CLINICAL STUDY PROTOCOL

Protocol Title:	A Randomized, Controlled, Open-label, Global Phase 3 Study Comparing the Efficacy of the anti-PD-1 Antibody Tislelizumab (BGB-A317) versus Chemotherapy as Second Line Treatment in Patients with Advanced Unresectable/Metastatic Esophageal Squamous Cell Carcinoma
Protocol Identifier:	BGB-A317-302
Phase:	3
Investigational Product:	Tislelizumab (BGB-A317)
Indication:	Advanced Unresectable/Metastatic Esophageal Squamous Cell Carcinoma (ESCC)
EudraCT:	2017-003699-30
Sponsor:	BeiGene, Ltd. c/o BeiGene USA, Inc. 1900 Powell Street, 5th Fl., Suite 500 Emeryville, CA 94608 USA
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Original Protocol:	13Jul2017
Amendment 1.0:	07Nov2017
Amendment 2.0:	06Dec2017
Amendment 3.0:	08Nov2018
Amendment 4.0:	20Mar2020

FINAL PROTOCOL APPROVAL SHEET

A Randomized, Controlled, Open-label, Global Phase 3 Study Comparing the Efficacy of the anti-PD-1 Antibody Tislelizumab (BGB-A317) versus Chemotherapy as Second Line Treatment in Patients with Advanced Unresectable/Metastatic Esophageal Squamous Cell Carcinoma

BeiGene, Ltd., Approval:

[redacted]

Mar. 20th

Date

INVESTIGATOR SIGNATURE PAGE

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Protocol Identifier: BGB-A317-302

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 Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd., or one of its subsidiaries.

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

I have read the entire protocol and agree to carry out the study according to this protocol.

Investigator's Signature: _____

Investigator's Printed Name: _____

Date (dd mmm yyyy): _____

Name of the center in which the study will be conducted: _____

SYNOPSIS

Name of Sponsor/Company: BeiGene, Ltd.

Investigational Product: Tislelizumab (BGB-A317)

Title of Study: A Randomized, Controlled, Open-label, Global Phase 3 Study Comparing the Efficacy of the anti-PD-1 Antibody Tislelizumab (BGB-A317) versus Chemotherapy as Second Line Treatment in Patients with Advanced Unresectable/Metastatic Esophageal Squamous Cell Carcinoma

Protocol Identifier: BGB-A317-302

Phase of Development: 3

Number of Patients: Approximately 500

Study Centers: Approximately 140 global centers

Study Objectives:

Primary:

- To compare the overall survival (OS) in the Intention-to-Treat (ITT) population following treatment with tislelizumab versus investigator chosen chemotherapy (ICC) when given as second line treatment in patients with advanced unresectable/metastatic Esophageal Squamous Cell Carcinoma (ESCC)

Secondary:

Key Secondary:

- To compare the OS in programmed cell death protein ligand-1 (PD-L1) positive population following treatment with tislelizumab versus ICC

Other Secondary:

- The following will be compared between tislelizumab and ICC based on assessment by investigator per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria:
    - Overall response rate (ORR)
    - Progression-free survival (PFS)
    - Duration of response (DOR)
- To compare patient reported outcomes of health-related quality of life (HRQoL) between the tislelizumab and the chemotherapy treatments
- To compare the safety and tolerability between tislelizumab and the chemotherapy treatments

Exploratory**:**

- To characterize the disease control rate (DCR) with tislelizumab compared to chemotherapy
- To characterize the pharmacokinetics (PK) of tislelizumab
- To determine host immunogenicity to tislelizumab
- To explore potential predictive biomarkers (including but not limited to PD-L1 expression, gene expression profiling, tumor mutation burden, microsatellite instability (MSI), tumor-infiltrated immune cells) and resistance mechanism

Study Endpoints:

Primary:

- OS in the ITT analysis set- defined as the time from the date of randomization until the date of death due to any cause in all randomized patients

Secondary:

Key Secondary:

- OS in the PD-L1 positive analysis set - defined as the time from the date of randomization until the date of death due to any cause in the PD-L1 positive population

Other Secondary:

- ORR in both the ITT analysis set and the PD-L1 positive analysis set - defined as the proportion of patients who had complete response (CR) or partial response (PR) assessed by the investigators per RECIST v1.1
- PFS in both the ITT analysis set and the PD-L1 positive analysis set - defined as the time from the date of randomization to the date of first documentation of disease progression assessed by the investigators per RECIST v1.1 or death, whichever occurs first
- DOR in both the ITT analysis set and the PD-L1 positive analysis set - defined as the time from the first determination of an objective response until the first documentation of progression as assessed by the investigator per RECIST v1.1, or death, whichever comes first
- HRQoL assessment of the subject's overall health status using European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 index, the EORTC QLQ esophageal cancer module OES18, and the generic health state instrument Euroqol 5D (EQ-5D-5L) in both the ITT analysis set and the PD-L1 positive analysis set
- The incidence and severity of adverse events according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03

Exploratory:

- Disease control rate (DCR) in both the ITT analysis set and the PD-L1 positive analysis set - defined as the proportion of patients who have CR, PR, and stable disease

(SD) assessed by the investigators per RECIST v1.1

- Pharmacokinetic endpoints: summary of serum concentration of tislelizumab to include but not limited to trough serum concentration (C_{trough})
- Assessments of immunogenicity of tislelizumab to determine the incidence of anti-drug antibodies (ADA)
- Predictive biomarkers (including but not limited to PD-L1 expression, gene expression profiling, tumor mutation burden, MSI, and tumor-infiltrated immune cells) and resistance mechanism

Study Design:

This is a randomized, controlled, open-label, global Phase 3 study comparing overall survival following treatment with the anti-PD-1 monoclonal antibody tislelizumab to ICC given as a second line treatment in patients with advanced unresectable/metastatic ESCC that has progressed during or after first line therapy.

Before initiating this Phase 3 study in Japan, a substudy investigating the safety, tolerability, PK and preliminary efficacy in Japanese patients is planned (see Appendix 13 for details).

After providing written informed consent, completing all screening assessments, and being confirmed as eligible for study participation, approximately 500 patients will be randomized 1:1 to receive either tislelizumab monotherapy or investigator chosen chemotherapy (paclitaxel/docetaxel/irinotecan). The choice of chemotherapy must be determined prior to randomization.

At randomization, patient enrollment will be stratified by the following 3 factors:

- Region (Asia [excluding Japan] vs Japan vs United States [US]/European Union [EU])
- Eastern Cooperative Oncology Group performance status (0 vs 1)
- ICC option (paclitaxel vs docetaxel vs irinotecan)

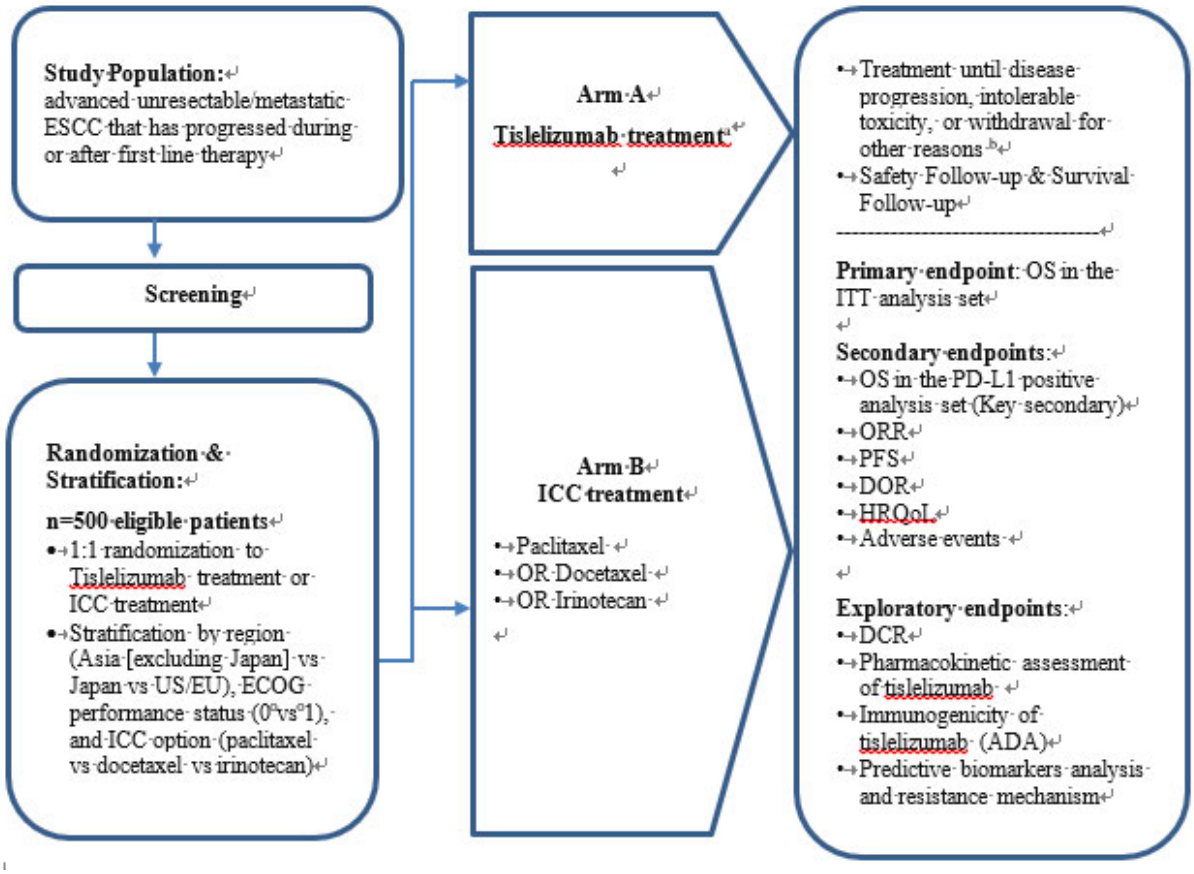
After randomization, patients will then begin open-label treatment with one of the following regimens.

- Arm A: Tislelizumab 200 mg intravenously (IV) on Day 1, given every 21 days
- Arm B: One of the following three single-agent chemotherapies as determined by the investigator
    - paclitaxel 135-175 mg/m² IV on Day 1, given every 21 days
        - NOTE: paclitaxel may also be given in doses of 80-100 mg/m^2 IV on a weekly schedule, according to local and/or country specific guidelines for standard of care
        - Japan: 100 mg/m^2 IV on Day 1, 8, 15, 22, 29, and 36, followed by one week of rest
    - **OR** docetaxel 75 mg/m^2 IV on Day 1, given every 21 days
        - Japan: 70 mg/m^2 IV on Day 1, given every 21 days
    - **OR** irinotecan 125 mg/m^2 IV on Days 1 and 8, given every 21 days

Cross-over between chemotherapy treatments or between chemotherapy and tislelizumab treatment arms during the study treatment period will not be allowed.

Study treatment will be administered until disease progression, intolerable toxicity, or another treatment discontinuation criterion is met. Tislelizumab treatment beyond initial investigator-assessed RECIST v1.1 defined progression is permitted if the patient has evidence of "pseudo-progression" (Section 7.17.1).

The study design schema is as follows:



Abbreviations: ECOG, Eastern Cooperative Oncology Group; ESCC, Esophageal squamous cell carcinoma; ICC, investigator chosen chemotherapy; ITT, Intention-to-treat; OS, Overall survival; ORR, Overall response rate; PD-L1, Programmed cell death protein ligand-1; PFS, Progression-free survival; DOR, Duration of response; HRQoL, Health Related Quality of Life; DCR, Disease control rate;
ADA, Anti-drug antibody.

a. The initial infusion (Cycle 1, Day 1) will be administered over a period of 60 minutes. If this infusion is well tolerated, subsequent infusions may be administered over 30 minutes. After tislelizumab infusion, patients will be further monitored for at least 1 hour during Cycles 1 and 2. From Cycle 3 onward, a post-infusion monitoring period of at least 30 minutes will be required.
b. At the discretion of the investigator, patients randomized to receive tislelizumab may be treated beyond progression under protocol defined conditions. See Section 7.17.1.

Study Assessments:

PFS and tumor response will be assessed by the investigator using RECIST v1.1 criteria (Eisenhauer EA, 2009). Tumor imaging (CT with or without contrast or MRI) must be performed within 28 days prior to randomization. On-study tumor assessments will occur approximately every 6 weeks (± 7 days) for 6 months, then every 9 weeks (± 7 days) until

disease progression. If a patient discontinues study treatment due to reasons other than disease progression or death, tumor assessments will continue to be performed as scheduled until the start of new anti-cancer therapy, disease progression, loss to follow-up, withdrawal of consent, death, or until study completion, whichever occurs first.

Patient reported outcomes will be collected using the EORTC QLQ-C30, EORTC QLQ-OES18 and the EQ-5D-5L at baseline, Cycles 1-6 Day 1 or at the End-of-Treatment Visit (whichever occurs first), and at the Safety Follow-up Visit.

Patients will be evaluated for any AEs and serious adverse events (SAEs) occurring up to 30 days after the last dose of study drug (all severity grades, per NCI-CTCAE v.4.03) or initiation of a new anticancer therapy, whichever occurs first, and immune-related AEs (irAEs) occurring up to 90 days after the last dose of study drug regardless of initiation of a subsequent anticancer therapy. All drug-related SAEs will be recorded by the investigator after treatment discontinuation until patient death, withdrawal of consent, or loss to follow-up, whichever occurs first. All study drug related SAEs will be followed until they resolve to baseline or ≤ Grade 1, the investigator assesses the AE as stable and unlikely to improve, or the patient is lost to follow-up, whichever occurs first.

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

Key Eligibility Criteria:

The population under study is adult patients (≥18 years of age or acceptable age according to local regulations, whichever is older at the time of voluntarily signing of informed consent) with histologically confirmed diagnosis of ESCC with tumor progression during or after first-line treatment for advanced unresectable/metastatic disease. All patients are also required to have ≥ 1 evaluable lesion per RECIST v1.1 within 28 days prior to randomization, an Eastern Cooperative Oncology Group Performance Status score of ≤1, and adequate organ function.

Investigational Product, Dose, and Mode of Administration:

Tislelizumab will be administered at a dose of 200 mg IV on Day 1, given every 21 days.

Reference Therapy, Dose, and Mode of Administration:

- Paclitaxel will be administered at a dose of 135-175 mg /m² IV on Day 1, given every 21 days
    - NOTE: paclitaxel may also be given in doses of 80-100 mg/m^2 IV on a weekly schedule, according to local and/or country specific guidelines for standard of care
    - Japan: 100 mg/m^2 IV on Days 1, 8, 15, 22, 29, and 36, followed by one week of rest
- Docetaxel will be administered at a dose of 75 mg/m^2 IV on Day 1, given every 21 days
    - Japan: 70 mg/m^2 IV on Day 1, given every 21 days
- Irinotecan will be administered at a dose of 125 mg/m^2 IV on Days 1 and 8, given

every 21 days

Statistical Methods:

Analysis Sets:

- The Intention-to-Treat (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 ≥ 1 dose of study treatment. It will be the primary analysis set for safety analysis
- Per-Protocol (PP) analysis set includes patients who have received ≥ 1 dose of study medications and had no major protocol deviations that impact efficacy evaluation. Major protocol deviations will be determined and documented before the database lock for the primary analysis
- The PD-L1 positive analysis set includes patients whose tumor and immune cell score (TIC score) met the pre-defined cutoff (specified in the statistical analysis plan) using VENTANA PD-L1 (SP263) Cdx Assay. TIC score is the total percentage of the tumor area covered by tumor cells with PD-L1 membrane staining and tumor-associated immune cells with PD-L1 staining at any intensity.
- The PK analysis set includes all patients who received ≥ 1 dose of tislelizumab per the protocol, for whom any post-dose PK data are available
- The ADA analysis set includes all patients who have a baseline and ≥ 1 post-baseline ADA result

Statistical and Analytical Methods:

The primary endpoint (OS) will be tested at a one-sided alpha of 0.025. If the null hypothesis for overall survival in the ITT analysis set is rejected, the key secondary endpoint will be tested sequentially for OS in the PD-L1 positive analysis set. The inferential test for OS in the PD-L1 positive analysis set will be stopped at the non-significant endpoint of OS in the ITT analysis set. The familywise type I error will be strongly controlled at one-sided level 0.025.

Primary Efficacy Analysis:

The primary efficacy endpoint is overall survival (OS) in the ITT analysis set as defined in the primary endpoint section. In the absence of death, patients will be censored either at the date that the patient was last known to be alive or the date of data cut-off, whichever comes earlier.

OS will be compared between the tislelizumab and ICC arms in a stratified log-rank test using a significance level of one-sided 0.025.

The null hypothesis to be tested is:

H_0: OS in tislelizumab = OS in ICC

against the alternative:

H_1: OS in tislelizumab $\neq$ OS in ICC

This will be the primary analysis once the targeted event number of approximately 400 is reached. The p-value from one-sided log-rank test will be calculated, stratified by selected stratification factors of ECOG performance status (0 vs 1) and ICC option (paclitaxel vs

docetaxel vs irinotecan).

The median OS and the cumulative probability of OS at every 3 months if estimable, will be calculated for each treatment arm and presented with 2-sided 95% confidence intervals (CIs). Kaplan-Meier survival probabilities over time for each arm will be plotted.

The treatment effect will be estimated by fitting a Cox regression model with treatment arm as a factor and with ICC and ECOG performance status as strata. From this model, the hazard ratio (HR) of OS will be estimated and presented with a 2-sided 95% CI.

These analyses will be performed in the ITT analysis set as the primary analysis. Outcomes in the Per Protocol analysis set will be evaluated as a sensitivity analysis.

Secondary Efficacy Analysis

The key secondary endpoint is OS in the PD-L1 positive analysis set.

The OS in the PD-L1 positive analysis set will be analyzed similarly as described in the primary analysis for OS in the ITT analysis set.

Cochran-Mantel-Haenszel (CMH) test adjusting for selected stratification factors (ECOG and ICC option) in the ITT analysis set and the PD-L1 positive analysis set will be provided for ORR per RECIST v1.1. The 2-sided 95% CIs for the odds ratio in ORR will be calculated, as well as Clopper-Pearson 95% CIs of ORR for each treatment arm.

PFS based on assessment by investigator per RECIST v1.1 will be estimated using the Kaplan-Meier (KM) method in the ITT analysis set and the PD-L1 positive analysis set. 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 (2007). 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 anti-cancer therapy prior to disease progression will be censored at the last tumor assessment date prior to the introduction of new therapy.

A log-rank test stratified by selected stratification factors (ECOG and ICC option) will be used to test the PFS differences between two treatment arms. The stratified Cox regression will be used to estimate the hazard ratios of PFS. A 95% confidence interval (CI) of HR in PFS will be constructed. Median PFS and PFS at every 3 months for each treatment arm, if estimable, will be presented.

Duration of response based on assessment by investigator will be analyzed similarly as PFS in the responders.

EORTC QLQ-C30 and EORTC QLQ-OES18 will be summarized using functional scale/symptom scale/single item. Observed values and changes from baseline for functional scale/symptom scale/single item will be summarized using descriptive statistics. Time to clinically meaningful worsening in HRQoL domains will be estimated using Kaplan-Meier method. Log-rank test will be employed for testing treatment difference.

EQ-5D-5L will be compared between tislelizumab and ICC arms. Descriptive statistics will be used to show the changes from baseline in each arm. These HRQoL assessments will be analyzed in both the ITT analysis set and the PD-L1 positive analysis set.

Exploratory Efficacy Analysis

Best overall response (BOR) is defined as the best response per RECIST v1.1 recorded from randomization until data cut or start of new anti-cancer treatment. Patients with no post-baseline response assessment (for any reason) will be considered non-responders for

BOR. The proportion and its corresponding Clopper-Pearson 95% CI for each of the response categories (CR, PR, SD and PD) will be presented by treatment arm.

DCR will be analyzed similarly to ORR in the ITT analysis set and the PD-L1 positive analysis set.

PD-L1 expression, gene expression profiling, tumor mutation burden, MSI, and tumor infiltrated immune cells may be examined in the ITT analysis set. Efficacy analyses, including but not limited to OS, PFS, and ORR, may be explored according to biomarker status. Other potential predictive markers may also be assessed.

Safety Analysis

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

Verbatim description of AEs will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA®) terms and graded per NCI-CTCAE v.4.03. All treatment-emergent AEs (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 drug up to 30 days following study drug discontinuation or initiation of a new anticancer therapy. TEAEs also include all irAEs and drug-related serious AEs recorded up to 90 days after the last dose of study drug regardless of whether or not the patient starts a new anticancer therapy.

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 Analysis

PK samples will be collected in this study as outlined in the schedule of assessments (Appendix 1).

Tislelizumab serum concentration data, including but not limited to C_{trough}, will be tabulated and summarized for each cycle at which pharmacokinetics are to be measured. Descriptive statistics will include means, medians, ranges, and standard deviations, as appropriate.

Additional PK analyses may be conducted as appropriate.

Exposure-response (efficacy or safety endpoints) analysis may be carried out if supported by data.

Immunogenicity Analysis

Immunogenicity samples will be collected in this study as outlined in schedule of assessments.

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

Sample Size

The sample size calculation is based on the primary efficacy analysis of OS comparison between tislelizumab and ICC arms in the ITT analysis set. Assuming an OS-HR (Arm Tislelizumab/Arm ICC) of 0.75 and a dropout rate of 5% per year, approximately 500 patients will be enrolled and randomized in a 1:1 ratio to Arm Tislelizumab and Arm ICC over a 26-month period to accumulate approximately 400 deaths, which is estimated to occur approximately 30.2 months after the first patient is enrolled when median OS in the

tislelizumab and ICC arms are 8 months and 6 months, respectively. Assuming OS-HR is 0.75, based on recently published results of anti-PD-1 therapies in second line treatment of ESCC (Kojima et al 2019; Kato et al 2019; Huang et al 2019), the study will have a power of 82% with a one-sided alpha of 0.025.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the curve-time curve
BGB-A317	Tislelizumab, a humanized monoclonal antibody directed at PD-1
BOR	Best overall response
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CSR	Clinical Study Report
DCR	Disease control rate
DOR	Duration of response
EAC	Esophageal adenocarcinoma
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EORTC QLQ-OES18	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Oesophagus Cancer Module
EOT	End of Treatment
EQ-5D-5L	European Quality of Life 5-Dimensions (EQ-5D-5L Version)
ESCC	Esophageal squamous cell carcinoma
Fc	Fragment crystallizable region
FcγR	Fc Gamma receptor (eg, Fcγ-RI, Fcγ-R2I)
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
GCP	Good Clinical Practice

Abbreviation	Definition
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HRQoL	Health Related Quality of Life
ICC	Investigator chosen chemotherapy
ICF	Informed consent form
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgG	Immunoglobulin G (eg, IgG1, IgG2, IgG3, IgG4); other types of immunoglobulins include IgD and IgM
IMP	Investigational medicinal product
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intention-to-Treat
IV	Intravenous (Intravenously)
K_D	Dissociation constant
KM	Kaplan-Meier
LDH	Lactic dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death protein-1
PD-L1	Programmed cell death protein ligand-1
PET	Positron emission tomography

Abbreviation	Definition
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PR	Partial response
PT	Preferred term
Q2W	Once every 2 weeks
Q3W	Once every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SD	Stable disease
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States

1. INTRODUCTION

1.1. Esophageal Carcinoma

Esophageal cancer is the eighth most common cancer worldwide and the sixth most common cause of death from cancer (GLOBOCAN, 2012). The incidence, prevalence, and histologic type of esophageal cancer varies between geographic regions, particularly between Western countries (US 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 M, 2015). To illustrate, an estimated 16,940 people in the US will be diagnosed with esophageal cancer and 15,690 people will eventually die of their disease in 2017 (Siegel RK, 2017). The predominant histologic type of these new diagnoses in the US will be adenocarcinoma. The 5-year survival rates are 18.4% in the United States (Siegel RK, 2017) and 12 % in Europe (De Angelis R, 2014). In contrast, in China, an estimated 477,900 people will be diagnosed with esophageal cancer, 90% of which will be of the squamous cell carcinoma histology, and 375,000 people will die of this disease (Chen W, 2016; Arnold M, 2015). The age-standardized five-year relative survival rate for patients in China diagnosed in 2003–2005 is 20.9% (Li M, 2017).

Recognized risk factors for developing both adenocarcinoma and squamous cell esophageal carcinoma include poor nutritional status, low intake of fruits and vegetables, drinking alcohol, smoking tobacco, chewing betel quid, and drinking liquids, such as mate, at high temperatures, obesity, and chronic gastroesophageal reflux disease (GERD). Esophageal cancer of either histology is much more prevalent in men and more common in an older patient population (Shah MA, 2015).

Advanced esophageal cancer is a rapidly fatal disease. Approximately 40% of patients diagnosed with esophageal cancer will have advanced or metastatic disease, with a median survival of 8-10 months and an expected 5-year survival rate < 5% (Lin M, 2016; Drahos J, 2013). These data, combined with the relative lack of highly effective treatment, are indicative of the large unmet medical need in patients diagnosed with esophageal cancer.

1.1.1. Treatment Options for Esophageal Carcinoma

Esophageal cancer treatment 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 F, 2016; NCCN Guidelines Version 1, 2017; Japanese Gastric Cancer Association Gastric Cancer, 2017; Stahl M, 2009). Chemoradiation therapy may be given to those with larger tumors in the neo-adjuvant, peri adjuvant or in the adjuvant setting. Post-operative 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 regimens given in the pre-operative or peri-operative setting commonly include chemotherapy doublets which include taxanes, platinum agents, fluorouracil, or irinotecan. Triplet combinations may also be considered, such as epirubicin, oxaliplatin and fluorouracil/capecitabine, but are more toxic and restricted to those patients with good performance status. In the pre-operative or peri-operative

setting, the choice of chemotherapy regimen is made independent of the tumor histology (Lordick F, 2016; NCCN Guidelines Version 1, 2017; Japanese Gastric Cancer Association Gastric Cancer, 2017; Stahl M, 2009).

The choice of systemic chemotherapy agents for patients who are not surgical candidates or those who have recurrent or metastatic disease that cannot be adequately treatment with local therapy are similar to those described above, and also similar to those treatments given to patients with advanced gastric cancer (Lordick F, 2016). The choice of agents or regimen may be based on the patient's performance status, and underlying comorbidities. Fluoropyrimidines (either 5-Flourouracil or capecitabine) as monotherapy or in combination with either cisplatin or oxaliplatin, taxanes (either paclitaxel or docetaxel) given as monotherapy or with platinum agents, or irinotecan in combination with 5-fluorouracil are suitable front-line treatments. The only difference in treatment recommendations between different esophageal histologic subtypes is the use of ramucirumab, which is indicated in combination with paclitaxel for patients with adenocarcinoma of the esophagus.

The overall response rate (ORR) to first-line chemotherapy for advanced or metastatic disease ranges from 20% to 48% and 5 -year survival rates of lower than 30% with significant toxicity rates (Grunberger B, 2007). There is no global consensus on the optimal second-line treatment. Very few prospective clinical studies have been completed evaluating second line treatments in esophageal carcinoma. Clinical studies have not shown that combination chemotherapy impart an overall survival advantage compared to monotherapy, and have shown that combination chemotherapies are associated with more toxicities (Song ZB, 2014; Thallinger CM, 2011; Albertsson M, 2007). Chemotherapy monotherapy is typically given, and include paclitaxel, docetaxel or irinotecan (Thallinger CM, 2011). There are regional preferences for the chemotherapy of choice and may be based on the toxicity profile of each agent. The following table (Table1) summarizes the efficacy outcomes between the 3 chemotherapies allowed in this protocol. It should be noted that some publications are summarizing data from retrospective analyses (Shirakawa T, 2014; Song ZB, 2014; Mizota A, 2011; Fukushima R, 2014). Given these caveats, the ORR and median survival appear comparable amongst paclitaxel, docetaxel, and irinotecan.

Table1: Second-Line Treatment and Outcomes for Esophageal Squamous Cell Carcinoma

Agent (Reference)	Sample Size by Histology (n)	Treatment setting	Regimen	ORR (%)	OS (median months)
Paclitaxel (Ilson DH, 2007)	ESCC (n=32)	1st/2nd line	80 mg/m^2 weekly x 4 weeks every 28 days	13% (1L); 8% (2L)	NR for ESCC subset
Paclitaxel (Mizota A, 2011)	ESCC (n=35) EAC (n=3)	2nd line	80 -100 mg/m^2 Day 1, 8, 15 every 28 days	25.7%*	7.2*
Paclitaxel (Kato K, 2011)	ESCC (n=52) EAC (n=1)	NR**	100 mg/m^2 Days 1,8, 15, 22, 29, and 36 every 49 days	44%	10.4
Paclitaxel (Shirakawa T, 2014)	ESCC (n= 31)	2nd line	100 mg/m^2 weekly x 6 1-week rest	19.4%	6.1
Docetaxel (Song ZB, 2014)	ESCC (n=41)	2nd line	Not specified	19.5%	5.2
Docetaxel (Mizota A, 2011)	ESCC (n=84) EAC (n=2)	2nd line	60- 70 mg/m^2 Q3W	10.3%*	6.1*
Docetaxel (Shirakawa T, 2014)	ESCC n=132	2nd line	70 mg/m^2 Q3W	5.3%	5.5
Docetaxel (Muro K, 2004)	ESCC (n=46) EAC (n=1) Other (n=1)	Advanced	70 mg/m^2 Q3W	20%	8.1
Irinotecan (Mühr-Wilkenshoff F, 2003)	ESCC (n=10) EAC (n=3)	1st/2nd line	125 mg/m^2 Weekly x 4 with 2 weeks' rest	20% ESCC only	6.4*
Irinotecan (Burkart C, 2007)	ESCC (n=7) EAC (n=7)	2nd line	100 mg/m^2 Weekly x 3 every 4 weeks	15%*	5*
Irinotecan (Fukushima R, 2014)	ESCC n=29	NR**	Not specified	4%	4.1

Abbreviations: ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma.
*Combined ESCC and EAC histology
** line of therapy not specified; all patients received prior treatment for esophageal cancer

1.1.1.1. Anti-PD-1/Anti-PD-L1 Therapy for Advanced Esophageal Squamous Cell Carcinoma

Clinical outcome data are available from early phase studies evaluating tislelizumab, nivolumab, and pembrolizumab in patients with advanced esophageal carcinoma.

