, sponsor, and site will maintain confidentiality and privacy standards for the collection, storage, transmission, and processing of patients' personal and medical information by following applicable laws and regulations related to the confidentiality, use, and protection of such information, including the ICH Good Clinical Practice Guideline, as implemented locally. Such laws may be more stringent than the requirements in this protocol.

The investigator and site shall code the personal and medical information obtained during the study with a unique patient identification number assigned to each patient enrolled in the study. The investigator must ensure that patients' confidentiality will be strictly maintained and that their identities are protected from unauthorized parties. Unless required to be provided by laws or regulations or specifically requested in exceptional circumstances by the sponsor or its representatives, the investigator and site must ensure that any personal and medical information transmitted to or collected by the sponsor or its service providers is: 1) required by the protocol, and 2) appropriately deidentified (eg, via redaction and/or coding with the patient identification number) to ensure the following information about patients is NOT shared:

- Names or initials (full or partial);
- Full dates of birth;
- Contact information (such as phone numbers or home or email addresses);
- Numerical identifiers (eg, hospital or medical record, government, health insurance, or financial account numbers) other than patient identification numbers assigned as part of this study;
- Geographic identifiers smaller than a state, province, or local equivalent (such as city, county, zip code, or other equivalent geographic identifiers); or

- Information about marital status, family, or household members; employment, sex life, sexual preference, or other sensitive data that is not relevant to the study.

Upon enrollment, patients will be required to provide their names, phone and contact information, and similar information on secondary contacts. This information will be stored separately from the study clinical database. Documents generated by the site that will be shared with the sponsor, such as patient enrollment logs, need to have this information redacted before being shared. This information will only be used to obtain patients vital status and disposition if the patients becomes lost to follow-up or in other specific circumstances specified in the ICF provided to the patient at the time of the collection of informed consent for participation in the study (eg, for purposes of expense reimbursement or mailing the latest version of the ICF to the patients when he or she cannot travel to the site).

Patients' personal and medical information obtained during 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.

Patient tissue samples (blocks or slides) that are collected before and during the study will be assigned a unique identification number by the hospital where the biopsy procedure was done. This identification number is sometimes called a "block ID." This identification number is necessary for the laboratory to keep track of the patient's sample during testing, and therefore this identification number will be collected together with the patient's tissue sample. This identification number will not contain any of the patient's personal information or identity, but it can be traced back to records held by their study doctor.

In certain circumstances, such as in connection with insurance purposes or patient support services ancillary to certain study sites (eg, for patient travel or reimbursement), the investigator and site may provide certain uncoded personal information to the sponsor and/or its representatives. Such personal information may not be provided as part of the study protocol (eg, as part of the eCRF, on samples or reports submitted to the central laboratory, on safety reporting forms, or on product dispensing logs provided to the sponsor, etc.).

Investigator and site must use only the specific forms and clinical study systems (eg, the EDC system and any secure file transfer platforms) designated by the sponsor for sharing and transfer of personal and medical information. Should a site use its own form, it must be reviewed and redacted in accordance with this section before being shared with the sponsor.

In the event of a breach of the confidentiality of a patient's personal and medical information, the investigator, site, and sponsor, as appropriate, shall fulfill all risk containment and remediation steps and reporting obligations under applicable laws. If the sponsor identifies personal or medical information that was not properly de-identified, it may be required to report the disclosure under local applicable laws.

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 where allowed by local law or the patient's signed ICF.

Data generated during this study must be available for inspection upon request by representatives of the China National Medical Product Association; 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. Every effort will be made to keep the patient's personal data confidential.

In any presentations or in publications of the results of the study, the participants'/patients' identities will remain anonymous and confidential.

BeiGene Confidential Information

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, are confidential and remain the sole and exclusive property of the 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.

In cases of discrepancies between the confidentiality or data privacy provisions contained in a written contract for the conduct of the study and this Section 13.4 of the protocol, that contract's provisions shall apply to the extent that they provide for a higher level of protection of patients' rights to confidentiality and data privacy or of BeiGene's confidential information.

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 electronic data capture (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.

14.1.2. Data Management/Coding

All final patient data, both eCRF and external data (eg, laboratory data), collected according to the protocol, will be stored by 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 that 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 20.1 or higher. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. Concomitant diseases/medical history will be coded using the MedDRA Version 20.1 or higher.

14.2. Data Integrity and In-house Blinding

In this double-blind, placebo-controlled 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 to the treatment assignment. 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 persons per SOPs until the time of unblinding.

