CLINICAL STUDY PROTOCOL TITLE PAGE

A Randomized, Placebo-Controlled, Double-Blind Phase 3 Study to Evaluate the Efficacy and Safety of Tislelizumab (BGB-A317) in Combination With Chemotherapy as First-Line Treatment in Patients with Unresectable, Locally Advanced Recurrent or Metastatic Esophageal Squamous Cell Carcinoma

Brief Title:

A study of tislelizumab (BGB-A317) in combination with chemotherapy as first-line treatment in participants with advanced esophageal squamous cell carcinoma

Protocol Number:	BGB-A317-306
Amendment Number:	5.0
Investigational Medicinal Product:	Tislelizumab (BGB-A317)
Regulatory Agency Identification Number(s):	EudraCT Number 2018-000587-28
Sponsor:	BeiGene, Ltd. c/o BeiGene USA, Inc. 1840 Gateway Drive, 3rd Floor San Mateo, California 94404 USA
Approval Date:	*See electronic signature*
Contact Information:	BeiGene Medical Officer Phone: 1.877.828.5568 Email: clinicaltrials@beigene.com
NCT Number	NCT03783442

INVESTIGATOR SIGNATURE PAGE

I have read the protocol, appendices, and accessory materials related to study BGB-A317-306 and agree to the following:

- To conduct this study as described by the protocol and any accessory materials.
- To protect the rights, safety, and welfare of the patients under my care.
- To provide oversight to all personnel to whom study activities have been delegated. This includes personnel at my site as well as personnel working in any facility where study activities are my responsibility.
- To control all investigational products provided by the sponsor and maintain records of the disposition of those products.
- To conduct the study in accordance with all applicable laws and regulations, the requirements of the ethics committee of record for my clinical site, and current GCP as outlined by ICH E6(R2).
- To obtain approval for the protocol and all written materials provided to patients before initiating the study at my site.
- To obtain informed consent – and updated consent in the event of new information or amendments – from all patients enrolled at my study site before initiating any study-specific procedures or administering investigational products to those patients.
- To maintain records of each patient's participation and all data required by the protocol in an accurate and timely manner.

Acceptance of this protocol constitutes my agreement that no confidential information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd. or one of its affiliates, unless and only to the extent required by applicable laws and regulations.

Name:	**Title:**	**Institution:**
Signature:		**Date:**

DOCUMENT HISTORY

Amendment Version Number	Approval Date	Type of Protocol Amendment
BGB-A317-306 Amendment 4.0	30 April 2021	Substantial
BGB-A317-306 Amendment 3.0	25 May 2020	Substantial
BGB-A317-306 Amendment 2.0	15 August 2019	Substantial
BGB-A317-306 Amendment 1.0	19 September 2018	Substantial
Original protocol	13 February 2018	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

This Protocol Amendment 5.0 replaces the previous Protocol Amendment 4.0. The amendment is considered substantial based on the criteria set forth in Regulation (EU) No 536/2014 of the European Parliament and the Council of the EU. The primary purpose of this amendment is to:

- Add description of unblinding and placebo discontinuation of the study after its interim analysis.

A few clarifications or non-substantial updates have also been made and summarized in this summary.

Additionally, some editorial and formatting changes or corrections have also been made but are not included in this summary.

Protocol Amendment Summary of Changes Table

Section Number and Title	Summary of Change	Brief Rationale for Change
Section 3.1 Summary of Study Design, Section 5.5.3 Blinding	Added IDMC recommendation of unblinding based on interim analysis results. Added the conduct of official unblinding on 20 April 2022 and subsequent activities. Added description of unblinding after analysis.	The study was unblinded according to IDMC recommendation after interim analysis in 2022, and placebo was discontinued after the unblinding. Amendment here is intended to reflect those changes at that time.
Section 3.7 End of Study	Added description of a rollover study. Updated the language regarding patients who may benefit from tislelizumab could be offered the option to continue treatment after study closeout.	Clarify there would be options for patients to continue treatment after study closeout.
Section 1.4.2 Toxicology	Updated the language to comply with GLP.	Text was revised for consistency with sponsor's protocol template.
Section 3.4 End of Treatment/Safety Follow-up, Appendix 1 Schedule of Assessments	Added the requirement of patients completing an End-of-Treatment/Safety Follow-up Visit before continuing in a long-term extension/posttrial supply study.	Clarify the request for the End-of-Treatment/Safety Follow-up Visit
Section 9.2.2 Secondary Efficacy Analysis	Updated the patient-reported outcome endpoint language	Text was revised for consistency with sponsor's protocol template.
Appendix 1 Schedule of Assessments	Added language that allows for PK and ADA sample collection and patient-reported outcome collection to stop after patients finish the 3-year follow up.	Remove unnecessary examinations after the 3-year follow-up
Throughout document	Changed "immune-related adverse events" to "immune-mediated adverse events."	Text was revised for consistency with sponsor's protocol template.
Section 5.1.3 Cisplatin, Section 5.1.4 Oxaliplatin, Section 5.1.5 5-Fluorouracil, Section 5.1.6 Capecitabine, Section 5.1.7 Paclitaxel	Added that the labels described are for drugs supplied by the sponsor or its designee.	Clarified the labels are for drugs supplied by the sponsor or the designee.

Section Number and Title	Summary of Change	Brief Rationale for Change
Section 5.1.7 Paclitaxel	Added that the appearance and composition of the product may depend on the respective marketed product sourced for the participating country.	Updated the text for clarity.
Section 5.2 Dosage, Administration, and Compliance	Added language that the sponsor or designee will either supply or reimburse sites where the sponsor is required to provide chemotherapy doublet products.	Updated the text for clarity.
Section 13 Ethics/Protection of Human Patients	Updated language to comply with ICH GCP and local regulations.	Text was revised for consistency with the protocol template.
Clinical Study Title Page, Investigator Signature Page, Protocol Synopsis	Updated the current study information per the current regulations and guidance.	To update for administrative purposes
Document History	Added Document History page	Text was revised for consistency with the protocol template.

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SYNOPSIS

Name of Sponsor/Company: BeiGene, Ltd.
Investigational Medicinal Product: Tislelizumab (BGB-A317)
Title of Study: A randomized, placebo-controlled, double-blind Phase 3 study to evaluate the efficacy and safety of tislelizumab (BGB-A317) in combination with chemotherapy as first-line treatment in patients with unresectable, locally advanced, recurrent or metastatic esophageal squamous cell carcinoma
Protocol Identifier: BGB-A317-306
Amendment Version: 5.0
Regulatory Agency Identifier Number(s): EudraCT Number 2018-000587-28
Number of Patients: Approximately 622
Study Centers: At least 120 centers internationally

Study Objectives:

Primary:

- To evaluate and compare the overall survival (OS) following treatment with tislelizumab in combination with chemotherapy compared to placebo in combination with chemotherapy when given as first-line treatment in patients with unresectable, locally advanced recurrent or metastatic ESCC

Secondary:

- To evaluate and compare the efficacy of tislelizumab in combination with chemotherapy compared to placebo in combination with chemotherapy as a first-line treatment in unresectable, locally advanced recurrent or metastatic ESCC as measured by progression-free survival (PFS), objective response rate (ORR), and duration of response (DOR) assessed by the investigator per Response Evaluation Criteria in Solid Tumors (RECIST) version (v) 1.1
- To evaluate and compare the efficacy of tislelizumab in combination with chemotherapy with the efficacy of placebo in combination with chemotherapy as a first-line treatment in unresectable, locally advanced recurrent or metastatic ESCC as measured by OS in the programmed cell death protein ligand-1 (PD-L1) visually estimated combined positive score (vCPS) ≥ 10% subgroup
- To evaluate and compare health-related quality of life (HRQoL) based on patient-reported outcomes (PROs) between tislelizumab in combination with chemotherapy and placebo in combination with chemotherapy
- To compare the safety between tislelizumab in combination with chemotherapy and placebo in combination with chemotherapy

Exploratory:

- To characterize the disease control rate (DCR) with tislelizumab in combination with chemotherapy assessed by the investigator per RECIST v1.1

- To evaluate PFS, ORR, DOR, and DCR assessed by blinded independent review committee (BIRC) per RECIST v1.1
- To assess PFS after next line of treatment (PFS2)
- To evaluate the potential association of biomarkers with patient prognosis, response, or resistance to tislelizumab in combination with chemotherapy
- To assess the pharmacokinetics of tislelizumab in combination with chemotherapy
- To assess host immunogenicity to tislelizumab in combination with chemotherapy

Study Endpoints:

Primary:

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

Secondary:

- PFS - 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
- ORR - defined as the proportion of patients whose best overall response (BOR) is complete response (CR) or partial response (PR) assessed by the investigator per RECIST v1.1
- OS in the PD-L1 vCPS ≥ 10% subgroup
- HRQoL - defined as scores of the European EORTC QLQ-C30 (QLQ-C30), its esophageal cancer module - EORTC QLQ-OES18 (OES18), and the European Quality of Life 5-Dimension 5-Level (EQ-5D-5L)
- DOR - defined as the time from the first determination of an objective response until the first documentation of progression assessed by the investigator per RECIST v1.1 or death, whichever comes first
- The incidence and severity of adverse events (AEs) according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03

Exploratory:

- DCR - defined as the proportion of patients whose BOR is CR, PR, and stable disease (SD) assessed by the investigator per RECIST v1.1
- PFS, ORR, DOR, and DCR assessed by BIRC per RECIST v1.1
- PFS2 - defined as the time from randomization to the objective disease progression after next line of treatment or death from any cause, whichever occurs first
- To explore biomarkers in tumor tissues and/or blood samples before and after study treatment and/or at progressive disease (PD)/reoccurrence, and the association between these biomarkers and clinical efficacy, disease status, and resistance. Biomarker assessment will consist of PD-L1 expression, gene expression profiling (GEP), tumor mutation burden (TMB)/microsatellite instability (MSI)/mutation profile, and tumor-infiltrating immune cells. Other assessments may be conducted as allowed by local regulations.
- Assessments of pharmacokinetics of tislelizumab when given with chemotherapy
- Assessments of immunogenicity of tislelizumab to determine the incidence of anti-drug

antibodies (ADA)

Study Design:

This is a randomized, placebo-controlled, double-blind, global Phase 3 study comparing OS following treatment with the anti-programmed cell death protein-1 (PD-1) monoclonal antibody tislelizumab in combination with standard chemotherapy compared to placebo in combination with chemotherapy when given as the first-line treatment in patients with unresectable, locally advanced recurrent or metastatic ESCC who have Stage IV unresectable ESCC at first diagnosis (ie, Stage IV disease at the original diagnosis of ESCC) or who have unresectable, locally advanced recurrent or metastatic disease with at least a 6-month treatment-free interval, if definitive treatment (neo-adjuvant or adjuvant treatment chemotherapy, chemo-radiation therapy and/or surgery) was given. Staging criteria for this study are defined by the American Joint Committee on Cancer (AJCC), 7th Edition (Edge et al 2010).

After providing written informed consent, completing all screening assessments, and being confirmed as eligible for study participation, approximately 622 patients will be randomized 1:1 to receive either tislelizumab in combination with a chemotherapy doublet (Arm A) or placebo with a chemotherapy doublet (Arm B). The choice of chemotherapy must be determined prior to randomization.

Patient randomization will be stratified by the following 3 factors:

- Geographic region (Asia [excluding Japan] vs Japan vs Rest of World)
- Prior definitive therapy (yes vs no)
- Investigator choice of chemotherapy (platinum with fluoropyrimidine vs platinum with paclitaxel)

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

- Arm A:
  - Tislelizumab + chemotherapy doublet
  - The chemotherapy doublet will consist of:
    - Platinum (cisplatin or oxaliplatin) and a fluoropyrimidine (capecitabine or 5-fluorouracil [5-FU])

    OR

    - Platinum (cisplatin or oxaliplatin) and paclitaxel
- Arm B:
  - Placebo + chemotherapy doublet
  - The chemotherapy doublet will consist of:
    - Platinum (cisplatin or oxaliplatin) and a fluoropyrimidine (capecitabine or 5-FU)

    OR

    - Platinum (cisplatin or oxaliplatin) and paclitaxel

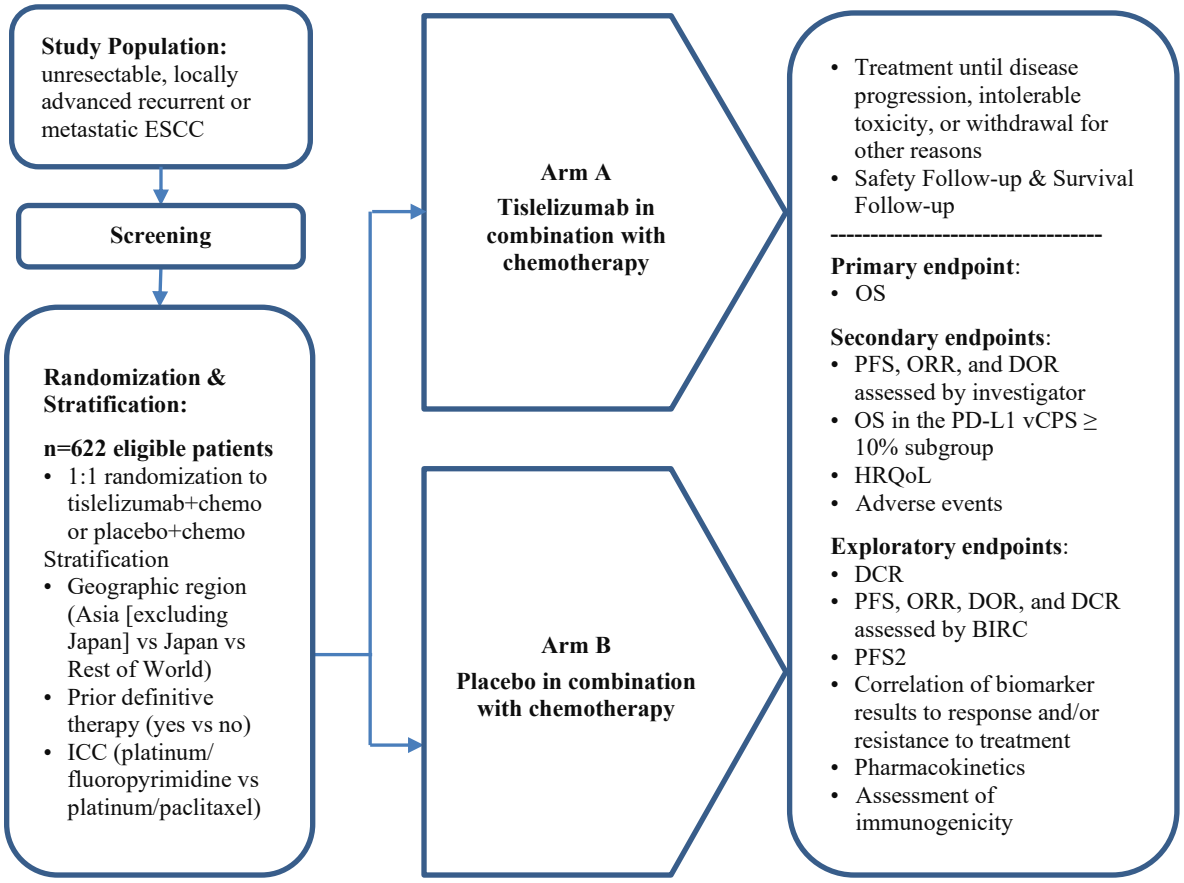
The platinum agent may be cisplatin or oxaliplatin (except in China, Taiwan, Japan, and countries where oxaliplatin substitution is not permitted) according to site or investigator preference or standard

practice as determined prior to randomization.

Cross-over between treatment arms or between fluoropyrimidine and paclitaxel during the study treatment period will not be allowed.

Study treatment will be administered until disease progression, intolerable toxicity, or another reason for treatment discontinuation criterion is met. Platinum therapy may be stopped after 6 cycles, per site or investigator preference or standard practice. If platinum treatment is stopped, the non-platinum agent (fluoropyrimidine or paclitaxel) may continue at the regular schedule.

The study design schema is as follows:



Abbreviations: BIRC, blinded independent review committee; chemo, chemotherapy; DCR, disease control rate; DOR, duration of response; ESCC, esophageal squamous cell carcinoma; HRQoL, health-related quality of life; ICC, investigator choice of chemotherapy; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death protein ligand-1; PFS, progression-free survival; PFS2, PFS after next line of treatment; vCPS, visually estimated combined positive score.

Study Assessments:

Response to treatment will be assessed by the investigator and BIRC. Tumor imaging (computed tomography [CT] with or without contrast or magnetic resonance imaging [MRI]) must be performed within 28 days prior to randomization. On-treatment tumor assessments will occur every 6 weeks (± 7 days) for the first 48 weeks, then every 9 weeks (± 7 days) based on RECIST v1.1, regardless of treatment delays, until disease progression. Patients who discontinue study treatment early for reasons other than documented radiographic disease progression (eg, toxicity) will continue to undergo tumor assessments following the original plan until the patient experiences disease progression, withdraws consent, is lost to follow-up, or dies, or until the study completes, whichever occurs first. Investigators

must obtain written informed consent for treatment beyond radiologic disease progression and inform patients that this practice is not considered standard in the treatment of cancer.

HRQoL will be measured via 3 validated patient-reported outcomes (PROs) instruments: the QLQ-C30, OES18, and the EQ-5D-5L at baseline, after randomization, prior to dosing or any clinical activities at every treatment cycle for the first 6 cycles, then every other cycle afterwards, and at the End-of-Treatment (EOT) Visit.

All AEs will be reported during the study (AEs from the time of the first dose and serious adverse events (SAEs) from the time of signing of informed consent) and for up to 30 days after the last dose of study drug(s) (including chemotherapy) or until initiation of another anticancer therapy, whichever occurs first. Immune-mediated AEs (serious or non-serious) should be reported up to 90 days after the last dose of tislelizumab, regardless of whether the patient starts a new anticancer therapy. The investigator should report any SAEs that are assessed as related to tislelizumab treatment, at any time after treatment discontinuation. AEs will be graded according to NCI CTCAE v4.03.

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.

The IDMC convened on 20 April 2022 to review the efficacy and safety data of the preplanned interim analysis (data cutoff date of 28 February 2022, with 422 death events which corresponds to 86.5% of the number of total planned death events for the final analysis [488 OS events]). After reviewing the data, the IDMC confirmed that the study met the specified 1-sided p-value boundary for superiority of the primary endpoint and recommended to unblind/unmask the study due to compelling efficacy. Based on the IDMC recommendation, a decision was made to unblind all patients, and inform all investigators and IRB/IEC as required. Patients randomized to Arm B were to discontinue placebo after unblinding.

Duration of Patient Participation:

Duration of study participation will vary by patient, depending on the duration of treatment and treatment outcomes. Each patient treatment course will include:

- Screening up to 28 days
- Treatment until disease progression (or other reason for discontinuation before progression)
    - In select cases, patients may continue treatment beyond disease progression. See Section 3.6.1 for requirements related to treatment beyond disease progression.
    - Platinum therapy may be stopped after 6 cycles, per site or investigator preference or standard practice. If platinum treatment is stopped, the non-platinum agent (fluoropyrimidine or paclitaxel) may continue at the regular schedule, if appropriate.
- End of Treatment (EOT)/Safety Follow-up Visit up to 30 days after the last dose
- Survival Follow-up Visits every 3 months until death (or other reason before death)

Study Population: Patients with unresectable, locally advanced recurrent or metastatic ESCC who have Stage IV unresectable ESCC at first diagnosis (ie, Stage IV disease at the original diagnosis of ESCC) or who have unresectable, locally advanced recurrent or metastatic disease with at least a 6-month treatment-free interval, if prior definitive therapy (chemotherapy, chemo-radiation therapy or surgery) was given. Appendix 13 contains a flow chart to help determine which patients are appropriate for this study.

Prior to opening full enrollment in Japan, close monitoring measures will be taken to observe the safety

and tolerability of the combination of tislelizumab with cisplatin and 5-FU in ESCC in Japanese patients as described in Section 3.8.

Key Eligibility Criteria:

The following are key disease-specific criteria. For the complete list of eligibility criteria for this study, please refer to Section 4.

- Key inclusion criteria
  - Pathologically (histologically) confirmed diagnosis of ESCC
  - Stage IV unresectable ESCC at first diagnosis OR unresectable, locally advanced recurrent or metastatic disease (per AJCC 7th Edition, Appendix 14), if there is prior neoadjuvant/adjuvant therapy with platinum-based chemotherapy, a treatment-free interval of at least 6 months is required
- Key exclusion criteria
  - Palliative radiation treatment for ESCC within 4 weeks of study treatment initiation
  - Prior systemic therapy for unresectable, locally advanced recurrent or metastatic ESCC
  - Uncontrollable pleural effusion, pericardial effusion, or ascites requiring frequent drainage or medical intervention (clinically significant recurrence requiring an additional intervention within 2 weeks of intervention)
  - Evidence of complete esophageal obstruction not amenable to treatment
  - Received prior therapies targeting PD-1, PD-L1 or PD-L2
  - Unintentional weight loss ≥ 5% within 1 month prior to randomization or Nutritional Risk Index (NRI) < 83.5 (Appendix 15) per investigator's choice

Investigational Product, Dose, and Mode of Administration:

Tislelizumab will be administered at a dose of 200 mg intravenously (IV) on Day 1 of every 21-day cycle. Tislelizumab will be given in combination with 1 of the 3 chemotherapy doublets listed below. The platinum agent may be cisplatin or oxaliplatin (except in China, Taiwan, Japan, and countries where oxaliplatin substitution is not permitted) according to site and investigator preference or standard practice as determined prior to randomization.

- Platinum (cisplatin or oxaliplatin) + 5-FU:
  - Cisplatin 60 to 80 mg/m^2 OR oxaliplatin 130 mg/m^2 IV on Day 1 Q3W
  - 5-FU 750 to 800 mg/m^2 IV continuous infusion over 24 hours daily on Days 1 to 5 Q3W
- Platinum (cisplatin or oxaliplatin) + capecitabine:
  - Cisplatin 60 to 80 mg/m^2 OR oxaliplatin 130 mg/m^2 IV on Day 1 Q3W
  - Capecitabine 1000 mg/m^2 orally (PO) twice daily (BID) on Days 1 to 14 Q3W
- Platinum (cisplatin or oxaliplatin) + paclitaxel:
  - Cisplatin 60 to 80 mg/m^2 OR oxaliplatin 130 mg/m^2 IV on Day 1 or 2 Q3W
    - Depending on local guidelines, cisplatin may be given in 3 divided doses on Days 1, 2, and 3. The total dose given must be between 60 to 80 mg/m^2 per cycle.
  - Paclitaxel 175 mg/m^2 IV on Day 1 Q3W

Reference Therapy, Dose, and Mode of Administration:

Matched placebo will be administered on Day 1 of every 21-day cycle. Matched placebo will be given in combination with 1 of the 3 chemotherapy doublets listed below. The platinum agent may be cisplatin or oxaliplatin (except in China, Taiwan, Japan, and countries where oxaliplatin substitution is not permitted), according to site or investigator preference or standard practice as determined prior to randomization.

- Platinum (cisplatin or oxaliplatin) + 5-FU:
  - Cisplatin 60 to 80 mg/m^2 OR oxaliplatin 130 mg/m^2 IV on Day 1 Q3W
  - 5-FU 750 to 800 mg/m^2 IV continuous infusion over 24 hours daily on Days 1 to 5 Q3W
- Platinum (cisplatin or oxaliplatin) + capecitabine:
  - Cisplatin 60 to 80 mg/m^2 OR oxaliplatin 130 mg/m^2 IV on Day 1 Q3W
  - Capecitabine 1000 mg/m^2 orally BID on Days 1 to 14 Q3W
- Platinum (cisplatin or oxaliplatin) + paclitaxel:
  - Cisplatin 60 to 80 mg/m^2 OR oxaliplatin 130 mg/m^2 IV on Day 1 or 2 Q3W
    - Depending on local guidelines, cisplatin may be given in 3 divided doses on Days 1, 2, and 3. The total dose given must be between 60 to 80 mg/m^2 per cycle.
  - Paclitaxel 175 mg/m^2 IV on Day 1 Q3W

Statistical Methods

The primary endpoint of OS in the Intention-to-Treat (ITT) analysis set will be tested at a one-sided alpha of 0.025. By using the graphic approach of Bretz et al (2009), if the null hypothesis for OS in the ITT analysis set is rejected, the corresponding alpha will be shifted to the hypothesis tests of the secondary endpoints PFS by the investigator in the ITT analysis set, ORR by the investigator in the ITT analysis set, OS in the PD-L1 vCPS ≥ 10% subgroup, and HRQoL in the ITT analysis set, which will be tested sequentially. The inferential test will be stopped at the first non-significant endpoint.