Tislelizumab

As of 20 May 2019, there are 22 ongoing clinical studies with tislelizumab with over 1705 patients treated. Of these, 13 studies have preliminary data available in the Investigator's Brochure (IB): 7 monotherapy studies, 2 chemotherapy combination therapy studies, and 4 investigational agent combination therapy studies. Information about the safety and efficacy signals in these clinical studies may be found in the Tislelizumab Investigator's Brochure.

Tislelizumab in advanced esophageal carcinoma

As of 20 May 2019, 54 patients with advanced esophageal carcinoma (adenocarcinoma, n=23; squamous, n=26; other, n=5; missing, n=1) were enrolled in a Phase 1 clinical study (Study BGB-A317_Study_001). The median age of these enrolled patients is 62 years (range 30-80 years), 41 patients are men and 28 patients are white, 21 patients are Asian, and 5 are other races. Prior to study enrollment, these patients had received a median of 2 (range 0-7) prior treatment regimens for their esophageal cancer, with 12 patients having received at least 3 prior treatments.

Tislelizumab was administered for a median of 2.1 months (range 0.2-31.7 months) in this patient cohort. Patients received BGB-A317 at a variable dose of 5 mg/kg; 1 patient was treated at the 2 mg/kg dose or a fixed dose of 200 mg.

The majority (n=52 [96.3%]) of patients experienced at least 1 treatment-emergent adverse event. Twenty-eight (51.9%) patients experienced a treatment-related adverse event. The most common treatment-emergent adverse events reported in ≥ 5% of patients in the esophageal cohort of any grade or causality included fatigue (27.8%); decreased appetite (22.2%); nausea (20.4%); cough and constipation (18.5% each); back pain (13.0%); diarrhoea, vomiting, dyspnoea and pyrexia (11.1% each); abdominal pain upper, anaemia, arthralgia, gastroesophageal reflux disease, hypercalcaemia, hypothyroidism, pneumonia, upper respiratory infection, and weight decreased (9.3% each); abdominal pain and musculoskeletal pain (7.4% each); dysphagia, headache, hypokalaemia, infusion-related reaction, insomnia, myalgia, neck pain, oedema peripheral, oesohageal obstruction, pleural effusion, proteinuria, and pruritus (5.6% each).

Serious adverse events were reported in 19 patients (35.2%). The serious adverse events that occurred in more than 1 patient included esophageal obstruction in 2 patients (3.7%), pneumonia in 4 patients (7.4%), and lower respiratory tract infections in 2 patients (3.7%). One patient experienced a treatment-related NCI-CTCAE Grade 3 event of dermatitis.

Three patients reported adverse events with fatal outcome: mediastinitis (1), sepsis (1), and hemoptysis (1). These events are recognized complications of esophageal carcinoma; none were considered related to study treatment.

Of 54 esophageal carcinoma patients, 53 patients were evaluable for response. Confirmed complete and partial responses were observed in 1 patient (1.9%) and 5 patients (9.4%), respectively. The resulting ORR was 11.3%. In addition, 14 patients (26.4%) had a best overall response of stable disease (SD). A total of 24 patients (45.3%) had a best response of progressive disease (PD) in this cohort, and the assessments for 8 patients (15.1%) were missing.

Nivolumab

Efficacy results in ESCC patients treated with nivolumab, an anti-PD-1 monoclonal antibody, were reported from an open-label, single-arm, multi-center phase 2 study (Kudo T, 2017). This study enrolled 65 patients with squamous cell esophageal carcinoma 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 (Q2W). Tumor response was assessed approximately every 6 weeks. Median follow-up was 10.8 months (Interquartile range 4.9–14.3) and patients received a median of

3 nivolumab cycles (range 1-10). The ORR by central radiology assessment was 17% (95% CI:10-28) and 22% (95% CI:14-33) by investigator assessment. The DCR, defined as the number of patients with a complete or partial response, and those with stable disease of any duration was 42% (95% CI: 31-54) by centrally assessment and 53% (95% CI:41-65) patients by investigator assessment. The median duration of overall survival was 10.8 months (95% CI 7.4–13.3). The median durations of progression-free survival were 1.5 (95% CI: 1.4-2.8) and 2.3 (95% CI:1.5–3.0) months, by central and investigator assessment, respectively. IrRECIST objective response and disease control were reported in 16 patients (25%, 95% CI: 16-37) and 43 patients (67%, 95% CI: 55-77), respectively, and median irRECIST progression-free survival was 2.9 months (95% CI:1.9-5.6).

Pembrolizumab

KEYNOTE-028 (NCT02054806), a multicohort, phase 1b study recruited advanced esophageal squamous cell carcinoma and adenocarcinoma patients with disease progression following standard therapy. Patients received pembrolizumab 10 mg/kg Q2W. Response was assessed every 8 weeks for the first 6 month and every 12 weeks thereafter. Primary endpoint was ORR per RECIST v1.1 by investigator review. In this cohort of 23 patients, 87% received ≥ 2 prior therapies for metastatic disease and 17 patients had esophageal squamous cell carcinoma. After a median follow-up of 7.1 months (range, 1.3-19.4 months), ORR was 30% (95% CI: 13%-53%) (five patients with a response had ESCC and 2 patients had adenocarcinoma) and the stable disease rate was 9% (95% CI, 1%-28%). The median duration of response was not reached (range, 5.5-11.8 months). The median time to response was 3.7 months (range, 1.8-8.3 months) (Doi T, 2016).

1.2. Background Information on Tislelizumab

1.2.1. Pharmacology

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

Tislelizumab acts by binding to the extracellular domain of human PD-1 with high specificity as well as high affinity (dissociation constant [K_D] = 0.15 nM). It competitively blocks binding by both programmed cell death protein ligand-1 (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.

In addition, tislelizumab is an IgG4 variant antibody to gamma fragment crystallizable region (Fc) receptors (FcγR) such as FcγRI and FcγRIIIA, and has very low binding affinity to Complement 1q (C1q), a subunit of complement 1. In vitro assays with tislelizumab suggest either low or no antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular

phagocytosis (ADCP), or complement-dependent cytotoxicity (CDC) effects in humans (Labrijn et al 2009; Zhang et al 2018).

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

1.2.2. Clinical Pharmacology

1.2.2.1. Pharmacokinetics

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

Preliminary population PK analysis using a 2-compartment model with first-order elimination shows a systemic plasma clearance (CL) of tislelizumab of 0.173 L/day, volume of distribution (Vd) 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 CL of tislelizumab, which supports fixed-dosing across different ethnic groups.

1.2.2.1.1. Lack of Ethnic Differences in Exposure

Based on the information available to date, tislelizumab exposure in Asian and Caucasian patients is similar, and the safety profile at clinically relevant doses is tolerable and manageable.

Preliminary PK data from Study BGB-A317_Study_001 are summarized in Section 1.2.2.1 above. Comparison of PK parameters indicates that after a single intravenous (IV) infusion of tislelizumab, dose-normalized exposure ($AUC_{0\text{-}14day}$) was consistent between Study 001 with non-Chinese (n=91 mostly Caucasian) and Study 102 with Chinese (n=20) patients in the study, which was conducted in the US, Australia, New Zealand, Korea, and Taiwan. Additionally, dose-normalized exposure ($AUC_{0\text{-}14day}$) was consistent between BGB-A317_Study_ 001 across Asian (n=27, including 20 Chinese and 7 non-Chinese Asian) and Caucasian (n=80).

These preliminary findings indicate that ethnic differences are unlikely to affect the exposure of tislelizumab.

Furthermore, these data are consistent with findings of limited ethnic differences in studies of therapeutic monoclonal antibodies (Chiba et al 2014, Matsushima et al 2015, Zhou et al 2012). In addition, there do not appear to be clinically relevant differences in PK exposures from studies of 2 other anti-PD-1 antibodies, nivolumab and pembrolizumab (Shimizu et al 2016; Yamamoto et al 2017).

1.2.3. Summary of Relevant Clinical Experience With Tislelizumab

As of 20 May 2019, there are 22 ongoing studies with tislelizumab, 13 ongoing with available preliminary data: monotherapy studies BGB-A317_Study_001, BGB-A317-102, BGB-A317-203, BGB-A317-204, BGB-A317-207, BGB-A317-208, and BGB-A317-209; chemotherapy combination therapy studies BGB-A317-205 and BGB-A317-206; and investigational agent combination therapy studies BGB-A317/BGB-290_Study_001 (tislelizumab in combination with BGB-290 [also known as pamiparib, a poly (ADP-ribose) polymerase (PARP) inhibitor]), BGB-3111_BGB-A317_Study_001 (tislelizumab in combination with zanubrutinib [also known as BGB-3111, a Bruton's tyrosine kinase (BTK) inhibitor]), and BGB-900-101 (BGB-A333 [an anti-PD-L1 monoclonal antibody] alone and in combination with tislelizumab), and BGB-900-103 (tislelizumab in combination with sitravatinib [also known as MGCD516, a receptor tyrosine kinase inhibitor]).

The 9 ongoing studies without available clinical data include BGB-A317-301, BGB-A317-302, BGB-A317-303, BGB-A317-304, BGB-A317-305, BGB-A317-306, BGB-A317-307, BGB-900-102, and BGB-900-104.

A pooled analysis of monotherapy studies was conducted to provide a comprehensive safety assessment separately from combination therapy. For monotherapy, the safety profile is similar across tumor types. There is no pattern in the incidence, severity, or causality of adverse events (AEs) to tislelizumab dose level. The safety profile for single-agent tislelizumab is similar to those observed in other PD-1 inhibitors. The initial data collected in these studies suggest that tislelizumab can result in antitumor activity across a variety of tumor types. Antitumor activity has been observed across the dose ranges evaluated in patients. In Phase 3 controlled studies, the safety profile of tislelizumab monotherapy is acceptable in the context of the observed clinical efficacy, and manageable using established safety guidelines. Please find the overview of safety and efficacy in Section 1.2.3.1 and Section 1.2.3.2.

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

1.2.3.1. Overview of Safety

There were 1,273 patients in the Pooled Monotherapy studies. Of the 1,273 enrolled, 544 patients (42.7%) remained on study as of 20 May 2019; 272 patients (21.4%) were still receiving tislelizumab treatment, and 272 patients (21.4%) were in follow-up. At the time of data cut-off, 785 patients had a dosing period of ≥ 2 months, ie, evaluable for treatment assessment beyond 2 months. Among them, 261 patients (33.2%) continued to receive tislelizumab treatment.

All patients in the pooled monotherapy analysis had a median treatment exposure duration of 3.58 months (range: 0.1 to 43.6) and median study follow-up duration of 8.34 months (range: 0.1 to 47.5). Overall, the total pooled monotherapy population had a median age of 59 years and was 66.9% male.

The median number of prior systemic anti-cancer therapy regimens for the solid tumor, hematologic malignancy, and total populations were 1.0 (range: 0 to 12), 3.0 (range: 0 to 11), and 1.0 (range: 0 to 12), respectively.

Preliminary Safety

Of the 1,273 total patients treated in the Pooled Monotherapy studies, 846 (66.5%) experienced at least one treatment-related TEAE. The most commonly occurring TEAEs assessed as related to tislelizumab were aspartate aminotransferase (AST) increased (128 patients, 10.1%), alanine aminotransferase (ALT) increased (123 patients, 9.7%), hypothyroidism (113 patients, 8.9%), rash (96 patients, 7.5%), and pyrexia (94 patients, 7.4%).

Related TEAEs by Severity

Of the 1,273 total patients treated in the Pooled Monotherapy studies, 163 (12.8%) experienced at least one Grade 3 or higher TEAE assessed as related to tislelizumab. The only Grade 3 or higher TEAEs that occurred in ≥ 1% (12 or more patients) in the total study population were AST increased (19 patients, 1.5%) and ALT increased (15 patients, 1.2%).

As of the data cutoff 20 May 2019, 105 patients (8.2% of the total population) died within 30 days of the last study drug dose in the Pooled Monotherapy studies. Of these 105 patients, there were 21 patients (1.6% of the total population) who had an AE with a fatal outcome within 30 days of the last study drug dose. Of the 536 patients (42.1% of the total population) who died more than 30 days after the last study drug dose, 14 patients (1.1% of the total population) died as a result of an AE.

1.2.3.2. Overview of Efficacy

1.2.3.2.1. Study BGB-A317_Study_001 (Data Cutoff 20 May 2019)

Study BGB-A317_Study_001 was a 2-stage study consisting of a Phase 1a dose-escalation and dose-finding component with 3 parts to establish the maximum tolerated dose (MTD), if any, a recommended Phase 2 dose (RP2D) for the Phase 1b, and a flat dose (fixed dose) followed by a Phase 1b component to investigate efficacy in select tumor types in indication expansion arms and to further evaluate safety and tolerability of tislelizumab.

As of the data cutoff 20 May 2019, there were 451 patients treated in the study and 441 patients were included in the efficacy evaluable set.

Across all disease cohorts, there were 5 patients (1.1%) with a complete response (CR). A total of 55 patients (12.5%) had a confirmed partial response (PR). The resulting overall clinical response rate was 13.6%. Additionally, there were 142 patients (32.2%) with a best overall response of SD. A total of 199 patients (45.1%) had a best response of PD in this study.

1.2.3.2.2. Study BGB-A317-102 (Data Cutoff 20 May 2019)

This is a two-phase, non-randomized, Phase 1/2 study of tislelizumab monotherapy in Chinese patients with advanced solid tumors. Phase 1 includes a dose verification substudy and a substudy of PK evaluation of the investigational products derived from 2 manufacturing processes and scales. Phase 2 is an indication expansion study.

As of the data cutoff 20 May 2019, of the 300 patients treated in Study BGB-A317-102, 249 patients were included in the Efficacy Evaluable Analysis Set. Across all disease cohorts and study phases, there was 1 patient (0.4%) with a CR. A total of 44 patients (17.7%) had a confirmed PR. The resulting overall clinical response rate was 18.1%. Additionally, there were

91 patients (36.5%) with a best overall response of SD. A total of 113 patients (45.4%) had a best response of PD in this study.

1.2.3.3. Immune-Related Reactions

Of the 1273 total patients for the Pooled Monotherapy studies, 602 (47.3%) experienced at least one immune-related adverse events (irAEs) of any grade. The most commonly occurring irAEs of any grade were AST increased (129 patients, 10.1%), ALT increased (124 patients, 9.7%), hypothyroidism (113 patients, 8.9%), rash (97 patients, 7.6%), and pruritus (78 patients, 6.1%). Analysis of the total patients with at least one irAE that also was ≥ Grade 3 in severity showed that 121 patients (9.5%) experienced such events. The most commonly occurring irAEs ≥ Grade 3 in severity were AST increased (21 patients, 1.6%), gamma-glutamyltransferase increased (17 patients, 1.3%), ALT increased (16 patients, 1.3%), pneumonitis and pneumonia (9 patients each, 0.7%).

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

1.2.4. Benefit-Risk Assessment

Patients with advanced unresectable/metastatic ESCC represent a population with a high unmet medical need. There is no globally accepted standard of care regimen for patients with previously treated unresectable/metastatic ESCC. Single-agent chemotherapy is typically administered, but the choice of agent differs by geography and is often tailored to patient needs.

Data from clinical studies of immune checkpoint inhibitors and the data collected in the Phase 1 Study BGB-A317_ Study_001 suggest that evaluating tislelizumab in ESCC may have potential benefit for these patients. The safety profile across immune checkpoint inhibitors is consistent, supporting an acceptable tolerability profile.

Given the unmet medical need and limited treatment options for this indication, the benefit/risk assessment based on available tislelizumab Phase 1 data and published data from the PD-1 antibodies may be considered acceptable and support the conduct of this study.

An Independent Data Monitoring Committee (IDMC) will be established to regularly monitor the safety of tislelizumab when compared with investigator chosen chemotherapy (ICC).

1.3. Study Conduct

This study will be conducted in compliance with the protocol approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and in accordance with Good Clinical Practice (GCP) standards.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

To compare the overall survival (OS) in the Intention-to-Treat (ITT) population following treatment with tislelizumab vs. investigator chosen chemotherapy (ICC) when given as second line treatment in patients with advanced unresectable/metastatic esophageal squamous cell carcinoma (ESCC)

2.1.2. Secondary Objectives

Key Secondary Objective:

- To compare the OS in the PD-L1 positive population following treatment with tislelizumab versus investigator chosen chemotherapy (ICC).

Other Secondary Objectives:

- The following will be compared between the tislelizumab and the chemotherapy treatments based on assessment by investigator per RECIST v1.1 criteria:
  - ORR
  - Progression-free survival (PFS)
  - Duration of response (DOR)
- To compare HRQoL endpoints between the tislelizumab and the chemotherapy treatments as assessed by patient reported outcome (PRO) measures: European EORTC QLQ-C30 index (EORTC QLQ-C-30), the European esophageal cancer specific module OES18 (EORTC QLQ-OES18), and the generic health state instrument Euroqol 5D (EQ-5D-5L)
- To compare the safety and tolerability between tislelizumab and the chemotherapy treatments

2.1.3. Exploratory Objectives

- To characterize the disease control rate (DCR) with tislelizumab compared to chemotherapy
- To characterize the PK of tislelizumab
- To determine host immunogenicity to tislelizumab
- To explore potential predictive biomarkers (including but not limited to PD-L1 expression, gene expression profiling, tumor mutation burden, microsatellite instability [MSI], and tumor-infiltrated immune cells) and resistance mechanism

2.2. Endpoints

2.2.1. Primary Endpoint

- Overall survival (OS) in the ITT analysis set- defined as the time from the date of randomization until the date of death due to any cause in all randomized patients.

2.2.2. Secondary Endpoints

Key Secondary Endpoint:

- OS in the PD-L1 positive analysis set - defined as the time from the date of randomization until the date of death due to any cause in PD-L1 positive population

Other Secondary Endpoints:

- ORR in both the ITT analysis set and the PD-L1 positive analysis set - defined as the proportion of patients who had CR or PR assessed by the investigator per RECIST v1.1.
- PFS in both the ITT analysis set and the PD-L1 positive analysis set - defined as the time from the date of randomization to the date of first documentation of disease progression assessed by the investigator per RECIST v1.1 or death, whichever occurs first
- DOR in both the ITT analysis set and the PD-L1 positive analysis set - defined as the time from the first determination of an objective response until the first documentation of progression as assessed by the investigator per RECIST v1.1, or death, whichever comes first
- HRQoL assessment of the subject's overall health status using EORTC QLQ-C-30, EORTC QLQ-OES18, and EQ-5D-5L in both the ITT analysis set and the PD-L1 positive analysis set
- The incidence and severity of adverse events according to NCI-CTCAE v4.03

2.2.3. Exploratory Endpoints

- Disease control rate (DCR) in both the ITT analysis set and the PD-L1 positive analysis set - defined as the proportion of patients who have CR, PR and SD assessed by the investigator per RECIST v1.1
- Pharmacokinetic endpoints: summary of serum concentration of tislelizumab to include but not limited to C_{trough}
- Assessments of immunogenicity of tislelizumab to determine the incidence of anti-drug antibodies (ADA)
- Predictive biomarkers (including but not limited to PD-L1 expression, gene expression profiling, tumor mutation burden, MSI, and tumor-infiltrated immune cells) and resistance mechanism

3. STUDY DESIGN

3.1. Summary of Study Design

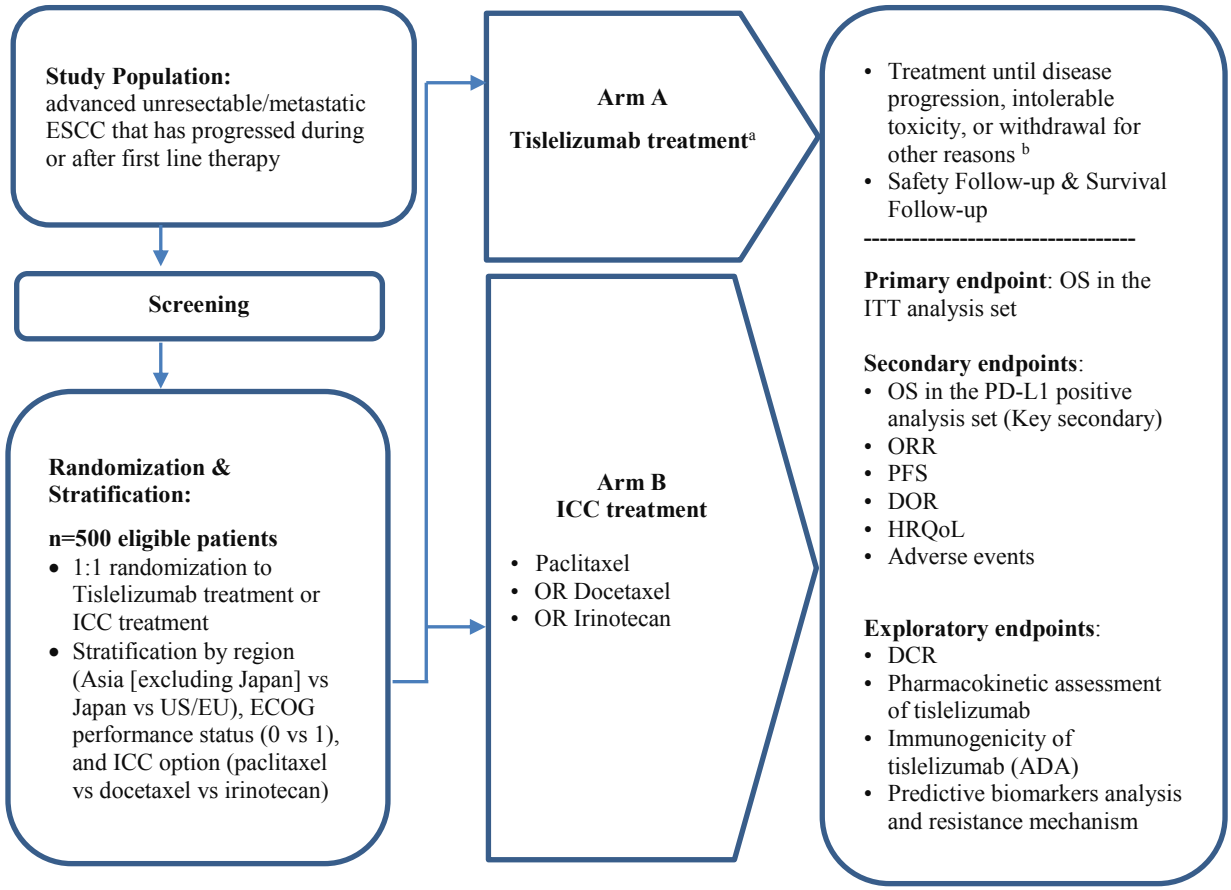
This is a randomized, controlled, open-label, global Phase 3 study of the PD-1 monoclonal antibody tislelizumab compared to investigator chosen chemotherapy given as second line treatment in patients with advanced unresectable/metastatic ESCC that has progressed during or after first line therapy. A substudy investigating the safety, tolerability, PK, and preliminary efficacy in Japanese patients is planned; preliminary safety and tolerability will be evaluated before Japanese patients are recruited in this Phase 3 study (see Appendix 13).

Patient randomization and enrollment will be stratified by region (Asia [excluding Japan] vs Japan vs US/EU), ECOG performance status (0 vs 1), and ICC option (paclitaxel vs docetaxel vs irinotecan).

3.2. Study Schematic

The study design schematic is presented in Figure 1

Figure 1: Study Design Schematic



Abbreviations: ECOG, Eastern Cooperative Oncology Group; ESCC, Esophageal squamous cell carcinoma; ICC, investigator chosen chemotherapy; ITT, Intention-to-treat; OS, Overall survival; ORR, Overall response rate;

PD-L1, Programmed cell death protein ligand-1; PFS, Progression-free survival; DOR, Duration of response; HRQoL, Health Related Quality of Life; DCR, Disease control rate; ADA, Anti-drug antibody.

a. The initial infusion (Cycle 1, Day 1) will be administered over a period of 60 minutes. If this infusion is well tolerated, subsequent infusions may be administered over 30 minutes. After tislelizumab infusion, patients will be further monitored for at least 1 hour during Cycles 1 and 2. From Cycle 3 onward, a post-infusion monitoring period of at least 30 minutes will be required.
b. At the discretion of the investigator, patients randomized to receive tislelizumab may be treated beyond progression under protocol defined conditions. See Section 7.17.1.

3.3. Duration of Study

Total duration of study participation will vary by patient. Each study phase is further discussed below.

3.3.1. Screening Phase

Screening evaluations will be performed within 28 days prior to randomization. Patients who voluntarily agree to participate will be required to sign the informed consent form (ICF) prior to undergoing any screening procedure (refer to Appendix 1 for details). Rescreening under limited conditions may be allowed after consultation with BeiGene, eg, when a patient narrowly misses a laboratory criterion and it is correctable and not due to rapidly deteriorating condition or disease progression. Rescreening is allowed only once. The investigator is to assess patient eligibility according to the latest screening assessment results.

Patients who are suspected to have serious respiratory illness or exhibit significant respiratory symptoms should undergo pulmonary function testing (refer to Appendix 1 for details).

Archival tissue is required to be collected for the purpose of biomarker analysis if available. If archival tumor tissue samples are not available, collection of a fresh tumor biopsy at baseline is requested if accessible. Please refer to Section 7.12 for details.

Radiologic images performed within 28 days prior to randomization will be reviewed by the investigators for tumor characterization according to RECIST v1.1 criteria.

3.3.2. Treatment Phase

After completing all screening activities, patients confirmed eligible will be randomized in a 1:1 ratio to receive either tislelizumab or ICC treatment (paclitaxel/docetaxel/irinotecan).

Investigator chosen chemotherapy (ICC, paclitaxel/docetaxel/irinotecan) should be determined prior to randomization. The treatment plan is presented in Table 2.

Table 2: Treatment Plan

Arm	Drug	Treatment Regimen	Treatment Discontinuation
Tislelizumab	Tislelizumab	200 mg IV on Day 1, given every 21 days	until disease progression, intolerable toxicity, or withdrawal for other reasons
ICC	Paclitaxel	135-175 mg/m² IV on Day 1, given every 21 days • NOTE: Paclitaxel may also be given in doses of 80-100 mg/m² IV on a weekly schedule according to local and/or country specific guidelines for standard of care • Japan: 100 mg/m² IV on Day 1, 8, 15, 22, 29, and 36, followed by one week of rest	
	Docetaxel	75 mg/m² IV on Day 1, given every 21 days • Japan: 70 mg/m² IV on Day 1, given every 21 days	
	Irinotecan	125 mg/m² IV on Days 1 and 8, given every 21 days	

Tislelizumab treatment beyond initial investigator-assessed, RECIST v1.1 defined progression may be permitted if, in the judgement of the investigator, the patient is anticipated to benefit from continued treatment, eg, the patient has evidence of "pseudo-progression". Specific requirements for post-progression continuation of patients treated with tislelizumab are described in Section 7.17.1.

Radiologic assessment of tumor-response status will be performed approximately every 6 weeks (± 7 days) for 6 months, then every 9 weeks (± 7 days) until disease progression. Tumor response will be assessed by the investigator using RECIST v1.1 (see Appendix 2) (Eisenhauer EA, 2009). Details are provided in Section 7.4.

Patients randomized to tislelizumab treatment will undergo blood sampling for PK assessment at predetermined timepoints, as outlined in Appendix 1. Procedures for collection of tislelizumab PK samples are described in the Laboratory Manual.

The HRQoL measurement will be performed using the EORTC-QLQ-C30, EORTC QLQ-OES18 and the EQ-5D-5L at baseline, prior to study treatments on Day 1 of Cycles 1 through 6 or at the End-of-Treatment Visit (whichever occurs first), and at the Safety Follow-up Visit.

Safety will be assessed throughout the study by monitoring AEs/SAEs (toxicity grades assigned per National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] v4.03), new physical examination findings, and clinically significant changes in laboratory assessments. Adverse events of special interest in this study will include the incidence and severity of irAEs. Vital signs, Eastern Cooperative Oncology Group (ECOG) performance status change, and electrocardiogram (ECG) results will also be used for safety assessment. Safety assessments are further detailed in Section 7 and the Schedule of Assessments (Appendix 1).

Optional blood samples will be taken to explore the association of blood-based biomarkers. Please refer to Section 7.12 for details.

3.3.3. End of Treatment

The End-of-Treatment (EOT) Visit is conducted when the investigator determines that tislelizumab or ICC will no longer be used, at which time all of the assessments listed for the EOT Visit will be performed. If a patient withdraws from treatment at a study visit when all assessments required for EOT have been completed, EOT assessments do not need to be repeated.

Patients randomized to tislelizumab treatment who have RECIST-defined PD by investigator assessment, but who, in the opinion of the investigator, have evidence of continued clinical benefit from tislelizumab may continue to receive this drug only after review and agreement by the medical monitor. In such cases, patients must complete the EOT visit only after permanent discontinuation of tislelizumab.