Depending on the recommendation from IDMC based on interim analysis, the Sponsor may prepare a regulatory submission; limited sponsor personnel may be unblinded to the treatment assignment, if required, in order to act on the recommendations of the IDMC and facilitate regulatory filling. The extent to which individuals are unblinded with respect to results of interim analysis will be documented. Key aspects of the interim analyses are described in Section 9.7.

14.3. 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 1 of the following categories: 1) investigator's study file, and/or 2) 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 re-generating a hard copy, if required. Furthermore, the investigator must ensure 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 the 15 years.

The investigator must notify the sponsor of any changes in the archival arrangements, including but not limited to the following: 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 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.

14.4. 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 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.

14.5. Publication and Data Sharing Policy

A CSR 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. For multicenter studies, 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).

After conclusion of the study and without prior written approval from BeiGene, investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media *only after the following conditions have been met:*

- The results of the study in their entirety have been publicly disclosed by or with the consent of BeiGene in an abstract, manuscript, or presentation form; or
- The study has been completed at all study sites for at least 2 years.
- No such communication, presentation, or publication will include BeiGene's confidential information.
- Each investigator agrees to submit all manuscripts or congress abstracts and posters/presentations to the sponsor prior to submission. 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 details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this trial will be presented in the investigator's clinical study agreement.

14.6. 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.

14.7. 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 that becomes publicly available through no fault of the investigator or study center personnel
- Information that is necessary to disclose in confidence to an IEC/IRB solely for the evaluation of the study
- Information is necessary to disclose to provide appropriate medical care to a patient Study results which may be published as described in Section 14.5.

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								Safety Follow-up[3]	Survival Follow-up[4]
		Treatment Period of During cCRT (Cycle1, 2) (every week)						Treatment Period After cCRT (Cycle3) up to 24 months (every 21 days)	EOT Visit[2]		
Days (Window)	**-28 to ~ -1**	**C1D1 D1**	**C1D8 D8 (± 3)**	**C1D15 D15 (± 3)**	**C2D1 D22 (± 3)**	**C2D8 D29 (± 3)**	**C2D15 D36 (± 3)**	**Day 1 of each 21-day cycle from Cycle 3 (± 3)**	**0 to 7 Days**	**30± 7 Days After Last Dose**	**Every 3 Months**
Informed consent	x										
Inclusion/exclusion criteria evaluation	x										
Randomization		x[5]									
Demographics/medical history/prior medications[6]	x										
Vital signs/ height[7]	x	x	x	x	x	x	x	x	x	x	
Physical examination[8]	x	x	x	x	x	x	x	x	x	x	
ECOG Performance Status	x	x			x			x	x	x	
12-lead ECG[9]	x	As clinically indicated								x	
Adverse events[10]	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x	
Hematology[11]	x[1]	x	x	x	x	x	x	x	x[2]	x	
Serum chemistry[11]	x[1]	x	x	x	x	x	x	x	x[2]	x	

Assessment	Screening[1]	Treatment								Safety Follow-up[3]	Survival Follow-up[4]
		Treatment Period of During cCRT (Cycle1, 2) (every week)						Treatment Period After cCRT (Cycle3) up to 24 months (every 21 days)	EOT Visit[2]		
Days (Window)	**-28 to ~ -1**	**C1D1 D1**	**C1D8 D8 (± 3)**	**C1D15 D15 (± 3)**	**C2D1 D22 (± 3)**	**C2D8 D29 (± 3)**	**C2D15 D36 (± 3)**	**Day 1 of each 21-day cycle from Cycle 3 (± 3)**	**0 to 7 Days**	**30± 7 Days After Last Dose**	**Every 3 Months**
Coagulation parameters[11,12]	x	x			x			x	x[2]	x	
Urinalysis[11]	x	As clinically indicated									
Pregnancy test[13]	x	x			x			x			
Thyroid function[14]	x[1]							x		x	
HBV/HCV tests[15]	x	As clinically indicated									
Pulmonary function tests[16]	x										
Pharmacokinetics[17]		x			x			x		x	
Anti-tislelizumab antibodies[18]		x			x			x		x	
Tumor assessment[19]	x							x	x[2]		x
Archival tumor tissue (if feasible)[20]	x										
Fresh tumor tissue (optional)[21]	x							x			
Blood collection[22]	refer to Appendix 2										
Tislelizumab/ placebo administration[23]		x			x			x			
Chemotherapy[24]		x			x						