Analysis Sets:

- The ITT analysis set includes all randomized patients. It will be the primary analysis population for the efficacy analysis
- The Safety analysis set includes all patients who received at least 1 dose of study treatment. It will be the primary analysis population for safety analysis
- The Pharmacokinetics (PK) analysis set includes all patients who are receive 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 a baseline and at least 1 post-baseline ADA result

Primary Efficacy Endpoint Analysis:

OS in the ITT analysis set:
The null hypothesis to be tested is:

H_0: OS in Arm A ≤ OS in Arm B

against the alternative:

H_1: OS in Arm A > OS in Arm B

The primary analysis of OS will be carried out when approximately 488 OS events are reached. In absence of confirmation 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 Arm A and Arm B in a one-sided, stratified log-rank test using stratification factors of pooled geographic region (Asia [including Japan] vs Rest of World), prior definitive therapy (yes vs no), and the investigator's choice of chemotherapy (ICC) option (platinum with fluoropyrimidine vs platinum with paclitaxel). A one-sided significance level of 0.025 will be used for the OS testing.

The median OS and the cumulative probability of OS at every 3 months including 9-month OS and 18-month OS, if estimable, will be calculated for each treatment arm and presented with 2-sided 95% confidence intervals (CIs). Kaplan-Meier survival probabilities for each arm will be plotted over time. OS rate at 9 and 18 months based on Kaplan-Meier estimate will be compared between 2 treatment arms for landmark analysis.

The treatment effect will be estimated by fitting a Cox regression model to the OS times including treatment arm as a covariate and region of enrollment and prior definitive therapy as strata. From this model, the HR of OS will be estimated and presented with a 2-sided 95% CI.

Primary Analyses of OS

There will be 1 interim analysis of OS utilizing the O'Brien-Fleming boundary approximated by Hwang-Shih-DeCani spending function with the gamma parameter set at -4. The interim analysis will be performed at the time when approximately 423 death events (87% of the target number of OS events) among the 2 treatment arms are observed. It is estimated that it will take approximately 33 months to observe 423 death events. An IDMC will oversee the interim analysis of OS. The final analysis of OS will take place after approximately 488 OS events have been observed. Stopping boundaries in p-value and Z score for primary analyses of OS are shown in the table below. The boundaries will be updated according to the actual numbers of events in the interim and final analyses, and the revised alpha level due to alpha shifting as described above, using the above pre-specified alpha spending function.

Stopping Boundaries (in p-value and Z score) of Primary Analysis of Overall Survival

Endpoint	Analysis	Analysis Time (month)	# Events	p-value[1] (Z score) for Efficacy	Approximate HR Threshold
OS	Interim analysis	33	423	< 0.0145 (> 2.18)	0.809
	Final analysis	40	488	< 0.0216 (> 2.02)	0.833

Abbreviations: HR = hazard ratio; OS = overall survival
[1]one-sided

Secondary Efficacy Endpoint Analyses:

Progression Free Survival (PFS)

There will be one analysis of PFS in the ITT analysis set, which will be carried out after superiority of OS in the ITT analysis set has been demonstrated. Similar statistical analysis methods used for OS testing will be applied to PFS analysis.

The p-value from one-sided, stratified log-rank test will be presented using the stratification factors of pooled geographic regions (Asia [including Japan] vs Rest of World), prior definitive therapy (yes vs no), and ICC option.

PFS assessed by the investigator will be estimated using the Kaplan-Meier method in the ITT analysis set. The PFS censoring rule will follow United States (US) Food and Drug Administration (FDA) Guidance for Industry, Clinical Trial Endpoints for Approval of Cancer drugs and Biologics (FDA 2018). Data for patients without disease progression or death at the time of analysis will be censored at the time of the last tumor assessment. Data for patients who are lost to follow-up prior to documented disease progression will be censored at the last tumor assessment date when the patient is known to be free of disease progression. 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 a new therapy.

The median PFS and the cumulative probability of PFS at every 3 months, including 6-month PFS, if estimable, will be calculated for each treatment arm and presented with 2-sided 95% CIs. Kaplan-Meier estimates of PFS for each arm will be plotted over time. The PFS rate at 6 months based on the Kaplan-Meier estimate will be compared between the 2 treatment arms for landmark analysis.

HR estimated from a Cox regression model will be presented with its 95% CI.

OS in the vCPS ≥ 10% subgroup:

This analysis for the PD-L1 vCPS ≥ 10% subgroup is similar as the OS analysis in the ITT analysis set.

Other secondary efficacy endpoints

ORR per RECIST v1.1 by the investigator in the ITT analysis set will be tested in a Cochran-Mantel-Haenszel (CMH) test, adjusting for stratification factors of pooled geographic region, prior definitive therapy, and ICC options. Patients with no post-baseline response assessment (for any reason) will be considered non-responders. The 2-sided 95% CIs for the odds ratio in ORR will be calculated along with Clopper-Pearson 95% CIs of ORR for each treatment arm.

DOR assessed by the investigator will be calculated similarly to PFS by the investigator in the responders. Median DOR per arm, if estimable, will be presented.

HRQoL will be analyzed and compared between the treatment arms via the post-baseline scores of QLQ-C30's Global Health Status/QoL (GHS), functional scales and symptom scores and symptoms single item scores, QLQ-OES18's index score and symptoms scales and single item scores, and EQ-5D-5L descriptive scale scores as well as the visual analogue scale (VAS) scores. Observed values and changes from baseline will be summarized using descriptive statistics. A mixed-effect model analysis for measuring clinically meaningful changes post-baseline will be performed using the patient-reported outcome endpoints of GHS, physical function, and fatigue domains of QLQ-C30 and dysphagia, reflux, pain and eating of QLQ-OES18.

Time to clinically meaningful deterioration in the aforementioned scales will be estimated using the Kaplan-Meier method and Cox regression model. Deterioration thresholds will be defined based on the published 10-point EORTC threshold, and a secondary deterioration threshold based on data may be explored.

Exploratory Efficacy Analyses:

BOR is defined as the best response per RECIST v1.1 by the investigator recorded from randomization till data cut, progressive disease (PD) or start of new anti-cancer treatment. 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.

To calculate PFS2, data from patients without disease progression after next line of treatment or death at the time of analysis will be censored at the last time known to be alive. Kaplan-Meier method as described in the PFS and OS analyses will be used in the analysis of PFS2.

In addition, PFS, ORR, DOR, and DCR assessed by the BIRC per RECIST v1.1 are summarized similarly the data assessed by the investigator for exploratory analysis.

Exploratory biomarkers may also be assessed.

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), dosing, 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.

Extent of exposure to each study drug will be summarized descriptively as the number of doses 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 v4.03. 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 (pre-treatment) on or after the first dose of study drug up to 30 days following study drug discontinuation or initiation of new anti-cancer therapy, whichever occurs first. TEAEs also include immune-mediated AEs recorded up to 90 days after the last dose of tislelizumab or placebo, regardless of whether the patient starts a new anticancer therapy. SAEs, deaths, TEAEs that are Grade 3 or above, infusion-related reactions, treatment-related TEAEs, TEAEs that led to treatment discontinuation, dose reduction, dose interruption or dose delay, and immune-mediated AEs will be summarized.

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

Sample Size Considerations:

The initial sample size calculation was based on the primary efficacy analysis of PFS and OS in the comparison between tislelizumab in combination with chemotherapy arm and placebo plus chemotherapy arm in the ITT analysis set. Hazard ratios in PFS and OS were assumed as 0.65 and 0.73, respectively, with median PFS of 5 months and OS of 9 months in the comparator arm. A total of 480 patients would be enrolled in a 1:1 randomization over a 17-month period at enrollment rates of 10 patients/month in the first month, 20 patients/month in the second month and 30 patients/month in the

next 15 months. Approximately 319 PFS events were planned in the PFS hypothesis testing to have a power of 90% with an alpha of 0.005. A group sequential testing of OS would be performed. The interim analysis was planned after approximately 67% of the total planned death events had occurred (241). The final analysis of OS would be performed when approximately 360 death events have been observed. The sample size calculation of OS was based on overall power of 82% and an alpha level of 0.02.

The previous version of protocol amendment 3.0 was amended on 25 May 2020. The study sample size was increased from 480 to 622 to allow increased targeted numbers of events in the PFS and OS analyses, which was to account for the delayed treatment effect and increased usage of subsequent immunotherapies that were observed in the newly published immuno-oncology trials in the second-line ESCC (Kojima et al 2019; Kato et al 2019; Huang et al 2019).

By 24 November 2020, enrollment was completed with 649 randomized patients. In the current protocol amendment, BIRC-assessed PFS has been removed from the primary efficacy analysis based on the results from KEYNOTE-590 (Kato et al 2020) in the first-line treatment of ESCC. OS is the sole primary efficacy endpoint. The HR for OS is assumed to be 0.74 at the time of final analysis after an initial 1-month delayed treatment effect (eg, assuming HR = 1 in the first month), the number of deaths required in the final analysis will be approximately 488 with 90% power by simulation. The planned interim analysis with a power of 81% will occur after 423 events have been observed. A 5% annual dropout rate is assumed and one-sided alpha of 0.025 is used in the sample size calculation.

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
5-FU	5-fluorouracil
ADA	antidrug antibody
AE	adverse event
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BGB-A317	humanized monoclonal antibody directed at PD-1; tislelizumab
BID	twice daily
BIRC	blinded independent review committee
BSA	body surface area
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	Clearance
CMH	Cochran-Mantel-Haenszel
CR	complete response
CT	computed tomography
DCR	disease control rate
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture (system)
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EORTC QLQ-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-Dimension 5-Level
ESCC	esophageal squamous cell carcinoma
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FDG-PET	fluorodeoxyglucose-positron emission tomography
GC	gastric carcinoma
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBcAb	hepatitis B core antibody

Abbreviation	Definition
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HR	hazard ratio
HRQoL	health-related quality of life
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
INR	international normalized ratio
imAE	immune-mediated adverse event
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IV	intravenous(ly)
MedDRA	Medical Dictionary for Regulatory Activities
MMF	mycophenolate mofetil
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OCT	optical coherence tomography
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein-1
PD-L1	programmed cell death protein ligand-1
PD-L2	programmed cell death protein ligand-2
PET	positron emission tomography
PFS	progression-free survival
PFS2	PFS after next line of treatment
PK	pharmacokinetic(s)
PR	partial response
Q2W	once every 2 weeks
Q3W	once every 3 weeks
Q4W	once every 4 weeks

Abbreviation	Definition
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
T4	thyroxine
TEAE	treatment-emergent adverse event
TFT	thyroid function tests
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	United States
vCPS	visually estimated combined positive score

1. INTRODUCTION

1.1. Background Information on Esophageal Carcinoma

Esophageal cancer is the eighth most common cancer worldwide and the sixth most common cause of death from cancer (Ferlay et al 2012). The incidence, prevalence, and histologic type of esophageal cancer varies between geographic regions, particularly between Western countries (United States [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 et al 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 et al 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 et al 2017) and 12% in Europe (De Angelis et al 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 et al 2016; Arnold et al 2015). The age-standardized 5-year relative survival rate for patients in China diagnosed in 2003 to 2005 is 20.9% (Li et al 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. Esophageal cancer of either histology is much more prevalent in men and more common in an older patient population (Shah 2015).

Advanced esophageal cancer is a rapidly fatal disease. More than two-thirds of patients diagnosed with esophageal cancer will have advanced or metastatic disease, with a median survival of 8 to 10 months and an expected 5-year survival rate < 5% (Lin et al 2016; Drahos et al 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.

1.2. Current Treatment of Esophageal Carcinoma and Unmet Clinical Needs

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 et al 2016; NCCN Guidelines Version 1, 2017; Japanese Gastric Cancer Association 2017; Stahl et al 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 et al 2016; NCCN Guidelines Version 1, 2017; Japanese Gastric Cancer Association 2017; Stahl et al 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 treated with local therapy are like those described above, and are similar to treatments given to patients with advanced gastric cancer (Lordick et al 2016). The choice of agents or regimen may be based on the patient's performance status, and underlying comorbidities. Fluoropyrimidines (either 5-Fluorouracil [5-FU] 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-FU are suitable front-line treatments.

The overall response rate 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 et al 2007). There is no global consensus on the optimal first-line treatment; but combination chemotherapy combination therapy is typically given. Treatment regimens commonly include a platinum agent (cisplatin or oxaliplatin) in combination with paclitaxel or 5-FU (NCCN Guidelines Version 1, 2017). There are regional preferences for the chemotherapy of choice and may be based on the toxicity profile of each agent. The following table (Table 1) summarizes the efficacy outcomes between the chemotherapy regimens allowed in this protocol. It should be noted that one publication summarizes data from retrospective analysis (Liu et al 2016). Given these caveats, the ORRs and median survival durations appear comparable amongst the various regimens.

Table 1. First-Line Treatment and Outcomes for Esophageal Squamous Cell Carcinoma

Reference	Sample Size by Histology (n)	Treatment setting	Regimen	ORR (%)	PFS (median months	OS (median months)
Cisplatin + 5-fluorouracil						
Bleiberg, 1997	ESCC (44)	1st line	Cisplatin 100 mg/m^2 IV Day 1 Q3W 5-FU 1000 mg/m^2 IV infusion over 24h Days 1-5 Q3W	35	6.8	8.3
Hayashi, 2001	ESCC (36)	85% 1st line	Cisplatin 20 mg/m^2 IV Day 1-5 Q4W 5-FU 800 mg/m^2 IV infusion over 24h Days 1-5 Q4W	33.3	N/A	7.2
Lorenzen, 2009	ESCC (30)	1st line	Cisplatin 75-100 mg/m^2 IV Day 1 Q4W 5-FU 250-1000 mg/m^2 IV infusion over 24h Days 1-4 Q4W	13	3.6	5.5
Liu, 2016	ESCC (203)	1st line	Cisplatin 75 mg/m^2 IV Day 1 Q3W 5-FU 750 mg/m^2 IV over 24h Days 1-5 Q3W	38.4	6.5	12.7
Wang, 2017	ESCC (48)	85% 1st line	Cisplatin 15 mg/m^2 IV Day 1-5 Q3W 5-FU 750 mg/m^2 IV infusion over 24h Days 1-5 Q3W	46.8	4.9	8.9
Cisplatin + capecitabine						
Lee, 2008	ESCC (45)	1st line	Cisplatin 60 mg/m^2 IV Day 1 Q3W Capecitabine 1250 mg/m^2 BID PO Day 1-14 Q3W	57.8	4.7	11.2
Lee, 2015	ESCC (46)	1st line	Cisplatin 75 mg/m^2 IV Day 1 Q3W Capecitabine 1000 mg/m^2 BID PO Day 1-14 Q3W	57	5.1	10.5
Cisplatin + paclitaxel						
Petrasch, 1998	ESCC (18) EAC (6)	1st line	Cisplatin 50 mg/m^2 IV Day 1 Q2W Paclitaxel 90 mg/m^2 IV Day 1 Q2W	40	N/A	7.0
Cho, 2005	ESCC (32)	31% 1st line	Cisplatin 50 mg/m^2 IV Day 1 Q2W Paclitaxel 90 mg/m^2 IV Day 1 Q2W	41	5.0	7.0
Huang, 2013	ESCC (46)	1st line	Cisplatin 50 mg/m^2 IV Day 2 Q2W Paclitaxel 150 mg/m^2 IV Day 1 Q2W	56.5	5.6	17.0
Liu, 2016	ESCC (195)	1st line	Cisplatin 75 mg/m^2 IV Day 1 Q3W Paclitaxel 175 mg/m^2 IV Day 1 Q3W	42.5	7.9	13.5

Abbreviations: 5-FU, 5-fluorouracil; BID, twice daily; EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; IV, intravenous; N/A, not applicable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, orally; Q2W, once every 2 weeks; Q3W, once every 3 weeks; Q4W, once every 4 weeks

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

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

Tislelizumab

As of 28 August 2017, 49 patients with advanced esophageal carcinoma have been enrolled to an ongoing Phase 1 clinical study. The median age of these enrolled patients is 62 years (range: 30 to 80 years), 36 patients are men and 28 patients are of the white race. Prior to study enrollment, these patients had received a median of 2 (range: 0 to 7) prior treatment regimens for their

esophageal cancer, with 12 patients receiving at least 3 prior treatments. The duration of follow-up in this study was 3.4 months (range: 0.2 to 10.6 months).

Tislelizumab was administered for a median of 2 months (range: 0.2 to 10.6 months) in this patient cohort. All but 1 patient received tislelizumab at a dose of 5 mg/kg; 1 patient was treated at the 2 mg/kg dose.

The majority (n = 46) of patients experienced at least 1 treatment-emergent adverse event (TEAE). Twenty-three patients experienced a treatment-related adverse event (AE). The most common AEs reported in at least 3 patients in the esophageal cohort of any grade or causality included nausea, constipation, dysphagia, abdominal pain (including upper abdominal pain), diarrhea, vomiting, pneumonia, upper respiratory tract infection, cough, dyspnea, pleural effusion, decreased appetite, hypercalcemia, fatigue, pyrexia, peripheral edema, back pain, arthralgia, myalgia, weight decrease, alkaline phosphatase increase, pruritus, headache, hypothyroidism, insomnia, proteinuria, infusion related reaction, and anemia. Of these events, nausea, fatigue, hypothyroidism, infusion related reaction, decreased appetite, and myalgia were reported as related to tislelizumab in more than 2 patients. Twenty-two patients experienced an AE that was reported as National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grade 3 or higher; none of these events occurred in more than 3 patients.

Serious adverse events (SAEs) were reported in 25 patients. The only SAE that occurred in more than 2 patients was pneumonia in 4 patients.

Six patients who received tislelizumab at the 5 mg/kg dose died of causes reported as AEs: mediastinitis, sepsis, esophageal hemorrhage, pleural effusion, tumor hemorrhage, and hemoptysis. These events are recognized complications of esophageal carcinoma; none were considered related to study treatment.

Radiographic anti-tumor activity results were available for 42 of the 49 enrolled patients. Of these patients, 6 experienced a partial response (PR). Three of these patients had squamous cell carcinoma and 3 had adenocarcinoma. Three of these responses were confirmed, and the remaining PRs were not confirmed per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria. Twelve additional patients had confirmed a best response of stable disease (SD). There were no complete responses (CR) reported.

At the time of the data cutoff, 12 patients were still receiving tislelizumab treatment.

Nivolumab

Efficacy results in esophageal squamous cell carcinoma (ESCC) patients treated with nivolumab, an anti-programmed cell death protein-1 (PD-1) monoclonal antibody, were reported from an open-label, single-arm, multi-center Phase 2 study (Kudo et al 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 IV once every 2 weeks (Q2W). Tumor response was assessed every 6 weeks. Median follow-up was 10.8 months (interquartile range: 4.9 to 14.3 months) and patients received a median of 3 nivolumab cycles (range: 1 to 10 cycles). The ORR by central radiology assessment was 17% (95% confidence interval [CI]: 10 to 28%) and 22% (95% CI: 14 to 33%) by investigator assessment. The disease

control rate (DCR), defined as the number of patients with a CR or PR, and those with SD of any duration was 42% (95% CI: 31 to 54%) by central assessment and 53% (95% CI: 41 to 65%) patients by investigator assessment. The median duration of OS was 10.8 months (95% CI:7.4 to 13.9 months). The 2-year OS was 17.2%. The median durations of progression-free survival (PFS) were 1.5 months (95% CI: 1.4 to 2.8 months) and 2.3 months (95% CI: 1.5 to 3.0 months), by central and investigator assessment, respectively.

Pembrolizumab

KEYNOTE-028 (NCT02054806), a multicohort, Phase 1b trial recruited advanced ESCC and adenocarcinoma patients with disease progression (PD) following standard therapy. Patients received pembrolizumab 10 mg/kg Q2W. Response was assessed every 8 weeks for the first 6 months 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 78% of 17 patients had ESCC. After a median follow-up of 7 months (range: 1 to 33 months), ORR was 30% (95% CI: 13 to 53%). Median PFS was 1.8 months and median OS was 7 months. The median duration of response (DOR) was 15 months (range: 6 to 26 months) (Doi et al 2017).

KEYNOTE-590 (NCT03189719) is a multicenter, randomized, double-blind, placebo-controlled Phase 3 study that enrolled 749 patients with metastatic or locally advanced esophageal or esophagogastric junction (GEJ) carcinoma who were not candidates for surgical resection or definitive chemoradiation. Patients were randomized (1:1) to receive either pembrolizumab (200 mg on Day 1 every three weeks [Q3W]) or placebo (on Day 1 Q3W) in combination with cisplatin (80 mg/m^2 on Day 1 Q3W for ≤ 6 cycles) plus 5-FU (800 mg/m^2 per day on Days 1 to 5 Q3W, or per local standard for 5-FU administration, for ≤ 35 cycles). Treatment with pembrolizumab or chemotherapy continued until unacceptable toxicity, disease progression, withdrawal, or 2 years. The major efficacy outcome measures were OS and PFS (assessed by the investigator). The pre-specified analyses of OS and PFS were performed in the following subgroups: patients with ESCC, patients with ESCC with PD-L1-positive tumors with combined positive score (CPS) ≥ 10, and all patients. Additional efficacy outcome measures were ORR and DOR assessed by the investigator. Both patients with squamous (ESCC, 73%) and adenocarcinoma (27%) histologies were accrued. After a median follow-up of 10.8 months, the interim analysis of KEYNOTE-590 demonstrated that pembrolizumab combined with chemotherapy showed statistically significant and clinical meaningful improvement in OS compared with chemotherapy alone in the all-patient population (HR 0.73, median OS 12.4 months [pembro+chemo] versus 9.8 months [chemo], $p < 0.0001$), ESCC subgroup (HR 0.72, median OS 12.6 months [pembro+chemo] versus 9.8 months [chemo], $p = 0.0006$), and ESCC PD-L1 CPS ≥ 10 subgroup (HR 0.57, median OS 13.9 months [pembro+chemo] versus 8.8 months [chemo], $p < 0.0001$). A superior PFS in both the all-patient population (HR 0.65, median PFS 6.3 months [pembro+chemo] versus 5.8 months [chemo], $p < 0.0001$) and the ESCC subgroup (HR 0.65, median PFS 6.3 months [pembro+chemo] versus 5.8 months [chemo], $p < 0.0001$) was also observed in the pembrolizumab combined with chemotherapy group. ORR was 45% (95% CI: 39.9% to 50.2%) versus 29.3% (95% CI: 24.7% to 34.1%) and DOR was 8.3 months (range: 1.2+ to 31.0+ months) versus 6.0 months (range: 1.5+ to 25.0+ months) for pembrolizumab combined with chemotherapy and chemotherapy alone groups, respectively (Kato et al 2020).

1.4. Background Information on Tislelizumab

1.4.1. Pharmacology

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

Tislelizumab acts by binding to the extracellular domain of human PD-1 with high specificity as well as high affinity (dissociation constant [K_D] = 0.15 nM). It competitively blocks binding efforts by both 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 cell were co-injected with human cancer cells (A431 [epidermoid carcinoma]) or tumor fragments (BCCO-028 [colon cancer]) into immunocompromised mice.

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

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

1.4.2. Toxicology

The toxicity and safety profile of tislelizumab was characterized in single-dose intravenous (IV) toxicology studies in mice and monkeys, and in two separate repeated-dose IV toxicology studies in cynomolgus monkeys dosed once every two weeks for 13 weeks. The tissue cross-reactivity was evaluated in the normal frozen tissues from both humans and monkeys. In addition, the potential off-target binding of tislelizumab was screened using the Retrogenix microarray and subsequently verified by Biacore assays. The cytokine release assays were also evaluated using fresh human whole blood cells. Cynomolgus monkey was the only relevant species based on the target sequence homology and binding activity.

Overall, no apparent toxicity was noted in mice or monkeys at single doses up to 100 mg/kg. No apparent tislelizumab-related toxicity was noted in the 13-week repeated-dose monkey toxicology studies at doses up to 30 mg/kg. Apparent but likely immunogenicity-related toxicity was noted in individual monkeys given 60 mg/kg repeatedly. However, immunogenicity-related changes due to formation of antidrug antibodies (ADAs) and immune complex formation in nonhuman primates is generally considered not translatable to humans (Vahle 2018). The No-Observed-Adverse-Effect Level of tislelizumab in the 13-week monkey toxicology studies was considered to be 30 mg/kg, approximately 10-fold higher than the clinical dose (200 mg, once every 3 weeks). The toxicokinetic profile was well characterized in cynomolgus monkeys with dose-proportional increases in systemic exposure, without apparent accumulation or sex difference.