If routine laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the End of Treatment Visit, tests need not be repeated. In subjects who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (± 4 weeks window). If a previous scan was obtained within 6 weeks prior to the date of discontinuation, then a scan at treatment discontinuation is not required.

If patients refuse to return for these visits or are unable to do so, every effort should be made to contact them to determine the survival status.

Optional biopsies and/or blood samples will be taken for the patients who have confirmed disease progression to explore resistance mechanism as outlined in Section 7.12.

3.3.4. Safety Follow-up Phase

In both study arms, patients who discontinue treatment for any reason will be asked to return to the clinic for the Safety Follow-up Visit within 30 days (± 7 days) after the last dose of study drug or before the initiation of a new anticancer therapy (whichever occurs first) to collect AEs or SAEs that may have occurred after the patient discontinued from the study treatment. All drug-related SAEs will be recorded by investigator after treatment discontinuation until patient death, withdrawal of consent, or lost to follow-up, whichever occurs first. In addition, telephone contacts with patients should be conducted to assess irAEs and concomitant medications (if appropriate, ie, associated with an irAE or is a new anticancer therapy) at 60 days (± 14 days), and 90 days (± 14 days) after the last dose of study drug, regardless of whether or not the patient starts a new anticancer therapy. If patients report a suspected irAE 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 8.4.

The End of Treatment (EOT) Visit may be combined with the Safety Follow-up visit, provided that the EOT occurred 30 days (± 7 days) after the last study treatment; the assessments for both visits should be performed. Patients who discontinue study treatment prior to disease progression will have their tumors assessed as outlined in Section 7.4.

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

3.3.5. Survival Follow-up Phase

Patients who discontinue study drug for reasons other than radiographically confirmed disease progression (eg, toxicity) will continue to undergo tumor assessments according to Section 7.4 and the Schedule of Assessments (Appendix 1), until radiographically confirmed disease progression, withdrawal of consent, loss to follow-up, death, or until the study completes, whichever occurs first.

Patients will be followed for survival and further anticancer therapy information after discontinuation of study treatment via telephone contact, email, or other communications; review of patient medical records; and/or in-person clinic visits approximately 1 month (4 weeks ± 7 days) after the Safety Follow-up Visit and every month thereafter (Section 7.16).

3.3.6. End of Study

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

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

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

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

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

The sponsor has the right to close a site at any time. The decision will be 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 (GCP), applicable laws and regulations
- Study activity is completed (ie, all patients have completed and all obligations have been fulfilled)]

3.4. Study Rationale

3.4.1. Rationale for Tislelizumab in the Treatment of ESCC

High levels of FcγR-expressing myeloid derived cells (eg, M2 macrophage, MDSC) 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 ADCC or antibody-dependent cellular phagocytosis (ADCP) depletion of effector T cells (Gül and van Egmond 2015; Prieto et al 2015; Makarova-Rusher et al 2015; Beers et al 2016; Dahan et al 2015). As a no- to low-FcγR-binding agent (thus causing minimal ADCC/ADCP effect), tislelizumab may show superior efficacy and lower toxicity in esophageal carcinoma. Available data from a clinical study with other anti-PD-1 monoclonal antibodies, nivolumab and pembrolizumab, have shown drugs targeting the PD-1 pathway to have both a manageable safety profile and promising antitumor activity in patients with advanced unresectable or metastatic ESCC (Section 1.1.1.1).

Finally, according to the latest data collected from the Phase 1 Study 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 (Section 1.2.3).

Given the unmet medical need and limited treatment options in this indication, the benefit/risk assessment based on available tislelizumab Phase 1 data and published data from the PD-1 antibodies may be considered acceptable and support continued development.

3.4.2. Rationale for Selection of Tislelizumab Fixed 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 IV Q3W was selected for further evaluation.

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

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

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

In conclusion, tislelizumab 200 mg Q3W is the recommended dose for this Phase 3 global study.

3.4.3. Rationale for Selection of Paclitaxel/Docetaxel/Irinotecan as Comparator

Current guidelines recommend the combination of fluorouracil and cisplatin, either alone or in combination with a third drug such as epirubicin or a taxane, as the most effective first-line treatment option (Ando N, 2015). In China, cisplatin with a taxane is also preferred to treat ESCC as first-line therapy. Approximately 40% of patients for whom first-line treatment fails will be potential candidates for second line therapy (Thallinger CM, 2011). In a relapsed or refractory disease setting, however, data in the second-line ESCC treatment setting are scarce, and there is no established consensus on the optimal second-line chemotherapy treatment so far.

National Comprehensive Cancer Network (NCCN, 2017) guidelines endorse use of docetaxel, paclitaxel and irinotecan in the second-line treatment of esophageal carcinoma. While these agents are widely used, there are recognized geographic differences in the choice of treatment in this disease setting despite the lack of clinically significant differences in response rates, PFS and OS between agents. In Japan, taxanes are widely used as second-line treatment of esophageal carcinoma (Kuwano H, 2015). In China, irinotecan is often chosen as second-line treatment.

As discussed in Section 1.1.1, ORR to single-agent chemotherapy with paclitaxel, docetaxel, or irinotecan range between 4% and 44% (Table1). Progression-free survival, being less than 4 months, in the 13 single-agent studies reviewed by Thallinger et al (2011). In addition, combination chemotherapy as second line therapy showed more serious adverse events than single regimen, suggesting an unfavorable risk benefit profile. So, new well-designed, adequately powered clinical second-line studies may lead to improved outcome, but Phase 3 studies for comparison of the different forms of therapy are indispensable.

3.4.4. Rationale of Stratification Factors

Patient enrollment will be stratified by geographic region of enrollment (Asia excluding Japan vs Japan vs US/EU), ECOG performance status (0 vs 1), and by ICC option (paclitaxel vs docetaxel vs irinotecan).

The highest incidence of esophageal cancer is seen along two geographical belts, one from north central China through the central Asian republics to northern Iran, and one from eastern to southern Africa (Arnold M, 2015). Patient enrollment will be stratified by geographic region of enrollment to account for potential differences in the prior standard medical care that are not easily quantifiable, as well as other factors associated with those geographic regions (ie betel quid exposure, nutritional factors).

Patients with an ECOG performance score (PS) of 0 or 1 may be enrolled to this study if other entry criteria are met. As with many other malignancies, performance status has been shown to be prognostic for survival in patients with both limited and advanced squamous esophageal carcinoma (Tustumi F, 2016; Uchinami Y, 2016). In a retrospective analysis, Tustumi et al (2016) observed a 1-year survival rate of 62.3% in patients with an ECOG PS <2 vs. 31.7% in patients with an ECOG PS ≥2. These results are consistent with that published by Nomura et al (2016) who found a significant association of PS with outcome in a univariate analysis, but not in a multi-variate analysis, as well as data published by Shirakawa et al (2014).

The ICC option will be determined for all patients prior to the randomization. Since 3 comparator drugs are included in the control arm to reflect the real-world choices made by physicians and their patients, the type of ICC chosen prior to the randomization will be included

as a stratification factor in the randomization and statistical analysis to adjust any potential confounding factors due to the heterogeneity of these three drugs used in the control arm.

4. MATERIALS AND METHODS

4.1. Selection of Study Population

The specific eligibility criteria for selection of the approximately 500 patients planned for randomization (1:1 to tislelizumab or ICC treatment) are provided in Section 4.1.1 and Section 4.1.2, respectively.

4.1.1. Inclusion Criteria

To be eligible to participate in this study, a patient must meet all of the following criteria:

1. Is male or female, aged ≥ 18 years on the day the patient voluntarily agrees to participate in the study (or acceptable age according to local regulations, whichever is older)
2. Able to provide written informed consent and can understand and agree to comply with the requirements of the study and the schedule of assessments
3. Histologically confirmed diagnosis of esophageal squamous cell carcinoma (ESCC)
4. Tumor progression during or after first-line systemic treatment for advanced unresectable/metastatic ESCC (Appendix 12)

   NOTE: Patients with disease progression that occurs during treatment or within ≤ 6 months (180 days) of cessation of neoadjuvant/adjuvant treatment (chemotherapy or chemoradiotherapy) are eligible provided all other criteria are met

   NOTE: A line of treatment begins with the administration of the first agent in a regimen and ends with disease progression. A line of therapy is preserved when chemotherapy is switched due to toxicities
5. At least one measurable/evaluable lesion by RECIST v1.1 as determined by local site investigator/radiology assessment within 28 days prior to randomization

   NOTE: Lesions that have been previously irradiated may be considered evaluable provided there is evidence of disease progression following the completion of radiation therapy.
6. Eastern Cooperative Oncology Group (ECOG) performance status (Appendix 3) of 0 or 1 prior to randomization
7. Laboratory data meeting the criteria below within 14 days prior to randomization. Laboratory data will not be valid if the patient has received growth factors or blood transfusion for prophylactic use within 7 days before the laboratory testing:
   - Absolute neutrophil count (ANC) ≥1500 cells/mm^3
   - Platelet count ≥100,000 cells/mm^3
   - Hemoglobin ≥9 g/dL or ≥5.6 mmol/L
   - Estimated glomerular filtration rate (GFR) ≥ 30 mL/min/1.73 m^2 by Chronic Kidney Disease Epidemiology Collaboration equation (Appendix 11)

- Serum total bilirubin ≤1.5 x upper limit of normal (ULN) (or < 3 x ULN in patients with Gilbert's syndrome)
- Prothrombin time/International normalized ratio (PT/INR) ≤1.5 x ULN unless the patient is receiving anti-coagulant therapy
- Aspartate transaminase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN (or ≤ 5.0 x ULN in patients with liver metastases)

8. HBV or HCV infection and meets the following criteria as applicable to the infection type:

   For patients with inactive/asymptomatic carrier, chronic, or active HBV:

   HBV deoxyribonucleic acid (DNA) < 500 IU/mL (or 2500 copies/mL) at screening.

   NOTE: Patients with detectable hepatitis B surface antigen (HBsAg) or detectable HBV DNA should be managed per treatment guidelines. Patients receiving antivirals at screening should have been treated for > 2 weeks and HBV < 500 IU/ml prior to randomization and should continue treatment for at least 6 months after study drug treatment discontinuation.

   For patients with HCV:

   Patients with detectable HCV RNA and who are receiving treatment at screening should remain on continuous, effective antiviral therapy during the study.

9. Females of childbearing potential must have a negative serum pregnancy test within 7 days of randomization and must be willing to have additional pregnancy tests during the study. Females of childbearing potential must be willing to use highly effective methods of birth control for the duration of the study, and for at least 120 days after the last dose of tislelizumab and 180 days after the last dose of ICC
10. Non-sterile males who have female sexual partner(s) of childbearing potential (Appendix 5) must use highly effective form of birth control for the duration of the study, and for at least 120 days after the last dose of tislelizumab and 180 days after the last dose of ICC
    - A sterile male is defined as one for whom known azoospermia, in a semen sample examination, has been previously demonstrated as definitive evidence of infertility.
    - Males with known 'low sperm counts' (consistent with 'sub-fertility) are not to be considered sterile for purposes of this study.

4.1.2. Exclusion Criteria

To be eligible to participate in this study, a patient cannot meet any of the following exclusion criteria:

1. Ineligible for treatment with any of the treatments of protocol-specified chemotherapy
2. Receipt of 2 or more prior lines of systemic treatments for advanced/metastatic unresectable ESCC
3. Palliative radiation treatment for ESCC within 14 days of study treatment initiation (C1D1)

4. History of gastrointestinal perforation and /or fistula or aorto-esophageal fistula within 6 months prior to randomization
5. Tumor invasion into organs located adjacent to the esophageal disease site (eg, aorta or respiratory tract) at an increased risk of fistula in the study treatment assessed by investigator
6. Uncontrollable pleural effusion, pericardial effusion, or ascites requiring frequent drainage (recurrence within 2 weeks of intervention)
7. Current or past history of severe hypersensitivity reactions to other humanized monoclonal antibodies
8. Received prior therapies targeting PD-1 or PD-L1
9. Has 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) exceptions are to be determined by investigator in consultation with the medical monitor
10. Prior malignancy active within the previous 2 years before randomization (exceptions include the tumor under investigation in this study and surgically excised non-melanoma skin cancer, curatively treated carcinoma in situ of the cervix, localized prostate cancer treated with curative intent, curatively treated low-stage bladder cancer, ductal carcinoma in situ treated surgically with curative intent, or a malignancy diagnosed >2 years ago, with no current evidence of disease and no therapy ≤ 2 years prior to randomization)
11. Active brain or leptomeningeal metastasis. Patients with equivocal findings or with confirmed brain metastases are eligible for enrollment provided that they are asymptomatic and radiologically stable without the need for corticosteroid treatment for at least 4 weeks prior to randomization. CT/MRI of the head at baseline is required for patients who are suspected to have central nervous system (CNS) metastases.
12. Has active autoimmune disease or history of autoimmune diseases at high risk for relapse

    NOTE: Patients with following diseases may be enrolled if they meet all other eligibility criteria: controlled type I diabetes, hypothyroidism managed with hormone replacement therapy only, controlled celiac disease, skin diseases not requiring systemic treatment (such as vitiligo, psoriasis or alopecia), or diseases not expected to recur in the absence of external triggering factors.
13. Has a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone or equivalents) or other immunosuppressive medications within 14 days prior to randomization
    - Patients who have a history of organ transplant, including stem cell allograft are not permitted to enroll
    - Adrenal replacement steroid dose ≤ 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease
    - Patients are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption).

- A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted.

14. Undergone surgery requiring general anesthesia or epidural anesthesia within 28 days prior to randomization
15. Undergone surgery involving local anesthesia within 14 days prior to randomization. Exceptions to this exclusion criteria include:
    a. Placement of a central venous access device that requires up to a 3-day surveillance period.
    b. A biopsy procedure performed under local anesthesia during the screening period that require a 7-day post procedure surveillance period.
16. Received any radiopharmaceuticals - (except for examination or diagnostic use of radiopharmaceuticals) within 42 days prior to randomization.
17. Has received:
    a. Within 28 days or 5 half-lives (whichever is shorter but at least 14 days) of the first study drug administration: any chemotherapy, any immunotherapy (eg, interleukin, interferon, or thymoxin) or any investigational therapies
    b. Within 14 days of the first study drug administration: any Chinese herbal medicine or Chinese patent medicines used to control cancer or boost immunity
18. Any serious or unstable pre-existing medical conditions (aside from malignancy exceptions specified above), psychiatric disorders, or other conditions that could interfere with the subject's safety, obtaining informed consent, or compliance with study procedures
19. Receipt of a live vaccine within 4 weeks prior to Cycle 1 Day 1

    NOTE: Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live viruses and are not allowed.
20. Known history of, or any evidence of interstitial lung disease, non-infectious pneumonitis, pulmonary fibrosis diagnosed based on imaging or clinical findings, or uncontrolled systemic diseases, including diabetes, hypertension, acute lung diseases, etc

    NOTE: Patients with radiation pneumonitis may be randomized if the radiation pneumonitis has been confirmed as stable (beyond acute phase) and is unlikely to recur. Patients with severe but stable radiation-induced pneumonitis may be required to undergo routine pulmonary function studies
21. Has severe chronic or active infection (including tuberculosis infection, etc) requiring systemic antibacterial, antifungal or antiviral therapy, within 14 days prior to Cycle 1 Day 1

    NOTE: Patients who require systemic antiviral therapy for HBV are excepted
22. Known history of Human Immunodeficiency Virus (HIV)

23. Has any of the following cardiovascular risk factors:
    - Ongoing cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living
    - Symptomatic pulmonary embolism within 28 days before randomization
    - Any history of acute myocardial infarction within 6 months before randomization
    - Any history of heart failure meeting New York Heart Association Classification III or IV (Appendix 6) within 6 months before randomization
    - Any event of ventricular arrhythmia > Grade 2 in severity within 6 months before randomization
    - Any history of cerebrovascular accident or transient ischemic attack within 6 months before randomization
    - Uncontrolled hypertension: systolic pressure ≥ 160 mmHg or diastolic pressure ≥ 100 mmHg despite anti-hypertension medications ≤ 28 days before randomization or first dose of study drug

      Any episode of syncope or seizure ≤ 28 days before randomization
24. Severe malnutrition despite enteral or parenteral nutritional supplementation
25. Known, active alcohol or drug abuse or dependence
26. Pregnant or breastfeeding woman.

5. STUDY TREATMENT

5.1. Formulation, Packaging, Handling, and Storage

The interactive response technology (IRT) system will be used for drug supply management. The study drug will be dispatched to a study center only after receipt of the required documents in accordance with applicable regulatory requirements and the sponsor's procedures. The investigator or pharmacist/designated personnel is responsible for maintaining the drug supply inventory and acknowledgement receipt of all study drug shipments. All study drugs must be stored in a secure area with access limited to the investigator and authorized study center personnel and under physical conditions that are consistent with study drug-specific requirements.

Only patients enrolled in the study may receive study drug, in accordance with all applicable regulatory requirements. Only authorized study center personnel may supply or administer study drug.

5.1.1. Tislelizumab

Tislelizumab is a monoclonal antibody formulated for IV injection in a single-use vial (20R glass, United States Pharmacopeia [USP] type I), containing a total of 100 mg 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. One vial is packaged in a single carton box.

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

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

5.1.2. Paclitaxel

Paclitaxel will be provided in vials for infusion. The contents of the label will be in accordance with all applicable local regulatory requirements.

Paclitaxel must be kept at room temperature in original package as specified on the label.

Please refer to the Pharmacy Manual for details regarding administration, accountability, and disposal.

5.1.3. Docetaxel

Docetaxel will be provided in vials for infusion. The contents of the label will be in accordance with all applicable local regulatory requirements.

Docetaxel must be kept at 20 to 25℃ in original package to protect from light as specified on the label.

Please refer to the Pharmacy Manual for details regarding administration, accountability, and disposal.

5.1.4. Irinotecan

Irinotecan will be provided in vials for infusion. The contents of the label will be in accordance with all applicable local regulatory requirements.

Irinotecan must be kept at room temperatures condition and protected from light as specified on the label.

Please refer to the Pharmacy Manual for details regarding administration, accountability, and disposal.

5.2. Dosage, Administration, and Compliance

Dosing schedules for both arms, broken out by individual arm, are provided in Table 3. The first dose of study drug should be administered within 3 business days of randomization. The day of the 1st dose treatment will be documented as Cycle 1 Day 1. All patients will be monitored continuously for AEs. Treatment modifications (eg, dose delay, reduction, interruption, or discontinuation) will be based on specific laboratory assessment and AE criteria, as described in Section 8.6.

Table 3: Selection and Timing of Dose for Each Patient

Study Drug	Dose	Frequency of Administration	Route of Administration	Duration of Treatment
Tislelizumab	200 mg	Day 1, given every 21 days	IV	See Section 3.3.2
Paclitaxel	135-175 mg/m²	Day 1, given every 21 days	IV	See Section 3.3.2
Paclitaxel	80-100 mg/m²	Weekly in accordance with local/country treatment guidelines	IV	
Paclitaxel (Japan)	100 mg/m²	Day 1, 8, 15, 22, 29, and 36, followed by one week of rest	IV	
Docetaxel	75 mg/m²	Day 1, given every 21 days	IV	
Docetaxel (Japan)	70 mg/m²	Day 1, given every 21 days	IV	
Irinotecan	125 mg/m²	Days 1 and 8, given every 21 days	IV	

5.2.1. Tislelizumab

Tislelizumab 200 mg will be administered on Day 1, given every 21 days.

Tislelizumab will be administered by IV infusion, using a volumetric pump 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 afterwards in an area with resuscitation equipment and emergency agents. From Cycle 3 onward, at least 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.

Guidelines for dose modification, treatment interruption, or discontinuation and for the management of irAEs and infusion-related reactions are provided in detail in Section 8.6 and Section 8.8, respectively.

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

5.2.2. Paclitaxel

After all procedures/assessments have been completed as detailed in Appendix 1 and Section 3.3.1, paclitaxel will be administered on Day 1, given every 21 days at a dose of 135 to 175 mg/m^2 by IV infusion over 3 hours or 1 hour, or in doses ranging between 80 to 100 mg/m^2 IV on a weekly basis consistent with local or country-specific treatment guidelines, or according to manufacturer standards or institutional standards. The labeled dose and schedule for paclitaxel in Japan is 100 mg/m^2 IV infusion over 1 hour on Days 1, 8, 15, 22, 29, and 36, followed by one week of rest. The initial treatment of paclitaxel should be administered within 3 business days of randomization. The first dose of paclitaxel is dependent upon the patient's baseline body surface area. Subsequent doses of paclitaxel must be recalculated if the change of body surface area (increase or decrease) from baseline ≥ 10%. Subsequent doses should not be recalculated if the change (increase or decrease) of body surface area from baseline < 10%.

Premedication is recommended prior to infusion of paclitaxel according to the manufacturer's instructions and local standards. The premedication regimen should be determined by the investigator and administered as close to randomization as possible. Premedication may consist of an oral steroid (such as dexamethasone 8-20 mg or equivalent administered 6-12 hours orally or 30-60 minutes intravenously before paclitaxel), an antihistamine (H1 antagonist) such as diphenhydramine hydrochloride 50 mg IV or equivalent or H2 antagonist, such as cimetidine 300 mg IV or equivalent), and an antiemetic (such as ondansetron 8 mg/kg IV or equivalent administered 30 to 120 minutes before paclitaxel). Premedication may be provided per local guidance and all medications will be documented on the case report form (CRF).

There is a 3-day window for all treatments in subsequent cycles if the cycle length is 21 days. If paclitaxel is given on a weekly schedule, there will be a 2-day treatment window. If dosing is delayed due to administrative or other reasons (holidays, intercurrent illnesses, etc.), the subsequent dosing visit should be scheduled as clinically appropriate.

Patients will be monitored continuously for adverse events and will be instructed to notify their physician for new adverse events, such as worsening of pre-existing conditions, or adverse events that cause any change in performance status or activities of daily living. Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of paclitaxel therapy. Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 8.6.

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

5.2.3. Docetaxel

Docetaxel will be administered on Day 1, given every 21 days after all procedures/assessments have been completed as detailed in Appendix 1 and Section 3.3.1. The initial treatment of docetaxel should be administered within 3 business days of randomization. Docetaxel should be administered at a dose of 75 mg/m^2 by IV infusion over 60 minutes according to manufacturer standards. Doses lower than 75 mg/m^2 are allowed if considered appropriate for any given patient. The labeled dose and schedule for docetaxel in Japan is 70 mg/m^2 IV on Day 1, given every 21 days. The first dose of docetaxel is dependent upon the patient's baseline body surface area. Subsequent doses of docetaxel must be recalculated if the change of body surface area (increase or decrease) is ≥ 10% from baseline. Subsequent doses should not be recalculated if the change (increase or decrease) of body surface area is < 10% from baseline.

Premedication might be recommended prior to infusion of docetaxel according to the manufacturer's instructions and local standards. To alleviate the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions, premedication of oral corticosteroids, such as dexamethasone 16 mg per day (eg, 8 mg twice daily) for 3 days should be given prior to infusion of docetaxel. The premedication regimen should be determined by the investigator and administered as close to randomization as possible. All medications will be documented on the appropriate CRF.

There is a 3-day window for all treatment in subsequent cycles if the cycle length is 21 days. If dosing is delayed due to administrative or other reasons (holidays, intercurrent illnesses, etc.), the subsequent dosing visit should be scheduled as clinically appropriate.

Patients will be monitored continuously for adverse events and will be instructed to notify their physician for new adverse events, such as worsening of pre-existing conditions, or adverse events that cause any change in performance status or activities of daily living. Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of docetaxel therapy. Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 8.6.

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

5.2.4. Irinotecan

Irinotecan will be administered on Days 1 and 8, given every 21 days after all procedures/assessments have been completed as detailed in Appendix 1 and Section 3.3.1. The initial treatment of irinotecan should be administered within 3 business days of randomization.

Irinotecan should be administered at a dose of 125 mg/m^2 by IV infusion over 90 minutes or according to manufacturer standards. The first dose of irinotecan is dependent upon the patient's baseline body surface area. Subsequent doses of irinotecan must be recalculated if the change of body surface area (increase or decrease) is ≥ 10% from baseline. Subsequent doses should not be recalculated if the change (increase or decrease) of body surface area is < 10% from baseline. Alternate doses/schedules of irinotecan according to local or country-specific standards of care may be used as long as the 21-day cycle length (or multiples of that) are maintained.

Premedication is recommended prior to infusion of irinotecan according to the manufacturer's introductions and local standards. The premedication regimen should be determined by the investigator and administered as close to randomization as possible. To reduce the incidence and severity of fluid loss, premedication may include atropine and antiemetic agents, such as dexamethasone 10 mg along with another antiemetic agent (eg, ondansetron) on the day of irinotecan administered. All medications will be documented on the appropriate CRF.

There is a 3-day window for all treatment in subsequent cycles if the cycle length is 21 days. If dosing is delayed due to administrative or other reasons (holidays, intercurrent illnesses, etc.), the subsequent dosing visit should be scheduled as clinically appropriate.

Patients will be monitored continuously for adverse events and will be instructed to notify their physician for new adverse events, such as worsening of pre-existing conditions, or adverse events that cause any change in performance status or activities of daily living. Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of irinotecan therapy. Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 8.6.

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

5.3. Handling of Overdose

Any overdose (defined as ≥ 600 mg of tislelizumab in a 24-hour period) or incorrect administration of any study drug should be noted on the study drug administration 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 8.8. Supportive care measures should be administered as appropriate.

5.4. Investigational Medicinal Product Accountability

The investigational medicinal product (IMP) required for completion of this study (tislelizumab, paclitaxel, docetaxel and irinotecan) will be provided by the sponsor, as required by local or country-specific guidance. The investigational site will acknowledge receipt of IMP. Any damaged shipments will be replaced.

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

Compliance will be assessed by the investigator and/or study personnel at each patient visit and by information provided by the patient.

The investigator and/or study personnel will keep accurate records of drug dispensed and used by each patient. This information must be captured in the source document at each patient visit. The investigator is responsible for tislelizumab, paclitaxel, docetaxel and irinotecan, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the investigator or designated study center personnel must maintain tislelizumab, paclitaxel, docetaxel and irinotecan accountability records throughout the course of the study. This person will document the amount of tislelizumab, paclitaxel, docetaxel and irinotecan received from the sponsor, the amount supplied, and/or administered (and returned by patients, if applicable).

5.5. Disposal and Destruction

After completion of the study, all unused tislelizumab, paclitaxel, docetaxel and irinotecan will be inventoried and packaged for return shipment by the hospital unit pharmacist or other designated study center personnel. The inventoried supplies may also be destroyed on site or at the depot according to institutional policies, after receiving written sponsor approval.

6. PRIOR, CONCOMITANT AND SUPPORTIVE THERAPY

6.1. Prior Therapy

All prior cancer treatments and treatments for underlying active medical conditions must be recorded on the appropriate case report form.

6.2. Concomitant Therapy

6.2.1. Permitted Therapy

Most concomitant medications and therapies deemed necessary 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 prescription, over-the-counter, herbal supplements, and IV medications and fluids. If changes (stop or start) in concomitant medication occur during the study, documentation of drug 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 irAEs must be tapered over at least 1 month and be at non-immunosuppressive doses (≤ 10 mg/day of prednisone or equivalent) before the next tislelizumab administration. The short-term use of steroids as prophylactic treatments (eg, patients with contrast allergies to diagnostic imaging contrast dyes) is permitted.

Patients with active hepatitis B defined as either detectable HBsAg or HBV DNA at baseline must initiate treatment 2 weeks prior to randomization or first dose and continue until 6 months after the last dose. Patients should continue effective antiviral treatment during the study to decrease potential viral re-activation 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; AASLD/IDSA HCV Guidance Panel, 2015). The investigator might use other antiviral agents, if appropriate, following local guidelines. Management of antiviral therapy is at the discretion of the investigator; however, reason(s) must be provided in the CRF if a patient with active hepatitis B is not treated with antiviral prophylaxis.

BeiGene does not require patients with active hepatitis C to receive treatment with antiviral therapy. Patients with detectable HCV RNA and who are receiving treatment at screening should remain on continuous, effective antiviral therapy during the study. Investigators 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 HCV is not permitted on study. Patients who are given antiviral therapy must initiate treatment at least 2 weeks prior to randomization or first dose.

Patients may continue to receive hormone replacement or supportive care if initiated prior to enrollment. Bisphosphonates and RANK-L inhibitors are allowed for bone metastases if initiated prior to enrollment and at a stable dose. Bisphosphonates are permitted during the study for a non-malignant indication.

For those patients randomized to the ICC arm of the study, premedication with steroids is acceptable.

Palliative (limited-field) radiation therapy is permitted, but only for pain control or prophylaxis of bone fracture to sites of bone disease present at baseline. If repeat imaging demonstrates new sites of bone metastases and the criteria for disease progression has been met, according to the investigator, then the patient should discontinue study treatment, and receive appropriate treatment

- If the lesion being considered for palliative radiation is a target or non-target lesion per RECIST v1.1, it will become non-evaluable for response assessments
- The case should be discussed with the medical monitor to ensure that the patient is still eligible to continue on study treatment

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

6.2.2. Prohibited Concomitant Medications/Procedures

6.2.2.1. Therapies Excluded during Tislelizumab Treatment

The following medications are prohibited or restricted at the time of screening and during the administration of tislelizumab:

- 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 or for short-term use as prophylactic treatment
- Live vaccines within 28 days prior to the first dose of tislelizumab and 60 days following the last dose of tislelizumab
- Herbal remedies with immune-stimulating properties (eg, mistletoe extract) or that are known to potentially interfere with liver or other major organ functions (eg, hypericin). Patients must notify the investigator of all herbal remedies used during the study.