Assessment	Screening[1]	Treatment								Safety Follow-up[3]	Survival Follow-up[4]
		Treatment Period of During cCRT (Cycle1, 2) (every week)						Treatment Period After cCRT (Cycle3) up to 24 months (every 21 days)	EOT Visit[2]		
Days (Window)	-28 to ~ -1	C1D1 D1	C1D8 D8 (± 3)	C1D15 D15 (± 3)	C2D1 D22 (± 3)	C2D8 D29 (± 3)	C2D15 D36 (± 3)	Day 1 of each 21-day cycle from Cycle 3 (± 3)	0 to 7 Days	30± 7 Days After Last Dose	Every 3 Months
EORTC QLQ-C30[25]	x	x			x			x	x		
EORTC QLQ-OES18[25]	x	x			x			x	x		
Survival status											x

Abbreviations: AE, adverse event; cCRT: concurrent chemoradiotherapy; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-OES, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Oesophageal Cancer Module; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EOT: end of treatment; FFPE, formalin-fixed paraffin-embedded; FT3, free triiodothyronine; FT4, free thyroxine; 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; IRT, interactive response technology; IV, intravenous; MRI, magnetic resonance imaging; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; PET, positron emission tomography; PK, pharmacokinetic; Q3W, once every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; RNA, ribonucleic acid; SAE, serious adverse event; TSH, thyroid stimulating hormone.

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 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. Patients who discontinue study treatment prior to disease progression (confirmed by the investigator or BIRC, whichever is later) will need to undergo tumor assessments as outlined in Section 7.5.
3. The Safety Follow-up Visit is required to be conducted 30 days (± 7 days) after the last study treatment of tislelizumab/placebo or chemoradiotherapy (whichever occurs later), before the initiation of a new anticancer treatment, or before administration of the first dose in a long-term extension study or posttrial continued access program, whichever occurs first. In addition, telephone contacts with patients should be conducted to assess all AEs 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.
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. The schedule of survival follow-up may be adjusted

within the allowed time window to perform the planned survival follow-up between 2 scheduled tumor response assessments for patients who enter the survival follow-up period but still need to continue tumor response assessment per protocol requirement, especially after the completion of the 3-year tumor response assessment (eg, a survival follow-up is performed approximately 3 months after the last tumor response assessment when a 6-month interval is required between 2 tumor assessments). In these survival follow-ups, potential symptoms or signs indicating disease progression should be followed actively. If any suspected symptoms/signs are reported, the investigator should arrange an unscheduled on-site visit for further assessment. Tumor assessments will be at the discretion of the investigator, per local standards of care, at the time of symptoms or signs of disease progression.

5. Patients will be randomized into either the tislelizumab or placebo arms via IRT. All patients are required to receive study treatment within 3 days of randomization.
6. Includes history of treatment for the primary diagnosis, including prior medication, 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, heart rate, respiratory rate, weight, and blood pressure (systolic and diastolic) while the patient is in a seated position after resting for 10 minutes. The patient's vital signs are required to be recorded within 60 minutes before; during; and 30 minutes after the first infusion of tislelizumab or placebo. For subsequent infusions, vital signs will be collected within 60 minutes before infusion and if clinically indicated, during and 30 minutes after the infusion.
8. Please consider specifying that a complete physical examination is required at screening while subsequent visits entail limited, symptom-directed physical examinations (as detailed in Section 7.4.2).
9. The ECG recordings will be obtained during screening, the Safety Follow-up Visit, and as clinically indicated at other time points. Patients should be resting in semi-recumbent supine position for at least 10 minutes prior to each ECG collection.
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 treatment, only SAEs should be reported. After initiation of study treatment, all AEs and SAEs, regardless of relationship to study treatment, will be reported until 30 days after last study treatment (including chemoradiotherapy), or initiation of new anticancer therapy, whichever occurs first. Immune-mediated AEs (serious or non-serious) should be reported until 90 days after the last dose of tislelizumab, regardless of whether or not the patient starts a new anticancer therapy.
11. Local laboratory assessments on serum chemistry, hematology, coagulation, and urinalysis will be conducted, of which certain elements will be collected as specified in Appendix 3. If laboratory tests at screening are not performed within 7 days of Cycle 1 Day 1, these tests should be repeated and reviewed before Cycle 1 Day 1. Hematology and serum chemistry (including C reactive protein) will be performed weekly for the cCRT period and then at the beginning of subsequent cycles (data collected as specified in Appendix 3). After Cycle 1, results are to be reviewed within 72 hours before study drug administration. 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. Coagulation parameters include international normalized ratio, prothrombin time, and activated partial thromboplastin time.
13. Urine pregnancy test (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. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.
14. Analysis of FT3, FT4, and TSH will be performed by the local study site laboratory. Thyroid function tests will be performed at Screening and every 3 cycles (ie, Day 1 of Cycles 4, 7, 10, etc), and at the Safety Follow-up Visit.
15. Testing will be performed by the local laboratory at Screening and will include HBV/HCV serology (HBsAg, HBsAb, HBcAb, and HCV antibody), and may also include viral load assessment (HBV DNA and HCV RNA) as per relevant local guidance and/or clinical practice.
16. All patients will have pulmonary function testing which may include, but is not limited to, spirometry and assessment of diffusion capacity done during the screening period to assist in determining suitability for the study.