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

The safety profile of tislelizumab is considered adequate to support the current Study BGB-A317-306.

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

1.4.3. Clinical Pharmacology

In the Phase 1 BGB-A317_Study_001 study and Study BGB-A317-102, interim pharmacokinetics (PK) analysis (with a cut-off date of 28 August 2017) was conducted using non-compartmental methods, using serum concentrations from patients who received doses of 0.5, 2.0, 5.0, 10 mg/kg Q2W and 2.0 mg/kg, 5.0 mg/kg, 200 mg once every 3 weeks (Q3W) (Phase 1a Part 1, 2, 3, and Phase 1b in Study 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, after single-dose administration at steady state. Preliminary PK data from 27 patients who were administered 1 dose of 200 mg Q3W (Phase 1a, Part 3 and Study BGB-A317-102) showed tislelizumab concentrations between the range of concentrations observed for patients who were administered 2 mg/kg and 5 mg/kg doses. The PK profile of tislelizumab was consistent between Chinese patients and Caucasian patients.

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 (V_d) in the central and peripheral compartments of 2.89 L and 1.76 L, respectively, and half-life of approximately 19 days. Race, gender, and body weight are not significant covariates on the CL of tislelizumab, which supports fixed-dosing across different ethnic groups.

For more detailed information, please refer to the tislelizumab Investigator's Brochure.

1.4.4. Prior Clinical Experience of Tislelizumab

As of 28 February 2018, there are 13 ongoing studies with tislelizumab, including monotherapy and combination studies in solid tumors and hematological malignancies. Of the ongoing monotherapy studies in solid tumors, available data from BGB-A317_Study_001 and BGB-A317-102 are summarized below (with a data cutoff date of 28 August 2017). Of the ongoing combination studies, available data from BGB-A317-206 (data cutoff date of 21 February 2018) and BGB-A317-205 (data cutoff date of 13 June 2018) are summarized below. Please refer to the tislelizumab Investigator's Brochure for the most current data set.

1.4.4.1. BGB-A317_Study_001 (Data Cutoff 28 August 2017)

Study BGB-A317_Study_001 is a 2-stage study consisting of a Phase 1a dose-escalation and dose-finding component with 3 parts to establish the maximum tolerated dose (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 28 August 2017, in Phase 1a, 116 patients had received tislelizumab at dose regimens including 0.5 mg/kg, 2 mg/kg, 5 mg/kg, or 10 mg/kg Q2W; 2 mg/kg or 5 mg/kg Q3W; and 200 mg Q3W. In Phase 1b, 323 patients had received tislelizumab across 9 indication-expansion cohorts.

Overall, for the 439 patients in the study, the median age was 60.0 years, 53.8% of the population was male, and 65.6% of patients were white. The median number of prior anticancer therapy regimens was 2 (range: 0 to 12). The median treatment exposure duration was 2.50 months (range: 0 to 23.0), and the median study follow-up duration was 5.56 months (range: 0.0 to 26.9). The recommended Phase 2 dose (RP2) was established as fixed dose of 200 mg IV Q3W. As of 28 August 2017, there were 210 patients (47.8%) remaining on study.

Preliminary Safety

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

Preliminary Efficacy

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

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

1.4.4.2. Study BGB-A317-102 (Data Cutoff 28 August 2017)

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

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

Preliminary Safety

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

Preliminary efficacy data are not yet available.

1.4.4.3. Study BGB-A317-206 (Data Cutoff 21 February 2018)

This multi-arm Phase 2 study, consisting of safety run-in and dose-extension phases, assessed tislelizumab in combination with platinum-based chemotherapy (by tumor histology) as a potential first-line treatment for Chinese patients with lung cancer.

As of 21 Feb 2018, 48 patients (median age: 62 years [range: 36 to 75]; 71% male; 71% current/former smokers) received tislelizumab treatment (median: 3 cycles [range: 1 to 7]); 44 patients remain on the study.

Preliminary Safety

The most frequent AEs were chemotherapy-related hematologic toxicities. The most commonly reported ≥ 3 Grade treatment-related AEs were neutropenia (20.8%) and anemia (12.5%); the most common Grade 3 immune-mediated AEs (imAEs) were pyrexia (6.3%) and rash (6.3%). One sq-NSCLC patient experienced a fatal myocarditis/myositis following 1 cycle of paclitaxel/cisplatin; all other treatment-related AEs were managed/resolved by study-drug interruption (n=15) or discontinuation (n=4) and appropriate treatment.

Preliminary Efficacy

Across the 4 cohorts, confirmed and unconfirmed partial responses were observed in 13 and 9 patients, respectively.

1.4.4.4. Study BGB-A317-205 (Data Cutoff 13 June 2018)

This is a Phase 2, multi-cohort study to investigate the safety, pharmacokinetics and preliminary antitumor activity of the anti-PD-1 monoclonal antibody tislelizumab in combination with chemotherapy as first-line treatment in adults with inoperable, locally advanced or metastatic esophageal, gastric, or gastroesophageal junction (GEJ) carcinoma.

As of 13 June 2018, in the ESCC cohort, 15 patients (median age: 61 years) were enrolled (93% male; median treatment duration: 108 [21, 201] days; 3 patients received prior chemotherapy). In the GC (gastric carcinoma)/GEJ cohort, 15 GC/GEJ patients (median age: 57.9 years) were enrolled (73% male; median treatment duration: 171 [21, 251] days). There were 5 patients (33.3%) remaining on study treatment.

Preliminary Safety

In the ESCC cohort, a total of 22 patients experienced ≥1 tislelizumab- (n=8) or chemotherapy- (n=14) related AE. Two patients experienced a tislelizumab-related SAE (abnormal hepatic

function, pneumonitis); 4 patients experienced ≥1 chemotherapy-related SAE (thrombocytopenia, atrial fibrillation, fatigue, abnormal hepatic function, lung infection, decreased appetite). Rash (n=2) was the only imAE reported in ≥2 patients. One patient experienced ≥ 3 Grade increased AST and a fatal abnormal hepatic function.

In the GC/GEJ cohort, 14 patients (93.3 %) experienced treatment-related AEs of any grade, most commonly asthenia (n=8, 53.3%), nausea (n=7, 46.7%), AST increased (n=7, 46.7%), vomiting (n=6, 40.0%), ALT increased (n=6, 40.0%), Blood bilirubin increased (n=5, 33.3%), platelet count decreased (n=5, 33.3%), thrombocytopenia (n=5, 33.3%), decreased appetite (n=5, 33.3%). Nine patients (60.0 %) experienced ≥ 3 Grade treatment-related AEs including AST increased, ALT increased, blood bilirubin increased, neutrophil count decreased, amylase increased, lipase increased, vomiting, diarrhea, thrombocytopenia, granulocytopenia, decreased appetite, paronychia, all of which occurred in 1 patient. Tislelizumab (BGB-A317) treatment-related AEs occurred in 10 patients (66.7%), commonly asthenia (n=4, 26.7%) ALT increased (n=3, 20.0%), AST increased (n=3, 20.0%). Tislelizumab (BGB-A317) treatment-related ≥ 3 Grade AEs were observed in 5 patients including AST increased, ALT increased, neutrophil count decreased, amylase increased, lipase increased, decreased appetite, all of which occurred in 1 patient. One tislelizumab (BGB-A317) treatment-related SAE was reported (AST increased, ALT increased).

Preliminary Efficacy

Preliminary efficacy data are not yet available.

1.4.4.5. Immune-Mediated Reactions

In patients treated with tislelizumab monotherapy, the following imAEs were observed:

Acute hepatitis and abnormal liver function have been reported, including 1 patient with fatal hepatitis. Additionally, 3.2% of patients experienced treatment-related abnormal liver function tests, and 1.4% of patients experienced immune-mediated hepatitis or hyperbilirubinaemia.

Pneumonitis has been reported in 2.1% of patients, including 1 patient with fatal pneumonitis.

Colitis has been reported in approximately 2% of patients treated. Diarrhoea has been reported in 6.6% of patients.

Endocrinopathies have been reported including diabetes mellitus (hyperglycemia and ketoacidosis). In addition, thyroiditis, including thyrotoxicosis and hypothyroidism has been reported. Furthermore, hypophysitis has been reported in < 1% of patients treated.

Other immune-mediated events (< 1% of patients with tislelizumab monotherapy except where noted): skin reactions (20.5%, including rash and pruritus); arthralgia (2.5%); haemolytic anaemia, nephritis, proteinuria (1.8%); encephalitis, neuropathy, arthritis, pancreatitis, stomatitis, uveitis, and dry eye (1.4%).

Beyond patients treated with tislelizumab monotherapy, a case of fatal myocarditis and polymyositis was reported in 1 patient who received a single dose of tislelizumab, in combination with paclitaxel and cisplatin. 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.

1.5. Study Rationales

1.5.1. Rationale for Tislelizumab in the Treatment of Esophageal Carcinoma

High levels of FcγR-expressing myeloid derived cells (eg, M2 macrophage, myeloid-derived suppressor cell [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 antibody-dependent cell-mediated cytotoxicity (ADCC) or antibody-dependent cellular phagocytosis (ADCP) depletion of effector T-cells (Gül and van Egmund 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 theoretically show superior efficacy and lower toxicity in esophageal carcinoma. Available data from a clinical trial with other anti-PD-1 monoclonal antibodies, nivolumab and pembrolizumab, have shown the drugs to have both manageable safety profiles and promising antitumor activity in patients with esophageal carcinoma (Section 1.6).

Finally, according to the latest data collected from the Phase 1 BGB-A317_Study_001, tislelizumab monotherapy has established a manageable safety profile, with the most common side effects consistent with known class effects of other anti-PD-1 antibodies, as well as evidence for anti-tumor activity (Section 1.6).

1.5.2. Rationale for Selection of Tislelizumab Dose

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

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 objective 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% and 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 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 best overall response (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 pivotal studies.

1.5.3. Rationale for Matched Placebo in Combination with Chemotherapy as the Comparator

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

1.6. Benefit-Risk Assessment

Patients with unresectable recurrent or metastatic ESCC represent a population with a great unmet medical need.

Data from a Phase 1/2 clinical trial of nivolumab, a similar anti-PD-1 antibody, indicated an objective response of 22% (95% CI: 14% to 33%) that is durable, which suggests the potential efficacy of anti-PD-1 antibody for the treatment of patients with advanced ESCC (for additional discussion, see Section 1.1) (Kudo et al 2017). In a cohort of patients (n=49, 42 evaluable) with esophageal carcinoma treated with tislelizumab at 5 mg/kg in Phase 1b of Study BGB-A317_Study_001, PR was observed in 6 patients as of the 28 August 2017 data cut-off date. These patients had received a median of 2 prior lines of therapy. Responses were assessed after every 9 weeks on therapy. Confirmation of response required occurred at least 4 weeks after initial response assessment. Three of these patients had squamous cell carcinoma and 3 had adenocarcinoma. Twelve additional patients had confirmed a best response of SD. There were no CRs reported.

More than 800 patients have been treated with tislelizumab monotherapy at clinically relevant doses (≥ 2 mg/kg) and in combination. The safety profile is consistent with known class effects of anti-PD-1 antibodies and included mostly mild/moderate AEs. Very few Grade 3/4 imAEs have been observed, and they have been generally reversible and manageable with study drug interruption and/or steroid treatment. For further discussion on safety profile of tislelizumab, please refer to the Investigator's Brochure.

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

An Independent Data Monitoring Committee (IDMC) will be established to regularly monitor the safety of tislelizumab when compared with placebo. An interim analysis for OS superiority test is planned in the study (Section 9.7).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

- To evaluate and compare the overall survival (OS) following treatment with tislelizumab in combination with chemotherapy compared to placebo in combination with chemotherapy when given as first-line treatment in patients with unresectable, locally advanced recurrent or metastatic ESCC

2.1.2. Secondary Objectives

- To evaluate and compare the efficacy of tislelizumab in combination with chemotherapy compared to placebo in combination with chemotherapy as a first-line treatment in unresectable, locally advanced recurrent or metastatic ESCC as measured by PFS, ORR, and DOR assessed by the investigator per RECIST v1.1
- To evaluate and compare the efficacy of tislelizumab in combination with chemotherapy with the efficacy of placebo in combination with chemotherapy as a first-line treatment in unresectable, locally advanced recurrent or metastatic ESCC as measured by OS in the PD-L1 visually estimated combined positive score (vCPS) ≥ 10% subgroup. PD-L1 expression will be assessed centrally using the VENTANA PD-L1 (SP263) assay. The vCPS 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
- To evaluate and compare health-related quality of life (HRQoL) based on patient-reported outcomes (PROs) between tislelizumab in combination with chemotherapy and placebo in combination with chemotherapy
- To compare the safety between tislelizumab in combination with chemotherapy and placebo in combination with chemotherapy

2.1.3. Exploratory Objectives

- To characterize the DCR with tislelizumab in combination with chemotherapy assessed by the investigator per RECIST v1.1
- To evaluate PFS, ORR, DOR, and DCR assessed by blinded independent review committee (BIRC) per RECIST v1.1
- To assess PFS after next line of treatment (PFS2)
- To evaluate the potential association of biomarkers with patient prognosis, response, or resistance to tislelizumab in combination with chemotherapy
- To assess the pharmacokinetics of tislelizumab in combination with chemotherapy
- To assess host immunogenicity to tislelizumab in combination with chemotherapy

2.2. Study Endpoints

2.2.1. Primary Endpoint

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

2.2.2. Secondary Endpoints

- PFS - 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
- ORR - defined as the proportion of patients whose BOR is CR or PR assessed by the investigator per RECIST v1.1
- OS in the PD-L1 vCPS ≥ 10% subgroup
- HRQoL - defined as scores of the European EORTC QLQ-C30 (QLQ-C30), its esophageal cancer module - EORTC QLQ-OES18 (OES18), and the European Quality of Life 5-Dimension 5-Level (EQ-5D-5L)
- DOR - defined as the time from the first determination of an objective response until the first documentation of progression assessed by the investigator per RECIST v1.1 or death, whichever comes first
- The incidence and severity of adverse events according to NCI-CTCAE v4.03

2.2.3. Exploratory Endpoints

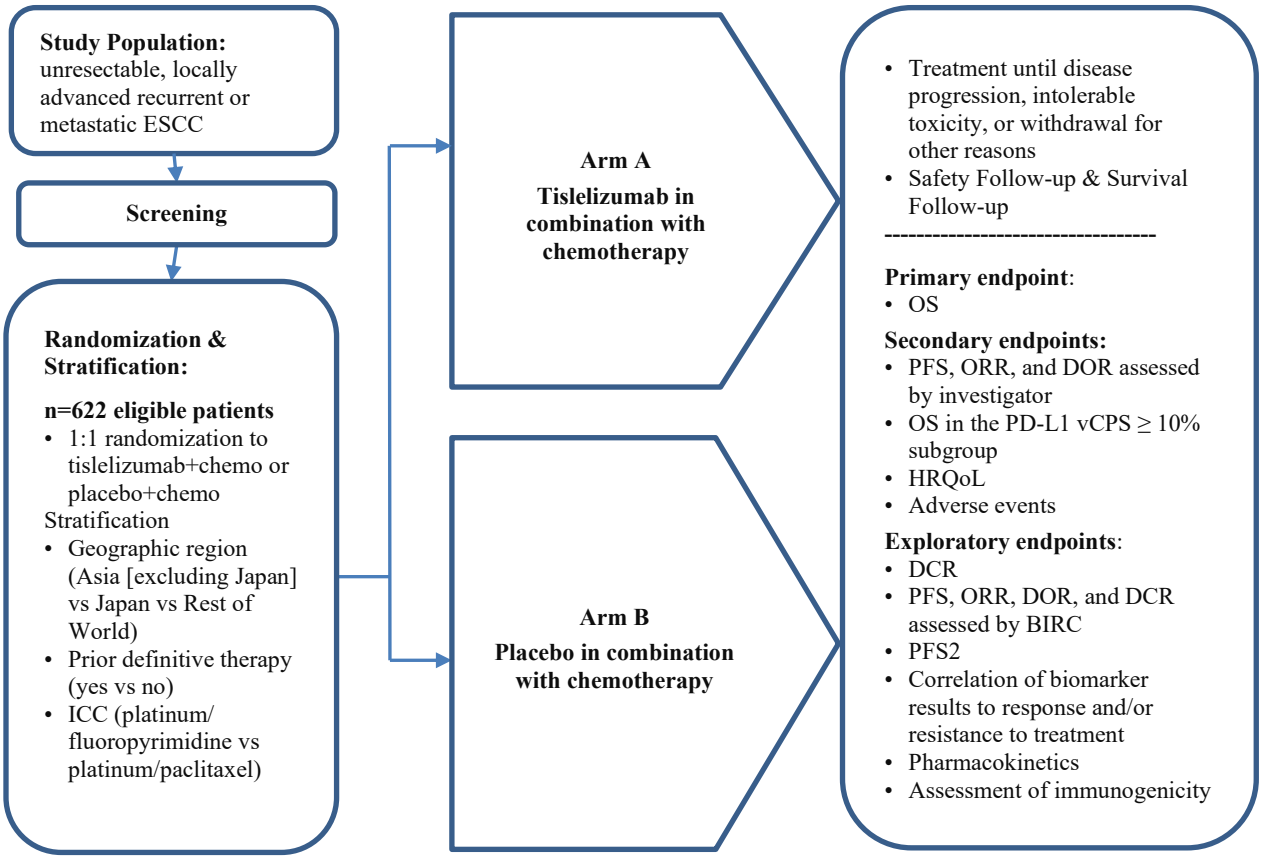
- DCR - defined as the proportion of patients whose BOR is CR, PR, and SD assessed by the investigator per RECIST v1.1
- PFS, ORR, DOR, and DCR assessed by BIRC per RECIST v1.1
- PFS2 - defined as the time from randomization to the objective disease progression after next line of treatment or death from any cause, whichever occurs first
- To explore biomarkers in tumor tissues and/or blood samples before and after study treatment and/or at PD/reoccurrence, and the association between these biomarkers and clinical efficacy, disease status, and resistance. Biomarker assessment will consist of PD-L1 expression, gene expression profiling (GEP), tumor mutation burden (TMB)/microsatellite instability (MSI)/mutation profile, and tumor-infiltrating immune cells. Other assessments may be conducted as allowed by local regulations.
- Assessments of pharmacokinetics of tislelizumab when given with chemotherapy
- Assessments of immunogenicity of tislelizumab by determining the incidence of antidrug antibodies (ADA)

3. STUDY DESIGN

3.1. Summary of Study Design

The study design schematic is presented in Figure 1.

Figure 1. Study Schema



Abbreviations: BIRC, blinded independent review committee; chemo, chemotherapy; DCR, disease control rate; DOR, duration of response; ESCC, esophageal squamous cell carcinoma; HRQoL, health-related quality of life; ICC, investigator choice of chemotherapy; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death protein ligand-1; PFS, progression-free survival; PFS2, PFS after next line of treatment; vCPS, visually estimated combined positive score.

The IDMC convened on 20 April 2022 to review the efficacy and safety data of the preplanned interim analysis (data cutoff date of 28 February 2022, with 422 death events which corresponds to 86.5% of the number of total planned death events for the final analysis [488 planned death events]). After reviewing the data, the IDMC confirmed that the study met the specified 1-sided p-value boundary for superiority of the primary endpoint and recommended to unblind/unmask the study due to compelling efficacy. Based on the IDMC recommendation, a decision was made to unblind all patients, and inform all investigators and IRB/IEC as required. Patients randomized to Arm B were to discontinue placebo after unblinding.

For all study procedures see Section 7 and Appendix 1.

3.2. Screening Period

Screening evaluations will be performed within 28 days prior to randomization. Patients will sign the informed consent form (ICF) prior to undergoing any screening procedure. Patients who are suspected to have serious respiratory concurrent illness or exhibit significant respiratory symptoms unrelated to underlying cancer or with a history of thoracic radiotherapy will also take a pulmonary function test (refer to Section 7.1.4 and Appendix 1 for details). Screening evaluations may be repeated once within the screening period; the investigator is to assess preliminary patient eligibility according to the latest screening assessment results.

Archival tumor tissue (formalin-fixed paraffin-embedded block or approximately 15 [at least 6] unstained slides) must be collected for purpose of biomarker analysis. If no archival samples are available, a fresh tumor biopsy at baseline is needed. Refer to Section 7.7 for details.

3.3. Treatment Period

After completing all screening activities, eligible patients will be randomized in a 1:1 ratio to receive either tislelizumab in combination with a chemotherapy doublet or placebo with a chemotherapy doublet. Randomization will be stratified according to geographic region (Asia [excluding Japan] vs Japan vs Rest of World), prior definitive therapy (yes vs no), and investigator choice of chemotherapy (platinum with fluoropyrimidine vs platinum with paclitaxel; see Section 5.2).

Patients will receive blinded treatment with one of the following:

Tislelizumab 200 mg IV Q3W in combination with chemotherapy doublet until disease progression assessed by the investigator per RECIST v1.1, unacceptable toxicity, or withdrawal of informed consent, whichever should occur first

Placebo IV Q3W in combination with a chemotherapy doublet until disease progression assessed by the investigator per RECIST v1.1, unacceptable toxicity, or withdrawal of informed consent, whichever should occur first

Platinum therapy may be stopped after 6 cycles, per site or investigator preference or standard practice. If platinum treatment is stopped, the non-platinum agent (fluoropyrimidine or paclitaxel) may continue at the regular schedule, if appropriate. In both arms, treatment beyond the initial investigator-assessed, RECIST v1.1-defined disease progression is permitted provided that the patient a) has investigator-assessed clinical benefit and b) is tolerating study drug. Specific requirements for post-progression continuation of patients treated with tislelizumab (or placebo) and chemotherapy are described in Section 3.6.1.

Radiological assessment of tumor-response status will be performed every 6 weeks (± 7 days) for the first 48 weeks, then every 9 weeks (± 7 days) after 48 weeks, based on RECIST v1.1. Tumor response will be assessed by BIRC and by investigators. Details are provided in Section 7.5.

Safety will be assessed throughout the study by monitoring AEs/SAEs (toxicity grades assigned per National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] v4.03), and laboratory results. Vital signs, physical examinations, Eastern Cooperative Oncology Group (ECOG) performance status change, electrocardiogram (ECG) results, and other examinations will also be used for safety assessment. Safety assessments are further detailed in Section 7.4 and the Schedule of Assessments (Appendix 1).

When a patient reaches 24 months of treatment (as measured from Cycle 1 Day 1):

Patients may continue study therapy beyond 2 years if the investigator considers this to be in the best interest of the patient based on an assessment of clinical benefit and potential risks. Continuation of study therapy beyond 2 years has to be explicitly approved by the sponsor, and will be contingent on the continued availability of study treatment. The study assessment and procedures schedule will remain the same.

After 2 years of study treatment, if patients have confirmed CR, PR, or SD, the treatment can be stopped if the patient wishes. The decision should be based on the investigator's evaluation, with the patient's clinical benefit and risk taken into consideration. A treatment-interruption informed consent form must be signed by patients who stop treatment. The investigator should notify the sponsor that treatment will be stopped prior to the event. In such a case, the study assessments and procedures will be performed every 12 weeks (in conjunction with repeat radiographic imaging, as described in Section 7.5) rather than every cycle.

[redacted]

Blood samples of approximately 10 mL will be taken at baseline (predose on Day 1 of Cycle 1) for all randomized patients to explore the association of blood-based biomarkers with response and prognosis to tislelizumab in combination with chemotherapy or chemotherapy alone. Written patient consent is required for blood sample collections.

3.4. End of Treatment/Safety Follow-up

The End-of-Treatment (EOT) Visit and Safety Follow-up Visit may be a combined visit. The EOT/Safety Follow-up is conducted when the investigator determines that tislelizumab or placebo with chemotherapy will no longer be used. If routine laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the EOT/Safety Follow-up visit, these tests need not be repeated. Tumor assessment is not required at the EOT/Safety Follow-up Visit provided that fewer than 6 weeks have passed since the last assessment.

Patients who discontinue treatment for any reason will be asked to return to the clinic for the EOT/Safety Follow-up Visit (to occur within 30 days [± 7 days] after the last dose of study treatment (including chemotherapy), or before the initiation of a new anticancer treatment, or before the first dose administration in the long-term extension/posttrial supply study for patients who are going to rollover to those studies, whichever occurs first. In addition, telephone contacts with patients should be conducted to assess imAEs and concomitant medications (if appropriate, ie, associated with an imAE or is a new anticancer therapy) at 60 and 90 days (± 14 days) after the last dose of study drug (including chemotherapy), regardless of whether the patient starts a new anticancer therapy. If patients report a suspected imAE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated.