6.2.2.2. Therapies Excluded during Paclitaxel/Docetaxel/Irinotecan Treatment

Caution should be exercised for patients receiving paclitaxel concomitantly with substrates, inhibitors or inducers of CYP2C8 or CYP3A4. The metabolism of paclitaxel is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Caution should be exercised when paclitaxel is concomitantly administered with known substrates (eg, midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam), inhibitors (eg,

atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin), and inducers (eg, rifampin and carbamazepine) of CYP3A4. Caution should also be exercised when paclitaxel is concomitantly administered with known substrates (eg, repaglinide and rosiglitazone), inhibitors (eg, gemfibrozil), and inducers (eg, rifampin) of CYP2C8. Potential interactions between paclitaxel, a substrate of CYP3A4, and protease inhibitors (ritonavir, saquinavir, indinavir, and nelfinavir), which are substrates and/or inhibitors of CYP3A4, have not been evaluated in clinical studies.

Patients receiving docetaxel should avoid concomitant use of strong inhibitors of CYP3A4 (eg, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole).; however, if strong inhibitors of CYP3A4 cannot be avoided, the docetaxel dose should be reduced per the product label.

Do not administer strong CYP3A4 inducers (phenytoin, phenobarbital, carbamazepine, or St. John's wort) with irinotecan unless there are no therapeutic alternatives. Do not administer strong CYP3A4 inhibitors (clarithromycin, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, voriconazole) and UGT1A1 inhibitor (eg, atazanavir, gemfibrozil, indinavir) or both CYP3A4 and UGT1A1 inhibitors (such as ketoconazole) when patients treated by irinotecan unless there are no therapeutic alternatives.

6.2.2.3. Therapies Excluded during All Study Treatment

The following medications are to be prohibited or restricted at the time of screening and during the administration of study treatment:

- Any concurrent antineoplastic therapy (eg, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents [including Chinese herbal medicine and Chinese patent medicines] for the treatment of cancer)
- Extensive radiation therapy (except for local, palliative radiotherapy; refer to Section 6.2.1)

The following guidelines should be also followed during the study:

- Surgical procedures required during study participation will be reported as treatments for adverse events. If a surgical procedure is considered elective (eg, Cosmetic surgery), the procedure should be reported on the appropriate eCRF
- Patients should not abuse alcohol or other drugs during the study

6.3. Rescue Medication and Supportive Care

6.3.1. Supportive Care guidelines for Tislelizumab

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined in Section 8.8.2, Section 8.8.3, and Appendix 10. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder,

attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to tislelizumab.

6.3.2. Supportive Care guidelines for Paclitaxel, Docetaxel and Irinotecan

Palliative and supportive care for other disease-related symptoms and for toxicity associated with treatment will be offered to the subjects in ICC arm of this study. Supportive care measures may include but are not limited to antidiarrheal agents, antiemetic agents, opiate and non-opiate analgesic agents, appetite stimulants, and granulocyte and erythroid growth factors. Non-drug supportive care procedures may be performed as medically necessary and appropriate in the opinion of the investigator. Details of interventions, procedures, or blood products (eg, blood cells, platelets, or fresh frozen plasma transfusions) should be recorded on the eCRF. Appropriate management of hypersensitivity reactions is described in Section 8.8.5. The use of other specific supportive care agents is presented as below.

Diarrhea: In the event of Grade 3 or 4 diarrhea, supportive measures may include hydration, loperamide, octreotide, or other antidiarrheals. If diarrhea is severe (ie, requires intravenous hydration) and associated with fever or severe (Grade 3 or 4) neutropenia, broad – spectrum antibiotics may be prescribed as clinically necessary. Subjects with severe diarrhea or any diarrhea associated with severe nausea or vomiting should be hospitalized for intravenous hydration and correction of electrolyte imbalance. In cases of irinotecan induced diarrhea, antibiotic therapy should be initiated if the subject develops ileus, fever or sever neutropenia.

Nausea/Vomiting: The use of antiemetic agents is permitted at the discretion of the investigator (Hesketh PJ, 2016).

Additional Supportive Care Guidelines:

Analgesic Agents: The use of analgesic agents is permitted at the discretion of the investigator. The chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) with a high risk of bleeding (eg, indomethacin, ibuprofen, naproxen, or similar agents) is strongly discouraged unless at the discretion and responsibility of the investigator after careful assessment of the individual bleeding risk of the subject. Chronic use of analgesic agents with no or low bleeding risk (eg, paracetamol/acetaminophen, metamizole, dipyrone, propyphenazone) is acceptable.

Granulocyte-Colony Stimulating Factors (G-CSF): The use of G-CSF is permitted during the study at the discretion of the investigator according to the standard of care practice guidelines. G-CSF or similar agents are recommended following Grade 3 or 4 neutropenia of duration > 5 days or following any incidence of febrile neutropenia (ANC $< 0.5 \times 10^9$/L or $< 1.0 \times 10^9$/L with predicted decline to $< 0.5 \times 10^9$/L over the next 48 hours with a single temperature ≥ 38.5°C or a sustained temperature ≥ 38.0°C over 1 hour) (Smith TJ, 2015).

Erythroid Growth Factors: The use of erythroid-stimulating factors (eg, erythropoietin) is permitted at the discretion of the investigator based on American Society of Clinical Oncology (ASCO) and Food and Drug Administration (FDA) guidelines, or according to local guidelines (Rizzo JD, 2010; Bokemeyer et al, 2007).

Please refer to the product label or local standards of care for additional paclitaxel, docetaxel, or irinotecan supportive measures.

7. STUDY ASSESSMENTS AND PROCEDURES

The timing of all study procedures is provided in the Schedule of Assessments (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 and eCRF for each patient.

Dosing will occur only if the clinical assessment and laboratory test values (which must be available before any dosing) have been reviewed and found to be acceptable per protocol guidelines. 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 dosing continued on the scheduled 21-day intervals accordingly.

Results of standard-of-care tests or examinations performed prior to obtaining informed consent and ≤ 7 days prior to randomization may be used for the purposes of screening rather than repeating the standard-of-care tests.

7.1. Informed Consent Form and Screening Log Completion

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.

7.2. Medical History and Demographic Data Collection

Medical history should include any history of clinically significant disease, surgery, reproductive status (ie, of childbearing potential or no childbearing potential [Appendix 5]); history of alcohol consumption (ie, presence or absence); history of smoking; weight loss history, and all medications (eg, prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 30 days before the first dose.

Demographic data will include age, gender, and self-reported race/ethnicity.

Cancer history will include stage at initial diagnosis using current American Joint Committee on Cancer criteria, tumor location, location of metastatic disease at study baseline, dates of prior surgery, prior radiotherapy, prior drug therapy, including start and stop dates, best response and the date(s) of disease progression. The presence or absence of symptoms of esophageal carcinoma as well as the severity grade will be collected at baseline.

New or worsening conditions are to be recorded as adverse events on the Adverse Event eCRF. Refer to Section 8.2 regarding AE definitions and reporting and follow-up requirements.

7.3. Eastern Cooperative Oncology Group Performance Status Grading

Eastern Cooperative Oncology Group Performance Status (Appendix 3) will be assessed at the Screening Visit (within 7 days prior to randomization), pretreatment on Day 1 of each treatment cycle, EOT Visit and Safety Follow-up Visit.

7.4. Antitumor Activity and Response Assessment

Tumor imaging will be performed within 28 days prior to randomization. Results of standard-of-care tests or examinations (Appendix 1) 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, patients will undergo tumor assessments approximately every 6 weeks (± 7 days) for 6 months, then every 9 weeks (± 7 days). All radiographic assessments performed to assess tumor status at baseline and during study treatment to assess response should be performed at the same investigative site.

Screening assessments and each subsequent assessment must include computed tomography (CT) scans (with oral/IV contrast, unless contraindicated) or magnetic resonance imaging (MRI) of at least the neck, chest and abdomen. 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) 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.

Subjects with previously treated brain metastases may participate provided they have stable brain metastases, ie, without evidence of progression by imaging (confirmed by MRI if MRI was used at prior imaging, or confirmed by CT imaging if CT used at prior imaging) for at least four weeks prior to randomization. Any neurologic symptoms must have returned to baseline and subjects must have no evidence of new or enlarging brain metastases, and have not used steroids for brain metastases for at least 28 days prior to randomization. This exception does not include carcinomatous meningitis, as subjects with carcinomatous meningitis are excluded regardless of clinical stability. CT/MRI of the head at baseline is required for patients who are suspected to have central nervous system (CNS) metastases.

Bone scans (Technetium-99m [TC-99m]) or sodium fluoride-PET (NaF-PET) should be performed at screening if clinically indicated. If bone metastases are present at screening and cannot be seen on subsequent CT or MRI scans, or if clinically indicated, TC-99m or NaF PET bone scans should be repeated when either progression in bone or a CR in the target lesion is suspected.

CT scans of the extremities and all other known sites should also be performed if clinically indicated and followed throughout the study, if there is evidence of metastatic disease in these regions at screening.

For subsequent tumor assessments, 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.

Response will be assessed by the investigator using RECIST v1.1 (Appendix 2). The same evaluator should perform assessments, if possible, to ensure internal consistency across visits.

At the investigator's discretion, additional radiographic scans or more frequent assessments should be performed if clinically indicated.

Patients who discontinue study treatment early for reasons other than disease progression or death will continue to undergo tumor assessments as scheduled until the patient begins a new anticancer treatment, experiences disease progression, withdraws consent, dies, lost to follow-up, or the study completes, whichever occurs first. If previous tumor imaging was obtained within 6 weeks prior to the date of discontinuation, then additional tumor imaging at treatment discontinuation is not required.

After signing a separate informed consent, patients who continue tislelizumab treatment beyond the initial diagnosis of radiographic disease progression (Section 7.17.1) will be monitored with a follow-up scan at least 4 weeks later or at the next scheduled tumor assessment (not to exceed 6 weeks) from the prior radiographic scan date.

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

7.5. Adverse Event Collection

All adverse events, including SAEs, will be collected as described in Section 8.2.

7.6. Physical Examinations

A complete physical examination, including an evaluation of the head, eyes, ears, nose, throat, cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems is required to be performed at screening. Any abnormality identified at baseline will be recorded on the Medical History eCRF with appropriate disease/condition terms. Height (baseline only) will be measured and recorded in the eCRF.

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

7.7. Ophthalmologic Examinations

Eye examination, visual acuity test, and optical coherence tomography (or equivalent diagnostic test) will be assessed at the Screening Visit in all patients. Eye examination, visual acuity test, and optical coherence tomography (or equivalent diagnostic test for retinal examination) captured as standard of care prior to obtaining written informed consent and within 28 days of randomization may be used for the screening evaluation. Patients on the tislelizumab arm will undergo repeated assessments approximately every 15 weeks (± 7 days) during study treatment and a final assessment < 30 days (± 7 days) after the last dose of study treatment.

In addition, investigators should solicit patients regarding changes in vision, visual disturbance, or ocular inflammation at each scheduled study visit during tislelizumab treatment. For any change in vision, referral to an appropriate specialist will be made for further management guidance (see Appendix 10).

7.8. Vital Signs Assessment

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

For all infusions of tislelizumab, vital signs will be assessed before the infusion, and between 30 to 45 minutes after the infusion. Vital signs must be collected during the infusion if clinically indicated. Weight should be collected once at each of these visits. Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms. Refer to Section 8.8.3 regarding management of infusion-related reactions.

7.9. Electrocardiograms

A 12-lead ECG is required at screening, End of Treatment, and as clinically indicated. All ECG recordings should be performed after the patient has been resting in a sitting or supine position for at least 10 minutes, and a repeat ECG should be performed to confirm findings, if any.

7.10. Clinical Laboratory Tests and Pharmacokinetic Blood Sampling

Clinical laboratory assessments will include the following, of which certain elements will be collected:

- Hematology (complete blood count [CBC], including red blood cell [RBC] count, hemoglobin, hematocrit, white blood cell [WBC] count with automated differential [neutrophils, eosinophils, lymphocytes, monocytes, and basophils], and platelet count). A manual differential can be done if clinically indicated
- Serum chemistry (glucose, blood urea nitrogen [BUN] or serum urea, creatinine, sodium, potassium, chloride, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase [LDH] [optional], total protein, albumin). All patients will have creatine kinase (CK) and creatine kinase-cardiac muscle isoenzyme (CK-MB) testing at screening and at all scheduled visits during the first 3 treatment cycles, all pre-dose assessments from Cycle 4 onwards, and at the EOT and Safety Follow-up Visits.

  NOTE: In the event that CK-MB fractionation cannot be evaluated in the local laboratory, troponin I and/or troponin T should be assessed instead; the same test should be administered throughout the study.
- Prothrombin time and international normalized ratio (PT/INR)
- Serum 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, EOT Visit and at Safety Follow-up. Urine pregnancy test 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
- Urinalysis (complete [including, but not limited to glucose, protein, ketones, and blood] and/or microscopic, if clinically indicated)

- Thyroid function testing (thyroid-stimulating hormone [TSH], free T3, free T4)
- Thyroid function testing performed during the study and at the Safety Follow-up Visit will only be for patients on the tislelizumab arm
- HBV and HCV serology (HBsAg, HBcAb and HCV antibody)

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 liver function tests) as specified above should be performed weekly for the first 2 cycles and at the beginning of each subsequent cycle; results are to be reviewed within 3 business days before study drug administration. Weekly peripheral blood cell counts should be performed on all patients receiving paclitaxel, docetaxel, and irinotecan.

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.

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

7.11. Anti-drug Antibody Evaluation Procedures

Tislelizumab may elicit an immune response. Patients with signs of any potential immune response to tislelizumab will be closely monitored with repeat sampling for anti-drug antibody (ADA detection as well as clinical evaluations.

Validated screening and confirmatory assays will be employed to detect ADAs at multiple timepoints throughout the study (Appendix 1). The immunogenicity evaluation will utilize a risk-based immunogenicity strategy (Bai S, 2012; Worobec A, 2004) to characterize ADA responses to tislelizumab in support of the clinical development program.

7.12. Tumor Tissue and Biomarker Assessment Procedures

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

Archival tumor tissues (representative tumor specimens in paraffin blocks (preferred) or approximately 10 unstained tumor specimen slides) are required to be sent to central laboratory for biomarker analysis such as immunohistochemistry (IHC) analysis of PD-L1 status if available. In addition to PD-L1 expression, other exploratory predictive biomarkers, such as gene expression profiling, tumor mutation burden, MSI, and tumor-infiltrated immune cells, that are related to response or clinical benefit of tislelizumab may also be evaluated.

In the absence of available archival tumor tissue samples, collection of fresh tumor biopsy at baseline is recommended if accessible. 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.

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

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

Optional blood samples (approximately 10 mL each timepoint) will be taken at the time of first tumor response (tumor assessment is CR or PR), and/or disease progression for all randomized patients, to explore the association of blood-based biomarkers (such as ctDNA, cytokine, immune cell profiling, etc) with response, resistance, and prognosis to tislelizumab or chemotherapy. Written patient consent is required for blood sample collections.

Refer to the Schedule of Assessment (Appendix 1) for detailed schedule.

7.13. Health-Related Quality of Life Assessment

Patients will be asked to complete the EORTC-QLQ-C30 (Appendix 7), EORTC-QLQ-OES18 (Appendix 8) and EQ-5D-5L questionnaires (Appendix 9) prior to study treatment initiation, Cycle 1 through Cycle 6 Day 1 (± 7 days) or at treatment discontinuation (whichever occurs first), and at the Safety Follow-up visit according to the schedule in Appendix 1. The questionnaires will be provided in the patient's preferred language and given to the patient prior to being seen by a health care professional.

7.14. Timing of Assessments during the Treatment Phase

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

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 dosing rescheduled to meet the requirement of interval for dosing visit.

7.15. Safety Follow-up

In both treatment arms, patients who discontinue treatment for any reason will be asked to return to the clinic for a Safety Follow-up Visit within 30 days (± 7 days) after the last study treatment or before the initiation of a new anticancer treatment, whichever comes first. In addition, telephone contacts with patients should be conducted to assess irAEs and concomitant medications (if appropriate, ie, associated with an irAE or is a new anticancer therapy) at 60 (±14 days), and 90 days (±14 days) after the last dose of tislelizumab, regardless of initiation of a new anticancer treatment. Beyond 90 days, investigators should continue to report any SAEs that are believed to be related to study drug(s) if they become aware of them. If patients report a suspected immune-related AE 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 8.4.

The EOT Visit may be combined with the Safety Follow-up visit, provided that the EOT occurred 30 days (± 7 days) after the last study treatment; the assessments for both visits should be performed. Patients who discontinue study treatment prior to disease progression will have their tumors assessed as outlined in Section 7.4.

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

7.16. Survival Follow-up

Following discontinuation of the study treatment, all patients will be followed for survival status and study drug-related SAEs, beginning approximately 1 month (4 weeks ± 7 days) after the Safety Follow-up Visit and approximately monthly thereafter or as directed by the sponsor. Information on Survival Follow-up and the subsequent anticancer treatment will be collected via telephone calls, email, or other communications; patient medical records; and/or clinic visits approximately every month until death, loss to follow-up, withdrawal of consent, or study termination by the sponsor.

7.17. Patient, Treatment, Study, and Site Discontinuation

Patients who discontinue study treatment early, but who have not withdrawn consent for follow-up, should be followed for assessments of antitumor activity (unless a new anti-cancer treatment is initiated - see Section 7.4), safety (Section 7.15), and survival (Section 7.16), if possible.

7.17.1. Discontinuation of Patients

Patients have the right to voluntarily withdraw from the study or 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. Reasons that a patient may be discontinued from the study treatment may include, but are not limited to the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or sponsor determines may jeopardize the patient's safety, if he or she were to continue in the study

- Investigator or sponsor determines it is in the best interest of the patient
- Patient noncompliance

Every effort should be made to obtain information on patients who discontinue from study treatment. The primary reason for discontinuation should be documented on the appropriate eCRF.

Patients should discontinue study treatment if they experience any of the following:

- Symptomatic deterioration (eg, uncontrollable pain secondary to disease or unmanageable ascites, etc.) attributed to disease progression
- Patients must discontinue study treatment if they experience any of the following:
- Intolerable toxicity related to tislelizumab, paclitaxel, docetaxel or irinotecan, including development of an immune-mediated or paclitaxel/docetaxel/ irinotecan-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient's safety if he or she continues on study treatment
- Use of another non-protocol anticancer therapy (Section 6.2.2)
- Pregnancy

Patients will be permitted to continue tislelizumab if pseudo-progression is suspected and/or there is a reasonable belief that the patient could derive benefit from tislelizumab after RECIST v1.1 criteria for progressive disease are met, and all of the following criteria are met:

- Absence of clinical symptoms and signs of disease progression (including clinically significant worsening laboratory values)
- ECOG PS ≤ 1
- Absence of rapid progression of disease or progression at a critical anatomical site (eg, progression of a spinal lesion with impending cord compression) or that necessitates urgent alternative medical intervention

If, in the judgement of the investigator, the patient is anticipated to benefit from continued treatment, the patient must re-sign an informed consent, agreeing to continue treatment beyond radiographical disease progression. If patients agree to continue treatment beyond radiographical progression, a follow-up radiographic evaluation will be performed no later than 6 weeks after the initial scan that diagnosed progressive disease, as outlined in Section 7.4.

If, in the judgement of the investigator, rapid early progression is evident ("hyperprogression"), tislelizumab should be discontinued.

The primary reason for study drug discontinuation will be documented in the medical chart and on the appropriate eCRF. Patients who discontinue study drug prior to disease progression will not be replaced.

7.17.2. Study Termination and Study Site Closure

The primary analyses will be conducted when the predefined 400 death events have been observed (Section 9.6.1). The study will continue until the last patient has died, becomes lost to follow-up, or withdraws consent from the study, or until the sponsor decides to terminate the study (see Section 3.3.6 for End of Study).

At the end of study, any patient assigned to tislelizumab who, in the opinion of the investigator, may continue to benefit from tislelizumab at study termination, will be offered the option to continue treatment in a company-sponsored clinical trial until tislelizumab is commercially available in the country of the patient's residence.

8. SAFETY MONITORING AND REPORTING

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

8.1. Risks Associated With Study Drugs

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

8.1.1. Risks Associated With Tislelizumab

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

The PD-L1/PD-1 pathway is involved in peripheral immune tolerance; therefore, such therapy may increase the risk of irAEs, specifically the induction or enhancement of autoimmune conditions. Immune-related AEs commonly associated with anti-PD-1 therapy are presented in Table 5.

Although most irAEs 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 irAEs are provided in Appendix 10.

8.1.2. Risks Associated with Chemotherapy (Paclitaxel/Docetaxel/Irinotecan)

Most common adverse reactions across all paclitaxel indications are neutropenia, leukopenia, alopecia, anemia, arthralgia/myalgia, peripheral neuropathy, nausea, vomiting, diarrhea, mucositis, infections, alkaline phosphatase elevations, aspartate transaminase (AST) elevations, hypotension, infusion site reaction, or bleeding. Most frequent Grade 3 and 4 adverse events are neutropenia, anemia, leukopenia, infection, nausea, vomiting, hypersensitivity reactions. 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 studies. Fatal reactions have occurred in patients despite premedication. Patients who experience severe hypersensitivity reactions to paclitaxel should not be rechallenged with the drug.

Most common adverse reactions across all docetaxel indications are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions and myalgia. Most frequent grade 3 or 4 adverse events are neutropenia, anemia, leukopenia, infection, thrombocytopenia. Treatment-related mortality will increase if patients have abnormal liver function. Severe hypersensitivity, including very rare fatal anaphylaxis, has also been reported in patients despite receiving dexamethasone premedication.

Common adverse reactions of irinotecan observed in single-agent therapy clinical studies are: nausea, vomiting, abdominal pain, diarrhea, constipation, anorexia, neutropenia, leukopenia

(including lymphocytopenia), anemia, asthenia, fever, body weight decreasing, and alopecia. Most frequent Grade 3 or 4 adverse events are diarrhea, nausea, vomiting, leukopenia, neutropenia, abdominal pain and asthenia. Early and late forms of diarrhea can occur. Early diarrhea may be accompanied by cholinergic symptoms which may be prevented or ameliorated by atropine. Late diarrhea can be life threatening and should be treated promptly with loperamide. Monitor patients with diarrhea and give fluid and electrolytes as needed. If patients develop ileus, fever, or severe neutropenia, they should receive antibiotic therapy, per institution-specific guidelines. If severe diarrhea and myelosuppression occur, irinotecan should be interrupted and either discontinued or dose reduced for subsequent cycles to subsequent doses.

Patients should be tested locally for the UGT1A1*28 allele to determine if modifications to the starting dose are needed as outlined in the prescribing information or according to local guidelines.

Selected precautions:

- Neutropenia: Fever or other evidence of infection must be assessed promptly and treated aggressively following the local clinical practice and/or the guidelines.
  - Paclitaxel, Docetaxel and irinotecan therapy should not be given to patients with solid tumor who have baseline neutrophil counts of less than 1,500 cells/mm^3. To monitor the occurrence of bone marrow suppression, primary neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving paclitaxel, docetaxel, and irinotecan.
- Anaphylaxis reactions: Anaphylaxis reactions and severe hypersensitivity reactions have occurred in 2% to 4% of subjects treated with paclitaxel. Fatal reactions have occurred in subjects despite premedication. All subjects should be pretreated with corticosteroids, diphenhydramine, and H2 antagonists. Subjects who experience severe hypersensitivity reactions should not be rechallenged.
- Diarrhea: Early diarrhea (occurring during or shortly after infusion of irinotecan) is usually transient and infrequently severe. Late diarrhea (generally occurring more than 24 hours after administration of irinotecan) can be life threatening since it may be prolonged and may lead to dehydration, electrolyte imbalance, or sepsis. Monitor patients with diarrhea and give fluid and electrolytes as needed. Early diarrhea may be accompanied by cholinergic symptoms which may be prevented or ameliorated by atropine. Late diarrhea can be life threatening and should be treated promptly with loperamide. Avoid diuretics or laxatives in patients with diarrhea.

For toxicities not listed above, dose modifications are permitted per local standards.

8.1.3. General Plan to Manage Safety Concerns

8.1.3.1. Eligibility Criteria

Eligibility criteria were selected to guard the safety of patients enrolled to in this study. Results from the nonclinical toxicology studies and clinical data with tislelizumab, as well as the nonclinical/clinical data from other PD-L1/PD-1 inhibitors, were taken into account.

Specifically, patients at risk for study-emergent active autoimmune diseases or history of autoimmune diseases that may relapse, patients who have undergone allogenic stem cell or organ transplantation and patients who have received a live viral vaccine within 28 days before randomization, are excluded from the study. Patients must be eligible for at least one of the chemotherapy drugs in ICC treatment arm.

8.1.3.2. Safety Monitoring Plan

Safety will be evaluated in this study through reporting and monitoring of all AEs, defined and graded according to NCI-CTCAE v4.03. Patients will be assessed for safety (including laboratory values) according to the schedule in Appendix 1. Clinical laboratory results must be reviewed by the investigator or appropriate delegate prior to the start of each cycle. Patients receiving irinotecan will be monitored for diarrhea and given fluids and electrolytes at the investigator's discretion.

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. General safety assessments will include review of medical history, physical examinations, ophthalmologic examinations, and specific laboratory studies, including but not limited to serum chemistry and blood counts (see Appendix 1 for the Schedule of Assessments). In addition, patients will be closely monitored for the development of any signs or symptoms of autoimmune conditions and infection.

Serum samples will be drawn for determination of ADAs to tislelizumab in patients randomized to the tislelizumab arm, if treatment assignment is known. Administration of tislelizumab will be performed in a setting where emergency medical equipment and staff who are trained to respond to medical emergencies are available (see Section 5.1.4).

All AEs will be recorded during the study (AE from the time of the first dose and SAEs from the time of signing of informed consent) and for up to 30 days after the last dose of study drug(s) (including paclitaxel, docetaxel and irinotecan) or until the initiation of another anticancer therapy, whichever occurs first. At the end of treatment, ongoing AEs considered related to study treatment will be followed until the event has resolved to baseline or ≤ Grade 1, the event is assessed by the investigator as stable, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the AE.

Immune-related AEs will be recorded up to 90 days after the last dose of tislelizumab, regardless of whether the patient starts a new anticancer therapy. All drug-related SAEs will be recorded by the investigator after treatment discontinuation until patient death, withdrawal of consent, or loss to follow-up, whichever occurs first.

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

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

During the study, patients will be closely monitored for the development of any signs or symptoms of autoimmune conditions and infection. Patients will receive standard of care medications for any adverse event according to the judgement of the investigator.

Reporting requirements for SAEs are discussed in Section 8.4.2. In addition, the medical monitor or Safety Physician will review and evaluate observed AEs on a regular basis.

Patients who discontinue treatment for any reason will be asked to return to the clinic for a Safety Follow-up Visit within 30 days (± 7 days) after the last dose of study treatment or before the initiation of a new anticancer therapy, whichever occurs first.

8.2. Adverse Events

8.2.1. Definition and Reporting Guidelines

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

Examples of AEs include:

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

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

8.2.2. Assessing Severity

The investigator will assess the severity for each AE and SAE reported during the study. All AEs and SAEs are to be assessed and graded based upon NCI-CTCAE v4.03.

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 8.4.2.3.

8.2.3. 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

8.2.4. Assessing Causality

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

There may be situations when an SAE has occurred and the investigator has only limited information to include in the initial report to the sponsor. However, it is very important that the investigator always assesses 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 subsequently change his/her opinion of causality considering follow-up information and may amend the SAE report accordingly.

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

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

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

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

8.2.5. Laboratory Test Abnormalities

Abnormal laboratory findings (eg, clinical chemistry, CBC, coagulation, or urinalysis) or other abnormal assessments (eg, ECGs 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 judgement of the

investigator. In general, these are the laboratory test abnormalities assessments 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.

8.2.6. Follow up of 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 condition of the patient.

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. Once resolved, the appropriate AE or SAE will be updated. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, radiographic imaging, or consultation with other health care professionals.

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

New or updated information will be recorded on the originally completed SAE report, with all changes signed and dated by the investigator. The updated SAE report should be re-sent to the sponsor within the time frames outlined in Section 8.4.2.1.

8.3. 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.

8.4. Timing, Frequency, and Method of Capturing Adverse Events

8.4.1. Reporting All Adverse Events

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

After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until either 30 days after last dose of study treatment (including paclitaxel, docetaxel and irinotecan) or initiation of a new anticancer therapy, whichever occurs first. Immune-related AEs (serious or non-serious) should be reported for 90 days after the last dose of tislelizumab regardless of initiation of a subsequent anticancer therapy. After this period, the investigator should report any SAEs that are believed to be related to tislelizumab treatment.

8.4.2. Reporting Serious Adverse Events

8.4.2.1. 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 to the sponsor or designee as described in Table 4.

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

	Timeframe for Making Initial Report	Documentation Method	Timeframe for Making Follow-up Report	Documentation Method	Reporting Method
All SAEs	Within 24 hours of first knowledge of the 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.

8.4.2.2. 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 8.4.2.1. The SAE report will always be completed as thoroughly as possible with all available details of the SAE and forwarded to the sponsor or designee within the designated time frames.

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

The investigator must always provide an assessment of causality for each SAE as described in Section 8.2.4.

The sponsor will provide a list of project contacts for SAE receipt.

8.4.2.3. 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 8.4.2.1. 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. Prompt notification of SAEs by the investigator to the appropriate project contact for SAE receipt is essential so that legal obligations and ethical responsibilities towards the safety of other patients are met.