17. Procedures for collection of PK samples are described in the laboratory manual. 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/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 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/placebo. These tests for patients randomized to receive tislelizumab are required when it is allowed by local regulations/IRBs/IECs.
18. 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 for patients randomized to receive tislelizumab are required when it is allowed by local regulations/IRBs/IECs.
19. Radiological 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. All measurable and evaluable lesions are required to be assessed and documented at the Screening Visit. An MRI (or CT scan if MRI is contraindicated or not readily available) of the head may be required at screening based on clinical judgement; 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. During the study, tumor imaging will be performed approximately every 9 weeks (± 7 days) for the first 54 weeks, every 12 weeks (± 7 days) during Years 2 and 3, every 24 weeks (± 7 days) during Years 4 and 5, and then according to local standards with a minimum of 1 tumor response assessment annually thereafter based on RECIST v1.1, regardless of treatment delays, or until disease progression (confirmed by the investigator or BIRC, whichever is later). The investigator may perform additional scans or more frequent assessments if clinically indicated. See Section 7.5 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 begins a subsequent anticancer treatment, experiences disease progression (confirmed by the investigator or BIRC, whichever is later), withdraws consent, lost to follow up, death, or until the study terminates, whichever occurs first. Patients who continue tislelizumab/placebo treatment beyond radiographic disease progression assessed by BIRC per RECIST v1.1 (Section 7.5) will be monitored with a follow-up scan no more than 6 to 8 weeks beyond the initial BIRC assessment of radiographic disease progression before discontinuation of tislelizumab/placebo treatment.
    Screening assessments must include CT scans (with oral/intravenous contrast, unless contraindicated) or MRI of the neck, chest, and abdomen, ultrasound of cervical and supraclavicular lymph nodes, and esophagography. If feasible, esophagoscopy, including esophagoendoscopic ultrasonography should be included as well. Other known or suspected sites of disease must be included in the imaging assessments (bone, brain, etc).
    Tumor assessments must include CT scans (with oral/intravenous contrast, unless contraindicated) or MRI, with preference for CT, of the neck, chest, and abdomen, and esophagography. The same radiographic procedure used to assess disease sites at screening is required to be used throughout the study (eg, the same contrast protocol for CT scans). All known sites of disease must be documented at screening and reassessed at each subsequent tumor evaluation. The modality of tumor assessment at screening and subsequent assessment please refer to Section 7.5 for detailed instructions.
20. Patients are required to provide archival tumor tissues (FFPE blocks or approximately 15 [≥ 6] unstained slides) for biomarker analysis if feasible. The baseline tissue sample can be collected at any stage of study after local regulation approval.
21. Fresh biopsy: In the absence of archival tumor tissues, a fresh biopsy of a tumor lesion at baseline (within 28 days before randomization) is strongly recommended if feasible. For all randomized patients who have disease progression, a fresh biopsy will be optionally obtained (written informed consent is required prior to fresh tumor biopsies). See Section 7.7 for more information.
22. Blood biomarker: Refer to Appendix 2.
23. Tislelizumab/placebo will be given intravenously Q3W. The initial infusion (Cycle 1, Day 1) will be delivered over 60 minutes, and then can be administered over 30 minutes for subsequent infusions if well tolerated. Patients must be monitored for 60 minutes after infusion of tislelizumab/placebo on Day 1 of Cycle 1 and Cycle 2. From Cycle 3 onward, at least a 30-minute monitoring period is required. The first dose will be given on Cycle 1 Day 1 and subsequent dosing will continue on the scheduled 21-day intervals.