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

Patients who discontinue study treatment prior to disease progression will have their tumors assessed as outlined in Section 7.5.

Patients receiving paclitaxel will need to be followed for safety and pregnancy for 180 days following the last dose.

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

3.5. Survival Follow-up

Patients who discontinue study drug for reasons other than documented radiographic disease progression (eg, toxicity) will continue to undergo tumor assessments according to Section 7.5 and the Schedule of Assessments (Appendix 1), until the patient experiences radiographic disease progression, withdraws consent, is lost to follow-up, or dies, or until the study completes, whichever occurs first.

Patients will be followed for survival, and further anticancer therapy information after discontinuation of study treatment via telephone calls, patient medical records, and/or clinic visits at least every 3 months (± 14 days) or more frequently to ensure data collection feasibility after the Safety Follow-up Visit or as directed by the sponsor until death, loss to follow-up, withdrawal of consent, or study completion by the sponsor (Section 3.7). Confirmed loss to follow-up is defined as ≥ 3 consecutive failures of contacting attempts, any 2 of which are ≥ 1 month apart, via ≥ 2 different documented methods. At the time of site closure, one additional final attempt of contacting patients lost to follow-up should be made and documented for confirming the loss to follow-up.

3.6. Discontinuation From the Study Treatment or From the Study

3.6.1. Patient Discontinuation from Study Treatment

Patients have the right to discontinue study treatment at any time for any reason. In addition, the investigator has the right to discontinue a patient from the study treatment at any time. Patients who discontinue study treatment for reasons other than radiographic disease progression as documented by BIRC should be followed for assessments of antitumor activity (Section 7.5), safety (Section 7.4), and survival (Section 3.5), if possible.

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

- Withdrawal by patient from study treatment (survival/PFS2 data can still be collected and biospecimens analyzed beyond that date)
- Pregnancy
- Any medical condition that the investigator or sponsor determines may jeopardize the patient's safety, if he or she were to continue the study treatment
- Use of any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents [including Chinese herbal medicine and Chinese patent medicines] for the treatment of cancer)
- Patient noncompliance

Patients will be permitted to continue study drug(s) if pseudoprogression is suspected and/or there is a reasonable belief that the patient could derive benefit from study drug(s) after RECIST v1.1 criteria for progressive disease are met, and if they meet all of the following criteria:

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

The decision to continue study drug(s) beyond initial investigator-assessed progression must be discussed with the sponsor's medical monitor and documented in the study records. Tumor assessment should continue as planned in patients receiving study drug(s) beyond initial investigator-assessed progression. Tumor assessment in these patients should continue until study treatment discontinuation.

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

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

- Withdrawal by patient from study (no further data can be collected but biospecimens collected before that date can still be analyzed)
- Death
- Lost to follow up
- Patients have completed all study assessments

3.7. End of Study

The end of study is defined as the timepoint when the final data for a clinical study have been collected, which is after the last 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
- A rollover study becomes available

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

At the end of the study, any patient who, in the opinion of the investigator, continues to benefit from tislelizumab, will be offered the option to continue treatment in a company-sponsored rollover study or post-study drug supply program until tislelizumab is commercially available in the country of the patient's residence.

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

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

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

3.8. Enrollment of Japanese Patients

The safety of study treatment will be closely monitored in all patients throughout the course of the clinical study. Enrollment of Japanese patients will be gated to monitor for unexpected or new safety concerns. The safety cohort of approximately 10 Japanese patients (minimum of 5 per arm) will be treated and closely monitored during a 7-day hospitalization, according to local practice. Following discharge from this initial hospitalization, patients will be monitored with weekly assessments for safety, as detailed in Appendix 1 (Schedule of Assessments). The Sponsor unblinded Drug Safety and Pharmacovigilance group will review unblinded SAE reports, and the IDMC will review all safety data after this safety cohort of Japanese patients completes 1 cycle, or at any time there is a safety concern. DLT is defined in the IDMC charter and the occurrence of DLTs in patients who receive tislelizumab in combination with cisplatin and 5-FU will be assessed independently by the IDMC. During the IDMC review, enrollment in Japan will be held until the IDMC review is complete and the safety and tolerability is deemed acceptable.

4. STUDY POPULATION

The specific eligibility criteria for selection of patients are provided in Section 4.1 and Section 4.2. Appendix 13 contains a flow chart to help determine which patients are appropriate for this study. The sponsor will not grant any eligibility waivers.

4.1. Inclusion Criteria

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

1. Able to provide written informed consent and can understand and agree to comply with the requirements of the study and the Schedule of Assessments
2. Age ≥ 18 years on the day of signing the informed consent form (or the legal age of consent in the jurisdiction in which the study is taking place)
3. Pathologically (histologically) confirmed diagnosis of ESCC

   Note: Patients with adenocarcinoma differentiation < 5% of the viable tumor sample are eligible
4. Stage IV unresectable ESCC at first diagnosis OR unresectable, locally advanced recurrent or metastatic disease (per AJCC 7th Edition, Appendix 14), if there is prior neoadjuvant/adjuvant therapy with platinum-based chemotherapy, a treatment-free interval of at least 6 months is required
5. Measurable or evaluable disease as defined per RECIST v1.1

   Note: The target lesion(s) selected that are within the field of prior local therapy have subsequently progressed as defined by RECIST v1.1
6. ECOG Performance Status ≤ 1
7. Adequate organ function as indicated by the following laboratory values ≤ 14 days prior to randomization.
   a. Patients must have the following laboratory values:
      i. Absolute neutrophil count ≥ 1.5 x 10^9/L
      ii. Platelets ≥ 100 x 10^9/L
      iii. Hemoglobin ≥ 90 g/L

   NOTE: Patients must not have required a transfusion or growth factor support ≤ 14 days before sample collection for neutrophil counts, platelets, or hemoglobin that were lower than required for the study.

   b. Serum creatinine ≤ 1.5 mg/100 mL (equivalent 130 µmol/L).
   c. Serum total bilirubin ≤ 1.5 x upper limit of normal (ULN) (total bilirubin must be < 3 x ULN for patients with Gilberts syndrome).
   d. AST and ALT ≤ 3 x ULN, or AST and ALT ≤ 5 x ULN for patients with liver metastases
8. Have newly obtained or archival tissue sample available for biomarker assessment.

9. Females of childbearing potential must be willing to use a highly effective method of birth control for the duration of the study (in accordance with the Contraception Guidelines in Appendix 9), ≥ 120 days after the last dose of tislelizumab, and ≥ 180 days after the last dose of chemotherapy, and have a negative serum pregnancy test ≤ 7 days of randomization
10. Non-sterile males must be willing to use a highly effective method of birth control for the duration of the study, ≥ 120 days after the last dose of tislelizumab, and for ≥ 180 days after the last dose of chemotherapy

4.2. Exclusion Criteria

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

1. Ineligible for treatment with any of the chemotherapy doublets of protocol-specified chemotherapy
2. Prior systemic therapy for unresectable, locally advanced recurrent or metastatic ESCC

   Note: Patients with prior systemic concurrent chemotherapy in concurrent chemoradiotherapy are eligible
3. Palliative radiation treatment for ESCC within 4 weeks of study treatment initiation
4. Patients with evidence of fistula (either esophageal/bronchial or esophageal/aorta)
5. Uncontrollable pleural effusion, pericardial effusion, or ascites requiring frequent drainage or medical intervention (clinically significant recurrence requiring an additional intervention within 2 weeks of intervention)
6. Evidence of complete esophageal obstruction not amenable to treatment
7. Received prior therapies targeting PD-1, PD-L1, or PD-L2
8. Active leptomeningeal disease or uncontrolled brain metastasis.
   a. Patients with a history of treated and, at the time of screening, stable central nervous system (CNS) metastases are eligible, provided they meet all the following:
      i. Brain imaging at screening shows no evidence of interim progression, clinically stable for at least 2 weeks and have no evidence of new brain metastases
      ii. Have measurable and/or evaluable disease outside the CNS
      iii. No ongoing requirement for corticosteroids as therapy for CNS disease; off steroids 3 days prior to randomization; anticonvulsants at a stable dose are allowed
      iv. No stereotactic radiation or whole-brain radiation within 14 days prior to randomization
   b. Deleted
      i. Deleted
9. Active autoimmune diseases or history of autoimmune diseases that may relapse.

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

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

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

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

    a. Adrenal replacement steroid (dose ≤ 10 mg daily of prednisone or equivalent)
    b. Topical, ocular, intra-articular, intranasal, or inhaled corticosteroid with minimal systemic absorption
    c. Short course (≤ 7 days) of corticosteroid prescribed prophylactically (eg, for contrast dye allergy) or for the treatment of a non-autoimmune condition (eg, delayed-type hypersensitivity reaction caused by contact allergen)
12. With history of interstitial lung disease, non-infectious pneumonitis or uncontrolled lung diseases including pulmonary fibrosis, acute lung diseases, etc.
13. With infections (including tuberculosis infection, etc) requiring systemic antibacterial, antifungal or antiviral therapy within 14 days prior to randomization. Note: antiviral therapy is permitted for patients with chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection.
14. A known history of HIV infection
15. Any major surgical procedure requiring general anesthesia ≤ 28 days before randomization
16. Prior allogeneic stem cell transplantation or organ transplantation
17. Any of the following cardiovascular risk factors:

    a. Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living, ≤ 28 days before randomization
    b. Pulmonary embolism ≤ 28 days before randomization
    c. Any history of acute myocardial infarction ≤ 6 months before randomization
    d. Any history of heart failure meeting New York Heart Association Classification III or IV (Appendix 6) ≤ 6 months before randomization
    e. Any event of ventricular arrhythmia ≥ Grade 2 in severity ≤ 6 months before randomization

f. Any history of cerebrovascular accident ≤ 6 months before randomization
g. Uncontrolled hypertension: systolic pressure ≥ 160 mmHg or diastolic pressure ≥ 100 mmHg despite anti-hypertension medications ≤ 28 days before randomization
h. Any episode of syncope or seizure ≤ 28 days before randomization

18. A history of severe hypersensitivity reactions to other monoclonal antibodies
19. Has received any Chinese herbal medicine or Chinese patent medicines used to control cancer within 14 days of the first study drug administration
20. Was administered a live vaccine ≤ 4 weeks before randomization

    Note: Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed.
21. Underlying medical conditions (including laboratory abnormalities) or alcohol or drug abuse or dependence that will be unfavorable for the administration of study drug or affect the explanation of drug toxicity or AEs or might impair compliance with study conduct.
22. Concurrent participation in another therapeutic clinical trial
23. Unintentional weight loss ≥ 5% within one month prior to randomization or Nutritional Risk Index (NRI) < 83.5 (Appendix 15) per investigator's choice
24. Pregnant or breastfeeding woman
25. Patients receiving chemotherapy doublet C (platinum and paclitaxel) must not have peripheral neuropathy ≥ Grade 2 at baseline
26. With uncontrolled diabetes or > Grade 1 laboratory test abnormalities in potassium, sodium, or corrected calcium despite standard medical management or ≥ Grade 3 hypoalbuminemia ≤ 14 days before randomization.
27. Has received any chemotherapy, immunotherapy (eg, interleukin, interferon, thymosin, etc) or any investigational therapies within 14 days or 5 half-lives (whichever is shorter) of the first study drug administration
28. Patients with toxicities (as a result of prior anticancer therapy) which have not recovered to baseline or stabilized, except for AEs not considered a likely safety risk (eg, alopecia and specific laboratory abnormalities)
29. Locally advanced esophageal carcinoma that is resectable or potentially curable with radiation therapy per local investigator.
30. Patients with untreated chronic hepatitis B or chronic HBV carriers whose HBV DNA is ≥ 500 IU/mL or patients with active hepatitis C virus (HCV)

    Note: Patients who are inactive carriers or with treated and stable hepatitis B (detectable B surface antigen (HBsAg), HBV DNA < 500 IU/mL) and patients with non-active hepatitis C can be enrolled. Management of prophylaxis antiviral therapy should be as per local guidelines.

5. STUDY TREATMENT

5.1. Formulation, Packaging, and Handling

5.1.1. Tislelizumab

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

The label will include at a minimum, the drug name, dose strength, contents, sponsor, protocol number, kit number, batch/lot number, directions for use, storage conditions, caution statements, retest or expiry date, and space to enter the patient number and name of the investigator. The contents of the label will be in accordance with all applicable local regulatory requirements.

The study drug must be kept at the temperature condition as specified on the label. Tislelizumab must be stored at temperatures between 2ºC and 8ºC and protected from light.

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. Matched Placebo

All personnel at the study sites and all patients and the Sponsor will be blinded to study treatment.

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

The label will include at a minimum, sponsor, protocol number, kit number, batch/lot number, directions for use, storage conditions, caution statements, retest or expiry date, and space to enter the patient number and name of the investigator. The contents of the label will be in accordance with all applicable local regulatory requirements.

The vials must be kept at the temperature condition as specified on the label. Vials must be stored at temperatures between 2ºC and 8ºC and protected from light.

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

5.1.3. Cisplatin

Cisplatin will be supplied in vials for infusion; however, the actual appearance and composition of the product may depend on the respective marketed product sourced for the participating countries

For cisplatin supplied by sponsor or its designee, the label will include at a minimum, the drug name, dose strength, contents, sponsor, protocol number, kit number, lot number, directions for use, storage conditions, caution statements, retest or expiry date, and space to enter the patient number and name of investigator. The contents of the label will be in accordance with all applicable local regulatory requirements.

The study drug must be kept at the temperature condition as specified on the label. If diluted solution is not to be used within 6 hours, protect solution from light.

For further details, see the manufacturer's prescribing information for cisplatin.

5.1.4. Oxaliplatin

Oxaliplatin will be supplied in vials for infusion; however, the actual appearance and composition of the product may depend on the respective marketed product sourced for the participating countries.

For oxaliplatin supplied by sponsor or its designee, the label will include at a minimum, the drug name, dose strength, contents, sponsor, protocol number, kit number, lot number, directions for use, storage conditions, caution statements, retest or expiry date, and space to enter the patient number and name of investigator. The contents of the label will be in accordance with all applicable local regulatory requirements.

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

For further details, see the manufacturer's prescribing information for oxaliplatin.

5.1.5. 5-Fluorouracil

5-FU will be supplied in vials for infusion; however, the actual appearance and composition of the product may depend on the respective marketed product sourced for the participating countries.

For 5-FU supplied by sponsor or its designee, the label will include at a minimum, the drug name, dose strength, contents, sponsor, protocol number, kit number, lot number, directions for use, storage conditions, caution statements, retest or expiry date, and space to enter the patient number and name of investigator. The contents of the label will be in accordance with all applicable local regulatory requirements.

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

For further details, see the manufacturer's prescribing information for 5-FU.

5.1.6. Capecitabine

Capecitabine will be supplied as tablets; however, the actual appearance and composition of the product may depend on the respective marketed product sourced for the participating countries.

For capecitabine supplied by sponsor or its designee, the label will include at a minimum, the drug name, dose strength, contents, sponsor, protocol number, kit number, lot number, directions for use, storage conditions, caution statements, retest or expiry date, and space to enter the patient number and name of investigator. The contents of the label will be in accordance with all applicable local regulatory requirements.

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

For further details, see the manufacturer's prescribing information for capecitabine.

5.1.7. Paclitaxel

Paclitaxel will be supplied in vials for infusion; however, the actual appearance and composition of the product may depend on the respective marketed product sourced for the participating countries.

For paclitaxel supplied by sponsor or its designee, the label will include at a minimum, the drug name, dose strength, contents, sponsor, protocol number, kit number, lot number, directions for use, storage conditions, caution statements, retest or expiry date, and space to enter the patient number and name of investigator. The contents of the label will be in accordance with all applicable local regulatory requirements.

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

For further details, see the manufacturer's prescribing information for paclitaxel.

5.2. Dosage, Administration, and Compliance

Dosing schedules for both arms, broken out by individual arm, are provided in Table 2. One treatment cycle is 21 days in length.

Table 2. Selection and Timing of Dose for Each Patient

Intervention	Drug	Dose	Study Day(s)	Frequency of Administration	Route of Administration
Study Drug	Tislelizumab (BGB-A317)	200 mg	1	Q3W	Intravenous
Matched Placebo	None	N/A	1	Q3W	Intravenous
Chemotherapy Doublet A***	Cisplatin OR Oxaliplatin*	60-80 mg/m^2 (cisplatin) 130 mg/m^2 (oxaliplatin)	1	Q3W	Intravenous
	5-Fluorouracil	750-800 mg/m^2	1-5	Q3W	Intravenous
Chemotherapy Doublet B***	Cisplatin OR Oxaliplatin*	60-80 mg/m^2 (cisplatin) 130 mg/m^2 (oxaliplatin)	1	Q3W	Intravenous
	Capecitabine	1000 mg/m^2	1-14	Twice a day	Oral
Chemotherapy Doublet C***	Cisplatin OR Oxaliplatin*	60-80 mg/m^2 (cisplatin) 130 mg/m^2 (oxaliplatin)	1 or 2**	Q3W	Intravenous
	Paclitaxel	175 mg/m^2	1	Q3W	Intravenous

Abbreviations: 5-FU, 5-fluorouracil; N/A, not applicable; Q3W, every 3 weeks.

Note: Platinum therapy may be stopped after 6 cycles, per site or investigator preference or standard practice. If platinum treatment is stopped, the non-platinum agent (fluoropyrimidine or paclitaxel) may continue at the regular schedule.

* The platinum agent may be cisplatin or oxaliplatin (except in China, Taiwan, Japan, and countries where oxaliplatin substitution is not permitted) according to site or investigator preference or standard practice as determined prior to randomization.

** For Chemotherapy Doublet C, cisplatin may be administered on Days 1 or 2, or in 3 divided doses on Days 1, 2, and 3 depending on local guidelines. The total dose given must be between 60 to 80 mg/m^2 per cycle.

*** For sites where the sponsor is required to provide these products will either be supplied or reimbursed by the sponsor or designee. These products may be obtained by the investigational sites as local commercial products in certain countries if allowed by local regulations.

All regimens in Arm A will contain tislelizumab in combination with 1 of the 3 listed chemotherapy doublets. All of the regimens in Arm B will contain matched placebo in combination with 1 of the 3 listed chemotherapy doublets. The first dose of study drug is to be administered within 2 business days of randomization. Tislelizumab/placebo will be administered first, followed by at least a 30-minute observation period for safety surveillance, then the chemotherapy doublet will be administered. The chemotherapy doublet may be administered without regard to the sequence of chemotherapy or according to local standard treatment practices and guidelines. (note that in Chemotherapy Doublet B, capecitabine is given orally daily). All patients will be monitored continuously for AEs. Treatment modifications (eg, dose delay, reduction, interruption or discontinuation) will be based on specific laboratory and adverse event criteria, and the investigator's clinical assessment as described in Section 5.5.

Alternate dose and dosing schedules are allowed according to local and institutional guidelines.

According to clinical practice in Japan, only the cisplatin + 5-FU chemotherapy regimen will be used in Japan.

5.2.1. Tislelizumab

Tislelizumab 200 mg will be administered on Day 1 of each 21-day cycle Q3W.

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

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

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

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

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

5.2.2. Matched Placebo

All personnel at the study sites and all patients and the Sponsor will be blinded to study treatment. Administration of matched placebo will follow the guidance given for tislelizumab, as described in Section 5.2.1 above.

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

5.2.3. Chemotherapy Doublet A: Platinum (Cisplatin or Oxaliplatin) in Combination with 5-Fluorouracil

After all procedures/assessments have been completed as detailed in Appendix 1 and Section 3.2. Cisplatin will be administered on Day 1, given Q3W at a dose of 60 to 80 mg/m^2 by IV infusion over 6 to 8 hours (or in doses consistent with local or country-specific treatment guidelines, or according to manufacturer standards or institutional standards). Oxaliplatin 130 mg/m^2 IV on Day 1 Q3W, given over 2 hours may be substituted in place of cisplatin, according to site or investigator preference or standard practice as determined prior to randomization (except in China, Taiwan, Japan, and countries where oxaliplatin substitution is not permitted). Also, 5-FU will be administered on Days 1 to 5, given Q3W at a dose of 750 to 800 mg/m^2 by continuous IV infusion over 24 hours. The actual infusion time of 5-FU should be recorded, and a total infusion time of 120+/- 3 hours is acceptable. The initial treatment of platinum (cisplatin or oxaliplatin) in combination with 5-FU will be administered within 2 business days of randomization. Alternate dose and dosing schedules are allowed according to local and institutional guidelines.

The first doses of platinum and 5-FU are dependent upon the patient's baseline body weight. Subsequent doses must be recalculated if the change of body weight from baseline ≥ 10%. Subsequent doses should not be recalculated if the change (increase or decrease) of body weight from baseline < 10% unless there is persistent toxicity that requires dose adjustment. If the dose is recalculated because of a ≥ 10% change in body weight from baseline, this body weight will then be used as the new baseline to calculate the platinum and 5-FU dose in subsequent cycles.

Premedication is recommended prior to infusion of cisplatin according to the manufacturer's instructions. The premedication regimen should be determined by the investigator and administered as close to treatment as possible. Premedication may consist of hydration with 1 to 2 liters of fluid infused 8 to 12 hours prior to dosing. The use of diuretics for fluid maintenance is allowable.

There is a 3-day window for all treatments 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 AEs and will be instructed to notify their physician immediately for any and all AEs. Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of therapy.

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

5.2.4. Chemotherapy Doublet B: Platinum (Cisplatin or Oxaliplatin) in Combination with Capecitabine

After all procedures/assessments have been completed as detailed in Appendix 1 and Section 3.2, cisplatin will be administered on Day 1, given every 21 days at a dose of 60 to 80 mg/m^2 by IV infusion over 6 to 8 hours (or in doses consistent with local or country-specific treatment guidelines, or according to manufacturer standards or institutional standards). Oxaliplatin 130 mg/m^2 IV on Day 1 Q3W, given over 2 hours may be substituted in place of cisplatin, according to site or investigator preference or standard practice as determined prior to randomization (except in China, Taiwan, Japan, and countries where oxaliplatin substitution is not permitted).

Capecitabine will be self-administered orally twice daily, from the morning of Day 1 to the evening of Day 14 or from the evening of Day 1 to the morning of Day 15 of each 21-day cycle at the recommended dose of 1000 mg/m^2 twice daily (BID). The initial treatment of cisplatin in combination with capecitabine will be administered within 2 business days of randomization. Alternate dose and dosing schedules are allowed according to local and institutional guidelines.

The first doses of platinum and capecitabine are dependent upon the patient's baseline body weight. Subsequent doses must be recalculated if the change of body weight (increase or decrease) from baseline ≥ 10%. Subsequent doses should not be recalculated if the change (increase or decrease) of body weight from baseline < 10% unless the emergence of toxicity requires dose adjustment. If the dose is recalculated because of a ≥ 10% change in body weight from baseline, this body weight will then be used as the new baseline to calculate the platinum and capecitabine dose in subsequent cycles.

Premedication is recommended prior to infusion of cisplatin according to the manufacturer's instructions. The premedication regimen should be determined by the investigator and administered as close to treatment as possible. Premedication may consist of hydration with 1 to 2 liters of fluid infused 8 to 12 hours prior to dosing. Urinary output must be maintained according to local or institutional standards of care when administering cisplatin treatment.

An adequate amount of supply of capecitabine will be dispensed to patients on Day 1 of each new cycle (Q3W). Each time study drug is dispensed, compliance will be evaluated and encouraged. Treatment compliance will also be monitored by drug accountability and recorded in the patient's medical record and eCRF. If the number of capsules returned does not agree with the expected number, the patient should be counseled, and proper dosing reinforced. Capecitabine should be taken with water, within 30 minutes after a meal. Urinary output should be maintained according to local or institutional standards of care. If a dose of capecitabine is missed, the patient should take the next dose as scheduled. A double dose of capecitabine should not be administered to make up for missed individual doses. Refer to the capecitabine prescribing information for additional details.

Patients will be monitored continuously for AEs and will be instructed to notify their physician immediately for any and all AEs. Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of therapy.