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 8.3), will be submitted to all applicable regulatory authorities and investigators for tislelizumab studies.

This protocol is being filed under an Investigational New Drug (IND) protocol amendment with the US FDA. All IND safety reports submitted to the FDA will also be sent to all investigators conducting studies under this IND.

When a study center receives an initial or follow-up report or other safety information (eg, revised IB) from the sponsor, the responsible person according to local requirements 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.

8.4.3. Eliciting Adverse Event Information

The investigator or designee will ask about AEs by asking the patient 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?"

8.4.4. Recording Disease Progression

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

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

8.4.5. Recording 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 "unexplained death".

8.4.6. Recording Pregnancies

If a female patient or the partner of a male patient becomes pregnant while receiving investigational therapy or within 120 days after the last dose of tislelizumab or within 180 days after the last dose of paclitaxel/docetaxel/irinotecan, 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 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 or SAE, 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.

8.4.7. Recording Post-Study Adverse Events

A post-study AE or SAE is defined as any AE that occurs outside of the AE/SAE reporting period that is defined in Section 8.4.1.

Investigators are not obligated to actively seek AEs or SAEs in former patients. However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the SAE related to the study drug, the investigator will notify the sponsor.

8.4.8. 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 documents:

- Tislelizumab Investigator's Brochure
- Local prescribing information for paclitaxel
- Local prescribing information for docetaxel
- Local prescribing information for irinotecan

8.5. Independent Data Monitoring Committee

Regular safety monitoring (at least every 6 months) and efficacy monitoring will be performed by an Independent Data Monitoring Committee (IDMC). The first IDMC safety review will occur after at least 50 patients have been randomized to study treatment (ie, approximately 25 patients per treatment arm) and have been on treatment for at least one treatment cycle. The IDMC may recommend modifications to the study procedures or conduct based on available data. The function and membership of the IDMC will be described in the IDMC Charter.

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

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

8.6. Dose Delays or Modifications

Every effort should be made to administer the study drug(s) according to the planned dose and schedule every 3 weeks from Cycle 1 Day 1. 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 chart and recorded in the eCRF.

8.6.1. Dose Delay or Modification for Tislelizumab

There will be no dose reduction of tislelizumab in this study. Dose delays or interruption of < 12 weeks will be permitted. The investigators should make every effort to maintain dose intensity in patients.

Patients may temporarily suspend study treatment if they experience toxicity that is considered related to tislelizumab and requires that a dose be withheld. If the administration delay is ≤ 10 days, the delayed dose will be administered. If the delay is > 10 days, the delayed dose will be omitted in this cycle. As long as the AE resolves within 14 days, the next cycle will be administered as planned If the delay of tislelizumab is > 12 weeks, it will be stopped permanently.

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

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other event, the visit should be scheduled on the nearest feasible date (refer to the visit window in Appendix 1), with subsequent dosing continued on the 21-day intervals accordingly.

Management guidelines for irAEs and infusion-related reactions in patients treated with tislelizumab are presented in Section 8.8.2, Section 8.8.3, and Appendix 10 respectively.

8.6.2. Dose Delay, Interruption or Modification for Paclitaxel, Docetaxel and Irinotecan

Study drug 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. A maximum of 2 dose reductions for each chemotherapeutic agent are permitted. If additional reductions are required, that chemotherapeutic agent must be discontinued. Once the dose has been decreased, it should remain reduced for all subsequent administrations or further reduced if necessary. There will be no dose escalations in this study. Chemotherapy treatment may be delayed up to 21 days, if the reason for the delay is toxicity/adverse event. All subsequent chemotherapy doses must be rescheduled according to the last chemotherapy dose administration date. If any chemotherapy agent is held for more than 6 weeks from the anticipated treatment date, or the dose level -2 is not tolerated, chemotherapy should be permanently discontinued.

Dose Modifications for Paclitaxel

Dose Levels for Paclitaxel given every 3 weeks		
Dose Level	Dose (mg/m^2)	
1	175	135
-1	135	90
-2	90	75

Dose Levels for Weekly Paclitaxel	
Dose Level	Dose (mg/m^2)
1	80 -100
-1	65 - 80 (~20% decrease from Dose Level 1)
-2	50 - 60 (~25% decrease from Dose Level -1)

Paclitaxel dose modification for decreased neutrophils

Absolute Neutrophil Count ($cells/mm^3$)	Paclitaxel Dose
≥ 1500 (Grade 1)	Dose Level 1
1000 - 1499 (Grade 2)	• Hold paclitaxel until recovery to Grade 1 and restart paclitaxel at Dose Level -1. • If no recovery within 3 weeks of planned next cycle, consider appropriateness for growth factor support or discontinue paclitaxel.
500 - 999 (Grade 3)	• Hold paclitaxel until recovery to Grade 1 and restart paclitaxel at Dose Level -2. • Initiate growth factor support • If no recovery within 3 weeks of planned next cycle despite growth factor support, discontinue paclitaxel.
< 500 (Grade 4)	• Initiate growth factor support • If ANC < 500 for > 7 days despite growth factor support, discontinue paclitaxel

If a patient experiences febrile neutropenia or ≥ Grade 2 infection at any time, granulocyte colony stimulating factor (G-CSF) should be added initially and in advance of any dose reduction for the next cycle of paclitaxel. In the event of a second episode of febrile neutropenia or ≥ Grade 2 infection, paclitaxel should be dose reduced to the next lower level. For a third episode of febrile neutropenia or ≥ Grade 2 infection, paclitaxel should be discontinued. Any dose reductions for neutropenic fever are permanent.

Paclitaxel dose modification for decreased platelet counts

Platelet Count (cells/mm^3)	Paclitaxel Dose
> 100,000	Dose Level 1
75,000 - 100,000 (Grade 1)	• Hold until recovery to a platelet count > 100,000 cells/mm^3 • Restart paclitaxel at Dose level 1
50,000 - 74,999 (Grade 2)	• Hold until recovery to a platelet count > 100,000 cells/mm^3 • Restart paclitaxel at Dose Level -1
< 50,000 (Grade 3)	• Hold until recovery to a platelet count > 100,000 cells/mm^3 • Restart paclitaxel at dose level -2
< 25,000 (Grade 4) with clinically significant bleeding	• Discontinue paclitaxel

For any grade toxicity, if the platelet count does not recover by the next planned treatment cycle, paclitaxel must be discontinued.

Paclitaxel dose modification for neuropathy

Neuropathy Grade	Recommended Paclitaxel Dose
Grade 1	Dose Level 1
Grade 2 lasting > 7 days or Grade 3 lasting < 7 days	• Hold until neuropathy recovery to Grade 1 • Restart paclitaxel at Dose Level -1
Grade 3 lasting > 7 days or Grade 4	• Discontinue paclitaxel

All dose reductions for neuropathy are permanent.

Paclitaxel dose modification for hepatic impairment

Degree of Hepatic impairment			Recommended Paclitaxel Dose
Transaminase levels		Bilirubin Levels	
< 2.5 x ULN	And	≤ 1.25 x ULN	• Continue dosing at Dose Level 1
> 2.5 - 5 x ULN	And	1.26 - 2.0 x ULN	• Hold until recovery to Grade 1 • Restart paclitaxel at Dose Level -1
> 5 - < 10 x ULN	And	2.01 - 5 x ULN	• Hold until recovery to Grade 1 • Restart paclitaxel at Dose Level -2
≥ 10 x ULN	OR	> 5.0 x ULN	• Discontinue Paclitaxel

If the liver function test abnormalities do not recover by the next planned cycle, paclitaxel must be discontinued. All dose reductions for liver function abnormalities are permanent.

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. If symptoms recur with reinstitution of the paclitaxel in fusion, the infusion must be stopped.

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

Paclitaxel dose modification for other toxicities

For other non-hepatic or non-hematologic toxicities such as Grade 3 nausea, vomiting, diarrhea or stomatitis that occur despite supportive care, paclitaxel will be held at the first occurrence and subsequently dose reduced to the next level once the toxicity has recovered to Grade 0 to 1 in severity.

If paclitaxel is given on a weekly basis, dose reductions should be implemented according to the usual standard of care following to regional or country-specific guidelines and the guidelines described above. 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 instead of dose reductions for the next cycle.

Dose Modifications for Docetaxel

Dose Levels for Docetaxel	
Dose Level	Dose (mg/m^2), given Day 1, given every 21 days
1	75
-1	60 (20% decrease from Dose Level 1)
-2	45 (25% decrease from Dose Level -1)

Dose Levels for Docetaxel in Japan	
Dose Level	Dose (mg/m^2), given Day 1, given every 21 days
1	70
-1	60 (15% decrease from Dose Level 1)
-2	50 (17% decrease from Dose Level -1)

The following table provides guidance regarding docetaxel dose adjustments for specific adverse events.

Docetaxel Dose	Adverse event
70 – 75 mg/m^2	Starting Dose Administer only if neutrophil count is > 1500 cell/mm^3
60 mg/m^2	• Febrile neutropenia or neutrophils < 500 cells/mm^3 for more than 1 week (after fully recovering to a neutrophil count ≥ 1500 cells/mm^3 • Platelet count < 100,000 cells/mm^3 (after recovering to a platelet count of ≥ 100,000 cells/mm^3 • Severe or cumulative cutaneous reactions
45 mg/m^2	• Second episode febrile neutropenia or neutrophils < 500 cells/mm^3 for more than 1 week (after fully recovering to a neutrophil count ≥ 1500 cells/mm^3)
Permanently Discontinue Docetaxel	After any of the following toxicities: • Severe hypersensitivity reactions • Peripheral neuropathy > Grade 3 • Severe or cumulative cutaneous reactions that continue at a dose of 45 mg/m^2 without recovery • Febrile neutropenia or neutrophils < 500 cells/mm^3 without recovery • Platelet count < 100,000 cells/mm^3 without recovery • Total bilirubin > ULN without recovery • Serum transaminase (AST, ALT) levels > 1.5 x ULN concurrent with serum alkaline phosphatase levels > 2.5 x ULN without recovery

Abbreviations: ANC, absolute neutrophil count; ULN, upper limit of normal.

Dose Modifications for Irinotecan

Dose Levels for Irinotecan	
Dose Level	Dose (mg/m^2), given Days 1 and 8, given every 21 days
1	125
-1	100 (20% decrease from Dose Level 1)
-2	75 (25% decrease from Dose Level -1)

Irinotecan Dose given every 21 days	Adverse Event
125 mg/m^2	Starting Dose Administer only if neutrophil count is > 1500 cell/mm^3
100 mg/m^2 (Dose Level -1)	Reduction from Dose Level 1 for any of the following toxicities • Grade 3 neutropenia (neutrophils 500 cells/mm^3 – 999 cells/mm^3) • Grade 3 diarrhea (7-9 stools/day over pretreatment status) - hold dose until resolved to ≤ Grade 2 then restart at Dose Level -1 • Other Grade 2 or 3 non-hematologic toxicities except alopecia, anorexia, asthenia
75 mg/m^2 (Dose Level -2)	After any of the following toxicities: • Neutropenic fever - Omit dose until resolved, restart at Dose Level -2 • Grade 4 neutropenia (neutrophils < 500 cells/mm^3) - hold dose until neutrophil count is ≤ Grade 2 then restart at Dose Level -2 • Grade 4 diarrhea (≥ 10 stools/day over pretreatment status) - hold dose until recovery to ≤ Grade 2 then restart at Dose Level -2 • Other Grade 4 nonhematologic toxicities except alopecia, anorexia, asthenia - omit dose until resolved to ≤ Grade 2 then restart at Dose Level -2

The above tables for dose reduction match standard clinical practice and label guidelines for each agent, and the treating physician should use their clinical judgement when determining if the chemotherapy should be held or dose reduced. If considered in the best interest of the patient and consistent with local practice, investigators may use supportive measures or treatment and/or secondary prophylaxis instead of dose reductions for the next treatment cycle.

If any chemotherapy agent is held for more than 6 weeks from the anticipated treatment date, or the dose level - 2 is not tolerated, chemotherapy should be permanently discontinued.

8.7. Criteria for Permanent Discontinuing Chemotherapy Regimens

Except where specified below, chemotherapy regimen should be discontinued for any of the following criteria. If any of these criteria are met, the chemotherapy will be permanently discontinued.

- Any Grade 4 peripheral neuropathy
- Grade 4 drug-related thrombocytopenia associated with clinically significant bleeding
- Any Grade 4 drug-related adverse events or laboratory abnormality except as noted in Section 8.6.2.
  - Grade 4 neutropenia > 7 days despite growth factor support
  - Grade 4 electrolyte imbalances/abnormalities that are associated with clinical sequelae and are not correctable with supplementation/appropriate management within 72 hours of their onset
- Any drug-related liver function test abnormality value that meets one of the following criteria requires discontinuation:
  - AST or ALT > 5-10 x upper limit of normal (ULN) for > 2 weeks or
  - AST or ALT > 10 x ULN or
  - Total bilirubin > 5 x ULN
- Any drug-related AE which recurs after 2 prior dose reductions for the same drug-related AE requires discontinuation of the drug(s)
- Any Grade 3 or 4 drug-related hypersensitivity reaction or infusion reaction requires discontinuation of the drug(s) felt to be causing the reaction. The drug not considered to be related to the hypersensitivity reaction or infusion reaction may be continued
- Any Grade 4 AE which the investigator considers related to study drug and inappropriate to be managed by dose reduction(s) requires discontinuation of drug(s). The drug not considered to be related to the event may be continued
- If any toxicity does not resolve within 42 days, the targeted treatment will be discontinued unless the treating physicians determines that the patient is clinically stable, the toxicity has stabilized, and the benefit of continuing the treatment compared to the risk of the toxicity is favorable
- For any adverse event, laboratory abnormality, or intercurrent illness not listed above, the investigator should use their medical judgment to determine whether any individual chemotherapy agents should be discontinued, in accordance with subject's well-being and local standards

8.8. Management of AE of Special Interest

As a routine precaution, after infusion of tislelizumab on Day 1 of Cycle 1 and Cycle 2, patients must be monitored for at least 1 hour afterwards 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 for infusion-related reactions, severe hypersensitivity reactions and irAEs according to the NCI-CTCAE criteria are outlined below.

8.8.1. Assessing and Recording Immune-Related Adverse Events

Since treatment with anti-PD-1 therapy can cause autoimmune disorders, AEs considered by the investigator to be immune-related should be classified as irAEs and identified as such in the eCRF AE page, until day 90, after treatment discontinuation.

If the events listed below (Table 5) or similar events occur, appropriate diagnostic tests, which may include but is not limited to serologic, immunologic, and histologic (biopsy) data, should be ordered to exclude alternative causes such as infection, metabolic, toxin, disease progression or other neoplastic causes, and other drugs. If alternative explanations have been excluded, the AE required the use of systemic steroids, other immunosuppressants, or endocrine therapy and is consistent with an immune mediated mechanism of action, the irAE field in the eCRF should be checked. The purpose of this action is to assess the cumulative incidence and severity of irAEs in the study and to detect any correlation with efficacy. Any serious irAEs should be reported according to the seriousness criteria above in Section 8.4.2. For the investigator's guidance, a list of potential irAEs appears below in Table 5. All conditions similar to those listed should be evaluated to determine whether they are irAEs, based on a similar diagnostic process to those reactions that are presented in more detail in Appendix 10.

Recommendation for diagnostic evaluation and management of irAEs is based on a recent ESMO guideline (Haanen JBAG, 2017) and common immune-related toxicities are detailed in Appendix 10. For any adverse events not included in Appendix 10, please refer to the recent ESMO guideline (Haanen JBAG, 2017) for further guidance on diagnostic evaluation and management of immune-related toxicities.

Table 5: Immune-Related Adverse Events Associated with Anti-PD-1 Drugs

Body System Affected	Events
Skin (mild-common):	pruritus or maculo-papular 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
Ocular:	episcleritis; conjunctivitis; iritis/uveitis; retinal detachment
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.
Note: Refer to Weber JS 2015

Dose modification and management for irAEs are detailed in Appendix 10.

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.

8.8.2. Managing Immune-Related Adverse Events

Immune-related adverse events may develop during the course of the study, including following last dose of tislelizumab. Corticosteroids are usually prescribed at medium to high doses (0.5 to 1 mg/kg of prednisone) and should be continued until symptoms resolve, become mild, or return to baseline levels, whereupon the doses given can be tapered over at least 1 month (Boutros C, 2016; Champiat S, 2016). See Appendix 10 for irAE evaluation and management.

8.8.3. Managing Infusion-Related Reactions due to Tislelizumab

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

Treatment modification guidelines for suspected infusion-related reactions due to tislelizumab are summarized in Table 6.

Table 6: Treatment Modification Guidelines for Symptoms of Infusion-Related Reactions Due to Tislelizumab

NCI-CTCAE Grade	Guideline for Modification of Tislelizumab Treatment
Grade 1 or 2 Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease tislelizumab infusion rate by 50% and closely monitor any worsening. Manage medically as needed. Subsequent infusions should be given after premedication and at the reduced infusion rate.
Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	Decrease tislelizumab infusion rate by 50% of previous rate once infusion-related reactions have resolved or decreased to at least Grade 1 in severity and closely monitor any worsening. 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: IV, intravenous; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NSAID, nonsteroidal anti-inflammatory drug.

8.8.4. Medical Management Guidelines for Infusion-Related Reactions (All Grades)

- Immediate access to resuscitation equipment (including epinephrine, corticosteroids, IV antihistamines, bronchodilators, and oxygen) must be available to treat infusion-related reactions
- Patients should be instructed to seek emergency care if they experience lightheadedness, shortness of breath, wheezing, or swelling after they have left the treatment center

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

CTCAE Grade 1 or 2 infusion reaction: Proper medical management should be instituted, as indicated per type of the reaction. This includes but is not limited to an anti-histamine (eg, diphenhydramine or equivalent), anti-pyretic (eg, paracetamol or equivalent), and if considered indicated oral or IV glucocorticoids, epinephrine, bronchodilators, and oxygen. In the next cycle, patients should receive oral premedication with an antihistamine (eg, diphenhydramine or equivalent) and an antipyretic (eg, paracetamol or equivalent), and they should be closely monitored for clinical signs and symptoms of an infusion reaction.

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

8.8.5. 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 (eg, 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 (eg, paracetamol) may be given to patients at the discretion of the investigator.

8.8.6. Renal Function Abnormalities

Patients with moderate renal dysfunction (estimated glomerular filtration rate $\geq$ 30 mL/min/1.73 m^2 and < 60 mL/min/1.73 m^2 by Chronic Kidney Disease Epidemiology Collaboration equation) may be enrolled into the study. The following algorithm is proposed for the use of steroid treatment in the management of irAEs:

- If the serum creatinine is normal at baseline, please see Section 8.8.1 and refer to Appendix 10 for diagnosis and management of patients with abnormal renal laboratory values.
- If the serum creatinine is Grade 1 at baseline and increase in serum creatinine meets criteria for serum creatinine increase $\geq$ Grade 2 after starting treatment with

tislelizumab, refer to Appendix 10 for diagnosis and management of patients with abnormal renal laboratory values. Check the estimated GFR using Appendix 11 and the eGFR calculator link. In the setting of a Grade 2 serum creatinine increase only, study treatment can continue unless the serum creatinine increases by at least 50% from the baseline value OR the eGFR falls below 20 mL/min.

- If the serum creatinine is Grade 2 at baseline and increase in serum creatinine meets criteria for serum creatinine increase ≥ Grade 3 after starting treatment with tislelizumab, refer to Appendix 10 for diagnosis and management of patients with abnormal renal laboratory values. In the setting of a Grade 3 serum creatinine increase only, study treatment will be held until serum creatinine improves to baseline and treatment may resume only after discussion with the medical monitor.

9. STATISTICAL METHODS AND ANALYSIS PLAN

The statistical analyses will be performed by the sponsor or designee after the data collection for the primary efficacy and safety analyses are completed and the database is locked and released. Data will be listed and summarized per sponsor agreed reporting standards, where applicable. Details of the statistical analyses will be included in a separate Statistical Analysis Plan (SAP).

9.1. Analysis Sets

Intention-to-Treat (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 one dose of study treatment. It will be the primary analysis set for safety analysis.

Per-Protocol (PP) analysis set includes patients who have received ≥ 1 dose of study medications and had no major protocol deviations that impact efficacy evaluation. Major protocol deviations will be determined and documented before the database lock for the primary analysis

The PD-L1 positive analysis set includes patients whose tumor and immune cell score (TIC score) met the pre-defined cut-off (specified in the statistical analysis plan) using VENTANA PD-L1 (SP263) CDx Assay. TIC score is the total percentage of the tumor area covered by tumor cells with PD-L1 membrane staining and tumor-associated immune cells with PD-L1 staining at any intensity.

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

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

9.2. Patient Disposition

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

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

9.3. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized in the ITT analysis set and the PD-L1 positive analysis set using descriptive statistics. Continuous variables include age, weight, vital signs, time since initial cancer diagnosis, and time since advanced/metastatic disease diagnosis; categorical variables include, gender, ECOG status, geographical region of enrollment, country, race, age (<45 years old, ≥45 to ≤65 years old and >65 years old), TNM Classification of Malignant Tumors staging (smoking status [never, previous and current], alcohol consumption [never, previous and current], primary tumor location [cervical, upper,

middle, lower] and previous treatment [chemotherapy, radiation therapy, surgery]), anatomic locations of metastases, and number of metastatic lesions (≤ 1 site vs ≥ 2 sites).

9.4. Prior and Concomitant Therapies

Concomitant medications will be assigned an 11-digit code using the World Health Organization Drug Dictionary drug codes. Concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical 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 first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 days after the patient's last dose (Safety Follow-up visit). In addition, telephone contacts with patients should be conducted to assess irAEs and concomitant medications (if appropriate, ie, associated with an irAE or is a new anticancer therapy) at 60 and 90 days (± 14 days) after the last dose of study drugs regardless of whether or not the patient starts a new anticancer therapy. A listing of prior and concomitant medications will be included in the CSR for this study.

9.5. Efficacy Analyses

The primary endpoint of OS in the ITT analysis set will be tested once at a one-sided alpha of 0.025. If the null hypothesis for OS in the ITT analysis set is rejected, the key secondary endpoint will be tested sequentially for OS in the PD-L1 positive analysis set. The inferential test for OS in the PD-L1 positive analysis set will be stopped at the non-significant endpoint of OS in the ITT analysis set. The familywise type I error will be strongly controlled at one-sided level 0.025. More details will be given in the statistical analysis plan.

9.5.1. Primary Efficacy Analyses

The primary efficacy endpoint is OS in the ITT analysis set as defined in the primary endpoint section. In the absence of death, patients will be censored either at the date that the patient was last known to be alive or the date of data cut-off, whichever comes earlier.

OS will be compared between tislelizumab and ICC arms in a stratified log-rank test using a significance level of one-sided 0.025.

The null hypothesis to be tested is:

H_0: OS in tislelizumab = OS in ICC against the alternative:

H_1: OS in tislelizumab ≠ OS in ICC

This will be the primary analysis once the targeted event number of approximately 400 is reached. The p-value from one-sided log-rank test will be calculated, stratified by selected stratification factors of ECOG performance status (0 vs 1) and ICC option (paclitaxel vs docetaxel vs irinotecan). Sample size calculation is included in Section 9.9.

The median OS and the cumulative probability of OS at every 3 months, if estimable, will be calculated for each treatment arm and presented with two-sided 95% CIs. Kaplan-Meier survival probabilities for each arm will be plotted over time.

The treatment effect will be estimated by fitting a Cox regression model with treatment arm as a factor and with ICC and ECOG performance status as strata. From this model, the hazard ratio (HR) of OS will be estimated and presented with a two-sided 95% CI.

These analyses will be performed in the ITT analysis set as the primary analysis. Outcomes in the Per Protocol analysis set will be evaluated as a sensitivity analysis.

9.5.2. Secondary Efficacy Analyses

Key Secondary Efficacy Endpoint-OS in PD-L1 positive analysis set:

The OS in the PD-L1 positive analysis set will be analyzed similarly as described in the primary analysis for OS in the ITT analysis set.

Other Secondary Efficacy Endpoints:

Cochran-Mantel-Haenszel (CMH) test adjusting for selected stratification factors (ECOG and ICC option) in the ITT analysis set and the PD-L1 positive analysis set will be provided for ORR per RECIST v1.1. The two-sided 95% CIs for the odds ratio in ORR will be calculated, as well as Clopper-Pearson 95% CIs of ORR for each treatment arm.

PFS based on assessment by investigator per RECIST v1.1 will be estimated using the Kaplan-Meier (KM) method in the ITT analysis set and the PD-L1 positive analysis set. 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 (2007). 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 anti-cancer therapy will be censored at the last tumor assessment date prior to the introduction of new therapy.

A log-rank test stratified by selected stratification factors (ECOG and ICC option) will be used to test the PFS differences between two treatment arms. The stratified Cox regression will be used to estimate the hazard ratio of PFS. A 95% confidence interval (CI) of HR in PFS will be constructed. Median PFS and PFS every 3 months for each treatment arm, if estimable, will be presented.

Duration of response based on assessment by investigator will be analyzed similarly as PFS in the responders.

EORTC QLQ-C30 and EORTC QLQ-OES18 will be summarized using functional scale/symptom scale/single item. Observed values and changes from baseline for functional scale/symptom scale/single item will be summarized using descriptive statistics. Time to clinically meaningful worsening in HRQoL domains will be estimated using Kaplan-Meier method. Log-rank test will be employed for testing treatment difference.

EQ-5D-5L will be compared between tislelizumab and ICC arms. Descriptive statistics will be used to show the changes from baseline in each arm. These HRQoL assessment will be analyzed in both the ITT analysis set and the PD-L1 positive analysis set.

9.5.3. Exploratory Efficacy Analyses

Best overall response (BOR) is defined as the best response per RECIST v1.1 recorded from randomization till data cut or start of new anti-cancer treatment. Patients with no post-baseline response assessment (for any reason) will be considered non-responders for BOR. The proportion and its corresponding Clopper-Pearson 95% CI for each of the response categories (CR, PR, SD and PD) will be presented by treatment arm.

DCR will be analyzed similarly as ORR in the ITT analysis set and the PD-L1 positive analysis set.

PD-L1 expression and, gene expression profiling, tumor mutation burden, MSI, and tumor-infiltrated immune cells may be examined in the ITT analysis set. Efficacy analyses, including but not limited to OS, PFS, and ORR, may be explored according to biomarker status. Other potential predictive markers may also be assessed.

Methodology for exploratory analyses will be described in the statistical analysis plan.

9.6. Safety Analyses

Safety will be assessed by the monitoring and recording of all AEs graded by NCI-CTCAE v4.03. Laboratory values (eg, hematology, clinical chemistry, coagulation and urinalysis), vital signs, ECGs, and physician examinations will also be evaluated in defining the safety profile of each treatment arm. Descriptive statistics will be used to analyze all safety data in the Safety analysis set.

9.6.1. Extent of Exposure

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

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

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

9.6.2. Adverse Events

The AE verbatim descriptions (investigator's description from the eCRF) will be classified into standardized medical terminology using Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to MedDRA (Version 20.0 or higher) lower level term closest to the verbatim term. The linked MedDRA System Organ Class (SOC) and Preferred Term (PT) are also classified.

In this protocol, a treatment-emergent adverse event (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 drug up to 30 days following study drug discontinuation or initiation of a new anticancer therapy. TEAEs also include all irAEs and drug-related serious AEs recorded up to 90 days after the last dose of study drug regardless of whether or not the patient starts a new anticancer

therapy. Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in patient data listings.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by SOC and PT. A patient will be counted only once by the highest severity grade per NCI-CTCAEv.4.03 within an SOC and PT, even if the patient experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of patients with TEAEs will also be summarized by relationship to the study drug.

Serious adverse events, deaths, TEAE with grade 3 or above, irAE, related TEAE and TEAEs that led to treatment discontinuation, dose reduction, dose interruption or dose delay will be summarized.

9.6.3. Clinical Laboratory Analyses

Clinical laboratory (eg, hematology, serum chemistry) values will be evaluated 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 Clinical Study Report (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-CTCAEv.4.03 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 ranges (eg, glucose, potassium, sodium) will be summarized separately.

9.6.4. Vital Signs Analyses

Descriptive statistics for vital sign parameters (eg, blood pressure, temperature) and changes from baseline will be summarized.

9.6.5. Ophthalmologic Examination

Ophthalmologic examination results will be listed by patient.

9.7. Pharmacokinetic Analyses

Pharmacokinetic samples will be collected in this study as outlined in Appendix 1, and only from patients randomized to receive tislelizumab and in sites that are able to adequately perform sampling, handling and processing procedures outlined in the Laboratory Manual.

Tislelizumab serum concentration data, including but not limited to C_{trough}, will be tabulated and summarized for each cycle at which pharmacokinetics are collected. Descriptive statistics will include means, medians, ranges, and standard deviations, as appropriate.

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

9.8. Immunogenicity Analyses

Samples to assess anti-tislelizumab antibodies will be collected only in patients randomized to receive tislelizumab and in sites that are able to adequately perform sampling, handling and processing procedures outlined in the Laboratory Manual.

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

9.9. Determination of Sample Size

The sample size calculation is based on the primary efficacy analysis of OS comparison between tislelizumab and ICC arms in the ITT analysis set. Assuming an OS-HR (Arm Tislelizumab/Arm ICC) of 0.75 and a dropout rate of 5% per year, approximately 500 patients will be enrolled and randomized in a 1:1 ratio to Arm Tislelizumab and ICC over a 26-month period to accumulate approximately 400 deaths, which is estimated to occur approximately 30.2 months after the first patient is enrolled when median OS in the tislelizumab and ICC arms are 8 months and 6 months, respectively. Assuming OS-HR is 0.75, based on recently published results of anti-PD-1 therapies in second line treatment of ESCC (Kojima et al 2019; Kato et al 2019; Huang et al 2019), the study will have a power of 82% with a one-sided alpha of 0.025.