24. Chemotherapy will be given intravenously for all patients for 2 cycles. Cisplatin 25 mg/ m^2 intravenously on Day 1 to 3 Q3W; paclitaxel 135 mg/m^2, intravenously on Day 1 Q3W. Refer to Section 5.2.3 for detail dose and schedule.
25. EORTC QLQ-C30, EORTC QLQ-OES18 will be completed at screening or baseline, prior to dosing of every treatment cycle for first 6 Cycles, then every 2 cycles thereafter and at EOT. QoL will be completed prior to any clinical activities during on-study site visits.

APPENDIX 2. BLOOD BIOMARKER ANALYSIS

Assessment	Screening	Treatment		
Days	**-28 to ~ -1**	**Cycle 1 Day 1**	**Cycle 3 Day 1**	**EOT Visit**
ctDNA[1]		X	X	X
Flow cytometry[2]		X	X	X
PBMC[2]		X	X	X

Abbreviations: ctDNA: circulating tumor DNA; EOT, end of treatment; PBMC, peripheral blood mononuclear cells.

1. 10 mL blood will be collected mandatorily at predose stage (Cycle 1 Day 1) for all randomized patients. An optional additional blood collection will be collected at C3D1 (predose of Cycle 3 Day 1) for those who have disease progression.
2. 9 mL blood for flow cytometry test and 10 mL blood for PBMC isolation will be collected optionally at predose stage (Cycle 1 Day 1), C3D1 (predose of Cycle 3 Day 1), and for those who have disease progression, respectively.

APPENDIX 3. CLINICAL LABORATORY ASSESSMENTS

Serum Chemistry	Hematology	Coagulation	Urinalysis
CRP Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Albumin Total bilirubin Direct bilirubin Blood urea nitrogen or urea Potassium Sodium Total calcium [b] Creatinine Glucose Lactate dehydrogenase Total protein CK [c] CK-MB [c]	Hematocrit Hemoglobin Platelet counts WBC count Lymphocyte count Neutrophil count	Prothrombin time Partial thromboplastin time or activated partial thromboplastin time INR	Glucose Protein Blood 24-hour protein [a] Random urine protein-to-creatinine ratio

Abbreviations: CK, creatine kinase; CK-MB, creatine kinase cardiac isoenzyme; CRP, C reactive protein; INR, international normalized ratio; WBC, white blood cell.

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

b. Total calcium values will be corrected for patients with hypoproteinemia.

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

APPENDIX 4. ECOG PERFORMANCE STATUS

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 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 et al 1982). Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

APPENDIX 5. 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;45:228-47.

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 nonmeasurable 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 (irrespective of scanner type) 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 nonmeasurable.

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 nonmeasurable) 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 noncystic 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 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 complete response. 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 stable disease in order to differentiate between response (or stable disease) 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 complete response 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 nonmeasurable 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 nonmeasurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly nonmeasurable) 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 nonmeasurable 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 nonmeasurable 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 complete response. 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 treatment, 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 complete or partial response 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 complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. 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 stable disease 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 complete response 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

Stable disease is measured from the start of the treatment (in randomised 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 stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease 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 stable disease.

Note: The duration of response and stable disease 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 5.1 ESOPHAGEAL PRIMARY LESION ASSESSMENT AND RESPONSE EVALUATION

In this trial, the esophageal primary lesion will be considered nonmeasurable disease, thus should be identified as non-target lesion.

In order to ensure the accuracy of the assessment of esophageal primary lesion, esophagography is included into each tumor assessment and the objective criteria below are applied for response evaluation of esophageal primary lesion in the trial, with the reference of Chinese guideline of radiotherapy in esophageal cancer 2019 (Li et al 2019):

- Disappearance: when images of both enhanced CT/enhanced MRI and esophagography are evaluable, all below criteria are met:
  - On enhanced CT/enhanced MRI: disappearance of esophageal primary lesion.

    Note: If the esophageal primary lesion is not completely disappeared, but it can be well supported on esophagography as not contributing to tumor, eg, fibrotic/scarring related lesions, the evaluation can be overridden to be "disappearance" when below criteria for esophagography is met.
  - On esophagography: the tumor is completely disappeared, the lining of the esophagus is smooth, the barium meals pass smoothly, the wall of the esophagus can be slightly stiff, the lumen has little or no stenosis (the ratio of normal upper esophagus to the stenosis ≤ 3:2), and the mucosa is normal or slightly thickened.
- Unequivocal progression: when either images of enhanced CT/enhanced MRI or esophagography are evaluable, any of below criteria is met:
  - On enhanced CT/enhanced MRI: unequivocal progression (as detailed in prior sections of Appendix 5) of esophageal primary lesion, or dynamic enlargement of esophageal primary lesion in at least 3 consecutive CT/MRI scans.
  - On esophagography: significant worsening of mucosal destruction, filling defects, or stenosis in at least 3 consecutive esophagography, taking as reference the image of the best response on study (this includes the baseline images).
- Present: when images of enhanced CT/enhanced MRI are evaluable, persistence of esophageal primary lesion without meeting the above criteria of "disappearance" or "unequivocal progression".