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

5.2.5. Chemotherapy Doublet C: Platinum (Cisplatin or Oxaliplatin) in Combination with Paclitaxel

After all procedures/assessments have been completed as detailed in Appendix 1 and Section 3.2, cisplatin will be administered on Day 1 or 2, given every 21 days at a dose of 60 to 80 mg/m^2 by IV infusion over 6 to 8 hours (or in doses consistent with local or country-specific treatment guidelines, or according to manufacturer standards or institutional standards). Oxaliplatin 130 mg/m^2 IV on Day 1 Q3W, given over 2 hours may be substituted in place of cisplatin, according to site or investigator preference or standard practice as determined prior to randomization (except in China, Taiwan, Japan, and countries where oxaliplatin substitution is not permitted). Depending on local guidelines, cisplatin may be given in 3 divided doses on Days 1, 2, and 3. The total dose

given must be between 60 to 80 mg/m^2 per cycle. Also, paclitaxel will be administered on Day 1, given Q3W at a dose of 175 mg/mg^2 by IV infusion over 3 hours. The initial treatment of platinum (cisplatin or oxaliplatin) in combination with paclitaxel will be administered within 2 business days of randomization. Alternate dose and dosing schedules are allowed according to local and institutional guidelines.

The first doses of platinum and paclitaxel are dependent upon the patient's baseline body weight (increase or decrease) from baseline ≥ 10%. Subsequent doses should not be recalculated if the change (increase or decrease) of body weight from baseline < 10%. If the dose is recalculated because of a ≥ 10% change in body weight from baseline, this body weight will then be used as the new baseline to calculate the platinum and paclitaxel dose in subsequent cycles.

Premedication is recommended prior to infusion of cisplatin according to the manufacturer's instructions. The premedication regimen should be determined by the investigator and administered as close to treatment as possible. Premedication may consist of hydration with 1 to 2 liters of fluid infused 8 to 12 hours prior to dosing.

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 treatment as possible. Premedication may consist of an oral steroid (such as dexamethasone 8 to 20 mg or equivalent administered 6 to 12 hours orally or 30 to 60 minutes IV 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 CRF.

There is a 3-day window for all treatments 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 AEs and will be instructed to notify their physician immediately for any and all AEs. Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of therapy. Patients receiving paclitaxel will need to be followed for safety and pregnancy for 180 days following the last dose.

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

5.3. Overdose

Any overdose of tislelizumab (defined as ≥ 600 mg of tislelizumab in a 24-hour period) or incorrect administration of study drug should be noted in the patient's chart and on the appropriate eCRF. For chemotherapy, doses >20% of targeted total dose specified in this protocol represent an overdose, and the Sponsor should be notified as soon as possible. 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 8.6. Supportive care measures should be administered as appropriate.

5.4. Investigational Medicinal Product Accountability

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

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

5.5. Dose Delay or Modification

A dose delay is a deviation from prescribed dosing schedule (ie, the drug is withheld beyond visit window). A dose interruption is an interruption of the intravenous infusion.

Every effort should be made to administer the study drug(s) according to the planned dose and schedule. In the event of significant toxicities, dosing may be delayed and/or reduced based on the guidelines provided below. Reasons for dose modifications or delays, the supportive measures taken, and the outcome will be documented in the patient's chart and recorded in the eCRF.

The dose modification guidelines in this section are not intended to be a substitute for clinical judgment. Investigators may delay or modify doses in response to other reasons (eg, AEs, declining weight, lab findings, etc.) as appropriate.

In case of chemotherapy-related toxicity, chemotherapy will be delayed until it resolves to baseline or ≤ Grade 1 (whichever is more severe) prior to administering the next dose of chemotherapy, with the exception of alopecia, Grade 2 fatigue, or other AEs which, in the opinion of the investigator, would not affect the safety evaluation of the study drugs. Tislelizumab or placebo should continue as scheduled. If the AE resolves within 10 days, chemotherapy will be administered. The administration of chemotherapy and tislelizumab or placebo will be resynchronized at the subsequent cycle, which will be scheduled according to the chemotherapy dose administration date. If the AE does not resolve within 10 days, chemotherapy will be omitted. If the AE resolves within 21 days, chemotherapy and tislelizumab or placebo will be administered on Day 1 of the next treatment cycle according to the original schedule.

In case of tislelizumab or placebo-related toxicity, tislelizumab or placebo will be delayed until it resolves to baseline or ≤ Grade 1 (whichever is more severe) prior to administering the next dose of tislelizumab or placebo, with the exception of alopecia, Grade 2 fatigue, or other AEs which, in the opinion of the investigator, would not affect the safety evaluation of the study drugs. Chemotherapy should continue as scheduled. If the AE is resolves within 10 days, tislelizumab or placebo will be administered. The administration of chemotherapy and tislelizumab or placebo will be resynchronized at the subsequent cycle, which will be scheduled according to the chemotherapy dose administration date. If the AE does not resolve within 10 days, tislelizumab or placebo should not be given for the current cycle. If the AE resolves within 21 days, tislelizumab or placebo and chemotherapy will be administered on Day 1 of the next treatment cycle according to the original schedule.

In case of both tislelizumab/placebo and chemotherapy toxicity, treatment in any patient may be temporarily held if the toxicity is considered to be related to tislelizumab or placebo and chemotherapy. If the administration delay is ≤ 10 days for any delayed drug, the delayed drug will

be administered; if the delay is >10 days, the delayed drug will be omitted in this cycle and the next cycle will be administered as planned as long as the AE resolves within 21 days. Other study drug (tislelizumab or placebo) delay principles will be the same with that in Section 5.5.1; Other chemotherapy delay principles will be the same with that in Section 5.5.2.

5.5.1. Dose Delay or Modification for Tislelizumab/Placebo

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

Dose delays < 12 weeks will be permitted. 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 or placebo and requires a dose to be withheld. If the administration delay is ≤ 10 days, the delayed drug will be administered; if the delay is > 10 days, the delayed drug will be omitted in this cycle and the next cycle will be administered as planned as long as the AE resolves within 21 days. If the study drug (tislelizumab or placebo) delay is > 12 weeks, it will be stopped permanently.

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

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

5.5.2. Dose Delay, Interruption, or Modifications for Chemotherapy

Dose adjustments are based on nadir blood counts since the preceding chemotherapy administration.

Dose level adjustments are relative to that of the preceding administration. Study drug related toxicities must be resolved to baseline or Grade 0 to 1 prior to administering the next dose, with the exception of alopecia or Grade 2 fatigue or other stable AEs that are assessed by the investigator as neither unfavorable to patients' safety nor influential to the safety evaluation of the study drug(s). 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. All subsequent chemotherapy doses must be rescheduled according to the last chemotherapy dose administration date. If any chemotherapy agent is held for more than 2 cycles (6 weeks) from the anticipated treatment date, or the dose level -2 is not tolerated, chemotherapy should be permanently discontinued.

Table 3: BGB-A317-306 Dose Reduction Level of Chemotherapy

Drug Dose	Level 1 (Standard level) (Every 3 weeks as a cycle)	Level-1	Level-2
Cisplatin	60-80 mg/m^2	60 mg/m^2	40 mg/m^2
Oxaliplatin	130 mg/m^2	100 mg/m^2	80 mg/m^2
5-FU	750-800 mg/m^2	600 mg/m^2	400 mg/m^2
Capecitabine	1000 mg/m^2, twice daily (total 14 days)	750 mg/m^2	500 mg/m^2
Paclitaxel	175 mg/m^2	135 mg/m^2	90 mg/m^2

Dose Modifications for Cisplatin

A repeat course of cisplatin should not be given until the serum creatinine is below 1.5 mg/100 mL, and/or the blood urea nitrogen (BUN) is below 25 mg/100 mL. A repeat course should not be given until circulating blood elements are at an acceptable level (platelets ≥ 100 x 10^9 /L, white blood cell [WBC] ≥ 4 x 10^9 /L). Subsequent doses of cisplatin should not be given until an audiometric analysis indicates that auditory acuity is within normal limits.

Adverse Event	Recommended Cisplatin Dose
Serum creatinine ≥ 1.5 mg/100 mL	Hold treatment until serum creatinine < 1.5 mg/100 mL
BUN ≥ 25 mg/100 mL	Hold treatment until BUN < 25 mg/100mL
Platelets < 100 x 10^9/L	Hold treatment until platelets ≥ 100 x 10^9/L
WBC < 4 x 10^9/L	Hold treatment until WBC ≥ 4 x 10^9/L
Auditory acuity by audiometric analysis out of range	Hold treatment until auditory acuity is within normal limits

Abbreviations: BUN, blood urea nitrogen; WBC, white blood cell

Dose Modifications for Oxaliplatin

Prolongation of infusion from 2 hours to 6 hours may mitigate acute toxicities.

For patients who experience persistent Grade 2 neurosensory events that do not resolve, a dose reduction to 100 mg/m^2 should be considered. For patients with persistent Grade 3 neurosensory events, discontinuing therapy should be considered. The infusional 5-FU infusion regimen need not be altered.

A dose reduction to 100 mg/m^2 and infusional 5-FU to 300 mg/m^2 bolus and 500 mg/m^2 22-hour infusion is recommended for patients after recovery from Grade 3/4 gastrointestinal (despite prophylactic treatment) or grade 4 neutropenia or Grade 3/4 thrombocytopenia. The next dose should be delayed until neutrophils are ≥ 1.5 x 10^9 /L and platelets are ≥ 75 x 10^9 /L.

Adverse Event	Recommended Oxaliplatin Dose
Neutrophils < 1.5 x 10^9/L	Hold treatment until neutrophils ≥ 1.5 x 10^9/L
Platelets < 75 x 10^9/L	Hold treatment until platelets ≥ 75 x 10^9/L

In patients with normal renal function or mild to moderate renal impairment, the recommended dose is 130 mg/m^2. In patients with severe renal impairment, the initial recommended dose should be reduced to 100 mg/m^2.

Dose Modifications for 5-Fluorouracil

5-FU dose modification scheme as described below is recommended for the management of adverse events.

Adverse Event	Recommended 5-Fluorouracil Dose
Development of angina, myocardial infarction/ischemia, arrhythmia, or heart failure in patients with no history of coronary artery disease or myocardial dysfunction	Hold treatment until resolution
Hyperammonemic encephalopathy	Hold treatment until resolution
Acute cerebellar confusion, disorientation, ataxia, or visual disturbances	Hold treatment until resolution
Grade 3 or 4 diarrhea	Hold treatment until resolution to Grade 2 or lower
Grade 2 or 3 palmar-plantar erythrodysesthesia (hand-foot syndrome)	Hold treatment until resolution to Grade 1 or lower
Grade 3 or 4 mucositis	Hold treatment until resolution to Grade 2 or lower
Grade 4 myelosuppression	Hold treatment until resolution to Grade 3 or lower

Dose Modifications for Capecitabine

Capecitabine dose modification scheme as described below is recommended for the management of adverse reactions.

Toxicity NCIC Grades*	During a Course of Therapy	Dose Adjustment for Next Treatment (% of starting dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
1st appearance	Interrupt until resolved to Grade 0-1	100%
2nd appearance		75%
3rd appearance		50%
4th appearance	Discontinue treatment permanently	-
Grade 3		
1st appearance	Interrupt until resolved to Grade 0-1	75%
2nd appearance		50%
3rd appearance	Discontinue treatment permanently	-
Grade 4		
1st appearance	Discontinue permanently OR If physician deems it to be in the patient's best interest to continue, interrupt until resolved to Grade 0-1	50%

*National Cancer Institute of Canada (NCIC) Common Toxicity Criteria were used except for the hand-and-foot syndrome.

Dose Modifications for Paclitaxel

Paclitaxel Dose Modifications for Decreased Neutrophils

Absolute Neutrophil Count (x 10^9/L)	Paclitaxel Dose
≥ 1.500 (Grade 1)	Dose Level 1
1.000 – 1.499 (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.
0.500 – 0.999 (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.
< 0.500 (Grade 4)	Initiate growth factor support If absolute neutrophil count < 0.500 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 Modifications for Decreased Platelet Counts

Platelet Count (x 10^9/L)	Paclitaxel Dose
> 100	Dose Level 1
75 - 100 (Grade 1)	Hold until recovery to a platelet count > 100 x 10^9/L Restart paclitaxel at Dose level 1
50 - 74.999 (Grade 2)	Hold until recovery to a platelet count > 100 x 10^9/L Restart paclitaxel at Dose Level -1
< 50 (Grade 3)	Hold until recovery to a platelet count > 100 x 10^9/L Restart paclitaxel at dose level -2
< 25 (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 Modifications 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	
< 10 x ULN	And	≤ 1.25 x ULN	Continue dosing at Dose Level 1
< 10 x ULN	And	1.26 - 2.0 x ULN	Hold until recovery to Grade 1 Restart paclitaxel at Dose Level -1
< 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

Abbreviation: ULN = upper limit of normal.

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

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 0-1 in severity.

5.5.3. Blinding

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

Every effort should be made to avoid unblinding the patient's treatment assignment unless necessary. Unblinding may be indicated and permissible only in specific situations as described below and if it's necessary for the patient's welfare. Unblinding would occur through Interactive Response Technology (IRT) as per the instructions in the IRT site user manual. If unblinding has occurred, the sponsor must be notified immediately using the Unblinding Event Form. To ensure the continued blinding of study personnel, this form will not include the treatment assignment. Patients will remain on study for safety follow-up and, if applicable, for survival follow-up.

- Emergency unblinding

  In case of an emergency, such as when a patient has an AE suspected to be related to the investigational drug product and for which management of the AE with one or more drug products with substantial toxicity or invasive procedures is being considered, unblinding can occur. The investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to inform the medical monitor of their intent before unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient. If a patient's treatment assignment is unblinded, the sponsor must be notified immediately.

  The investigator performs the emergency unblinding for AEs through an IRT System. Unblinded patients may remain on study treatment at the discretion of the investigator in consultation with the medical monitor and only as permissible per definitions in the study protocol.

- Non-Emergency Unblinding

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

- Inadvertent unblinding

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

- Unblinding after interim analysis per IDMC recommendation

  Sponsor, investigators and site personnel, and patients will be unblinded to treatment arms after the preplanned interim analysis if a recommendation is made by IDMC and accepted by the sponsor. Placebo administration will be discontinued after the unblinding. Crossover between the treatment arms will not be allowed.

On 20 April 2022, upon reviewing the efficacy and safety data of preplanned interim analysis, IDMC confirmed that the study met the specified 1-sided p-value boundary for superiority of the primary endpoint and recommended to unblind/unmask the study due to compelling efficacy. The sponsor accepted the IDMC recommendation, and the study was unblinded after the interim analysis. An instruction was provided to investigators to discontinue placebo in Arm B after the unblinding.

6. PRIOR AND CONCOMITANT THERAPY

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

6.1. Concomitant Therapy

6.1.1. Permitted Concomitant Medications

Most concomitant medications and therapies deemed necessary and in keeping with local standards of medical care at the discretion of the investigator for supportive care (eg, anti-emetics, antidiarrheals) and in a patient's interest are allowed. Opiates and other medication required for palliative management of patients are allowed. Patients must notify the investigator of all concurrent medications used during the study.

Systemic corticosteroids given for the control of imAEs must be tapered gradually (see Appendix 7) 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 HBV DNA ≥ 500 IU/mL at screening must initiate treatment 2 weeks prior to randomization and continue until 6 months after the last dose, or per local guidelines/clinical practice. 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 2018; AASLD/IDSA HCV Guidance Panel 2015). Management of antiviral therapy is at the discretion of the investigator; however, reason(s) must be provided in the eCRF 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.

Palliative (limited-field) radiation therapy is permitted, but only for pain control or prophylaxis of bone fracture to sites of bone disease present at baseline provided the following criteria are met:

- Repeat imaging demonstrates no new sites of bone metastases
- The lesion being considered for palliative radiation is not a target lesion for RECIST v1.1
- The case is discussed with the medical monitor, and the medical monitor agrees that the conditions required to receive palliative radiation are met
- Additionally, palliative radiation or other focally ablative therapy for other non-target sites of the disease is permitted if clinically indicated per investigator's 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.

6.1.2. Prohibited Concomitant Medications/Procedures

The following medications are prohibited during the study:

- Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy [including IL-2, interferon, thymosin, etc.] or standard or investigational agents [including Chinese herbal and patent medicines] for the treatment of cancer) is not allowed.
- Live vaccines within 28 days before randomization, during treatment with tislelizumab and 60 days following the last dose of study drug(s).
- Herbal remedies with immune-stimulating properties (ie, mistletoe extract) or that are known to potentially interfere with liver or other major organ functions (ie, hypericin). Patients must notify the investigator of all herbal remedies used during the study.

6.1.3. Restricted Concomitant Medications/Procedures

The following medications are restricted during the study:

- Immunosuppressive agents (except to treat a drug-related AE).
- Systemic corticosteroids > 10 mg daily (prednisone or equivalent), except to treat or control a drug related AE (per protocol) or for short-term use as prophylactic treatment.
- Patients should avoid alcohol abuse or any other drug abuse during the study.
- Use of potentially hepatotoxic drugs in patients with impaired hepatic function should be carefully monitored.
- Radiation therapy is not allowed, except for palliative radiation therapy described in Section 6.1.1.

6.2. Potential Interactions Between the Study Drugs and Concomitant Medications

- Tislelizumab

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

- Cisplatin

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

effects of cisplatin on auditory function. The investigator should refer to the most current cisplatin Summary of Product Characteristics (SmPC) for all potential interactions with cisplatin.

- Oxaliplatin

  No specific cytochrome P-450-based drug interaction studies have been conducted. Increases of 5-FU plasma concentrations by approximately 20% have been observed with doses of 130 mg/m^2 dosed every 3 weeks. Because platinum-containing species are eliminated primarily through the kidney, clearance of these products may be decreased by coadministration of potentially nephrotoxic compounds; although this has not been specifically studied. The investigator should refer to the most current oxaliplatin SmPC for all potential interactions with oxaliplatin.

- 5-Fluorouracil

  Elevated coagulation times have been reported in patients taking fluorouracil concomitantly with warfarin. While pharmacokinetic data are not available to assess the effect of fluorouracil administration on warfarin pharmacokinetics, the elevation of coagulation times that occurs with the fluorouracil prodrug capecitabine is accompanied by an increase in warfarin concentrations. Thus, the interaction may be due to inhibition of cytochrome P450 2C9 by fluorouracil or its metabolites. The investigator should refer to the most current 5-fluorouracil SmPC for all potential interactions with 5-fluorouracil.

- Capecitabine

  Altered coagulation parameters and/or bleeding have been reported in patients taking capecitabine concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. These events occurred within several days and up to several months after initiating capecitabine therapy and, in a few cases, within 1 month after stopping capecitabine. These events occurred in patients with and without liver metastases. In a drug interaction study with single-dose warfarin administration, there was a significant increase in the mean AUC of S-warfarin. The maximum observed international normalized ratio (INR) value increased by 91%. This interaction is probably due to an inhibition of cytochrome P450 2C9 by capecitabine and/or its metabolites. The level of phenytoin should be carefully monitored in patients taking capecitabine and phenytoin dose may need to be reduced. Post-marketing reports indicate that some patients receiving capecitabine and phenytoin had toxicity associated with elevated phenytoin levels. Formal drug-drug interaction studies with phenytoin have not been conducted, but the mechanism of interaction is presumed to be inhibition of the CYP2C9 isoenzyme by capecitabine and/or its metabolites. Other than warfarin, no formal drug-drug interaction studies between capecitabine and other CYP2C9 substrates have been conducted. Care should be exercised when capecitabine is co-administered with CYP2C9 substrates. The investigator should refer to the most current capecitabine SmPC for all potential interactions with capecitabine.

- Paclitaxel

  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 trials. The investigator should refer to the most current paclitaxel SmPC for all potential interactions with paclitaxel.

- COVID-19 vaccine

  Potential immune reactivity to the coronavirus disease 2019 (COVID-19) vaccine in patients concurrently receiving checkpoint inhibitors or other immune-oncologic treatments cannot be ruled out, but current data suggest that instances are rare. As additional data emerge, the approach will be modified accordingly.

7. STUDY ASSESSMENTS AND PROCEDURES

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

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

7.1. Screening

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

Results of standard of care tests or examinations performed prior to obtaining informed consent and ≤ 28 days prior to randomization may be used for the purposes of screening rather than repeating the standard of care tests unless otherwise indicated (only applicable if the same radiographic procedure will be used throughout the study).

Procedures conducted during Screening only are described in this section. For the description of other assessments that are conducted during screening, as well as throughout the study, refer to Safety Assessments (Section 7.4), Tumor and Response Evaluations (Section 7.5) and Biomarkers (Section 7.8) sections. The PK sampling schedule is shown in Appendix 1.

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

7.1.1. Demographic Data and Medical History

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

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

Cancer history will include an assessment of prior surgery, prior radiotherapy, and prior drug therapy, including start and stop dates, best response, and reason for discontinuation. Cancer symptoms that are present at baseline will be recorded and assessed for severity using the NCI-CTCAE v4.03 criteria. Radiographic studies performed prior to study entry may be collected for review by the investigator.

7.1.2. Females of Childbearing Potential and Contraception

Childbearing potential is defined as being physiologically capable of becoming pregnant. Refer to Appendix 9 for contraception guidelines and definitions of "women of childbearing potential" and "no childbearing potential"

7.1.3. Informed Consent and Screening Log

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

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

7.1.4. Pulmonary Function Tests

Patients who are suspected or known to have serious/severe respiratory conditions or exhibit significant respiratory symptoms unrelated to the underlying cancer or with a history of thoracic radiotherapy will undergo 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 on the study.

7.2. Enrollment

7.2.1. Confirmation of Eligibility

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

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

7.2.2. Patient Numbering

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

7.2.3. Enrollment/Randomization

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

7.3. Tislelizumab and Comparator Drug Dispensation

Depending on the treatment arm and preferred chemotherapy doublet, tislelizumab (or matched placebo), cisplatin, oxaliplatin, 5-FU, capecitabine, and paclitaxel will be dispensed and administered as described in Section 5.2.

7.4. Safety Assessments

7.4.1. Vital Signs

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

7.4.2. Physical Examinations

During Screening, a complete physical examination will be conducted including evaluations of 1) head, eyes, ears, nose, throat, 2) cardiovascular, 3) dermatological, 4) musculoskeletal, 5) respiratory, 6) gastrointestinal, and 7) neurological systems. Any abnormality identified during screening will be graded according to NCI-CTCAE v4.03 and recorded on the eCRF with appropriate disease/condition terms.

At subsequent visits (and as clinically indicated), limited, symptom-directed physical examinations will be performed. Changes from baseline will be recorded. New or worsened clinically significant abnormalities are to be recorded as AEs on eCRF. Refer to Section 8.3 regarding AE definitions and reporting and follow-up requirements.

7.4.2.1. Ophthalmologic Examination

Due to an increased risk of ophthalmologic adverse events in patients receiving PD-1 inhibitors (including, but not limited to uveitis and retinal disorders), eye exam, visual acuity test, and optical coherence tomography (or equivalent diagnostic test) will be assessed by an appropriate specialist at screening. Eye exam, 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. All patients will undergo repeat assessments by an appropriate specialist approximately every 15 weeks (± 7 days) during study treatment and a final assessment at the EOT/Safety follow-up visit, 30 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 study treatment. For any change in vision, referral to an appropriate specialist will be made for further management guidance (see Appendix 7).

7.4.3. Eastern Cooperative Oncology Group Performance Status

ECOG Performance Status (Appendix 3) will be assessed during the study.

7.4.4. Laboratory Safety Tests

Local and/or central laboratory assessments of serum chemistry, hematology, coagulation, and urinalysis will be conducted, of which certain elements will be collected as specified in Appendix 2.

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 in Appendix 2 should be performed weekly for the first 3 cycles and at the beginning of subsequent cycles. After Cycle 1, results are to be reviewed within 48 hours before study drug administration.

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

7.4.5. Cardiac Enzyme Monitoring

Although immune-mediated myocarditis is a rare complication of immune checkpoint inhibitors, serum creatinine kinase (CK) and CK cardiac isoenzyme (CK-MB) are monitored in all tislelizumab studies to protect study participants and to quantify the risk of muscle inflammation (see Appendix 1 for the blood collection schedule and Appendix 7 for guidelines for management of suspected immune-mediated myocarditis). Serum troponins may be substituted per local guidelines if used consistently throughout the study.

7.4.6. Electrocardiograms

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

Patients should rest for at least 10 minutes prior to ECG collection.

7.4.7. Adverse Events

AEs will be graded and recorded throughout the study according to NCI-CTCAE, v4.03. Characterization of toxicities will include severity, duration, and time to onset.

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

7.4.8. Hepatitis B and C Testing

Testing will be performed by a central laboratory and/or the local laboratory at screening and will include HBV/HCV serology (HBsAg, hepatitis B surface antibody [HBsAb], hepatitis B core antibody [HBcAb], and HCV antibody). If HBsAg or HBcAb is positive, then an HBV DNA test will be triggered. If HCV antibody is positive, an HCV RNA test will be triggered.

Patients who have detectable HBV DNA or HCV RNA at screening will have the viral load retested every 4 cycles.