9.10. Interim Analysis

No interim analysis is planned for this study.

10. DATA HANDLING AND QUALITY ASSURANCE

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

10.1. Data Collection

Data required by the protocol will be entered into the eCRFs in an EDC system that is compliant with all regulatory requirements. All study-related data collected or received by the investigator or study team shall be promptly entered into the eCRFs. In no event should the entry of the study data into the eCRF be later than what is stipulated in the site contract after the data is collected or received by the investigator or study team without prior communication with and approval by sponsor.

Data collection in the eCRF must follow the instructions described in the eCRF Completion Guidelines (eCCGs). The investigator has ultimate responsibility for the collection and reporting of all clinical data entered in the eCRF. The investigator or designee must sign the completed casebooks 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.

10.2. Data Management/Coding

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

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

During the course of the study, a study monitor (ie, 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.

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 giving due consideration to data protection and medical confidentiality.

Adverse events and concomitant diseases/medical history will be coded using MedDRA version 20.0 or higher. Concomitant medications will be coded using the World Health Organization Drug Dictionary.

10.3. Quality Assurance

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

10.4. Data Integrity Protection Plan and In-house Blinding

Due to the open-label design of the study, access to the unblinded patient level clinical data in the EDC system will only be assigned to predefined study personnel. Functions/persons with access to the EDC system shall be prohibited from using the EDC system to generate unnecessary listings/summaries that may introduce unwanted bias, or share such outputs or the unblinded data from the EDC system with other functions/persons who do not have access to the EDC. Although the study is open label, analyses or summaries generated by randomized treatment assignment and actual treatment received will be limited and documented. More details will be described in a Data Integrity Protection Plan (DIPP).

10.5. Study Records Retention

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

The investigator's study file will contain the protocol/amendments, CRF 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 CRFs) would include (although not be limited to) the following: patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, electrocardiogram, electroencephalogram, radio imaging, 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 back up 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 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, transfer of ownership of the records in the event the investigator leaves the study center.

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

Biological samples at the conclusion of this study may be retained as outlined in the agreement with the CRO managing the biological samples, for the shorter of: a period of up to 10 years or as allowed by your IRB/IEC.

10.6. Publication and Data Sharing Policy

A clinical study report will be prepared and provided to the regulatory agency(ies). BeiGene will ensure that the report meets the standards set out in the International Council for Harmonization (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 regulator 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).

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 study will be presented in the investigator's clinical study agreement.

11. ETHICAL CONSIDERATIONS

11.1. Compliance with Laws and Regulations

This study will be conducted in full conformance with the International Council for Harmonization (ICH) E6 guideline for GCP 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).

11.2. Informed Consent

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

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

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

Patients must be re-consented 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.

11.3. Institutional Review Board/Independent Ethics Committee

This protocol, the ICFs, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/IEC by the principal investigator and reviewed and approved by the IRB/IEC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/IEC. Copies of the IEC/IRB correspondence and approval of the amended ICF/other information and the approved amended ICF/other information must be forwarded to the sponsor promptly.

The principal investigator is responsible for providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC. The investigator is also responsible for promptly informing the IRB/IEC of any protocol amendments (Section 12.5). In addition to the

requirements for reporting all adverse events to the sponsor, the investigator must comply with the requirements for reporting SAEs to the local health authority and IRB/IEC. The investigator may receive written IND safety reports or other safety-related communications from the sponsor.

The investigator is 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.

11.4. Confidentiality

The principal investigator and sponsor will maintain confidentiality and privacy standards by following applicable data privacy laws covering the collection, storage, transmission, and processing of patients' personal and medical information. The principal investigator will maintain confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This approach ensures that patients' names are not included in any data set transmitted to any sponsor location.

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the signed ICF (or a separate authorization for the use and disclosure of personal health information that has been signed by the patient), unless permitted or required by law. In the event of a breach of the confidentiality of a patient's personal and medical information, the principal investigator and sponsor, as appropriate, shall fulfill all remediation steps and reporting obligations under applicable data privacy 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.

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

The investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. The investigator agrees that all information received from sponsor, including but not limited to the Investigator's Brochure, this protocol, CRFs, the IND, and any other study information, remain the sole and exclusive property of sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from 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.

If a written contract for the conduct of the study is executed, and that contract includes confidentiality provisions inconsistent with this section, that contract's provisions shall apply to the extent they are inconsistent with this section.

11.5. Financial Disclosure

The investigator will provide the sponsor with sufficient and accurate financial information, in accordance, with local regulations to allow the sponsor to submit complete and accurate financial

certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information about their financial interests during the course of the study and for 1 year after completion of the study (ie, last patient, last visit).

12. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

12.1. Study Documentation

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.

12.1.1. Access to Information for Monitoring

In accordance with ICH GCP guidelines, the study monitor must have direct access to the investigator's source documentation to verify the data recorded in the CRFs for consistency.

The monitor is responsible for routine review of the CRFs 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 CRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

12.1.2. 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.

12.2. Case Report Forms

For each patient randomized/assigned to treatment, an eCRF must be completed and signed by the principal investigator or subinvestigator within a reasonable time period after data collection. If a patient withdraws from the study, the reason must be noted in the appropriate eCRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

The eCRF exists within an EDC system with controlled access managed by BeiGene or its authorized representative for this study. Study staff will be appropriately trained in the use of eCRFs and applications of electronic signatures before being given access to the EDC system. Original data and any changes of data will be recorded using the EDC system, with all changes tracked by the system and recorded in an electronic audit trail. The investigator attests that the information contained in the eCRF is true by providing an electronic signature within the EDC system. After final database lock, the investigator will receive a copy of the patient data from that site (eg, paper, CD, or other appropriate media) for archiving the data at the study site.

12.3. Protocol Deviations

The investigator is to document and explain any deviations from the IRB/Ethics committee 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, and shall report all protocol deviations to sponsor.

12.4. Study Site Inspections

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.

12.5. Protocol Amendments

Any protocol amendments will be prepared by the sponsor. Protocol amendments will be submitted to the IRB/IEC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/IEC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (eg, change in medical monitor or contact information).

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14. APPENDICES

APPENDIX 1. SCHEDULE OF ASSESSMENTS

Assessment Window (Days)	Screening[1]	All Treatment Cycles[2]				End of Treatment[3] (0-7 days)	Safety Follow-up[4] (30 ± 7 days after last dose)	Survival Follow-up[5] (Every month)
		Cycles 1-2			Cycle 3 and Subsequent Cycles			
	Day -28 to Day -1	Day 1 (± 3)	Day 8 (± 2)	Day 15 (± 2)	Day 1 (± 3)			
Informed consent[1]	x							
Inclusion/Exclusion criteria	x							
Randomization	x							
Demographic/Medical history/Prior medications	x							
Cancer Diagnosis and Treatment History[6]	x							
Concomitant medications[7]	x	x	x	x	x	x	x	x
Adverse events[8]	x	x	x	x	x	x	x	
Physical examination[9]	x	x			x	x	x	
ECOG performance status[10]	x[10]	x[10]			x[10]	x	x	
Vital signs/Weight[11]	x	x	x	x	x	x	x	
12-lead ECG[12]	x	As clinically indicated				x		
HBV and HCV serology[13]	x	As clinically indicated						
Hematology[14]	x	x[14]	x[14]	x[14]	x[14]	x[14]	x[14]	
Serum chemistry[14]	x	x[14]	x[14]	x[14]	x[14]	x[14]	x[14]	
Total CK and CK-MB[14]	x	x	x	x	x	x	x	
Coagulation parameters[14]	x	As clinically indicated				x	x	

Assessment Window (Days)	Screening[1]	All Treatment Cycles[2]				End of Treatment[3] (0-7 days)	Safety Follow-up[4] (30 ± 7 days after last dose)	Survival Follow-up[5] (Every month)
		Cycles 1-2			Cycle 3 and Subsequent Cycles			
	Day -28 to Day -1	Day 1 (± 3)	Day 8 (± 2)	Day 15 (± 2)	Day 1 (± 3)			
Urinalysis[14]	x	As clinically indicated				x	x	
Pregnancy test[15]	x	x[15]			x[15]	x	x	
Thyroid function[16]	x	x[16]			x[16]		x	
Pharmacokinetics[17]		x [17]			x [17]		x[17]	
Anti-tislelizumab antibodies[18]		x[18]			x[18]		x[18]	
Tumor assessment[19]	x (within 28 days)	Every 6 weeks for 6 months, then every 9 weeks[27]				x		
Tislelizumab administration[20]		x			x			
Chemotherapy administration[21]		x			x			
Archive/Fresh Tumor tissue collection[22]	x					x (optional)		
Optional blood sample for biomarker analysis[23]		x						
HRQoL Assessments[24]	x	x			Cycles 3-6 only	x	x	
Survival status								x
Pulmonary function tests[25]	x							
Optical coherence tomography (or equivalent diagnostic test) and visual acuity tests[26]	x	Every 15 weeks ± 7 days				x[28]	x[28]	

Abbreviations: x, to be performed; ECOG, Eastern Cooperative Oncology Group; ECHO, echocardiography; ECG, electrocardiogram; FEV_1, forced expiratory volume in the first second of expiration; HBV, hepatitis B virus; HCV, hepatitis C virus; HRQoL, Health Related Quality of Life; MRI, magnetic resonance imaging.

[1] Written informed consent is required prior to performing any study-specific tests or procedures. Results of standard-of-care laboratory tests and physical examinations performed prior to obtaining informed consent and within 7 days prior to randomization may be used for screening assessments rather than repeating such tests. Baseline radiologic examinations for tumor status may be performed within 28 days of randomization. Fresh tumor biopsy is permitted, if no archival tumor tissue is available.

[2] Cycle 1 treatment must be given within 3 business days of randomization. After Cycle 1 there is a 3-day window for all study treatment given on a 21-day cycle unless otherwise noted. There is a 2-day window for treatments given on a weekly schedule. Efficacy assessments will be performed approximately every 6 weeks for 6 months, then every 9 weeks regardless of the duration of a chemotherapy cycle.

[3] The End-of-Treatment (EOT) Visit is conducted when the investigator determines that tislelizumab or ICC will no longer be used, at which time all of the assessments listed for the EOT Visit will be performed. If routine laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the EOT Visit, tests need not be repeated. Tumor assessment is not required at the EOT Visit provided that fewer than 6 weeks have passed since the last assessment.

[4] The mandatory Safety Follow-Up Visit is required to be conducted 30 days (± 7 days) after the last dose of study therapy, or before initiation of a new anti-cancer treatment. At the end of treatment, ongoing AEs considered related to study treatment will be followed until the event has resolved to baseline or ≤ Grade 1, the event is assessed by the investigator as stable, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the AE. The EOT Visit may be combined with the Safety Follow-up Visit, provided that the EOT occurred 30 days (± 7 days) after the last study treatment; the assessments for both visits should be performed.

[5] Survival follow-up information will be collected via telephone calls, email or other communication; patient medical records; and/or clinic visits approximately 1 month (4 weeks ± 7 days) after the Safety Follow-up Visit and approximately monthly thereafter until death, loss to follow-up, withdrawal of consent, or study termination by sponsor. All patients will also be followed for new anti-cancer therapy information unless the patient requests to be withdrawn from follow-up.

[6] Includes history of treatment for the primary diagnosis, including prior systemic, radiation treatment and surgical treatment. Radiographic imaging performed prior to study entry may be collected for review by the investigator, as clinically appropriate.

[7] Concomitant medications include any prescription medications, over-the-counter medications, herbal supplements, and IV medications and fluids. All concomitant medications received within 30 days before the first dose of study drug and 30 days after the last infusion of study medication should be recorded. At subsequent visits, changes to current medications or medications used since the last documentation of medications will be recorded. Only new anti-cancer treatment will be collected at Survival Follow-up Visits.

[8] AEs and laboratory safety measurements will be graded per NCI-CTCAE version 4.03. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness. After the informed consent form has been signed, but prior to the administration of study drug, only SAEs should be reported. After the first dose of study drug, all AEs and SAEs, regardless of their assessed relationship to study drug, are to be reported until either 30 days after the last dose of study treatment or the initiation of a new anticancer therapy, whichever occurs first. Immune-related AEs should be reported for 90 days after the last dose of tislelizumab regardless of initiation of subsequent anticancer therapy. After this period, the investigator should report any SAEs that are believed to be related to tislelizumab treatment (Section 8.4.1). 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 (Section 8.2.6).

[9] A complete physical examination should include an evaluation of the head, eyes, ears, nose, throat, cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations are required to be performed. Height will only be measured and recorded at Screening Visit. Investigators should solicit patients regarding changes in vision, visual disturbance, or ocular inflammation at each scheduled study visit during tislelizumab treatment. For any change in vision, referral to an appropriate specialist will be made for further management guidance.

[10] ECOG performance status are required to be obtained within 7 days prior to randomization.

[11] Vital signs to include temperature, pulse, blood pressure, and weight; pulse and BP should be recorded while the patient is in a seated position after resting for 10 minutes. For all infusions of tislelizumab, the patient's vital signs should be recorded before the infusion, and between 30 to 45 minutes after the infusion. Vital signs must be collected during the infusion if clinically indicated. For the subjects randomized to Paclitaxel, patients will be monitored for anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension. Monitor diarrhea and give fluid and electrolytes as needed on all patients receiving irinotecan.

[12] Electrocardiogram (ECG) recordings will be obtained during screening, End of Treatment, and as clinically indicated at other timepoints. Patients should be resting and in a sitting or supine position for at least 10 minutes prior to ECG collection. A repeat ECG should be performed to confirm findings, if any.

[13] Testing will be performed at screening and as clinically indicated, including HBsAg, HBcAb, and HCV antibody. Patients who are HBsAg positive at screening must not be enrolled until further definite testing with HBV DNA titers < 500 IU/mL (or 2500 copies/mL).

[14] Local or central laboratory assessments on serum chemistry, hematology, coagulation, and urinalysis will be conducted, of which certain elements will be collected as specified in Section 7.10. Laboratory tests are required to be obtained within 14 days of randomization. If laboratory tests 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 liver function tests) will be performed weekly for the first 2 cycles and then at the beginning of each subsequent cycle. After Cycle 1, results are to be reviewed within 3 business days before study drug administration. It is recommended to perform weekly peripheral blood cell counts on all patients receiving paclitaxel, docetaxel, and irinotecan. All patients will have creatine kinase (CK) and creatine kinase-cardiac muscle isoenzyme (CK-MB) testing at screening and at all scheduled visits during the first 3 treatment cycles, all pre-dose assessments from Cycle 4 onwards, and at the EOT and Safety Follow-up Visits. In the event that CK-MB fractionation cannot be evaluated in the local laboratory, troponin I and/or troponin T should be assessed instead; the same test should be administered throughout the study. Urinalysis and coagulation parameters are to be assessed during the treatment period only if clinically indicated. Refer to Section 8.2.5 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.

[15] Serum 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, EOT Visit and at Safety Follow-up. Urine pregnancy test will be performed at each visit prior to study treatment; a serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.

[16] Thyroid function tests will be performed within 7 days prior to randomization with analysis of free T3, free T4 and TSH. They will be tested every 3 cycles thereafter (eg, Cycles 4, 7 and 10, etc.) from randomization and at the mandatory Safety Follow-Up Visit in tislelizumab arm. Thyroid function testing performed during the study and at the Safety Follow-up Visit will only be for patients on the tislelizumab arm.

[17] Only for patients randomized to tislelizumab. Only in sites that can adequately perform sampling, handling and processing procedures outlined in the Laboratory Manual. Procedures for collection of tislelizumab PK samples are described in the Laboratory Manual. Predose (within 60 min before start infusion) samples are required to be collected at Day 1 of Cycle 1, 2, 5, 9 and 17; post-dose (within 30 minutes after completing tislelizumab infusion) samples are 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 Visit. If a patient present with any immune-related adverse event, additional blood PK samples may be taken to determine the plasma concentration of BGB-A317. These tests are required when it is allowed by local regulations/IRBs/ECs.

[18] Only for patients randomized to tislelizumab. Blood used to test for anti-tislelizumab antibodies should be collected within 60 minutes before beginning the Day 1 infusion of Cycles 1, 2, 5, 9, and 17 and at the mandatory Safety Follow-Up Visit. All samples should be drawn at the same time as blood collection for predose PK analysis. These tests are required when it is allowed by local regulations/IRBs/ECs.

[19] Examinations performed as standard of care prior to obtaining informed consent at the same study site within 28 days prior to randomization may be used rather than repeating tests. CT/MRI of the head at baseline is required for patients who are suspected to have central nervous system (CNS) metastases. All measurable and evaluable lesions are required to be assessed and documented at the screening visit. The same radiographic procedure must be used throughout the study for each patient. Patients will undergo tumor assessments approximately every 6 weeks (± 7 days) for 6 months, then every 9 weeks (± 7 days) from last assessment afterwards. Patients who discontinue from treatment for reasons other than disease progression or death will continue scheduled tumor assessments until the start of a new anti-cancer therapy, disease progression, death, lost to follow-up, withdrawal of consent, or until the study completion, whichever occurs first. Investigators may perform additional scans or more frequent assessments if clinically indicated. If previous tumor imaging was obtained within 6 weeks prior to the date of discontinuation, then additional tumor imaging at treatment discontinuation is not required. Imaging timing should follow calendar days and should not be adjusted for delays in treatment. Patients who continue

tislelizumab treatment beyond radiographic disease progression will be monitored with a follow-up scan at least 4 weeks later or at the next regularly scheduled timepoint (not to exceed 6 weeks) before discontinuation of study treatment.

[20] The initial infusion of tislelizumab will be delivered over 60 min; if well-tolerated, second infusion and each subsequent infusion may be administered over 30 min which is the shortest period permissible for infusion. As a routine precaution, after infusion of tislelizumab on Day 1 of Cycle 1 and Cycle 2, patients must be monitored for at least 1 hour afterwards 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.

[21] Study treatment must begin within 3 business days of randomization for Cycle 1 Day 1. Patients may receive premedications prior to the initiation of chemotherapy according to the routine standard of care. The treatment window for paclitaxel given on a weekly schedule is ± 2 days. The dosing frequency in this appendix will not be applicable for patients receiving weekly paclitaxel as a chemotherapy regimen, and they should follow the dosing regimen described in Table 2 of Section 3.3.2 or Table 3 of Section 5.1.4, or other local guidelines, as applicable.

[22] Representative tumor specimens in paraffin blocks (preferred) or approximately 10 unstained slides are required to be submitted for biomarker analysis if available. In the absence of archival tumor tissues, a fresh biopsy of a tumor lesion at baseline is highly recommended. Optional biopsies will also be taken for the patients who have confirmed disease progression during the study from accessible tumor sites to obtain samples to explore resistance mechanism. If feasible, any follow-up biopsy should be ideally taken from the same tumor lesion at baseline. Written patient consent is required for fresh tumor biopsies.

[23] Optional blood samples (approximately 10 mL each timepoint) will be taken at the time of first tumor response (tumor assessment is CR/PR) and/or confirmed disease progression for all randomized patients, to explore the association of blood-based biomarkers with response, resistance, and prognosis to tislelizumab or chemotherapy. Written patient consent is required for blood sample collections.

[24] All HRQoL assessments are to be performed prior to study treatment initiation, Cycles 1-6 Day 1 or at the EOT Visit (whichever occurs first), and at the Safety Follow-Up Visit. A visit window of ± 7 days will apply to an HRQoL visit assessment. HRQoL instruments are to be given to the patient prior to being seen by a health care professional. NOTE: HRQoL assessments are to be conducted both at screening and C1D1 visit; if screening visit is < 7 days from C1D1 visit, the HRQoL assessment does not need to be repeated.

[25] Patients who are suspected or known to have serious/severe respiratory condition or exhibit significant respiratory symptoms unrelated to underlying cancer 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 the determination of suitability for enrollment on the study. Uncertain cases should be discussed with the medical monitor.

[26] Eye examination, visual acuity test, and optical coherence tomography (or equivalent diagnostic test for retinal examination) captured as standard of care prior to obtaining written informed consent and within 28 days of randomization may be used rather than repeating tests. Eye examination, visual acuity test, and optical coherence tomography (or equivalent diagnostic test) will be assessed at the Screening Visit. Patients on the tislelizumab arm will undergo repeated assessments approximately every 15 weeks (± 7 days) during study treatment and a final assessment < 30 days (± 7 days) after the last dose of study treatment. Investigators should solicit patients regarding changes in vision, visual disturbance, or ocular inflammation at each scheduled study visit during tislelizumab treatment. For any change in vision, referral to an appropriate specialist will be made for further management guidance.

[27] To avoid bias, tumor assessments should occur independently of treatment and the timing of the tumor assessments should be based on the date of randomization.

[28] For patients on the tislelizumab arm, ophthalmologic assessments including eye examination, visual acuity test, and OCT (or equivalent diagnostic test) should only be performed once at either the EOT or during safety follow up, within 30 days (± 7 days) of study treatment end.

APPENDIX 2. 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, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (Version 1.1). Eur J Cancer. 2009; 45:228-247.

DEFINITIONS

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (Version 1.1). Changes in only the largest diameter (uni-dimensional measurement) of the tumor lesions are used in the RECIST criteria.

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

Measurable Disease

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

- 10 mm by CT scan (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 examination (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 ≤ 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable 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 non-measurable disease. Leptomeningeal disease, ascites, pleural, or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques are all non-measurable.

Bone lesions:

- Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.
- Cystic lesions:
- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study 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 x 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 non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological 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.

Non-target 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 non-target 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 study.

- 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 studies 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 (PSA) 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 studies 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 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, 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 Non-target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the protocol.

- CR: Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
- PD: Unequivocal progression (as detailed below) of existing non-target lesions. (NOTE: the appearance of one or more new lesions is also considered progression.)
- Non-CR/Non-PD: Persistence of one or more non-target 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 non-target disease, there must be an overall level of substantial worsening in non-target 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 non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.
- When the patient has only non-measurable disease: This circumstance arises in some Phase 3 studies when it is not a criterion of study entry to have measurable disease. The same general concept apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase diameter in a measurable lesion).

Examples include an increase in a pleural effusion from "trace" to "large", an increase in lymphangitic disease from localized to widespread, or may be described in protocols as "sufficient to require a change in therapy". If "unequivocal progression" is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or 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 study 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 study 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: This 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 best overall response is the best response recorded from the start of the study drug treatment until the end of treatment taking into account any requirement for confirmation. On occasion, a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized studies where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "best overall response".

The best overall response is determined once all the data for the patient is known. Best response determination in studies where confirmation of complete or partial response IS NOT required: Best response in these studies is defined as the best response across all timepoints (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response 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 timepoint 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 unevaluable.

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" on the eCRF.

In studies where confirmation of response is required, repeated 'NE' timepoint assessments may complicate best response determination. The analysis plan for the study must address how missing data/assessments will be addressed in determination of response and progression. For example, in most studies it is reasonable to consider a patient with timepoint 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 study therapy.

Conditions that define "early progression, early death, and unevaluable response" are study 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 non-randomized studies 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 studies. However, in all other circumstances, ie, in randomized studies (phase 2 or 3) or studies 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 study results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study 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 randomized studies, 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 study, the protocol should specify the minimal time interval required between two 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 studies are to be made.

APPENDIX 3. ECOG PERFORMANCE STATUS-GRADING SYSTEM

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, eg, 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

As published by (Oken et al 1982). Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

APPENDIX 4. 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. Patients with a history of one or more of the conditions listed in the table below are excluded from participating in the study, with some possible exceptions, as follows:

- An exception may be made for patients with a medical history of such entities as atopic disease or childhood arthralgias, for which the clinical suspicion of autoimmune disease is low.
- Patients with a history of autoimmune-related hypothyroidism who are on a stable dose of thyroid replacement hormone may be eligible for this study.
- Patients with a history of transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent (eg, acute Lyme arthritis) are not excluded.

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

Acute disseminated encephalomyelitis	Addison's disease
Ankylosing spondylitis	Antiphospholipid antibody syndrome
Aplastic anemia	Autoimmune hemolytic anemia
Autoimmune hepatitis	Autoimmune hypoparathyroidism
Autoimmune hypophysitis	Autoimmune myocarditis
Autoimmune oophoritis	Autoimmune orchitis
Autoimmune thrombocytopenic purpura	Behcet's disease
Bullous pemphigoid	Chronic inflammatory demyelinating polyneuropathy
Chung-Strauss syndrome	Crohn's disease
Dermatomyositis	Diabetes mellitus Type 1
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	Sjögren's syndrome
Stiff person syndrome	Takayasu's arteritis
Ulcerative colitis	Vogt-Kovangai-Harada disease

APPENDIX 5. CONTRACEPTION GUIDELINES AND DEFINITIONS OF "WOMEN OF CHILDBEARING POTENTIAL" AND "WOMEN OF 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

  NOTE: This is only considered a highly effective form of birth control when the vasectomized partner is the sole partner of the study participant and there has been a medical assessment confirming surgical success.

  NOTE: A sterile male is one for whom azoospermia, in a semen sample examination, has been demonstrated as definitive evidence of infertility. Males with 'low sperm counts' (consistent with 'sub-fertility) are not to be considered sterile for purposes of this study.

- 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, post-ovulation 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 another highly effective form of birth control listed above.

Definitions of "Women of Childbearing Potential" and "Women of Non-Childbearing Potential" are applicable to both study participants and sexual partners of male participants.

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

Conversely, "women of non-childbearing potential" are defined as female patients meeting any of the following criteria:

- Surgically sterile (ie, through bilateral salpingectomy, bilateral oophorectomy, or hysterectomy)
- Post-menopausal, defined as:
  - $\geq$ 55 years of age with no spontaneous menses for $\geq$ 12 months OR
  - < 55 years of age with no spontaneous menses for $\geq$ 12 months AND with postmenopausal follicle-stimulating hormone concentration > 30 IU/mL

Study participants receiving chemotherapy have a potential risk of irreversible infertility. Patients should be advised to speak to their physician for further information about their locally available options for fertility preservation.

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

APPENDIX 6. NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity (eg, no shortness of breath when walking, climbing stairs, et cetera).
II	Mild symptoms (eg, mild shortness of breath and/or angina). Slight limitations during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, eg, walking short distances (20-100 meters). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound.

APPENDIX 7. 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 8. 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

APPENDIX 9. EQ-5D-5L QUESTIONNAIRE

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

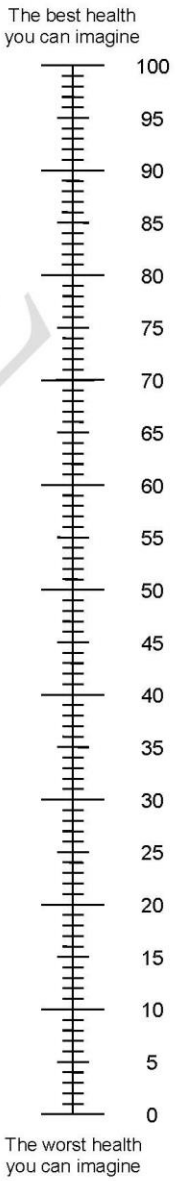
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



APPENDIX 10. IMMUNE-RELATED ADVERSE EVENT EVALUATION AND MANAGEMENT

The recommendations below for the diagnosis and management of any irAE 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. However, stopping rules for study drug must be followed as described below.

Criteria used to diagnose irAEs 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 irAE diagnosis:

- What was the temporal relationship between initiation of tislelizumab and the adverse event?
- How did the patient respond to withdrawal of 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 irAE field, associated with the AE in the eCRF should be checked.

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

Immune-related 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-related Adverse Events

Immune-related 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.
Ocular Disorders	If patients experience 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 or 4; every 2-3 days if Grade 2, until recovering). Review medications (eg, statins, antibiotics) and alcohol history. Perform liver screen including Hepatitis A/B/C serology, Hepatitis E PCR and assess anti-ANA/SMA/LKM/SLA/LP/LCI, iron studies. Consider imaging, eg, ultrasound scan for metastases or thromboembolism. Consult with a hepatologist and consider liver biopsy.
Renal toxicity	Review hydration status, and medication history. Test and culture urine. Consider renal ultrasound scan, protein assessment (dipstick/24-hour urine collection), or phase-contrast microscopy. Refer to nephrology for further management assistance.
Dermatology	Consider other causes by conducting a physical examination, consider dermatology referral for skin biopsy
Joint or muscle inflammation	Conduct musculoskeletal history and perform complete rheumatology examination. Consider joint X-ray and other imaging as required to exclude metastatic disease. Perform autoimmune serology and refer to rheumatology for further management assistance. For suspected myositis/rhabdomyolysis/myasthenia include: CK, ESR, CRP, troponin and consider a muscle biopsy
Myocarditis	Perform ECG, echocardiogram, CK/CK-MB, troponin (I and/or T), and refer to a cardiologist.