APPENDIX 6. 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 sponsor 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) nephropathy	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 7. 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 8. IMMUNE-MEDIATED ADVERSE EVENT EVALUATION AND MANAGEMENT

The recommendations below for the diagnosis and management of any 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: FBC, 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.
Rheumatology	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.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; CNS, central nervous system; CRP, C-reactive protein; CT, computed tomography; *D*LCO, diffusing capacity for carbon monoxide; FBC, full blood count; HIV, human immunodeficiency virus; INR, international normalized ratio; LCI, liver cystolic 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 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 Moderate-severe symptoms	Refer patient to an endocrinologist for assessment and treatment. Initiate pulse intravenous 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 intravenous 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 intravenous 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 intravenous 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: intravenous 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 intravenous 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 intravenous (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 intravenous 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 intravenous 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 intravenous (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 intravenous (methyl)prednisolone 2 mg/kg/day.	Discontinue study

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	Blindness (at least 20/200) in the affected eyes	Convert to oral 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 intravenous (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 intravenous (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 intravenous	Discontinue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	complications or dehydration	corticosteroids if not contraindicated by infection.	
Myoditis/ Rhabodomyolysis	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 intravenous (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 intravenous (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, chronic heart failure; 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 9. CHRONIC KIDNEY DISEASE EPIDEMIOLOGY COLLABORATION (CKD-EPI) EQUATION

In adults, the most widely used equations for estimating glomerular filtration rate (GFR) from serum creatinine are the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[1] and the Modification of Diet in Renal Disease (MDRD) Study equation. The National Kidney Disease Education Program (NKDEP) calculators rely on creatinine determinations which are isotope dilution mass spectrometry (IDMS) traceable. All laboratories should be using creatinine methods calibrated to be IDMS traceable.

This CKD-EPI equation calculator should be used when Scr reported in mg/dL. This equation is recommended when eGFR values above 60 mL/min/1.73 m^2 are desired.

$GFR = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times 1.159$ [if black]

where:

S_{cr} is serum creatinine in mg/dL,

κ is 0.7 for females and 0.9 for males,

α is -0.329 for females and -0.411 for males,

min indicates the minimum of S_{cr}/κ or 1, and

max indicates the maximum of S_{cr}/κ or 1.

The equation does not require weight because the results are reported normalized to 1.73 m^2 body surface area, which is an accepted average adult surface area.

The online calculator for CKD-EPI can be found here: https://www.niddk.nih.gov/health-information/communication-programs/nkdep/laboratory-evaluation/glomerular-filtration-rate-calculators

1. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.

APPENDIX 10. 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 a follicle-stimulating hormone 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 11. EORTC-QLQ-C30 QUESTIONNAIRE

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

APPENDIX 12. EORTC QLQ-OES18 QUESTIONNAIRE

EORTC QLQ – OES18

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at all	A little	Quite a bit	Very much
31.	Could you eat solid food?	1	2	3	4
32.	Could you eat liquidised or soft food?	1	2	3	4
33.	Could you drink liquids?	1	2	3	4
34.	Have you had trouble with swallowing your saliva?	1	2	3	4
35.	Have you choked when swallowing?	1	2	3	4
36.	Have you had trouble enjoying your meals?	1	2	3	4
37.	Have you felt full up too quickly?	1	2	3	4
38.	Have you had trouble with eating?	1	2	3	4
39.	Have you had trouble with eating in front of other people?	1	2	3	4
40.	Have you had a dry mouth?	1	2	3	4
41.	Did food and drink taste different from usual?	1	2	3	4
42	Have you had trouble with coughing?	1	2	3	4
43.	Have you had trouble with talking?	1	2	3	4
44.	Have you had acid indigestion or heartburn?	1	2	3	4
45.	Have you had trouble with acid or bile coming into your mouth?	1	2	3	4
46.	Have you had pain when you eat?	1	2	3	4
47.	Have you had pain in your chest?	1	2	3	4
48.	Have you had pain in your stomach?	1	2	3	4

Approved Date 9/30/2024

Signature Page

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