7.5. Tumor and Response Evaluations

Tumor imaging will be performed within 28 days before randomization. Results of standard of care tests or examinations performed prior to obtaining informed consent and ≤ 28 days prior to randomization may be used for the purposes of screening rather than repeating the standard of care tests (only applicable if the same radiographic procedure will be used throughout the study). During the study, tumor imaging will be performed every 6 weeks (± 7 days) for the first 48 weeks, then every 9 weeks (± 7 days) after 48 weeks based on RECIST v1.1. If a tumor assessment is missed or conducted outside of the specified assessment window, all subsequent scans should be conducted on the planned schedule.

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

Tumor assessments must include CT scans (with oral/IV contrast, unless contraindicated) or MRI, with preference for CT, of the neck, chest, and abdomen. All measurable and evaluable lesions should be assessed and documented at the Screening Visit and reassessed at each subsequent tumor evaluation. The same radiographic procedure used to assess disease sites at screening are required to be used throughout the study (eg, the same contrast protocol for CT scans). All known sites of disease must be documented at screening and reassessed at each subsequent tumor evaluation.

- Any patient with a history of CNS metastases will be required to undergo CT/MRI at baseline to ensure all sites of disease are evaluated per RECIST v1.1 criteria. Patients with newly diagnosed brain metastases on screening CT/MRI will be required to be treated for brain metastasis with standard of care treatments and be off corticosteroids prior to study entry.
- If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the study, a non-contrast CT of the chest plus a contrast-enhanced MRI (if possible) of abdomen and neck should be performed.
- If a CT scan for tumor assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan.
- Bone scans (Technetium-99m [Tc-99m]) or PET should be performed at Screening if clinically indicated. If bone metastases are present at Screening and cannot be seen on CT or MRI scans afterwards, TC-99m or PET bone scans should be conducted when a complete response (CR) is suspected in target lesion.
- CT scans of the extremities should also be performed if clinically indicated and followed throughout the study, if there is evidence of metastatic disease in these regions at Screening. At the investigator's discretion, other methods of assessment of target lesion and nontarget lesions per RECIST v1.1 may be used.

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

visits. For immune therapies such as tislelizumab, pseudoprogression 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. Also, some patients may benefit from additional immune therapies despite evidence of disease progression. The following criteria must be met in order to treat patients with suspected pseudoprogression or confirmed evidence of disease progression:

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

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

Tumor assessment should continue as planned in patients receiving study drug(s) beyond initial investigator-assessed progression. Tumor assessment in such patients should continue until study treatment discontinuation.

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

Tumor assessments are required to be performed on schedule regardless of whether study treatment has been administered or held. That is, assessments should not be adjusted for delays in cycles.

7.6. Pharmacokinetic and Anti-Drug Antibody Testing

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

The following assessments will be performed at a central laboratory:

- ADA assays: serum samples will be tested for the presence of ADAs to tislelizumab using a validated immunoassay

- PK assay: serum samples will be assayed for tislelizumab concentration with use of a validated immunoassay
- PK and ADA samples collected from patients randomized to receive placebo will not be analyzed.

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

7.7. On-Study Biopsies

If an on-study biopsy is performed for any reason while any patient is actively participating in the study, key histologic findings by local assessment will be collected. This information includes, at a minimum: date, type of biopsy (e.g. needle, surgical, etc.), location, and findings/results. This information will be collected regardless of whether the patient is actively receiving study treatment.

7.8. Biomarkers

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

Archival tumor tissues (formalin-fixed paraffin-embedded block or approximately 15 [at least 6] unstained slides) need to be sent to central laboratory for central immunohistochemistry assay of PD-L1 status. In the PD-L1 vCPS ≥ 10% population, PD-L1 expression will be assessed centrally using the VENTANA PD-L1 (SP263) assay. The vCPS 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. In addition to PD-L1 expression, other exploratory biomarkers consisting of gene expression profiling (GEP), tumor-infiltrating lymphocytes (TIL), TMB/MSI/gene mutation profile that are related to response or clinical benefit of tislelizumab in combination with chemotherapy may also be evaluated. Other assessments may be conducted as allowed by local regulations.

If no archival samples are available, a fresh tumor biopsy at baseline (within 28 days before randomization) is needed. 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.

An optional biopsy 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 mechanisms. If feasible, any follow-up biopsy should be ideally taken from the same tumor lesion as the baseline biopsy. Written patient consent is required for fresh tumor biopsies.

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

Blood samples will be taken at baseline (predose on Day 1 of Cycle 1) for all randomized patients to explore the association of blood-based biomarkers with response and prognosis to tislelizumab in combination with chemotherapy or chemotherapy alone. Blood samples are highly

recommended to be collected at first tumor response (CR/PR) and/or at confirmed disease progression to explore response and/or resistance mechanism to tislelizumab in combination with chemotherapy or chemotherapy alone. Written patient consent is required for optional blood sample collections. Blood-based biomarkers consist of TMB/MSI/gene mutation profile. Other assessments may be conducted as allowed by local regulations.

7.9. Patient-Reported Outcomes

Patients will be asked to complete the EORTC QLQ-C30, EORTC QLQ-OES18, and EQ-5D-5L questionnaires before any clinical activities are performed during on-study clinic visits according to the schedule in Appendix 1. The questionnaires will be provided in the patient's preferred language.

7.10. Visit Windows

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

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or justifiable events, the visit should be scheduled on the nearest feasible date (the visit window is provided in Appendix 1), with subsequent visits conducted according to the planned schedule Q3W from Cycle 1 Day 1 or from the last rescheduled date if resynchronization happens.

7.11. Unscheduled Visits

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

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

8. SAFETY MONITORING AND REPORTING

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

8.1. Risks Associated with Study Drugs

8.1.1. Risks Associated with Tislelizumab

Tislelizumab is an investigational agent that is currently in clinical development. The following recommendation is based on results from nonclinical and clinical studies with tislelizumab and published data on other molecules within the same biologic class.

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

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

8.1.2. Risks Associated with Comparator Drugs

Selected risks for each chemotherapy are listed below. Please refer to the package insert/prescribing information for each drug for more information.

Cisplatin

Cisplatin produces cumulative nephrotoxicity which is potentiated by aminoglycoside antibiotics. The serum creatinine, BUN, creatinine clearance, and magnesium, sodium, potassium, and calcium levels should be measured prior to initiating therapy, and prior to each subsequent course. At the recommended dosage, cisplatin should not be given more frequently than once every 3 to 4 weeks. Elderly patients may be more susceptible to nephrotoxicity. A urine output of 100 mL/hour or greater will tend to minimize cisplatin nephrotoxicity. This can be accomplished by increased hydration, before and after treatment.

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

Loss of motor function has also been reported.

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

Ototoxicity has been observed in patients treated with a single dose of cisplatin. Hearing loss can be unilateral or bilateral and tends to become more frequent and severe with repeated doses; however, deafness after initial dose of cisplatin has been reported rarely. It is unclear whether

cisplatin induced ototoxicity is reversible. Careful monitoring by audiometry should be performed prior to initiation of therapy and prior to subsequent doses of cisplatin.

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

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

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

Oxaliplatin

Grade 3/4 hypersensitivity to oxaliplatin, including anaphylactic/anaphylactoid reactions, has been observed in 2 to 3% of colon cancer patients (Oxaliplatin prescribing information). These allergic reactions which can be fatal, can occur within minutes of administration and at any cycle, and were similar in nature and severity to those reported with other platinum-containing compounds, such as rash, urticaria, erythema, pruritus, and, rarely, bronchospasm and hypotension. Symptoms associated with hypersensitivity reactions reported in previously untreated patients included urticaria, pruritus, flushing of the face, diarrhea associated with oxaliplatin infusion, shortness of breath, bronchospasm, diaphoresis, chest pains, hypotension, disorientation, and syncope. These reactions are usually managed with standard epinephrine, corticosteroid, antihistamine therapy, and require discontinuation of therapy. Rechallenge is contraindicated in these patients. Drug-related deaths associated with platinum compounds from anaphylaxis have been reported.

Oxaliplatin is associated with 2 types of neuropathy: acute, reversible, primarily peripheral sensory neuropathy and persistent (> 14 days) primarily peripheral sensory neuropathy.

- Acute, reversible, primarily peripheral, sensory neuropathy has an early onset (occurring within hours or 1 to 2 days of dosing), resolves within 14 days, and frequently recurs with further dosing. Symptoms may be precipitated or exacerbated by exposure to cold temperature or cold objects and they usually present as transient paresthesia, dysesthesia and hypoesthesia in the hands, feet, perioral area, or throat. Jaw spasm, abnormal tongue sensation, dysarthria, eye pain, and a feeling of chest pressure have also been observed. The acute, reversible pattern of sensory neuropathy was observed in about 56% of study patients who received oxaliplatin with 5-FU/leucovorin. In any individual cycle acute neurotoxicity was observed in approximately 30% of patients. In adjuvant patients, the median cycle of onset for Grade 3 peripheral sensory neuropathy was 9, and in previously treated patients, the median number of cycles administered on the oxaliplatin with 5FU/leucovorin combination arm was 6. An acute syndrome of pharyngolaryngeal dysesthesia, seen in 1 to 2% (Grade 3/4) of previously untreated and treated patients with advanced colorectal cancer, is characterized by subjective sensations of dysphagia or dyspnea, without any laryngospasm or bronchospasm (no stridor or wheezing). Ice

(mucositis prophylaxis) should be avoided during the infusion of oxaliplatin because cold temperature can exacerbate acute neurological symptoms.

- Persistent (> 14 days), primarily peripheral, sensory neuropathy is usually characterized by paresthesias, dysesthesias, and hypoesthesias, but may also include deficits in proprioception that can interfere with daily activities (eg, writing, buttoning, swallowing, and difficulty walking from impaired proprioception). These forms of neuropathy occurred in 48% of study patients receiving oxaliplatin with 5FU/leucovorin. Persistent neuropathy can occur without any prior acute neuropathy event. Most patients (80%) who developed Grade 3 persistent neuropathy progressed from prior Grade 1 or 2 events. These symptoms may improve in some patients upon discontinuation of oxaliplatin. Peripheral sensory neuropathy was reported in adjuvant patients treated with the oxaliplatin combination with a frequency of 92% (all grades) and 13% (Grade 3). At the 28-day follow-up after the last treatment cycle, 60% of all patients had any grade (Grade 1: 40%; Grade 2: 16%; Grade 3: 5%) peripheral sensory neuropathy decreasing to 39% at 6 months of follow-up (Grade 1: 31%; Grade 2: 7%; Grade 3: 1%) and 21% at 18 months of follow-up (Grade 1: 17%, Grade 2: 3%, Grade 3: 1%). Overall, neuropathy (all grades) was reported in 82% of previously untreated patients with advanced colorectal cancer (19% had Grade 3/4 neuropathy), and in 74% of previously treated patients (7% had Grade 3/4 neuropathy). Information regarding reversibility of neuropathy was not available from the trial for patients who had not been previously treated for colorectal cancer.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS, also known as Posterior Reversible Encephalopathy Syndrome [PRES]) has been observed in clinical trials (< 0.1%) and postmarketing experience. Signs and symptoms of RPLS can include headache, altered mental functioning, seizures, abnormal vision from blurriness to blindness, which may be associated with hypertension. Diagnosis of RPLS is based upon confirmation by brain imaging.

Oxaliplatin has been associated with pulmonary fibrosis (<1% of study patients), which may be fatal. In adjuvant colon cancer patients, the combined incidence of cough and dyspnea was 7.4% (any grade) and <1% (Grade 3) with no Grade 4 events in the oxaliplatin plus infusional 5-FU/leucovorin arm compared to 4.5% (any grade) and no Grade 3 and 0.1% Grade 4 events in the infusional 5-FU/leucovorin alone arm. In this study, 1 patient died from eosinophilic pneumonia in the oxaliplatin combination arm. In patients with previously untreated colorectal cancer, the combined incidence of cough, dyspnea and hypoxia was 43% (any grade) and 7% (Grade 3 and 4) in the oxaliplatin plus 5-FU/leucovorin arm compared to 32% (any grade) and 5% (Grade 3 and 4) in the irinotecan plus 5-FU/leucovorin arm of unknown duration. In case of unexplained respiratory symptoms such as non-productive cough, dyspnea, crackles, or radiological pulmonary infiltrates, oxaliplatin should be discontinued until further pulmonary investigation excludes interstitial lung disease or pulmonary fibrosis.

Hepatotoxicity was observed more commonly in the oxaliplatin combination arm than in the control arm, as evidenced in the adjuvant study by increase in transaminases (57% vs 34%, respectively) and alkaline phosphatase (42% vs 20%, respectively). The incidence of increased bilirubin was similar on both arms. Changes noted on liver biopsies include peliosis, nodular regenerative hyperplasia or sinusoidal alterations, perisinusoidal fibrosis, and veno-occlusive lesions. Hepatic vascular disorders should be considered, and if appropriate, should be

investigated in case of abnormal liver function test results or portal hypertension which cannot be explained by liver metastases.

Oxaliplatin may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of oxaliplatin in pregnant women. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with oxaliplatin.

5-Fluorouracil

The daily dose of fluorouracil is not to exceed 800 mg/m^2. It is recommended that patients be hospitalized during their first course of treatment. The first 10 patients enrolled in Japan will be hospitalized for the first course of treatment.

Fluorouracil should be used with extreme caution in poor risk patients with a history of high-dose pelvic irradiation or previous use of alkylating agents, those who have a widespread involvement of bone marrow by metastatic tumors or those with impaired hepatic or renal function.

Rarely, unexpected, severe toxicity (eg, stomatitis, diarrhea, neutropenia and neurotoxicity) associated with 5-FU has been attributed to deficiency of dipyrimidine dehydrogenase activity. A few patients have been rechallenged with 5-FU and despite 5-FU dose lowering, toxicity recurred and progressed with worse morbidity. Absence of this catabolic enzyme appears to result in prolonged clearance of 5-FU.

Investigator must advise patients to take measures to minimize exposure to UV light for the duration of the study as 5-FU has phototoxicity potential.

Fluorouracil may cause fetal harm when administered to a pregnant woman. Fluorouracil has been shown to be teratogenic in laboratory animals.

There are no adequate and well-controlled studies with fluorouracil in pregnant women. While there is no evidence of teratogenicity in humans due to fluorouracil, it should be kept in mind that other drugs which inhibit DNA synthesis (eg, methotrexate and aminopterin) have been reported to be teratogenic in humans. Women of childbearing potential should be advised to avoid becoming pregnant. If the drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be told of the potential hazard to the fetus. Fluorouracil should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Any form of therapy which adds to the stress of the patient, interferes with nutrition or depresses bone marrow function will increase the toxicity of fluorouracil.

Capecitabine

May result in bleeding, death. Monitor anticoagulant response (eg, INR) and adjust anticoagulant dose accordingly.

Diarrhea may be severe. Interrupt capecitabine treatment immediately until diarrhea resolves or decreases to Grade 1. Recommend standard antidiarrheal treatments.

Cardiotoxicity is common in patients with a prior history of coronary artery disease.

There is an increased risk of severe or fatal adverse reactions in patients with low or absent dihydropyrimidine dehydrogenase (DPD) activity. Withhold or permanently discontinue capecitabine in patients with evidence of acute early-onset or unusually severe toxicity, which

may indicate near complete or total absence of DPD activity. No capecitabine dose has been proven safe in patients with absent DPD activity.

In case of dehydration, interrupt capecitabine treatment until dehydration is corrected. There is a potential risk of acute renal failure secondary to dehydration. Monitor and correct dehydration.

Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception.

Severe mucocutaneous reactions, Steven-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), have been reported. Capecitabine should be permanently discontinued in patients who experience a severe mucocutaneous reaction during treatment. Capecitabine may induce hand-and-foot syndrome. Persistent or severe hand-and-foot syndrome can lead to loss of fingerprints which could impact patient identification. Interrupt capecitabine treatment until the hand-and-foot syndrome event resolves or decreases in intensity.

Interrupt capecitabine treatment immediately until the hyperbilirubinemia resolves or decreases in intensity.

Do not treat patients with neutrophil counts < 1.5 x 10^9/L or platelet counts < 100 x 10^9/L. If Grade 3 to 4 neutropenia or thrombocytopenia occurs, stop therapy until condition resolves.

Investigator must advise patients to take measures to minimize exposure to UV light for the duration of the study as capecitabine has phototoxicity potential.

Paclitaxel

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

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

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

8.2. General Plan to Manage Safety Concerns

8.2.1. Eligibility Criteria

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

at risk for study-emergent active autoimmune diseases, or with a history of autoimmune diseases that may relapse, patients who have undergone allogenic stem cell or organ transplantation and patients who have received a live vaccine ≤ 28 days before randomization are excluded from the study. Patients with contraindications for platinum (cisplatin or oxaliplatin), fluoropyrimidine (5-FU or capecitabine), and paclitaxel treatment are also excluded from the study (see Section 4.2 for the full list of exclusion criteria).

8.2.2. Safety Monitoring Plan

Safety will be evaluated in this study through the monitoring of all AEs, defined and graded according to NCI-CTCAE v4.03. Patients will be assessed for safety (including laboratory values) according to the schedule in Appendix 1. Clinical laboratory results must be reviewed prior to the start of each cycle.

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

Serum samples will be drawn for determination of ADAs to tislelizumab in patients randomized to the tislelizumab arm, if treatment assignment is known. Samples will be drawn from all patients but will only be analyzed in patients who are treated with tislelizumab. 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 (for additional information, see Section 5.2.1).

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 chemotherapy) or until the initiation of another anticancer therapy, whichever occurs first. At the EOT/Safety Follow-up Visit, all AEs 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-mediated 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.

8.3. Adverse Events

8.3.1. Definitions and Reporting

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

Examples of AEs include:

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

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

8.3.2. Assessment of Severity

The investigator will assess the severity of each AE and SAE reported during the study. AEs and SAEs should be assessed and graded based upon the 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 8.6.2.

8.3.3. Assessment of Causality

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

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

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

- Temporal relationship of the AE to the administration of study treatment/study procedure
- Whether an alternative etiology has been identified
- Mechanism of action of the study drug
- Biological plausibility
- An AE should be considered 'related' to study drug if any of the following are met, otherwise the event should be assessed as not related:
  - There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out
  - There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
  - There is some evidence to suggest a causal relationship (eg, the AE occurred within a reasonable time after administration of the study drug). However, the influence of other factors may have contributed to the AE (eg, the patient's clinical condition or other concomitant AEs).

8.3.4. Following Adverse Events

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

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

All AEs and SAEs will be followed until resolution, the condition stabilizes or is considered chronic, the AE or SAE is otherwise explained, the patient is lost to follow-up or the patient

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

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

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

8.3.5. Laboratory Test Abnormalities

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

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

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

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

8.4. Definition of a Serious Adverse Event

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

- Results in death
- Is life-threatening

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

- Requires hospitalization or prolongation of existing hospitalization

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

- Results in disability/incapacity

  Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere or prevent everyday life functions, but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect
- Is considered a significant medical AE by the investigator based on medical judgement (eg, may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The following are NOT considered SAEs:

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

8.5. Suspected Unexpected Serious Adverse Reaction

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

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

8.6.1. Adverse Event Reporting Period

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

After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until either 30 days after last dose of study drugs (including chemotherapy) or initiation of new anticancer therapy, whichever occurs first. Immune-mediated AEs (serious or non-serious) should be reported until 90 days after the last dose of tislelizumab, regardless of whether the patient starts a new anticancer therapy.

All SAEs considered related to the study drug(s) that are brought to the attention of the investigator should be reported regardless of time since the last dose of treatment.

AEs and SAEs should be recorded according to the details in Table 4. For the follow-up period for AEs, see Section 8.3.4. For the definition of TEAEs, see Section 9.3.2.

Table 4: Guidance for Duration of Recording New or Worsening Adverse Events in Both Treatment Arms

Event type	Record new or worsening events that occur during this period	
	Begin	End
SAEs [a]	Signing of informed consent	Up to 30 days after last dose, initiation of new anticancer therapy, death, withdrawal of consent, or loss to follow-up, whichever occurs first
Nonserious AEs due to PD	Do not record (see Section 8.6.4)	
All nonserious AEs, except those due to PD	First dose of study drug	Up to 30 days after last dose, initiation of new anticancer therapy, death, withdrawal of consent, or loss to follow-up, whichever occurs first
Immune-mediated AEs (serious or nonserious)		Up to 90 days after last dose (regardless of initiation of new anticancer therapy), death, withdrawal of consent, or loss to follow-up, whichever occurs first

Abbreviations: AE, adverse event; PD, progressive disease; SAE, serious adverse event.
All SAEs considered related to the study drug(s) that are brought to the attention of the Investigator should be reported regardless of time since the last dose of treatment.

8.6.2. Reporting Serious Adverse Events

8.6.2.1. Prompt Reporting of Serious Adverse Events

As soon as the investigator determines that an AE meets the protocol definition of an SAE, the event must be reported promptly (within 24 hours) to the sponsor or designee as described in Table 5.

Table 5. Timeframes and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

	Timeframe for Sending Initial Report	Documentation Method	Timeframe for Sending Follow-up Report	Documentation Method	Reporting Method
All SAEs	Within 24h of first knowledge of the AE	SAE Report	As expeditiously as possible	SAE Report	Email or fax SAE report form

Abbreviations: h, hours; SAE, serious adverse event.

8.6.2.2. Completion and Transmission of the Serious Adverse Event Report

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

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

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

The sponsor will provide contact information for SAE receipt.

8.6.2.3. Regulatory Reporting Requirements for Serious Adverse Events

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

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

All suspected unexpected serious adverse reactions (as defined in Section 8.5), will be submitted to all applicable regulatory authorities and investigators for tislelizumab studies.

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

8.6.3. Eliciting Adverse Events

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

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

8.6.4. Disease Progression

Disease progression, which is expected in this study population and measured as an efficacy endpoint, should not be recorded as an AE term. Similarly, nonserious AEs that are clearly consistent with the pattern of progression of the underlying disease and are considered unequivocally due to disease progression should not be recorded. However, if there is any uncertainty to whether a nonserious AE is due to disease progression, it should be recorded as an

AE. All SAEs and deaths regardless of relatedness to disease progression should be recorded and reported (see Section 8.6.2).

8.6.5. Deaths

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

8.6.6. Pregnancies

If a female patient or the partner of a male patient becomes pregnant while receiving investigational therapy or within 120 days after the last dose of tislelizumab or within 180 days after the last dose of chemotherapy, a pregnancy report form is required to be completed and expeditiously submitted to the sponsor to facilitate outcome follow-up. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow-up will be no longer than 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

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

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

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

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

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

- Tislelizumab Investigator's Brochure
- Cisplatin Package Insert
- Oxaliplatin Package Insert
- 5-FU Package Insert
- Capecitabine Package Insert
- Paclitaxel Package Insert

8.6.8. Assessing and Recording Immune-Mediated Adverse Events

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

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

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

8.6.9. Recording Infusion-Related Reactions

The symptoms of infusion-related reactions - may include, but are not limited to, 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, or cardiogenic shock. These infusion-related AEs should be recorded as “infusion-related reaction” instead of the individual signs and symptoms.

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

8.7.1. Managing Infusion-Related Reactions

Patients should be closely monitored for such reactions. Immediate access to an Intensive Care Unit (ICU) or equivalent environment and appropriate medical therapy (including epinephrine, corticosteroids, IV antihistamines, bronchodilators, and oxygen) must be available to treat infusion-related reactions.

Treatment modification for symptoms of infusion-related reactions due to study drug(s) is provided in Table 6.

Table 6. Treatment Modification for Symptoms of Infusion-Related Reactions Due to Study Drug(s)

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

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

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

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

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

8.7.2. Severe Hypersensitivity Reactions and Flu-Like Symptoms

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

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

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

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

8.7.3. Immune-Mediated Adverse Events

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

A list of potential imAEs is shown below in Table 7. All conditions like those listed should be evaluated in patients receiving tislelizumab to determine whether they are immune-mediated.

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

Table 7. Immune-Mediated Adverse Events

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

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

Recommendations for managing imAEs are detailed in Appendix 7.

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

9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

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

9.1. Statistical Analysis

9.1.1. Randomization Methods

As discussed in Section 7.2.3, patients will be randomized using the IRT system for this study by permuted block stratified randomization.

9.1.2. Analysis Sets

The Intent-to-Treat (ITT) analysis set includes all randomized patients. Patients will be analyzed according to their randomized treatment arms. This will be the primary analysis population for all efficacy analysis.

The Safety analysis set includes all patients who received at least 1 dose of study drug; it will be the primary population for the safety analyses.

The PK analysis set includes all patients who receive 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 1 non-missing postbaseline ADA results.