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

Treatment of Immune-related Adverse Events

- Immune-related AEs can escalate quickly; study treatment interruption, close monitoring, timely diagnostic work-up and treatment intervention, as appropriate, with patients is required
- Immune-related 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 irAEs, 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
- Tislelizumab must be permanently discontinued for any onset of Grade 4 or recurrent Grade 3 immune-related adverse events

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. For recurrent Grade 3: Discontinue study treatment. For Grade 4: Discontinue study treatment.
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.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3-4 Moderate-severe symptoms	Refer patient to an endocrinologist for assessment and treatment. Initiate pulse IV methylprednisolone 1 mg/kg for patients with headache/visual disturbance due to pituitary inflammation. Convert to oral prednisolone and taper over at least 1 month. Maintain hormone replacement according to endocrinology advice. Maintain hormone replacement according to endocrinology advice.	For Grade 3: Discontinue study treatment. For Grade 4: Discontinue study treatment.
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.
	3-4 Severe or life-threatening symptoms Breathless at rest	Admit to a hospital and initiate treatment with IV methylprednisolone 2-4 mg/kg/day. If there is no improvement, or worsening after 48 hours, add infliximab 5 mg/kg (if no hepatic involvement). Convert to oral prednisolone and taper over at least 2 months. Cover with empiric antibiotics and consider prophylaxis for Pneumocystis infection and other adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement.	Discontinue study treatment.

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

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	4 Life-threatening symptoms	perforation, sepsis, TB, hepatitis, NYHA Grade III/IV CHF or other immunosuppressive treatment: MMF or tacrolimus. Consult gastroenterologist to conduct colonoscopy/ sigmoidoscopy.	Discontinue study treatment.
Skin reactions	1 Skin rash, with or without symptoms, < 10% BSA	Avoid skin irritants and sun exposure; topical emollients recommended.	Continue study treatment.
	2 Rash covers 10%-30% of BSA	Avoid skin irritants and sun exposure; topical emollients recommended. Topical steroids (moderate strength cream once a day or potent cream twice a day) ± oral or topical antihistamines for itch. Consider a short course of oral steroids.	Continue study treatment.
	3 Rash covers > 30% BSA or Grade 2 with substantial symptoms	Avoid skin irritants and sun exposure; topical emollients recommended. Initiate steroids as follows based on clinical judgement: For moderate symptoms: oral prednisolone 0.5-1 mg/kg/day for 3 days then taper over 2-4 weeks. For severe symptoms: IV methylprednisolone 0.5-1 mg/kg/day; convert to oral prednisolone and taper over 2-4 weeks.	Hold study treatment. Re-treat when AE is resolved or improved to mild rash (Grade 1 or 2) after discussion with the study medical monitor. For recurrent Grade 3: Discontinue study treatment
	4 Skin sloughing > 30% BSA with associated symptoms (eg, erythema, purpura, epidermal detachment), including Stevens-Johnson Syndrome (all grades), and toxic epidermal necrolysis	Initiate IV methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Admit to a hospital and seek urgent dermatology consultation.	Discontinue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Myositis/ Rhabdomyolysis	1 Mild weakness with/without pain	Prescribe analgesics. If CK is significantly elevated above upper limit of normal but < 2.5 x ULN and patient has symptoms, consider oral steroids and treat as Grade 2	Continue study treatment.
	2 Moderate weakness with/without pain	If CK is 3 x ULN or worse initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks	Hold study treatment until improved to grade 0-1
	3-4 Severe weakness, limiting self-care	Admit to hospital and initiate oral prednisolone 1 mg/kg. Consider bolus IV (methyl)prednisolone and 1-2 mg/kg/day maintenance for severe activity restriction or dysphagia. If symptoms do not improve add immunosuppressant therapy. Taper oral steroids over at least 4 weeks	Discontinue if any evidence of myocardial involvement For recurrent Grade 3: Discontinue study treatment. For Grade 4: Discontinue study treatment.
Myocarditis	1 Asymptomatic but significantly increased CK-MB (an elevation of CK-MB would be any value above upper limit of normal) 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 refer to a cardiologist. Transfer all patients with moderate/severe cardiac symptoms or any increase in	Follow the same study drug management for Grade 1.
	3 Severe symptoms with mild exertion		Discontinue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	4 Life-threatening	cardiac serum markers to the coronary care unit. Initiate oral prednisolone or IV (methyl) prednisolone at 1-2 mg/kg/day. 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	Discontinue study treatment.
Hepatitis	1 ALT or AST > ULN to 3 x ULN	Check LFTs within 1 week and before the next dose to verify that there has been no worsening.	Based on clinical judgement, continue study treatment or hold. If study drug is held, recheck LFTs in 48-72 hours and restart study drug if LFTs did not worsen.
	2 ALT or AST 3-5 x 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.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3 ALT or AST 5-20 x ULN	ALT/AST < 400 IU/L and normal bilirubin/INR/albumin: Initiate oral prednisolone 1 mg/kg and taper over 2-4 weeks. ALT/AST > 400 IU/L or raised bilirubin/INR/low albumin: Initiate IV (methyl)prednisolone 2 mg/kg/day and recheck LFTs every day. When LFTs improve to Grade 2 or lower, convert to oral prednisolone and taper over at least 1 month. Recheck LFTs according to severity grade above.	Hold study treatment until improved to baseline grade; reintroduce only after discussion with the study medical monitor. If ALT or AST > 8xULN or rise in total bilirubin > 5xULN: Discontinue study treatment For recurrent Grade 3: Discontinue study treatment
	4 ALT or AST > 20X ULN	Initiate IV methylprednisolone 2 mg/kg/day and recheck LFTs every day. Convert to oral prednisolone and taper over at least 6 weeks. Recheck LFTs according to severity grade above.	Discontinue study treatment.
	Worsening LFTs despite steroids: • If on oral prednisolone, change to pulsed IV methylprednisolone • If on IV, add mycophenolate mofetil (MMF) 500-1000 mg twice a day • If worsens on MMF, consider addition of tacrolimus Duration and dose of steroid required will depend on severity of event		
Nephritis	1 Creatinine 1.5 x baseline or > ULN to 1.5 x ULN	Repeat creatinine weekly. If symptoms worsen, manage as per criteria below.	Continue study treatment.
	2 Creatinine > 1.5-3 x baseline or > 1.5-3 x 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.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3 Creatinine > 3 x baseline or > 3-6 x ULN	Hospitalize patient for monitoring and fluid balance; repeat creatinine every 24 hours; refer to a nephrologist and discuss need for biopsy. If worsening, initiate IV (methyl)prednisolone 1-2 mg/kg. Taper corticosteroids over at least 1 month.	Hold study treatment until the cause is investigated. If study drug suspected: Discontinue study treatment. For recurrent Grade 3: Discontinue study treatment
	4 Creatinine > 6 x 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. Checks 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. For recurrent Grade 3: Discontinue study treatment
	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.	Discontinue study treatment

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Ocular Toxicity	1 Asymptomatic eye examination/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.	Discontinue study treatment. For recurrent Grade 3: Discontinue study treatment
	4 Blindness (at least 20/200) in the affected eyes	Initiate IV (methyl)prednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks	Discontinue study treatment
Pancreatitis	2 Asymptomatic, blood test abnormalities	Monitor pancreatic enzymes	Continue study treatment
	3 Abdominal pain, nausea and vomiting	Admit to hospital for urgent management. Initiate IV (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when amylase/lipase improved to Grade 2, and taper over at least 4 weeks	Discontinue study treatment. For recurrent Grade 3: Discontinue study treatment
	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 to worsen, hold study treatment until symptoms improve to baseline or Grade 0-1

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	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. For recurrent Grade 3: Discontinue study treatment
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 guideline, treat with analgesics, topical treatments and oral hygiene care. Ensure adequate hydration. If symptoms worsen or there is sepsis or bleeding, manage as Grade 3.	Continue study treatment
	3 Severe pain, limited food and fluid intake, daily living activity limited	Admit to hospital for appropriate management. Initiate IV (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when symptoms improved to Grade 2 and taper over at least 4 weeks	Hold study treatment until improved to Grade 0 to 1. For recurrent Grade 3: Discontinue study treatment
	4 Life-threatening complications or dehydration	Admit to hospital for emergency care. Consider IV corticosteroids if not contraindicated by infection	Discontinue study treatment

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

APPENDIX 11. 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) equation1 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. Read more about creatinine standardization.

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 x min (Scr /κ, 1) α x max (Scr /κ, 1)-1.209 x 0.993Age x 1.018 [if female] x 1.159 [if black]

where:

Scr 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,

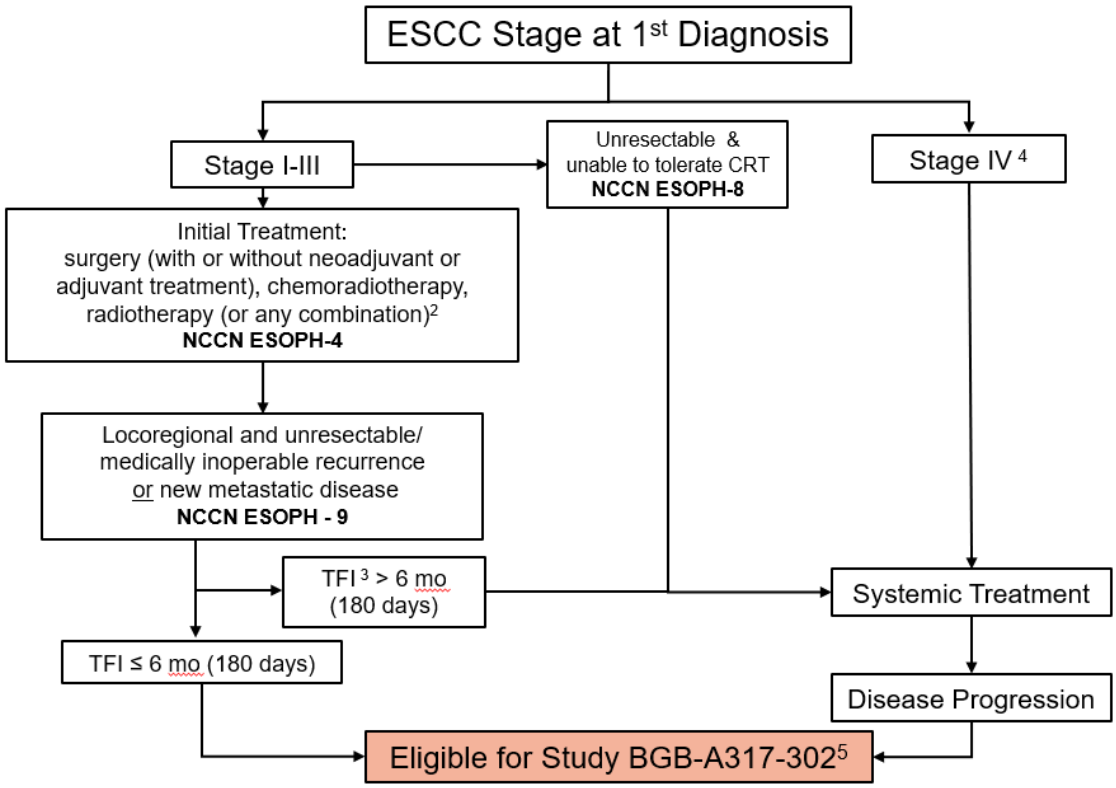
min indicates the minimum of Scr /κ or 1, and

max indicates the maximum of Scr /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

APPENDIX 12. DETERMINING LINE OF THERAPY IN ESCC [1]



Notes:

1. This is a general guide to determine the line of therapy and cannot cover all possibilities; if you have questions, please consult the medical monitor
2. The First Line or Front-Line systemic treatment is defined as "platinum-based regimen". Single drug regimen or non-platinum regimen which is used alone or used for radiotherapy sensitization (the dose is lower than the NCCN treatment guidance recommended standard systematic treatment dose) should not be considered as one line of therapy.

   Combination must include chemotherapy and may also include surgery and radiotherapy.
3. Treatment free interval (TFI) is defined as duration from the last day (given day/infusion day) of prior treatment to the date of progression.
4. Patients with stage IV disease at first diagnosis are eligible for this study when their cancer has progressed after the 1st line of systemic treatment, regardless of the length of the TFI.
5. Patients must meet all inclusion and exclusion criteria to be enrolled into this study.

APPENDIX 13. SAFETY RUN-IN SUBSTUDY INVESTIGATING SAFETY, TOLERABILITY, PHARMACOKINETICS AND PRELIMINARY ANTITUMOR ACTIVITY OF ANTI-PD-1 MONOCLONAL ANTIBODY TISLELIZUMAB IN JAPANESE PATIENTS WITH ADVANCED UNRESECTABLE/METASTATIC ESOPHAGEAL SQUAMOUS CELL CARCINOMA

SYNOPSIS FOR SUBSTUDY

Name of Sponsor: BeiGene, Ltd.
Investigational Product: Tislelizumab (BGB-A317)
Title of Study: Safety Run-in Substudy Investigating Safety, Tolerability, Pharmacokinetics and Preliminary Antitumor Activity of Anti-PD-1 Monoclonal Antibody Tislelizumab (BGB-A317) in Japanese Patients with Advanced Unresectable/Metastatic Esophageal Squamous Cell Carcinoma
Protocol Identifier: BGB-A317-302 Substudy
Number of Patients: A minimum of 6 and up to a maximum of 10 patients will be enrolled to assess pharmacokinetics (PK) and dose-limiting toxicity (DLT). (Up to 20 patients will be enrolled if more than one dose level is explored.)
Study Centers: To be determined
Study Objectives: Primary: • To assess the safety and tolerability of tislelizumab in Japanese patients with advanced unresectable esophageal squamous cell carcinoma (ESCC) • To confirm the pivotal Phase 3 dose of tislelizumab in Japanese patients • To characterize the pharmacokinetics of tislelizumab in Japanese patients Secondary: • To assess the preliminary antitumor activity of tislelizumab • To assess host immunogenicity to tislelizumab Exploratory: • To explore correlations between drug exposure and response

Study Endpoints:

Primary:

- Tislelizumab safety and tolerability: The safety of tislelizumab will be assessed throughout the study by monitoring adverse events (AEs) and serious adverse events (SAEs) per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version (v)4.03, relevant physical examination, electrocardiograms (ECGs) and laboratory assessments as needed
- The pivotal Phase 3 dose for tislelizumab will be confirmed based on safety, tolerability, pharmacokinetics, and other available data
- PK evaluations: Individual tislelizumab concentrations and PK parameters will be tabulated by visit/cycle and/or dose cohort

Secondary:

- Efficacy evaluations: Overall response rate (ORR), progression-free survival (PFS), and duration of response (DOR) will be determined based on assessment by investigator per Response Evaluation Criteria in Solid Tumors (RECIST) Version (v)1.1. Overall survival (OS) will be evaluated.
- Anti-BGB-A317 antibody: Assessments of immunogenicity of tislelizumab to determine the incidence of anti-drug antibodies (ADAs)

Exploratory:

- Assessments of the correlations between drug exposure and response (efficacy, safety endpoints)

Study Assessments:

Dose-limiting toxicities (DLTs) will be assessed among evaluable patients after 21 days on study. An evaluable patient is defined as the patient who has received at least 80% of the dose and completed all safety assessments required during the first 21 days, or any patient who has experienced a DLT within 21 days. The first six patients will be hospitalized for the first week of Cycle 1.

Tumor response will be evaluated by the investigator per RECIST v1.1 approximately every 6 weeks for the first 6 months and every 9 weeks thereafter. If a patient discontinues study treatment due to any reason other than disease progression or death, tumor assessments will continue as scheduled until disease progression, death, loss to follow-up, or withdrawal of consent, whichever occurs first.

Patients will be evaluated for any AEs and serious adverse events (SAEs) occurring up to 30 days after the last dose of study drug (all severity grades, per NCI-CTCAE v4.03) or initiation of a new anticancer therapy, whichever occurs first, and immune-related AEs (irAEs) occurring up to 90 days after the last dose of study drug regardless of initiation of a subsequent anticancer therapy. All drug-related SAEs will be recorded by the investigator after treatment discontinuation until patient death, withdrawal of consent, or loss to follow-up, whichever occurs first. All study drug-related SAEs will be followed until they resolve to baseline or ≤ Grade 1, the investigator assesses the AE as stable and unlikely to improve, or the patient is lost to follow-up, whichever occurs first.

Safety and efficacy monitoring will be performed by an Independent Data Monitoring Committee (IDMC) as per the main protocol (Section 8.5). The IDMC will additionally evaluate and confirm the Phase 3 dose based on the safety and tolerability of tislelizumab, and decide whether to add unscheduled dose levels for the study. The IDMC may recommend modifications to the study, including termination due to safety and/or efficacy concerns.

Dose Level

Based on the safety results of the Phase 1 studies of tislelizumab (Studies BGB-A317_Study_001 and BGB-A317-102), this study will initially assess the safety and PK characteristics of fixed dose 200 mg once every three weeks (Q3W) in Japanese patients with advanced unresectable/metastatic ESCC. Other dose levels may be further explored based on the tolerability in these patients.

Among the 6 patients in the 200 mg Q3W cohort, if 2 or more patients experience DLT in Cycle 1, that starting dose will be considered as exceeding the maximum tolerated dose (MTD), and a lower dose (eg, 150 mg Q3W), will be subsequently assessed in 3 to 6 patients.

If the 200-mg Q3W regimen passes the DLT assessment, the cohort at that dose level can be expanded to approximately 10 patients to further assess the safety, tolerability, pharmacokinetics and preliminary pharmacodynamic characteristics of tislelizumab. Up to 20 patients may be enrolled if a lower dose level is evaluated (such as 150 mg Q3W).

Dose-limiting Toxicity

All AEs will be graded according to the NCI-CTCAE v4.03. The occurrence of any of the following toxicities during Cycle 1 will be considered DLT, if judged by the investigator as related to study drug administration:

Hematologic Dose-limiting Toxicities:

1. Grade 4 neutropenia lasting > 7 days
2. Febrile neutropenia (defined as absolute neutrophil count [ANC] < 1000/mm^3 with a single temperature of 38.3°C or a sustained temperature of 38°C for > 1 hour)
3. Grade 3 neutropenia with infection
4. Grade 3 thrombocytopenia with bleeding

5. Grade 4 thrombocytopenia
6. Grade 4 anemia (life-threatening)

Non-hematologic Dose-limiting Toxicities:

1. Grade 4 or above toxicity
2. Grade 3 toxicity lasting > 7 days despite optimal supportive care

NOTE: The following AEs will not be considered as DLTs:

- Grade 3 endocrinopathy that is adequately controlled by hormonal replacement
- Grade 3 AE of tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumors)
- Grade 3 rash
- Grade 3 to Grade 4 laboratory abnormalities that are not associated with clinical sequelae (eg, LDH)

In addition, clinically important or persistent toxicities that are not included above may also be considered a DLT following review by IDMC.

Patients who received less than two-thirds (67%) of the assigned dose of tislelizumab (eg, because the infusion had to be discontinued due to an infusion reaction) and did not experience a DLT will not be taken into account in the assessment of the overall DLT rate for that particular dose level.

Key Eligibility Criteria:

The population under study is adult Japanese patients (≥ 20 years of age on the day the patient voluntarily agrees to participate in the study) with histologically confirmed diagnosis of ESCC with tumor progression during or after first-line treatment for advanced unresectable/metastatic disease. All patients are also required to have at least one evaluable lesion per RECIST v1.1 within 28 days prior to Cycle 1 Day 1, an Eastern Cooperative Oncology Group Performance Status score of 0 or 1.

Test Product, Dose, and Mode of Administration:

Tislelizumab will be administered at a dose of 200 mg intravenously (IV) Q3W. The proposed dose level can be further adjusted according to the safety and tolerability observed in the dose verification stage, and lower dose levels may be added if necessary.

Statistical Methods:

Descriptive statistics will be used to summarize the demographic, disease characteristic, efficacy and safety data. No statistical hypotheses are planned in this exploratory study.

All patients who have received tislelizumab will be included in the Safety analysis set. All patients with valid tislelizumab PK sampling after treatment will be included in the PK analysis set. For other parameters, all evaluable data will be included in the summaries.

Efficacy Analysis:

The efficacy per RECIST v1.1 (ie, ORR, PFS and DOR) will be summarized to explore the preliminary anti-cancer activities in Japanese patients.

The ORR is defined as the proportion of patients who had confirmed complete response (CR) or partial response (PR) assessed by the investigator using RECIST v1.1.

The DOR is defined as the time from the first determination of a confirmed objective response by investigator per RECIST v1.1 until the first documentation of progression or death, whichever comes first.

The PFS is defined as the time from the date of first dose of study drug to the date of first documentation of disease progression assessed by investigator using RECIST v1.1 or death, whichever occurs first.

The ORR and its 95% confidence interval will be summarized in the Safety analysis set. Both PFS and DOR will be estimated using the Kaplan-Meier method. Waterfall plot of maximum tumor shrinkage per patient will be presented.

Safety Analysis:

Safety will be determined by the reporting of AEs and by laboratory values (hematology, clinical chemistry, coagulation, and urinalysis). Vital signs, physical examinations, and ECG findings will also be used in determining safety. The severity of AEs will be graded per NCI-CTCAE v4.03. The incidence of DLT events and treatment-emergent adverse events (TEAEs) will be reported as the number (percentage) of patients with TEAEs by System Organ Class and Preferred Term. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) and changes from baseline will be determined for laboratory parameters and vital signs.

Statistical methods will be described in detail in the Statistical Analysis Plan.

1. INTRODUCTION

Before initiating this Phase 3 study in Japan, a substudy investigating the safety, tolerability, pharmacokinetics (PK), and preliminary efficacy is planned. This study is a dose-validation clinical study of the monoclonal antibody BGB-A317 in Japanese patients with advanced unresectable/metastatic esophageal squamous cell carcinoma (ESCC), aiming to explore safety, tolerability, and pharmacokinetics. This study is carried out based on Phase 1 studies evaluating tislelizumab (BGB-A317_Study_001 and BGB-A317-102). Per the preliminary results of the Phase 1A Study BGB-A317_001, 0.5, 2, 5, and 10 mg/kg once every two weeks (Q2W) are all tolerable doses. In addition, 2 and 5 mg/kg Q3W (once every 3 weeks) and 200 mg Q3W have also been confirmed as tolerable. A 200 mg Q3W fixed dose was selected as the pivotal dose for Phase 3 studies. In the Phase 1 clinical study in China, six patients were administered the 200 mg Q3W fixed dose and PK analysis indicated that this is equivalent to 2.4 to 3.8 mg/kg, based on body weight. The comparison results of dose normalized C_{max} and area under the concentration-time curve from Day 0 to Day 14 (AUC0-14d) showed that the PK is consistent in Chinese and Caucasian patients. The available safety and PK data suggest that the proposed dose of 200 mg Q3W tislelizumab is expected to be a safe dose to investigate in Japanese patients.

The background on ESCC and on the monoclonal antibody, BGB-A317 is provided in the main study in Section 1 , Introduction.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objectives

- To assess the safety and tolerability of tislelizumab as second-line in treatment Japanese patients with advanced unresectable/metastatic ESCC
- To confirm the pivotal Phase 3 dose of tislelizumab in Japanese patients
- To characterize the pharmacokinetics of tislelizumab in Japanese patients

2.1.2. Secondary Objectives:

- To assess the preliminary antitumor activity of tislelizumab
- To assess host immunogenicity to tislelizumab

2.1.3. Exploratory Objectives

- To explore correlations between drug exposure and response

2.2. Endpoints

2.2.1. Primary Endpoints

- Tislelizumab safety and tolerability: The safety of tislelizumab will be assessed throughout the study by monitoring AEs and serious adverse events (SAEs) per

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE Version [v]4.03), relevant physical examination, electrocardiograms (ECGs) and laboratory assessments as needed

- The pivotal Phase 3 dose for tislelizumab will be determined based on safety and tolerability, and other available data (which may include PK and/or preliminary efficacy)
- PK evaluations: Individual tislelizumab concentrations and PK parameters will be tabulated by visit/cycle and/or dose cohort

2.2.2. Secondary Endpoints

- Efficacy evaluations: Overall response rate (ORR), progression-free survival (PFS), and duration of response (DOR) will be determined based on assessment by investigator per Response Evaluation Criteria in Solid Tumors (RECIST) Version (v)1.1. Overall survival (OS) will also be evaluated.
- Anti-tislelizumab antibody: Assessments of immunogenicity of tislelizumab to determine the incidence of anti-drug antibodies (ADAs)

2.2.3. Exploratory Endpoints

- Assessments of the correlations between drug exposure and response (efficacy, safety endpoints)

3. STUDY DESIGN

3.1. Summary of Study Design

This is an open-label, multicenter, non-randomized Phase 1 clinical study in Japanese patients with advanced unresectable/metastatic ESCC who have received prior treatment. Screening can last up to 28 days and treatment can last until the investigator considers the patient is no longer benefiting from tislelizumab, toxicity, or voluntary withdrawal of study treatment. A minimum of 6 patients and a maximum of 10 patients will be enrolled to assess dose-limiting toxicities (DLTs) and to adequately address the PK profile of tislelizumab in Japanese patients. Up to 20 patients may be enrolled if more than one dose level is explored. A Safety Follow-up phase will last 30 days (± 7 days) after the last dose of tislelizumab or before the initiation of a new anti-cancer treatment, whichever occurs first for any AEs, and up to 90 days following last dose of tislelizumab for irAEs, regardless of initiation of subsequent anticancer treatment. Survival follow-up information will be collected approximately 1 month (4 weeks ± 7 days) after the Safety Follow-up Visit and approximately monthly thereafter until death, loss to follow-up, withdrawal of consent, or study termination by sponsor. The first 6 patients will remain hospitalized during the first week of the first cycle of treatment.

3.2. Schedule of Study Assessments

A schedule of efficacy and safety assessments is presented in Table 7.

Table 7: Japan Substudy Schedule of Assessments

Assessment Window (Days)	Screening[1]	All Treatment Cycles[2]				End of Treatment[3] (0-7 days)	Safety Follow-up[3] (30 ± 7 days after last dose)	Survival Follow-up[4] (Every month)
		Cycles 1-2			Cycle 3 and Subsequent Cycles			
	Day -28 to -1	Day 1 (± 3)	Day 8 (± 2)	Day 15 (± 2)	Day 1 (± 3)			
Informed consent[1]	x							
Inclusion/Exclusion criteria	x							
Demographic/Medical history/Prior medications	x							
Cancer Diagnosis and Treatment History[5]	x							
Concomitant medications[6]	x	x	x	x	x	x	x	
Adverse events[7]	x	x	x	x	x	x	x	
Physical examination[8, 9]	x	x			x	x	x	
ECOG performance status[9]	x	x			x	x	x	
Vital signs[10]	x	x			x	x	x	
12-lead ECG[11]	x	As clinically indicated				x		
HBV and HCV serology[12]	x	As clinically indicated						
Hematology[13]	x	x	x	x	x	x	x	
Serum chemistry[13]	x	x	x	x	x	x	x	
Total CK and CK-MB[13]	x	x	x	x	x	x	x	
Coagulation parameters[13]	x	As clinically indicated				x	x	
Urinalysis[13]	x	As clinically indicated				x	x	
Pregnancy test[14]	x	x			x	x	x	
Thyroid function[15]	x	Every 3rd cycle					x	
Pharmacokinetics[16]		x	x	x	x		x	
Anti-drug antibodies[16]		x			x		x	
Tumor assessment[17]	x	Every 6 weeks for 6 months, then every 9 weeks				x		
Tislelizumab administration[18]		x						
Archive/Fresh Tumor tissue	x							

Assessment Window (Days)	Screening[1] Day -28 to -1	All Treatment Cycles[2] Cycles 1-2 Day 1 (± 3)	Day 8 (± 2)	Day 15 (± 2)	Cycle 3 and Subsequent Cycles Day 1 (± 3)	End of Treatment[3] (0-7 days)	Safety Follow-up[3] (30 ± 7 days after last dose)	Survival Follow-up[4] (Every month)
collection[19]								
HRQoL Assesments[20]	x	x			Cycles 3-6 only	x	x	
Survival status								x
Pulmonary function tests[21]	x							
Optical coherence tomography (or equivalent diagnostic test) and visual acuity tests[22]	x	Every 15 weeks ± 7 days				x[23]	x[23]	

Abbreviations: x, to be performed; ECOG, Eastern Cooperative Oncology Group; ECHO, echocardiography; ECG, electrocardiogram; HBV, hepatitis B virus; HCV, hepatitis C virus; MRI, magnetic resonance imaging; HRQoL, Health-Related Quality of Life.

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 Cycle 1 Day 1 may be used for screening assessments rather than repeating such tests. Fresh tumor biopsy is permitted if no archival tumor tissue is available.

2 After Cycle 1, there is a three-day window for all study treatment unless otherwise noted. Efficacy assessments will be performed approximately every 6 weeks for 6 months, then every 9 weeks.

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

The mandatory Safety Follow-Up visit is required to be conducted 30 days (± 7 days) after the last dose of study therapy, or before initiation of a new treatment. At the end of treatment, ongoing AEs considered related to study treatment will be followed until the event has resolved to baseline or ≤ Grade 1, the event is assessed by the investigator as stable, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the AE.

4 Survival follow-up information will be collected after discontinuation of the study treatment via email or other communication, patient medical records, and/or clinic visits approximately 1 month (4 weeks ± 7 days) after the Safety Follow-up Visit and approximately monthly thereafter until death, loss to follow-up, withdrawal of consent, or study termination by sponsor. All patients will also be followed for new anti-cancer therapy information unless the patient requests to be withdrawn from follow-up.

5 Includes history of treatment for the primary diagnosis, including prior systemic, radiation treatment and surgical treatment. Radiographic imaging performed prior to study entry may be collected for review by the investigator.

6 Concomitant medications include any prescription medications, over-the-counter medications, herbal supplements, and IV medications and fluids. All concomitant medications received within 30 days before the first dose of tislelizumab and 30 days after the last infusion of tislelizumab should be recorded. At subsequent visits, changes to current medications or medications used since the last documentation of medications will be recorded.