9.1.3. Patient Disposition

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

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

9.1.4. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics of the ITT analysis set will be summarized using descriptive statistics. Continuous variables include age, weight, vital signs, time since initial cancer diagnosis, and time since advanced/metastatic disease diagnosis; categorical variables include, region (Asia [excluding Japan] vs Japan vs Rest of World), prior definitive therapy (yes vs no), choice of chemotherapy doublet (platinum plus fluoropyrimidine vs platinum plus paclitaxel), ECOG (0 vs 1), previous radiotherapy (yes vs no), previous surgery (yes vs no), age ($\leq$ 65 vs > 65 years), gender (female vs male), number of metastatic sites (1 vs 2 vs > 2), metastatic site (eg, liver, lung, bone, lymph node, etc.), tumor location , smoking status, and alcohol use

9.1.5. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary drug codes. Concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical (ATC) code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class in the Clinical Study Report (CSR) for this protocol. Prior medications will be defined as medications that stopped before the day of first dose of study drug. Concomitant medications will be defined as medications that 1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or 2) started on or after the date of the first dose of study drug up to 30 days after the patient's last dose (as of Safety Follow-up Visit). In addition, telephone contacts with patients should be conducted to assess imAEs and concomitant medications (if appropriate, ie, associated with an imAE or is a new anticancer therapy) at 60 and 90 days (± 14 days) after the last dose of study drugs regardless of whether or not the patient starts a new anticancer therapy.

9.2. Efficacy Analyses

The primary endpoint of OS in the ITT analysis set will be tested at a one-sided alpha of 0.025. By using the graphic approach of Bretz et al (2009), if the null hypothesis for OS in the ITT analysis set is rejected, the corresponding alpha will be shifted to the hypothesis tests of the secondary endpoints PFS by the investigator in the ITT analysis set, ORR by the investigator in the ITT analysis set, OS in the PD-L1 vCPS ≥ 10% subgroup, and HRQoL in the ITT analysis set, which will be tested sequentially. The inferential test will be stopped at the first non-significant endpoint.

9.2.1. Primary Efficacy Analysis

OS in the ITT analysis set:

The null hypothesis to be tested is:

H_0: OS in Arm A ≤ OS in Arm B

against the alternative:

H_1: OS in Arm A > OS in Arm B

The primary analysis of OS will be carried out when approximately 488 OS events are reached. In absence of confirmation 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 Arm A and Arm B in a one-sided, stratified log-rank test using the stratification factors of pooled geographic region (Asia [including Japan] vs Rest of World), prior definitive therapy (yes vs no), and the investigator choice of chemotherapy (ICC) option (platinum with fluoropyrimidine vs platinum with paclitaxel). A significance level of one-sided 0.025 will be used in the OS testing.

The median OS and the cumulative probability of OS at every 3 months including 9-month OS and 18-month OS, if estimable, will be calculated for each treatment arm and presented with 2-sided 95% CIs. Kaplan-Meier survival probabilities for each arm will be plotted over time. OS rate at 9 and 18 months based on Kaplan-Meier estimate will be compared between the 2 treatment arms for landmark analysis.

The treatment effect will be estimated by fitting a Cox regression model to the OS times including treatment arm as a covariate and geographical region and prior definitive therapy as strata. From this model, the HR of OS will be estimated and presented with a 2-sided 95% CI.

Primary Analyses of OS

There will be 1 interim analysis of OS utilizing the O'Brien-Fleming boundary approximated by Hwang-Shih-DeCani spending function with the gamma parameter set at -4. The interim analysis will be performed at the time when approximately 423 death events (87% of the target number of OS events) among the 2 treatment arms are observed. It is estimated that it will take approximately 33 months to observe 423 death events. An IDMC will oversee the interim analysis of OS. The final analysis of OS will take place after approximately 488 OS events have been observed. Stopping boundaries in p-value and Z score for primary analyses of OS are shown in Table 8. The boundaries will be updated according to the actual numbers of events in the interim and final analyses, and the revised alpha level due to alpha shifting as described above, using the above pre-specified alpha spending function.

Table 8. Stopping Boundaries (in p-Value and Z Score) of Primary Analysis of Overall Survival

Endpoint	Analysis	Analysis Time (months)	# Events	p-value[1] (Z score) for Efficacy	Approximate HR Threshold
OS	Interim analysis	33	423	< 0.0145 (> 2.18)	0.809
	Final analysis	40	488	< 0.0216 (> 2.02)	0.833

Abbreviations: HR = hazard ratio; OS = overall survival
[1]one-sided

Subgroup Analyses

To determine if the treatment effect is consistent across various subgroups, the HR estimates of OS and their 95% CI will be estimated and plotted within each category of the following variables: region (Asia [excluding Japan] vs Japan vs Rest of World), region (Asia [including Japan] vs Rest of World), choice of chemotherapy doublet (platinum plus fluoropyrimidine vs platinum plus paclitaxel), ECOG (0 vs 1), age (≤ 65 vs > 65 years), gender (female vs male), smoking status, PD-L1 expression (vCPS ≥ 10% vs vCPS < 10%).

9.2.2. Secondary Efficacy Analysis

Progression Free Survival (PFS)

There will be one analysis of PFS in the ITT analysis set, which will be carried out after superiority of OS in the ITT analysis set has been demonstrated. Similar statistical analysis methods used for the OS testing will be applied to PFS analysis.

The p-value from one-sided, stratified log-rank test will be presented using the stratification factors of pooled geographic region, prior definitive therapy, and ICC option.

PFS assessed by the investigator will be estimated using the Kaplan-Meier method in the ITT analysis set. The PFS censoring rule will follow United States (US) Food and Drug Administration (FDA) Guidance for Industry, Clinical Trial Endpoints for Approval of Cancer

drugs and Biologics (FDA 2018). Data for patients without disease progression or death at the time of analysis will be censored at the time of the last tumor assessment. Data for patients who are lost to follow-up prior to documented disease progression will be censored at the last tumor assessment date when the patient is known to be progression-free. Data for patients who start to receive new anti-cancer therapy will be censored at the last tumor assessment date prior to the introduction of a new therapy.

The median PFS and the cumulative probability of PFS at every 3 months, including 6-month PFS, if estimable, will be calculated for each treatment arm and presented with 2-sided 95% CIs. Kaplan-Meier estimates of PFS for each arm will be plotted over time. The PFS rate at 6 months based on the Kaplan-Meier estimate will be compared between the 2 treatment arms for landmark analysis.

HR estimated from a Cox regression model will be presented with its 95% CI.

OS in the vCPS ≥ 10% subgroup

This analysis for the baseline vCPS ≥ 10% subgroup is similar to the OS analysis in the ITT analysis.

Other secondary efficacy endpoints

The null hypotheses of no difference in ORR per RECIST v1.1 by the investigator will be tested using Cochran-Mantel-Haenszel (CMH) method, adjusting for stratification factors of pooled geographic region, prior definitive therapy, and ICC options in the ITT analysis set. Patients with no post-baseline response assessment (for any reason) will be considered non-responders. The 2-sided 95% CIs for the odds ratio in ORR will be calculated along with Clopper-Pearson 95% CIs of ORR for each treatment arm.

DOR assessed by the investigator will be calculated similarly to PFS by the investigator in the responders. Median DOR per arm, if estimable, will be presented.

HRQoL will be analyzed and compared between treatment arms via the post-baseline scores of QLQ-C30's Global Health Status/QoL (GHS), functional scales and symptom scores and symptoms single item scores, QLQ-OES18's index score and symptoms scales and single item scores, and EQ-5D-5L descriptive scale scores as well as the visual analogue scale (VAS) scores. Observed values and changes from baseline will be summarized using descriptive statistics. A mixed-effect model analysis for measuring clinically meaningful changes post-baseline will be performed using the key patient-reported outcome endpoints of GHS, physical functioning, and fatigue domains of QLQ-C30 and dysphagia, reflux, pain and eating of QLQ-OES18.

Time to clinically meaningful deterioration in the aforementioned scales will be estimated using the Kaplan-Meier method and Cox regression model. Deterioration thresholds will be defined based on the published 10-point EORTC threshold utilizing key patient-reported outcome endpoints and a secondary deterioration threshold based on data may be explored.

9.2.3. Exploratory Efficacy Analysis

BOR is defined as the best response per RECIST v1.1 by the investigator recorded from randomization till data cut, progressive disease (PD) or start of new anti-cancer treatment. 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.

To calculate PFS2, data from patients without disease progression after next line of treatment or death at the time of analysis will be censored at the last time known to be alive. Kaplan-Meier method as described in the PFS and OS analyses will be used in the analysis of PFS2.

In addition, PFS, ORR, DOR, and DCR assessed by BIRC per RECIST v1.1 are summarized similarly as the data assessed by the investigator for exploratory analysis.

Exploratory biomarkers may also be assessed.

9.3. 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), dosing, 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.

9.3.1. Extent of Exposure

Extent of exposure to each study drug will be summarized descriptively as the number of doses 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.

9.3.2. Adverse Events

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

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 and up to 30 days following study drug discontinuation or initiation of new anti-cancer therapy, whichever occurs first. The TEAE classification also applies to imAEs that are recorded up to 90 days after discontinuation from tislelizumab or placebo, regardless of whether the patient starts a new anticancer therapy. Only those AEs that were treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in patient data listings.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by SOC and preferred term. A patient will be counted only once by the highest severity grade per NCI-CTCAE v4.03 within an SOC and preferred term, even if the patient experienced more than 1 TEAE within a specific SOC and preferred term. The number (percentage) of patients with

TEAEs will also be summarized by relationship to the study drug. Treatment-related AEs include those events considered by the investigator to be related to study treatment or with missing assessment of the causal relationship. SAEs, deaths, TEAE with ≥ Grade 3 severity, imAE, infusion-related reactions, treatment-related TEAEs and TEAEs that led to treatment discontinuation, dose interruption, dose reduction, or dose delay will be summarized.

9.3.3. Laboratory Analyses

Clinical laboratory (eg, hematology, serum chemistry, urinalysis) values will be evaluated for each laboratory parameter as appropriate. Abnormal laboratory values will be flagged and identified as those outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be included in the CSR for this protocol. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) for laboratory parameters and their changes from baseline will be calculated. Laboratory values will be summarized by visit and by worst postbaseline visit.

Laboratory parameters that are graded in NCI-CTCAE v4.03 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 directions (eg, glucose, potassium, sodium) will be summarized separately.

9.3.4. Vital Signs

Descriptive statistics for vital sign parameters (systolic and diastolic blood pressure, pulse rate, temperature) and changes from baseline will be presented by visit for all visits. Vital signs will be listed by patient and visit.

9.3.5. Ophthalmologic Examination

Ophthalmologic examination results will be listed by patient.

9.4. Pharmacokinetic Analysis

Individual tislelizumab concentrations will be tabulated by scheduled time of collection.

Additional PK analyses such as population PK analysis may be conducted as appropriate. Exposure-response (efficacy or safety endpoints) analysis may be carried out if supported by data. The results from these analyses will be reported separately from the main study report.

9.5. Immunogenicity Analyses

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

9.6. Sample Size Consideration

The initial sample size calculation was based on the primary efficacy analysis of PFS and OS in the comparison between tislelizumab in combination with chemotherapy arm and placebo plus chemotherapy arm in the ITT analysis set. Hazard ratios in PFS and OS were assumed as 0.65 and

0.73, respectively, with median PFS of 5 months and OS of 9 months in the comparator arm. A total of 480 patients would be enrolled in a 1:1 randomization over 17-month period at enrollment rates of 10 patients/month in the first month, 20 patients/month in the second month and 30 patients/month in the next 15 months. Approximately 319 PFS events were planned in the PFS hypothesis testing to have a power of 90% with an alpha of 0.005. A group sequential testing of OS would be performed. The interim analysis was planned after approximately 67% of the total planned death events had occurred (241). The final analysis of OS would be performed when approximately 360 death events had been observed. The sample size calculation of OS was based on overall power of 82% and an alpha level of 0.02.

The previous version of protocol amendment 3.0 was amended on 25 May 2020. The study sample size was increased from 480 to 622 to allow increased targeted numbers of events in the PFS and OS analyses, which was to account for the showed delayed treatment effect and increased usage of subsequent immunotherapies that were observed in the newly published immuno-oncology trials in the second-line ESCC (Kojima et al 2019; Kato et al 2019; Huang et al 2019).

By 24 November 2020, enrollment was completed with 649 randomized patients. In the current protocol amendment, BIRC-assessed PFS has been removed from the primary efficacy analysis based on the results from KEYNOTE-590 (Kato et al 2020) in the first-line treatment of ESCC. OS is the sole primary efficacy endpoint. The HR for OS is assumed to be 0.74 at the time of final analysis after an initial 1-month delayed treatment effect (e.g. assuming HR = 1 in the first month), the number of deaths required in the final analysis will be approximately 488 with 90% power by simulation. The planned interim analysis with a power of 81% will occur after approximately 423 events have been observed. A 5% annual dropout rate is assumed and one-sided alpha of 0.025 is used in the sample size calculation.

9.7. Interim Analyses

An interim analysis of OS (see Section 9.2.1) will be performed by an independent statistician external to the Sponsor. The independent statistician will work with the blinded study statistician to provide statistical outputs to the IDMC as described in the IDMC charter and perform any ad-hoc analyses requested by the IDMC.

10. STUDY COMMITTEES AND COMMUNICATION

10.1. Blinded Independent Review Committee

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

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

10.2. Independent Data Monitoring Committee

As described in Section 3.8, enrollment of Japanese patients will be gated to monitor for unexpected or new safety concerns. IDMC will review safety data of the safety cohort of approximately 10 Japanese patients after they complete 1 cycle of treatment or whenever there is a safety concerns. Enrollment will continue only when the safety and tolerability are deemed acceptable by the IDMC.

Regular safety monitoring (every 6 months or in longer, previously agreed on intervals after the first IDMC safety review if there are no significant safety concerns), and efficacy monitoring will be performed by an IDMC. The first IDMC safety review will occur after approximately 50 patients have been randomized to study treatment (ie, at least 25 patients per treatment arm) and have been on treatment for ≥ 1 month to determine if the proposed dosing schedule of tislelizumab is safe and tolerable. The IDMC may recommend study modification including termination of the study due to safety and/or efficacy concerns. The IDMC will also be responsible for reviewing the results from pre-defined analyses, including final analysis of PFS and interim analysis of OS and making the recommendations for stopping the study based on pre-defined efficacy boundaries. The function and membership of the IDMC will be described in the IDMC charter.

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

Following IDMC review and discussion, the sponsor will make all final decisions regarding any changes in study conduct.

11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

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

11.1. Access to Information for Monitoring

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

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

11.2. Access to Information for Auditing or Inspections

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

12. QUALITY ASSURANCE AND QUALITY CONTROL

12.1. Regulatory Authority Approval

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

12.2. Quality Assurance

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

12.3. Study Site Inspections

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

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

12.4. Drug Accountability

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

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, cisplatin, oxaliplatin, 5-FU, capecitabine, and paclitaxel reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the Investigator or designated study center personnel must maintain tislelizumab, cisplatin, oxaliplatin, 5-FU, capecitabine, and paclitaxel accountability records throughout the course of the study. This person will document the amount of tislelizumab, cisplatin, oxaliplatin, 5-FU, capecitabine, and paclitaxel received from the sponsor, the amount supplied, and/or administered (and returned by patients, if applicable).

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

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

13. ETHICS/PROTECTION OF HUMAN PATIENTS

13.1. Ethical Standard

This study will be conducted by the investigator and the study center in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the Definitions and Standards for Expedited Reporting (ICH E2A 1994).

13.2. Institutional Review Board/Independent Ethics Committee

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

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

13.2.1. Protocol Amendments

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

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

13.3. Informed Consent

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

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

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

Patients must reconsent to the most current version of the ICFs (or to a significant new information/findings addendum in accordance with applicable laws and IRB/IEC policy) during their participation in the study, if the updated information may be relevant to the patient's willingness to continue 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. All patients in the survival follow-up will reconsent to the updated ICF if the updates may be relevant to the patient's willingness to continue participation in the study, either during on-site visits or by phone/video-call/mail, according to local regulations. The IRB/IEC submission letters, if applicable, should specify the approach taken (phone, video-call, or mail) according to local regulations. The process by which the consent is obtained from a patient during the survival follow-up should be documented in the patient's case history or clinical records.

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

13.4. Patient and Data Confidentiality

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

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

- Names or initials (full or partial);
- Full dates of birth;
- Contact information (such as phone numbers or home or email addresses);

- Numerical identifiers (eg, hospital or medical record, government, health insurance, or financial account numbers) other than patient identification numbers assigned as part of this study;
- Geographic identifiers smaller than a state, province, or local equivalent (such as city, county, zip code, or other equivalent geographic identifiers); or
- Information about marital status, family, or household members; employment, sex life, sexual preference, or other sensitive data that is not relevant to the study.

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

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

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

13.5. Financial Disclosure

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

14. DATA HANDLING AND RECORD KEEPING

14.1. Data Collection and Management Responsibilities

14.1.1. Data Collection

Data required by the protocol will be entered into an electronic data capture (EDC) system.

Data collection in the eCRF should follow the instructions described in the eCRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered in the eCRF. The investigator or designee as identified on Form FDA 1572 must provide e-signature in the EDC system to attest to its accuracy, authenticity, and completeness.

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

14.1.2. Data Management/Coding

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

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

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

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

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

14.2. Data Integrity and In-House Blinding

Due to the blinded design of the study, access to the patient level clinical data in the EDC system will be assigned to predefined study personnel only. 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 from the EDC system with other functions/persons who do not have access to the EDC. In addition, the central imaging vendor will perform the central imaging review without knowledge of treatment arm assignment.

Analyses or summaries generated by randomized treatment assignment and actual treatment received will be limited and documented.

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

14.3. Study Records Retention

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

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

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

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

The sponsor will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that study center for the study, as dictated by any institutional requirements or local laws or regulations, or the sponsor's standards/procedures; otherwise, the retention period will default to the 15 years.

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

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

14.4. Protocol Deviations

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

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

14.5. Publication and Data Sharing Policy

A 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 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 the sponsor, regardless of the outcome of the study. The data generated in this clinical study are the exclusive property of the sponsor and are confidential. As this is a multicenter study, the first publication or disclosure of study results shall be a complete, joint multicenter publication or disclosure coordinated by the sponsor. Thereafter, any secondary publications will reference the original publication(s). Authorship will be determined by mutual agreement and all authors must meet the criteria for authorship established by the International Committee of Medical Journal Editors Uniform Requirements for Manuscripts or stricter local criteria (International Committee of Medical Journal Editors 2018).

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

14.6. Study and Study Center Closure

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

- Return of all study data to the sponsor
- Resolution and closure of all data queries

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

In addition, the sponsor reserves the right to suspend the enrollment or prematurely discontinue this study either at a single study center or at all study centers at any time for reasons including, but not limited to, safety or ethical issues or severe noncompliance. If the sponsor determines such action is needed, the sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. When feasible, the sponsor will provide advance notification to the investigator of the impending action prior to it taking effect.

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

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

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

14.7. Information Disclosure and Inventions

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

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

All information provided by the sponsor and all data and information generated by the study center as part of the study (other than a patient's medical records) are the sole property of the sponsor and will be kept confidential by the investigator and other study center personnel. This information and data will not be used by the investigator or other study center personnel for any purpose other than conducting the study without the prior written consent of the sponsor.

These restrictions do not apply to:

- Information that becomes publicly available through no fault of the investigator or study center personnel
- Information that is necessary to disclose in confidence to an IEC/IRB solely for the evaluation of the study

- Information that is necessary to disclose to provide appropriate medical care to a patient
- Study results that may be published as described in Section 14.5

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

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APPENDIX 1. SCHEDULE OF ASSESSMENTS

Assessment	Screening[1]	Treatment Cycles				Safety Follow-up[3]	Survival Follow-up[4]
		Cycles 1 to 3 (every 21 days)			Cycle 4 and Subsequent Cycles (Every 21 Days)	End of Treatment Visit[2]	
Days (Window)	**-28 to ~ -1**	**1 (± 3)**	**8 (± 2)**	**15 (± 2)**	**1 (± 3)**	**30 ± 7 Days After Last Dose**	**Every 3 Months (± 14 days)**
Informed consent	x						
Inclusion/exclusion criteria	x						
Randomization[5]	x						
Demographics/medical history/prior medications/ ongoing cancer symptoms[6]	x						
Cancer diagnosis and treatment history[6]	x						
Vital signs/height and weight[7]	x	x	x	x	x	x	
Physical examination[8]	x	x			x	x	
ECOG Performance Status	x	x			x	x	
12-lead ECG[9]	x	As clinically indicated				x	
Optical coherence tomography (or equivalent diagnostic test) and visual acuity tests[10]	x	Approximately every 15 weeks				x	
Adverse events[11]	x	x	x[25]	x[25]	x	x	
Concomitant medications[12]	x	x	x[25]	x[25]	x	x	
Hematology[13]	x[1]	x	x	x	x	x	
Serum chemistry[13]	x[1]	x	x	x	x	x	
Coagulation parameters [13]	x	x			x	x	
Urinalysis[13]	x	As clinically indicated					
Pregnancy test[14]	x	x			x	x	
Thyroid function[15]	x[1]				x	x	
HBV/HCV tests[16]	x	Every 4 cycles and as clinically indicated					
Pulmonary function tests[17]	x	As clinically indicated					
Pharmacokinetics[18]		x			x	x	
Anti-tislelizumab antibodies[19]		x			x	x	
Tumor assessment[20]	x				x	x	x

Assessment	Screening[1]	Treatment Cycles				Safety Follow-up[3]	Survival Follow-up[4]
		Cycles 1 to 3 (every 21 days)			Cycle 4 and Subsequent Cycles (Every 21 Days)	End of Treatment Visit[2]	
Days (Window)	**-28 to ~ -1**	**1 (± 3)**	**8 (± 2)**	**15 (± 2)**	**1 (± 3)**	**30 ± 7 Days After Last Dose**	**Every 3 Months (± 14 days)**
Archival tumor tissue[21]	x						
Fresh tumor tissue[22]	x		x[22] (when PD is assessed)				
Study drug administration[23]		x			x		
EQ-5D-5L[24]	x	x			x	x	
EORTC QLQ-C30[24]	x	x			x	x	
EORTC QLQ-OES18[24]	x	x			x	x	
Survival status							x
Blood sample collection		x[26]	x[27] (when CR/PR and/or PD is assessed)				

Abbreviations: ADA, antidrug antibodies; AE, adverse event; CT, computed tomography; DNA, deoxyribonucleic acid; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-OES18, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Oesophageal Carcinoma-18 Questions; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EOT, end of treatment; EQ-5D-5L, European Quality of Life 5 Dimensions (health questionnaire); FFPE, formalin fixed paraffin-embedded; HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HBsAb, hepatitis B surface antibody; imAE, immune-mediated adverse event; IRB, Institutional Review Board; IEC, Independent Ethics Committee; IRT, interactive response technology; MRI, magnetic resonance imaging; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; OCT, optical coherence tomography; PET, positron emission tomography; PK, pharmacokinetic; RECIST, Response Evaluation Criteria in Solid Tumors; RNA, ribonucleic acid; SAE, serious adverse event; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone; v, version.

1. Written informed consent is required prior to performing any study-specific tests or procedures. Results of standard of care tests or examinations performed prior to obtaining informed consent and within 28 days prior to randomization may be used for screening assessments rather than repeating such tests (only applicable if the same radiographic procedure will be used throughout the study).
2. The EOT/Safety Follow-up Visit is conducted when the Investigator determines that tislelizumab or chemotherapy will no longer be used. If routine laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the visit, tests need not be repeated. Tumor assessment is not required at the visit provided that fewer than 6 weeks have passed since the last assessment.
3. The EOT/Safety Follow-up Visit is required to be conducted 30 days (± 7 days) after the last dose of tislelizumab or chemotherapy, before the initiation of a new anticancer treatment, or before the first dose administration in the long-term extension/posttrial supply study for patients who are going to rollover to those studies, whichever occurs first. Patients receiving paclitaxel will need to be followed for safety and pregnancy for 180 days following the last dose.
4. Survival Follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months after the Safety Follow-up Visit until death, loss to follow-up, withdrawal of consent, or study termination by Sponsor. All patients will be followed for survival and subsequent anticancer therapy information unless a patient requests to be withdrawn from follow-up.