[7] AEs and laboratory safety measurements will be graded per NCI-CTCAE version v4.03. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness. After informed consent has been signed but prior to the administration of the study drug, only SAEs should be reported. After the first dose of study drug, all AEs and SAEs, regardless of their assessed relationship to study drug, are to be reported until either 30 days after the last dose of study treatment or the initiation of a new anticancer therapy, whichever occurs first. All immune-related AEs should be reported for 90 days after the last dose of tislelizumab, regardless of initiation of a new anticancer therapy. After this period, the investigator should report any SAEs that are believed to be related to tislelizumab treatment (Section 8.4.1). 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 (Section 8.2.6).

[8] A complete physical examination should include an evaluation of the head, eyes, ears, nose, throat, cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations are required to be performed. Investigators should solicit patients regarding changes in vision, visual disturbance, or ocular inflammation at each scheduled study visit during tislelizumab treatment. For any change in vision, referral to an appropriate specialist will be made for further management guidance.

[9] If screening ECOG performance status, physical examination and local laboratory assessments are obtained within seven days of Cycle 1 Day 1, these assessments do not have to be repeated at Cycle 1 Day 1.

[10] Vital signs to include temperature, pulse, blood pressure, height and weight. Height will only be measured and recorded at Screening Visit. Pulse and BP should be recorded while the patient is in a seated position after resting for 10 minutes. For all infusions of tislelizumab, the patient's vital signs should be recorded before the infusion, and between 30 to 45 minutes after the infusion. Vital signs must be collected during the infusion if clinically indicated.

[11] Electrocardiogram (ECG) recordings will be obtained during screening, End of Treatment, and as clinically indicated at other timepoints. Patients should be resting and in a sitting or supine position for at least 10 minutes prior to ECG collection.

[12] Testing will be performed by the local laboratory at screening and as clinically indicated. Include HBsAg, HBcAb, and HCV antibody. Patients who are HBsAg positive at screening must not be enrolled until further definite testing with HBV DNA titers < 500 IU/mL (or 2500 copies/mL).

[13] Local or central laboratory assessments on serum chemistry (including liver function tests), hematology, coagulation, and urinalysis will be conducted within 7 days prior to Cycle 1 Day 1, of which certain elements will be collected as specified in Section 7.10 of the main protocol. If laboratory tests at screening are not performed within 7 days prior to the administration of study drug on Cycle 1 Day 1, these tests should be repeated and reviewed before study drug administration. Serum chemistry (including liver function tests) and hematology will be performed weekly for the first 2 cycles and then at the beginning of each subsequent cycle. After Cycle 1, results are to be reviewed within 3 business days before study drug administration. All patients will have creatine kinase (CK) and creatine kinase-cardiac muscle isoenzyme (CK-MB) testing at screening and all scheduled visits during the first 3 treatment cycles, all pre-dose assessments from Cycle 4 onwards, and at the EOT and Safety Follow-up Visits. In the event that CK-MB fractionation cannot be evaluated in the local laboratory, troponin I and/or troponin T should be assessed instead; the same test should be administered throughout the study. Urinalysis and coagulation parameters are to be assessed during the treatment period only if clinically indicated. Refer to Section 8.2.5 of the main protocol for additional information regarding clinical assessment and management of clinical laboratory abnormalities.

[14] Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within seven days prior to Cycle 1 Day 1. Urine pregnancy tests will be performed at each visit prior to dosing while on treatment, and at Safety Follow-up. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.

[15] Analysis of T3, T4 and TSH will be performed by the local study site laboratory. Thyroid function tests will be performed within 7 days prior to Cycle 1 Day 1 and every three cycles thereafter (eg, Cycles 4, 7 and 10, etc.), and at the mandatory Safety Follow-Up Visit.

[16] Procedures for collection of tislelizumab PK and ADA samples are described in the Laboratory Manual. Refer to Table 8 for details on timing of PK and ADA sample collection; additional PK and ADA samples are required to be collected at the Safety Follow-Up Visit. If a patient presents with any immune-related adverse event, additional blood PK samples may be taken to determine the plasma concentration of tislelizumab. These tests are required when it is allowed by local regulations/IRBs/ECs.

[17] Examinations performed as standard of care prior to obtaining informed consent and within 28 days prior to Cycle 1 Day 1 may be used rather than repeating tests. CT/MRI of the head at baseline is required for patients who are suspected to have CNS metastases. All measurable and evaluable lesions are required to be assessed and documented at the screening visit. The same radiographic procedure must be used throughout the study for each patient. The investigator must review radiograph results before dosing at the next cycle. Patients will undergo tumor assessments approximately every 6 weeks (± 7 days) for 6 months, then every 9 weeks (± 7 days) afterwards. Patients who discontinue from treatment for reasons other than disease progression or death will continue scheduled tumor assessments until disease progression, withdrawal of consent, death or start of a new anti-cancer therapy. Investigators may perform additional scans or more frequent assessments if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Patients who continue tislelizumab treatment beyond radiographic disease progression will be monitored with a follow-up scan at least 4 weeks later or at the next regularly scheduled timepoint (not exceed 6 weeks) before discontinuation of study treatment.

[18] The initial infusion of tislelizumab will be delivered over 60 min; if well-tolerated, second infusion and each subsequent infusion may be administered over 30 min which is the shortest period permissible for infusion.

[19] Representative tumor specimens in paraffin blocks (preferred) or at least 10 unstained slides is required to be submitted for biomarker analysis if available. In the absence of archival tumor tissues, a fresh biopsy of a tumor lesion at baseline is highly recommended.

[20] All HRQoL assessments are to be performed prior to study treatment initiation, Cycles 1- 6 Day 1 or at the EOT Visit (whichever occurs first), and at the Safety Follow-up Visit. A visit window of ± 7 days will apply to a HRQoL visit assessment. HRQoL instruments are to be given to the patient prior to being seen by a health care professional. NOTE: HRQoL assessments are to be conducted both at screening and C1D1 visit; if screening visit is < 7 days from C1D1 visit, the HRQoL assessment does not need to be repeated.

[21] Patients who are suspected or known to have serious/severe respiratory condition or exhibit significant respiratory symptoms unrelated to underlying cancer 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 the determination of suitability for enrollment on the study. Uncertain cases should be discussed with the medical monitor.

[22] Eye examination, visual acuity test, and optical coherence tomography (or equivalent diagnostic test for retinal examination) captured as standard of care prior to obtaining written informed consent and within 28 days of Cycle 1 Day 1 may be used rather than repeating tests. Eye examination, visual acuity test, and optical coherence tomography (or equivalent diagnostic test) will be assessed at the Screening Visit. Patients will undergo repeated assessments approximately every 15 weeks (± 7 days) during study treatment and a final assessment < 30 days (± 7 days) after the last dose of study treatment.

[23] The ophthalmologic assessments including eye examination, visual acuity test, and OCT (or equivalent diagnostic test) should only be performed once at either the EOT or during safety follow up within 30 days (± 7 days) of study treatment end.

Table 8: Schedule of Japan Substudy Pharmacokinetic Sampling and Anti-Tislelizumab Antibody Sampling

Japan Substudy		Days	Timing in relation to dose	Timepoints	PK for Patients in the Fixed Dose Exploration Cohorts	Anti-Tslelizumab Antibody Samples
Treatment Period	Cycle 1	1	Predose	-60 min to 0 h	x	x
			Postdose	End infusion to 30 min[1]	x	—
		2	--	24 h[2]	x	—
		4	--	72 h[2]	x	—
		8 ± 2	--	any time in the window	x	—
		15 ± 2	--	any time in the window	x	—
	Cycle 2 and 3	1 ± 2	Predose	-60 min to 0 h	x	x
			Postdose	End infusion to 30 min[1]	x	—
	Cycle 5	1 ± 2	Predose	-60 min to 0 h	x	x
			Postdose	End infusion to 30 min[1]	x	—
		2	--	24 h[2]	x	—
		4	--	72 h[2]	x	—
		8 ± 2	--	any time in the window	x	—
		15 ± 2	--	any time in the window	x	—
	Cycle 6	1 ± 2	Predose	-60 min to 0 h	x	—
	Cycles 7, 9, 13, 17, 25, 33, and every 8 cycles thereafter[3]	1 ± 2	Predose	-60 min to 0 h	x	x
			Postdose	End infusion to 30 min[1]	x	—
Safety Follow-up	(30 days ± 7 days after last dose)	30 ± 7	--	any time in the window	x[4]	x

Please NOTE: Actual drug dosing and PK sampling times have to be documented by the sites and will be captured in the database.

Abbreviations: h, hour(s); irAE, immune-related adverse event; min, minutes; PK, pharmacokinetic(s).

[1] Sample collection must be from opposite arm to that used for study drug infusion. If drug was administered via a central venous catheter, sample collection for PK should be from a different site.

[2] Window: ±2 h.

[3] Cycle 7, Cycle 9 and subsequently every 4 cycles through Cycle 17, and then every 8 cycles thereafter.

[4] PK assays should be performed at the mandatory Safety Follow-up Visit (if there is an irAE, an additional PK sample may be taken per the Schedule of Assessments). These tests are required when it is allowed by local regulations/IRBs/ECs.

3.3. Duration of Study

Total duration of study participation will vary by patient. Each study phase is further discussed in the main protocol in Section 3.3.1 though Section 3.3.5.

3.4. Dose-Limiting Toxicities

Dose-limiting toxicities (DLTs) will be assessed among evaluable patients after 21 days on study. An evaluable patient is defined as the patient who has received at least 80% of the dose and completed all safety assessments required during the first 21 days, or any patient who has experienced a DLT within 21 days.

Among the six patients in the 200 mg Q3W cohort, if two or more patients experience DLT within 21 days, that dose will be considered as exceeding the maximum tolerated dose (MTD), and a lower dose (eg, 150 mg Q3W) will be subsequently assessed in three to six patients. The first six patients will remain hospitalized for the first week of Cycle 1; after the first week they will be monitored with weekly complete blood count (CBC) and serum chemistry through the end of the 21-day DLT assessment period. After the DLT assessment period, hematology and serum chemistry (including liver function tests) will be performed weekly for Cycle 2 and Cycle 3 and then at the beginning of each subsequent cycle for Cycle 4 and beyond.

If the 200 mg Q3W dose passes the DLT assessment, the cohort at that dose level can be expanded to approximately 10 patients to further assess the safety, tolerability, PK and preliminary pharmacodynamic characteristics of tislelizumab. Up to 20 patients may be enrolled if more than dose level is evaluated. To continuously monitor safety, if the cohort has been expanded to 10 patients and ≥ 33% of them have experienced DLT within 21 days, enrollment will be suspended, and an Independent Data Monitoring Committee (IDMC) meeting will be immediately held to discuss and determine whether that dose is safe.

3.5. Study Rationale

Before initiating a large Phase 3 study in Japan, this substudy in Japanese patients will provide additional safety information allowing the enrollment of patients into the larger Phase 3 study in Japan. Please see the main protocol, Section 3.4.1 and Section 3.4.2 for rationale on the evaluation of tislelizumab in ESCC and selection of dose.

4. MATERIALS AND METHODS

4.1. Selection of Study Population

4.1.1. Inclusion Criteria

To be eligible to participate in this study, a patient must meet **all** of the following criteria:

1. Age (at the time of signing informed consent): 20 years and older.
2. Able to provide written informed consent and can understand and agree to comply with the requirements of the study and the schedule of assessments.
3. Histologically confirmed diagnosis of esophageal squamous cell carcinoma (ESCC)
4. Tumor progression during or after first-line systemic treatment for advanced unresectable/metastatic ESCC (Appendix 12).

   NOTE: patients with disease progression that occurs during treatment or within ≤ 6 months (180 days) of cessation of neoadjuvant/adjuvant treatment (chemotherapy or chemoradiotherapy) are eligible provided all other eligibility criteria are met.

   NOTE: A line of treatment begins with the administration of the first agent in a regimen and ends with disease progression. A line of therapy is preserved when chemotherapy is switched due to toxicities.
5. At least one measurable/evaluable lesion by RECIST v1.1 as determined by local site investigator/radiology assessment within 28 days prior to Cycle 1 Day 1.

   NOTE: Lesions that have been previously irradiated may be considered evaluable provided there is evidence of disease progression following the completion of radiation and initiation of study treatment.
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 prior to Cycle 1 Day 1.
7. Laboratory data meeting the criteria below within seven days prior to Cycle 1 Day 1. Laboratory data will not be valid if the patient has received growth factors or blood transfusion for prophylactic use within 7 days before the laboratory testing:
   - Absolute neutrophil count (ANC) ≥ 1500 cells/mm^3
   - Platelet count ≥ 100,000 cells/mm^3
   - Hemoglobin ≥ 9 g/dL or ≥ 5.6 mmol/L
   - Estimated glomerular filtration rate (GFR) ≥ 30 mL/min/1.73 m^2 by Chronic Kidney Disease Epidemiology Collaboration equation (Appendix 11).
   - Serum total bilirubin ≤ 1.5 x ULN (or < 3 x ULN in patients with Gilbert's syndrome).
   - Prothrombin time/international normalized ratio (PT/INR) ≤ 1.5 x ULN unless the patient is receiving anti-coagulant therapy

- Aspartate transaminase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN (or ≤ 5.0 x ULN in patients with liver metastases).

8. HBV or HCV infection and meets the following criteria as applicable to the infection type:

   For 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 (HBsAg) or detectable HBV DNA should be managed per treatment guidelines. Patients receiving antivirals at screening should have been treated for > 2 weeks and HBV < 500 IU/mL prior to enrollment and should continue treatment for 6 months after study drug treatment discontinuation.

   For patients with HCV:

   Patients with detectable HCV RNA and who are receiving treatment at screening should remain on continuous, effective antiviral therapy during the study.

9. Females of childbearing potential must have a negative serum pregnancy test during screening and must be willing to have additional pregnancy tests during the study. Females of childbearing potential must be willing to use highly effective methods of birth control for the duration of the study, and for at least 120 days after the last dose of tislelizumab.

10. Non-sterile males who have female sexual partner(s) of childbearing potential (Appendix 5) must use a highly effective method of birth control for the duration of the study, and for at least 120 days after the last dose of tislelizumab.

    a. A sterile male is defined as one for whom known azoospermia, in a semen sample examination, has been previously demonstrated as definitive evidence of infertility.
    b. Males with known 'low sperm counts' (consistent with 'sub-fertility) are not to be considered sterile for purposes of this study.

4.1.2. Exclusion Criteria

To be eligible to participate in this study, a patient cannot meet **any** of the following exclusion criteria:

1. Palliative radiation treatment for ESCC within 14 days of study treatment initiation Cycle 1 Day 1 (C1D1).
2. History of gastrointestinal perforation and/or fistula or aorto-esophageal fistula within 6 months prior to Cycle 1 Day 1.
3. Tumor invasion into organs located adjacent to the esophageal disease site (eg, aorta or respiratory tract) at an increased risk of fistula in the study treatment assessed by investigator
4. Uncontrollable pleural effusion, pericardial effusion, or ascites requiring frequent drainage (recurrence within two weeks of intervention).

5. Current or past history of severe hypersensitivity reactions to other monoclonal antibodies.
6. Received prior therapies targeting PD-1 or PD-L1.
7. Has 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) exceptions are to be determined by investigator in consultation with the medical monitor
8. Prior malignancy active within the previous 2 years before the first dose of study drug (exceptions include the tumor under investigation in this study, and surgically excised non-melanoma skin cancer, curatively treated carcinoma in situ of the cervix, localized prostate cancer treated with curative intent, curatively treated low-stage bladder cancer, ductal carcinoma in situ treated surgically with curative intent, or a malignancy diagnosed >2 years ago, with no current evidence of disease and no therapy ≤2 years before the first dose of study drug).
9. Active brain or leptomeningeal metastasis. Patients with equivocal findings or with confirmed brain metastases are eligible for enrollment provided that they are asymptomatic and radiologically stable without the need for corticosteroid treatment for at least 4 weeks prior to the first dose of study drug(s). CT/MRI of the head at baseline is required for patients who are suspected to have central nervous system (CNS) metastases.
10. Has active autoimmune disease or history of autoimmune diseases at high risk for relapse.

    NOTE: Patients with following diseases may be enrolled if they meet all other eligibility criteria: controlled type I diabetes, hypothyroidism managed with hormone replacement therapy only, controlled celiac disease, skin diseases not requiring systemic treatment (such as vitiligo, psoriasis or alopecia), or diseases not expected to recur in the absence of external triggering factors.
11. Has a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone or equivalents) or other immunosuppressive medications within 14 days prior to Cycle 1 Day 1.
    - Patients who have a history of organ transplant, including stem cell allograft are not permitted to enroll
    - Adrenal replacement steroid dose ≤10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease
    - Patients are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption).
    - A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted.
12. Undergone surgery requiring general anesthesia or epidural anesthesia within 28 days prior to Cycle 1 Day 1.

13. Undergone surgery involving local anesthesia within 14 days prior to Cycle 1 Day 1. Exceptions to this exclusion criteria include:
    a. Placement of a central venous access device that requires up to a 3-day surveillance period.
    b. A biopsy procedure performed under local anesthesia during the screening period that require a 7-day post procedure surveillance period.
14. Received any radiopharmaceuticals (except for examination or diagnostic use of radiopharmaceuticals) within 42 days prior to Cycle 1 Day 1.
15. Has received:
    a. Within 28 days or 5 half-lives (whichever is shorter but at least 14 days) of the first study drug administration: any chemotherapy, immunotherapy (eg, interleukin, interferon, thymoxin) or any investigational therapies
    b. Within 14 days of the first study drug administration: any Chinese herbal medicine or Chinese patent medicines used to control cancer or boost immunity
16. Any serious or unstable pre-existing medical conditions (aside from malignancy exceptions specified above), psychiatric disorders, or other conditions that could interfere with the subject's safety, obtaining informed consent, or compliance with study procedures
17. Receipt of a live vaccine within 4 weeks prior to Cycle 1 Day 1.

    NOTE: Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live viruses and are not allowed.
18. Known history of, or any evidence of interstitial lung disease, non-infectious pneumonitis, pulmonary fibrosis diagnosed based on imaging or clinical findings, or uncontrolled systemic diseases, including diabetes, hypertension, acute lung diseases, etc

    NOTE: Patients with radiation pneumonitis may be enrolled if the radiation pneumonitis has been confirmed as stable (beyond acute phase) and is unlikely to recur. Patients with severe but stable radiation-induced pneumonitis may be required to undergo routine pulmonary function studies
19. Has severe chronic or active infection (including tuberculosis infection, etc) requiring systemic antibacterial, antifungal or antiviral therapy, within 14 days prior to Cycle 1 Day 1.

    NOTE: Patients who require systemic antiviral therapy for HBV are excepted
20. Known history of Human Immunodeficiency Virus (HIV).
21. Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study.
22. Has any of the following cardiovascular risk factors:
    - Ongoing cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living
    - Symptomatic pulmonary embolism within 28 days before study drug administration

- Any history of acute myocardial infarction within 6 months before study drug administration
- Any history of heart failure meeting New York Heart Association Classification III or IV (Appendix 6) within six months before study drug administration
- Any event of ventricular arrhythmia > Grade 2 in severity within 6 months before study drug administration
- Any history of cerebrovascular accident or transient ischemic attack within 6 months before study drug administration

23. Known, active alcohol or drug abuse or dependence.
24. Pregnant or breastfeeding woman.

5. STUDY TREATMENT

5.1. Formulation, Packaging, Handling, and Storage

Please refer to the Section 5.1 of the main protocol for information on the formulation, packaging, handling and storage of tislelizumab.

5.2. Dosage, Administration, and Compliance

Patients will be treated with 200 mg intravenous (IV) tislelizumab Q3W until intolerable toxicity, withdrawal of informed consent, or until the patient is no longer benefiting from study therapy in the opinion of the investigator. All patients will be monitored continuously for AEs. Treatment modifications (eg, dose delay, reduction, interruption, or discontinuation) will be based on specific laboratory assessments and AE criteria, as described in Section 8.6 of the main protocol.

5.3. Handling of Overdose

Please refer to Section 5.3 of the main protocol for detailed information.

5.4. Investigational Medicinal Product Accountability

Please refer to Section 5.4 of the main protocol for detailed information.

5.5. Disposal and Destruction

Please refer to Section 5.5 of the main protocol for detailed information.

6. PRIOR AND CONCOMITANT THERAPY

Please refer to Section 6 of the main protocol for detailed information.

7. STUDY ASSESSMENTS AND PROCEDURES

Study assessments and procedures will be similar to those in the main protocol, Section 7 (Section 7.1 through Section 7.17), with the exception that patients will not be randomized for the substudy and there is no second treatment arm. In addition, PK assessments have been increased in this substudy for thorough characterization of PK after a single dose and at steady state in Japanese patients and are provided in further detail in Section 9.7 of this substudy protocol. Patients will be closely monitored for safety and tolerability throughout the study and the first six patients will be hospitalized during Cycle 1 of treatment. All assessments must be performed and documented in the medical record and electronic case report form (eCRF) for each patient.

Tumor response will be assessed by investigators based on RECIST v1.1. For immune therapies such as tislelizumab, pseudo-progression may occur due to immune-cell infiltration and other mechanisms leading to an apparent increase of existing tumor masses or appearance of new tumor lesions. Thus, for progressive disease (PD) suspected by the investigator as pseudo-progression, the following criteria must be met to treat patients continuously until PD is confirmed by repeated imaging performed no more than six to eight weeks beyond the initial diagnosis of radiographic PD:

- Absence of clinical symptoms and signs of disease progression (including worsening laboratory values)
- ECOG PS $\leq$ 1
- Absence of rapid progression of disease or progression at a critical anatomical site (eg, progression of a spinal lesion with impending cord compression) or that necessitates urgent alternative medical intervention

If, in the judgement of the investigator, the patient is anticipated to benefit from continued treatment, the patient must re-sign an informed consent, agreeing to continue treatment beyond radiographical disease progression. If patients agree to continue treatment beyond radiographical progression, a follow-up radiographic evaluation will be performed no later than 6 weeks after the initial scan that diagnosed progressive disease, as outlined in Section 7.4 of the main protocol.

If, in the judgement of the investigator, rapid early progression is evident (“hyperprogression”), tislelizumab should be discontinued.

8. SAFETY MONITORING AND REPORTING

Safety monitoring and reporting procedures will follow those in the main protocol (Section 8). Another addition to this substudy is the definition of DLTs. All toxicities or AEs will be graded per NCI-CTCAE v4.03. The occurrence of any of the following toxicities within 21 days after the first dose of tislelizumab, if judged by the investigator as related to tislelizumab, will be considered a DLT. The first six patients will remain hospitalized for the first week of Cycle 1; after the first week, they will be monitored with weekly CBC and serum chemistry through the end of the 22-day DLT assessment period. After the DLT assessment period, the patients will be further assessed on a weekly basis for up to 3 cycles.

Hematologic:

1. Grade 4 neutropenia lasting > 7 days
2. Grade 3 febrile neutropenia (defined as absolute neutrophil count [ANC] < 1000/mm^3 with a single temperature of 38.3°C or a sustained temperature of 38°C for > 1 hour)
3. Grade 3 neutropenia with infection
4. Grade 3 thrombocytopenia with bleeding
5. Grade 4 thrombocytopenia
6. Grade 4 anemia (life-threatening)

Non-hematologic:

1. Grade 4 or above toxicity
2. Grade 3 toxicity lasting > 7 days despite optimal supportive care

   NOTE: The following AEs will not be considered as DLTs:

   - Grade 3 endocrinopathy that is adequately controlled by hormonal replacement
   - Grade 3 AE of tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumors)
   - Grade 3 rash
   - Grade 3 to Grade 4 laboratory abnormalities that are not associated with clinical sequelae (eg, LDH)

In addition, clinically important or persistent toxicities that are not included above may also be considered a DLT following review by IDMC.

Patients who received <two-thirds (67%) of the assigned dose of tislelizumab (eg, because the infusion had to be discontinued due to an infusion reaction) and did not experience a DLT will not be taken into account in the assessment of the overall DLT rate for the particular dose level.

Independent Data Monitoring Committee

An IDMC (described in Section 8.5 of the main protocol) will evaluate and confirm the Phase 3 dose based on the safety and tolerability of tislelizumab, and decide whether or not to add unscheduled dose levels for study. To confirm the pivotal Phase 3 dose, an IDMC meeting will be held within 6 weeks after the sixth patient is treated. If ≥ 33% of patients have experienced a

DLT within 21 days after the first dose of tislelizumab, enrollment will be suspended, and the IDMC will determine whether such a dose is safe or if a lower dose level should be tested. If < 33% have experienced DLT, the cohort will be expanded to 10 patients in total to provide more safety experience on treatment.

Safety review will then subsequently be followed as per the main protocol. The IDMC may recommend modifications to the study, including termination due to safety and/or efficacy concerns.

9. STATISTICAL METHODS AND ANALYSIS PLAN

As described in the main protocol, Section 9, the statistical analyses will be performed by the sponsor or designee after the data collection for the primary efficacy and safety analyses are completed and the database is locked and released. Data will be listed and summarized using SAS® Version 9.3 or higher (SAS Institute, Inc., Cary, North Carolina) per sponsor agreed reporting standards, where applicable. Details of the statistical analyses will be included in a separate Statistical Analysis Plan.

9.1. Analysis Sets

- DLT Evaluable Analysis Set: Includes all patients who have received at least 80% of the dose and completed all safety assessments required in Cycle 1, or any patient who has experienced DLT in Cycle 1
- PK Analysis Set: Includes all patients who receive at least one dose of tislelizumab per the protocol, for whom any post-dose PK data are available. To get an adequate sample size to characterize PK, patients will be replaced if necessary
- Safety Analysis Set: Includes all patients who received at least one dose of study drug and is the primary analysis set used for all safety analyses

9.2. Patient Disposition

Please refer to Section 9.2 of the main protocol for detailed information.

9.3. Demographic and Other Baseline Characteristics

Please refer to Section 9.3 of the main protocol for detailed information.

9.4. Prior and Concomitant Therapies

Please refer to Section 9.4 of the main protocol for detailed information.

9.5. Analyses

Descriptive statistics will be used to summarize the demographic, disease characteristic, efficacy and safety data. No statistical hypotheses are planned in this exploratory study.

All patients who have received tislelizumab will be included in the Safety analysis set. All patients with valid tislelizumab PK sampling after treatment will be included in the PK analysis set. For other parameters, all evaluable data will be included in the summaries.

9.5.1. Primary Analyses

Tislelizumab safety and tolerability: The safety of tislelizumab will be assessed throughout the study by monitoring AEs and serious SAEs per NCI-CTCAE v4.03, relevant physical examination, ECGs and laboratory assessments as needed.

The recommended dose for the Phase 3 for tislelizumab will be determined based on safety, tolerability, PK, and other available data.

9.5.2. Secondary Analyses

Efficacy evaluations per RECIST v1.1 (ie, ORR, PFS and DOR) will be summarized to explore the preliminary anti-cancer activity in Japanese patients.

The ORR is defined as the proportion of patients who had confirmed complete response (CR) or partial response (PR) assessed by the investigator using RECIST v1.1.

The DOR is defined as the time from the first determination of a confirmed objective response by investigator per RECIST v1.1 until the first documentation of progression or death, whichever comes first.

The PFS is defined as the time from the date of first dose of study drug to the date of first documentation of disease progression assessed by investigator using RECIST v1.1 or death, whichever occurs first.

The ORR and its 95% confidence interval will be summarized in the Safety analysis set. Both PFS and DOR will be estimated using the Kaplan-Meier method. Waterfall plot of maximum tumor shrinkage per patient will be presented.

Immunogenic responses to tislelizumab will be assessed by monitoring the incidence of ADAs.

9.5.3. Exploratory Analyses

Assessments of the correlations between drug exposure and response (efficacy and safety endpoints) will be made. Results of such exploratory analysis may be reported separately from the clinical study report (CSR).

9.6. Safety Analyses

As described in the main protocol (Section 9.6), safety will be assessed by monitoring and recording of all AEs graded per NCI-CTCAE v4.03. 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. Substudy Protocol Section 8 includes DLT definitions as well as specific information on the role of the IDMC in the assessment of DLTs and the confirmation of the Phase 3 dose.

9.7. Pharmacokinetic Analyses

Pharmacokinetic samples will be collected in this study as outlined in Table 8. The PK analysis will include, but is not limited to, area under the concentration-time curve from Day 0 to Day 21 ($AUC_{0\text{-}21d}$), C_{max} and T_{max}, C_{trough}, $t_{1/2}$, CL and Vd. Mean serum tislelizumab concentration data and PK parameters will be tabulated and summarized by visit/cycle at which these data are available. Concentrations of tislelizumab will be summarized descriptively. Descriptive statistics will include means, medians, ranges, and standard deviations, as appropriate. Additional PK analyses may be conducted as appropriate.

Details concerning handling of PK serum samples, including labeling and shipping instructions will be provided in the Laboratory Manual. Samples will be shipped to the central laboratory where all samples will be analyzed for serum tislelizumab concentrations using a validated

method. The actual time each sample was collected will be captured to the nearest minute in the eCRF and recorded in the database.

9.8. Immunogenicity Analyses

As described in the main protocol (Section 9.8), the immunogenicity results will be summarized using descriptive statistics by the number and percentage of patients who develop detectable anti-drug antibodies (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.

10. DATA HANDLING AND QUALITY ASSURANCE

Please refer to Section 10 of the main protocol for detailed information.

11. ETHICAL CONSIDERATIONS

Please refer to Section 11 of the main protocol for detailed information.

12. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

Please refer to Section 12 of the main protocol for detailed information.