5. Patients will be randomized into either the tislelizumab with chemotherapy or placebo with chemotherapy arms via IRT. All patients are required to receive study treatment within 2 business days of randomization.
6. Includes age or year of birth, gender, and self-reported race/ethnicity; history of treatment for the primary diagnosis, including prior medication, loco-regional treatment(s), and surgical treatment(s). Information on radiographic studies performed prior to study entry may be collected for review by the Investigator.
7. Vital signs collected on study include body temperature, pulse rate, and blood pressure (systolic and diastolic) while the patient is in a seated position after resting for 10 minutes. The patient's vital signs are required to be recorded within 60 minutes before, during, and within 30 minutes after the first infusion of tislelizumab. For subsequent infusions, vital signs will be collected within 60 minutes before infusion and if clinically indicated, during and 30 minutes after the infusion.
8. 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. The ECG recordings will be obtained during Screening, the Safety Follow-up Visit, and as clinically indicated at other time points. Patients should be resting in a for at least 10 minutes prior to each ECG collection.
10. Eye exam, visual acuity test, and optical coherence tomography (OCT; or equivalent diagnostic test for retinal examination) captured as standard of care prior to obtaining written informed consent and within 28 days of randomization or first dose of study drug may be used rather than repeating tests. Eye exam, including visual acuity test, and optical coherence tomography (or equivalent diagnostic test) will be assessed by an appropriate specialist at the Screening visit. All patients will undergo repeat assessments approximately every 15 weeks (± 7 days) during study treatment and a final assessment at the EOT/Safety follow-up visit.
11. The AEs and laboratory abnormalities will be graded per NCI-CTCAE v4.03. All AEs will also be evaluated for seriousness. After the informed consent form has been signed, but prior to the administration of study drug, only SAEs should be reported. After 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 drugs (including chemotherapy) or the initiation of new anticancer therapy, whichever occurs first. Immune-mediated AEs (serious or non-serious) should be reported until 90 days after the last dose of tislelizumab, regardless of whether the patient starts a new anticancer therapy. The investigator should report any SAEs that are assessed as related to tislelizumab treatment, at any time after treatment discontinuation.
12. Concomitant medications include any prescription medications or over-the-counter medications. All concomitant medications received within 30 days before the first dose of study medication 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.
13. Local and/or central laboratory assessments on serum chemistry, hematology, coagulation, and urinalysis will be conducted, of which certain elements will be collected as specified in Appendix 2. If laboratory tests at screening are not performed within 7 days of 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 3 cycles and then at the beginning of subsequent cycles (data collected as specified in Appendix 2). After Cycle 1, results are to be reviewed within 48 hours before study drug administration. Urinalysis is to be conducted during the treatment period only if clinically warranted. Refer to Section 8.3.5 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.
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 7 days prior to randomization. Serum pregnancy tests will be performed at each visit prior to dosing.
15. Analysis of FT3, FT4, and TSH will be performed by a central laboratory or the local study site laboratory. Thyroid function tests will be performed at Screening and every 3 cycles (ie, Day 1 of Cycles 4, 7, 10, et cetera), and at the Safety Follow-up Visit.

16. Testing will be performed by a central laboratory and/or the local laboratory at Screening and will include HBV/HCV serology (HBsAg, HBsAb, HBcAb, and HCV antibody). If HBsAg or HBcAb is positive, then an HBV DNA test will be triggered. If HCV antibody is positive, an HCV RNA test will be triggered.
17. Patients who are suspected or known to have serious/severe respiratory conditions or exhibit significant respiratory symptoms unrelated to the underlying cancer or with a history of thoracic radiotherapy 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 on the study.
18. Procedures for collection of PK samples are described in the Laboratory Manual. Predose (within 60 minutes before starting infusion) samples are required to be collected at Day 1 of Cycles 1, 2, 5, 9 and 17; A postdose (within 30 minutes after completing tislelizumab infusion) sample is required to be collected at Day 1 of Cycles 1 and 5. If IP treatment is not given, the predose PK samples are still recommended to be collected when patients are available at the study site. An additional PK sample is required to be collected at the Safety Follow-up Visit. Should a patient present with any ≥ Grade 3 imAE, an additional blood PK sample may be taken to determine the serum concentration of tislelizumab. These tests are required when it is allowed by local regulations/IRBs/ECs. PK sample collection will stop after patients finish 3-year follow up.
19. 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. If IP treatment is not given, the predose ADA samples are still recommended to be collected when patients are available at the study site. These tests are required when it is allowed by local regulations/IRBs/ECs. ADA sample collection will stop after patients finish 3-year follow up.
20. Radiological images captured as standard of care prior to obtaining written informed consent and within 28 days of randomization may be used rather than repeating tests (only applicable if the same radiographic procedure will be used throughout the study). All measurable and evaluable lesions are required to be assessed and documented at Screening and reassessed at each subsequent tumor evaluation. An MRI (or CT scan if MRI is contraindicated or not readily available) of the head may be required at screening based on clinical judgement; bone scan or PET is required if clinically indicated. The same radiographic procedure must be used throughout the study for each patient.
    The Investigator must review radiograph results before dosing at the next cycle. During the study, tumor imaging will be performed every 6 weeks (± 7 days) for the first 48 weeks, then every 9 weeks (± 7 days) after 48 weeks based on RECIST v1.1. If a tumor assessment is missed or conducted outside of the specified assessment window, all subsequent scans should be conducted on the planned schedule. The Investigator may perform additional scans or more frequent assessments if clinically indicated. See Section 7.5 for more information. Patients who discontinue study treatment early for reasons other than documented radiographic disease progression (eg, toxicity) will continue to undergo tumor assessments following the original plan until the patient experiences disease progression, withdraws consent, is lost to follow-up, dies, or until the study terminates, whichever occurs first. Tumor assessment should continue as planned in patients receiving study drug(s) beyond initial investigator-assessed progression. Tumor assessment in such patients should continue until study treatment discontinuation.
21. Patients are required to provide archival tumor tissues (FFPE blocks or approximately 15 [≥ 6] unstained slides) for biomarker analysis.
22. Fresh biopsy: In the absence of archival tumor tissues, a fresh biopsy of a tumor lesion at baseline (within 28 days before randomization) is needed (written informed consent is required prior to fresh tumor biopsies). An optional biopsy will be taken for patients with confirmed disease progression during the study. See Section 7.7 and Section 7.8 for more information.
23. Tislelizumab will be administered first, followed by an approximate 30-minute observation period for safety surveillance, then the chemotherapy doublet will be administered (see Section 5.2). The chemotherapy doublet may be administered without regard to the sequence of chemotherapy (note that in Chemotherapy Doublet B, capecitabine is given orally daily). Platinum therapy may be stopped after 6 cycles, per site or investigator preference or standard practice. If platinum treatment is stopped, the non-platinum agent (fluoropyrimidine or paclitaxel) may continue at the regular schedule.
24. To be completed prior to any clinical activities during on-study site visits. EQ-5D-5L, EORTC QLQ-C30, and EORTC QLQ-OES18 will be completed at baseline, after randomization, prior to dosing or any clinical activities at every treatment cycle for the first 6 cycles, then every other cycle thereafter, and at the EOT Visit. Patient-reported outcome collection will stop after patients finish 3-year follow up.

25. Review of AEs and concomitant medications may be conducted by telephone on Days 8 and 15.
26. Blood sample will be taken at baseline (predose on Day 1 of Cycle 1) for all randomized patients to explore the association of blood-based biomarkers with response and prognosis to tislelizumab in combination with chemotherapy or chemotherapy alone. Written patient consent is required for blood sample collection.
27. Blood samples are highly recommended to be collected at first tumor response (CR/PR) and/or at confirmed disease progression to explore response and/or resistance mechanism to tislelizumab in combination with chemotherapy or chemotherapy alone. Written patient consent is required for optional blood sample collection. See Section 7.8 for more information.

APPENDIX 2. CLINICAL LABORATORY ASSESSMENTS

Serum Chemistry	Hematology	Coagulation	Urinalysis	Thyroid Function	HBV and HCV Serology
- Alkaline phosphatase - Alanine aminotransferase - Aspartate aminotransferase - Albumin - Total bilirubin - Direct bilirubin - Blood urea nitrogen or urea - Potassium - Sodium - Chloride - Magnesium - Phosphorous - Total calcium[a] - Creatinine - Glucose - Lactate dehydrogenase - Total protein - Creatine kinase (CK)[b] - CK-MB[b] - Lipase and/or Amylase	- Hematocrit - Hemoglobin - Red blood cell count - Platelet counts - WBC count with automated differential - Lymphocyte count - Neutrophil count	- Prothrombin time - Partial thromboplastin time or activated partial thromboplastin time - International normalized ratio	- Glucose - Protein - Blood - Ketones	- TSH - Free T3 - Free T4	- HBsAb - HBsAg - HBcAb - HBV DNA[c] - HCV Ab - HCV RNA[c]

Abbreviations: Ab, antibody; CK-MB, creatine kinase cardiac isoenzyme; DNA, deoxyribonucleic acid; HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; pH, negative of the logarithm to base 10 of the activity of the (solvated) hydronium ion; RNA, ribonucleic acid; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone; WBC, white blood cells.

a. For patients with hypoproteinemia, this value needs to be corrected, which means a corrected calcium is needed
Formula to calculate the corrected calcium: Corrected Calcium = (0.8*(Normal Albumin-Pt's Albumin)) + Serum Calcium
Note: above formula assumes albumin units in g/dL. (online calculator is available at http://www.mdcalc.com/calcium-correction-hypoalbuminemia#evidence)

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

c. If HBsAg or HBcAb is positive, then an HBV DNA test will be triggered. If HCV antibody is positive, an HCV RNA test will be triggered.

APPENDIX 3. ECOG PERFORMANCE STATUS

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, 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
5	Dead

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

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

The text below was obtained from the following reference:

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (Version 1.1). Eur J Cancer. 2009;45:228-247.

DEFINITIONS

Response and progression will be evaluated in this trial using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (v1.1). Changes in only the largest diameter (unidimensional 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 exam (when superficial)
- 20 mm by chest X-ray (if clearly defined and surrounded by aerated lung)

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

Nonmeasurable Disease

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

Bone lesions:

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

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

- Blastic bone lesions are nonmeasurable

Cystic lesions:

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

Lesions with prior local treatment:

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

Target Lesions

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

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

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

Nontarget Lesions

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

GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE

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

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

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

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

where recurrence following complete response (CR) or surgical resection is an endpoint.

- Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in CR. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and prostate-specific antigen response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.
- Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or 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 nontarget) 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 1 or more new lesions is also considered progression).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study
- Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report recorded in a separate section where, to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD,

the actual short axis measurement of the nodes is to be included in the sum of target lesions.

- Target lesions that become "too small to measure". While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure".

  When this occurs, it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

- Lesions that split or coalesce on treatment: When non-nodal lesions "fragment", the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion".

Evaluation of Nontarget Lesions

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

- CR: Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (<10 mm short axis).
- PD: Unequivocal progression (as detailed below) of existing nontarget lesions. (Note: the appearance of 1 or more new lesions is also considered progression.)
- Non-CR/Non-PD: Persistence of 1 or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits
- When the patient also has measurable disease: In this setting, to achieve "unequivocal progression" on the basis of the nontarget disease, there must be an overall level of substantial worsening in nontarget disease such that, even in presence of SD or PR in

target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of 1 or more nontarget lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in nontarget disease in the face of SD or PR of target disease will therefore be extremely rare.

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

New Lesions

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

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

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

While fluorodeoxyglucose (FDG)-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible "new" disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
Negative FDG-PET at baseline, with a positive FDG-PET at follow-up, is a sign of PD based on a new lesion.

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

Evaluation of Best Overall Response

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

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

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

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

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

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

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

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

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

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

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

CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

Confirmation

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

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

Duration of Overall Response

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

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

Duration of Stable Disease

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

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

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

APPENDIX 5. PRE-EXISTING IMMUNE DEFICIENCIES OR AUTOIMMUNE DISEASES

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

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

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

APPENDIX 6. NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

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

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

APPENDIX 7. IMMUNE-MEDIATED ADVERSE EVENT EVALUATION AND MANAGEMENT

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

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

- What was the temporal relationship between initiation of tislelizumab and the adverse event?
- How did the patient respond to withdrawal 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 imAE field associated with the adverse event (AE) in the electronic case report form (eCRF) should be checked.

For any adverse events not included in this appendix, please refer to the recent guidelines (Haanen et al 2017; Brahmer et al 2018) for further guidance on diagnostic evaluation and management of immune-mediated toxicities.

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

Immune-mediated Toxicity	Diagnostic Evaluation Guideline
Thyroid Disorders	Scheduled and repeat thyroid function tests (TSH and T4).
Hypophysitis	Check visual fields and consider pituitary endocrine axis blood profile. Perform pituitary and whole brain MRI in patients with headache, visual disturbance, unexplained fatigue, asthenia, weight loss and unexplained constitutional symptoms. Consider consultation with an endocrinologist if an abnormality is detected.
Pneumonitis	All patients presenting with new or worsened pulmonary symptoms or signs, such as an upper respiratory infection, new cough, shortness of breath or hypoxia should be assessed by high-resolution CT. Consider pulmonary function test including *D*LCO. Radiographic appearance is often nonspecific. Depending on the location of the abnormality, bronchoscopy and bronchoalveolar lavage or lung biopsy may be considered. Consult with a respiratory medicine physician for cases of uncertain cause.
Neurological Toxicity	Perform a comprehensive neurological examination and brain MRI for all CNS symptoms; review alcohol history and other medications. Conduct a diabetic screen, and assess blood B12/folate, HIV status, TFTs, and consider autoimmune serology. Consider the need for brain/spine MRI/MRA and nerve conduction study for peripheral neuropathy. Consult with a neurologist if there are abnormal findings.
Colitis	Review dietary intake and exclude steatorrhea. Consider comprehensive testing, including the following: FBC, UEC, LFTs, CRP, TFTs, stool microscopy and culture, viral PCR, Clostridium difficile toxin, cryptosporidia (drug-resistant organism). In case of abdominal discomfort, consider imaging, eg, X-ray, CT scan. If a patient experiences bleeding, pain or distension, consider colonoscopy with biopsy and surgical intervention, as appropriate.
Eye Disorders	If a patient experiences acute, new onset, or worsening of eye inflammation, blurred vision, or other visual disturbances, refer the patient urgently to an ophthalmologist for evaluation and management.
Hepatitis	Check ALT/AST/total bilirubin, INR/albumin; the frequency will depend on severity of the AE (eg, daily if Grade 3-4; every 2-3 days if Grade 2, until recovering). Review medications (eg, statins, antibiotics) and alcohol history. Perform liver screen including Hepatitis A/B/C serology, Hepatitis E PCR and assess anti-ANA/SMA/LKM/SLA/LP/LCI, iron studies. Consider imaging, eg, ultrasound scan for metastases or thromboembolism. Consult with a hepatologist and consider liver biopsy.
Renal toxicity	Review hydration status and medication history. Test and culture urine. Consider renal ultrasound scan, protein assessment (dipstick/24-hour urine collection), or phase-contrast microscopy. Refer to nephrology for further management assistance.
Dermatology	Consider other causes by conducting a physical examination, consider dermatology referral for skin biopsy.

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

Immune-mediated Toxicity	Diagnostic Evaluation Guideline
Joint or muscle inflammation	Conduct musculoskeletal history and perform complete musculoskeletal examination. Consider joint X-ray and other imaging as required to exclude metastatic disease. Perform autoimmune serology and refer to rheumatology for further management assistance. For suspected myositis/rhabdomyolysis/myasthenia include: CK, ESR, CRP, troponin, and consider a muscle biopsy
Myocarditis	Perform ECG, echocardiogram, CK/CK-MB, troponin (I and/or T), and refer to a cardiologist.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; CK, creatine kinase; CK-MB, creatine kinase cardiac enzyme; 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-Mediated Adverse Events

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

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Thyroid Disorders	**1-2** Asymptomatic TFT abnormality or mild symptoms	Replace thyroxine if hypothyroid, until TSH/T4 levels return to normal range. Thyrotoxic patients should be referred to an endocrinologist. In cases with systemic symptoms: withhold study treatment, treat with a beta blocker and consider oral prednisolone 0.5 mg/kg/day for thyroid pain. Taper corticosteroids over 2-4 weeks. Monitor thyroid function regarding the need for hormone replacement.	Continue study treatment or withhold treatment in cases with systemic symptoms.
	3-4 Severe symptoms, hospitalization required	Refer patient to an endocrinologist. If hypothyroid, replace with thyroxine 0.5-1.6 µg/kg/day (for the elderly or those with co-morbidities, the suggested starting dose is 0.5 µg/kg/day). Add oral prednisolone 0.5 mg/kg/day for thyroid pain. Thyrotoxic patients require treatment with a beta blocker and may require carbimazole until thyroiditis resolves.	Hold study treatment; resume when resolved/improved to Grade 0-1.
Hypophysitis	**1-2** Mild-moderate symptoms	Refer patient to an endocrinologist for hormone replacement. Add oral prednisolone 0.5-1 mg/kg/day for patients with pituitary inflammation. Taper corticosteroids over at least 1 month. If there is no improvement in 48 hours, treat as Grade 3-4. Taper corticosteroids over at least 1 month.	Continue study treatment.
	3-4 Severe or life-threatening symptoms	Refer patient to an endocrinologist for assessment and treatment. Initiate pulse IV methylprednisolone 1 mg/kg for patients with headache/visual disturbance due to pituitary inflammation. Convert to oral prednisolone and taper over at least 1 month. Maintain hormone replacement according to endocrinology advice. Maintain hormone replacement according to endocrinology advice.	Hold study treatment for patients with headache/visual disturbance due to pituitary inflammation until resolved/improved to Grade 2 or less. Discontinuation is usually not necessary.
Pneumonitis	**1** Radiographic changes only	Monitor symptoms every 2-3 days. If appearance worsens, treat as Grade 2.	Consider holding study treatment until appearance improves and cause is determined.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	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.
Neurological Toxicity	**1** Mild symptoms	N/A	Continue study treatment.
	2 Moderate symptoms	Treat with oral prednisolone 0.5-1 mg/kg/day. Taper over at least 4 weeks. Obtain neurology consultation.	Hold study treatment; resume when resolved/improved to Grade 0-1.
	3-4 Severe/life-threatening	Initiate treatment with oral prednisolone or IV methylprednisolone 1-2 mg/kg/day, depending on symptoms. Taper corticosteroids over at least 4 weeks. Consider azathioprine, MMF, cyclosporine if no response within 72-96 hours.	Discontinue study treatment.
Colitis/Diarrhea	**1** Mild symptoms: < 3 liquid stools per day over baseline and feeling well	Symptomatic management: fluids, loperamide, avoid high fiber/lactose diet. If Grade 1 persists for > 14 days manage as a Grade 2 event.	Continue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	2 Moderate symptoms: 4-6 liquid stools per day over baseline, or abdominal pain, or blood in stool, or nausea, or nocturnal episodes	Oral prednisolone 0.5 mg/kg/day (non-enteric coated). Do not wait for any diagnostic tests to start treatment. Taper steroids over 2-4 weeks, consider endoscopy if symptoms are recurring.	Hold study treatment; resume when resolved/improved to baseline grade.
	3 Severe symptoms: > 6 liquid stools per day over baseline, or if episodic within 1 hour of eating	Initiate IV methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Consider prophylaxis for adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement. If no improvement in 72 hours or symptoms worsen, consider infliximab 5 mg/kg if no perforation, sepsis, TB, hepatitis, NYHA grade III/IV CHF or other immunosuppressive treatment: MMF or tacrolimus. Consult gastroenterologist to conduct colonoscopy/ sigmoidoscopy.	Hold study treatment; retreatment may be considered when resolved/improved to baseline grade and after discussion with the study medical monitor.
	4 Life-threatening symptoms		Discontinue study treatment.
Skin reactions	**1** Skin rash, with or without symptoms, < 10% BSA	Avoid skin irritants and sun exposure; topical emollients recommended.	Continue study treatment.
	2 Rash covers 10%-30% of BSA	Avoid skin irritants and sun exposure; topical emollients recommended. Topical steroids (moderate strength cream once a day or potent cream twice a day) ± oral or topical antihistamines for itch. Consider a short course of oral steroids.	Continue study treatment.
	3 Rash covers > 30% BSA or Grade 2 with substantial symptoms	Avoid skin irritants and sun exposure; topical emollients recommended. Initiate steroids as follows based on clinical judgement: For moderate symptoms: oral prednisolone 0.5-1 mg/kg/day for 3 days then taper over 2-4 weeks. For severe symptoms: IV methylprednisolone 0.5-1 mg/kg/day; convert to oral prednisolone and taper over at least 4 weeks.	Hold study treatment. Re-treat when AE is resolved or improved to mild rash (Grade 1-2) after discussion with the study medical monitor.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	4 Skin sloughing > 30% BSA with associated symptoms (eg, erythema, purpura, epidermal detachment)	Initiate IV methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Admit to a hospital and seek urgent dermatology consultation.	Discontinue study treatment.
Hepatitis	**1** ALT or AST > ULN to 3X ULN	Check LFTs within 1 week and before the next dose check LFTs to verify that there has been no worsening. If LFTs are worsening, recheck every 48-72 hours until improvement is seen.	Continue study treatment if LFTs are unchanged or improving. Hold study treatment if LFTs are worsening until improvement is seen.
	2 ALT or AST 3-5X ULN	Recheck LFTs every 48-72 hours: For persistent ALT/AST elevation: consider oral prednisolone 0.5-1 mg/kg/day for 3 days then taper over 2-4 weeks. For rising ALT/AST: start oral prednisolone 1 mg/kg/day and taper over 2-4 weeks; re-escalate dose if LFTs worsen, depending on clinical judgement.	Hold study treatment; treatment may be resumed when resolved/improved to baseline Grade and prednisolone tapered to ≤ 10 mg.
	3 ALT or AST 5-20X ULN	ALT/AST < 400 IU/L and normal bilirubin/INR/albumin: Initiate oral prednisolone 1 mg/kg and taper over at least 4 weeks. ALT/AST > 400 IU/L or raised bilirubin/INR/low albumin: Initiate IV (methyl)prednisolone 2 mg/kg/day. When LFTs improve to Grade 2 or lower, convert to oral prednisolone and taper over at least 4 weeks.	Hold study treatment until improved to baseline Grade; reintroduce only after discussion with the study medical monitor.
	4 ALT or AST > 20X ULN	Initiate IV methylprednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 6 weeks.	Discontinue study treatment.
	Worsening LFTs despite steroids: • If on oral prednisolone, change to pulsed IV methylprednisolone • If on IV, add MMF 500-1000 mg twice a day • If worsens on MMF, consider addition of tacrolimus Duration and dose of steroid required will depend on severity of event		
Nephritis	**1** Creatinine 1.5X baseline or > ULN to 1.5X ULN	Repeat creatinine weekly. If symptoms worsen, manage as per criteria below.	Continue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	2 Creatinine > 1.5X-3X baseline or > 1.5X-3X ULN	Ensure hydration and review creatinine in 48-72 hours; if not improving, consider creatinine clearance measurement by 24-hour urine collection. Discuss with nephrologist the need for kidney biopsy. If attributed to study drug, initiate oral prednisolone 0.5-1 mg/kg and taper over at least 2 weeks. Repeat creatinine/U&E every 48-72 hours.	Hold study treatment. If not attributed to drug toxicity, restart treatment. If attributed to study drug and resolved/improved to baseline grade: Restart study drug if tapered to < 10 mg prednisolone.
	3 Creatinine > 3X baseline or > 3X-6X 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 4 weeks.	Hold study treatment until the cause is investigated. If study drug suspected: Discontinue study treatment.
	4 Creatinine > 6X ULN	As per Grade 3, patient should be managed in a hospital where renal replacement therapy is available.	Discontinue study treatment.
Diabetes/ Hyperglycemia	**1** Fasting glucose value ULN to 160 mg/dL; ULN to 8.9 mmol/L	Monitor closely and treat according to local guideline. Check for C-peptide and antibodies against glutamic acid decarboxylase and islet cells are recommended	Continue study treatment.
	2 Fasting glucose value 160-250 mg/dL; 8.9-13.9 mmol/L	Obtain a repeat blood glucose level at least every week. Manage according to local guideline.	Continue study treatment or hold treatment if hyperglycemia is worsening. Resume treatment when blood glucose is stabilized at baseline or Grade 0-1.
	3 Fasting glucose value 250-500 mg/dL; 13.9-27.8 mmol/L	Admit patient to hospital and refer to a diabetologist for hyperglycemia management. Corticosteroids may exacerbate hyperglycemia and should be avoided.	Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1.
	4 Fasting glucose value > 500 mg/dL; > 27.8 mmol/L	Admit patient to hospital and institute local emergency diabetes management. Refer the patient to a diabetologist for insulin maintenance and monitoring.	

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	Diabetic Ketoacidosis	Admit patient to hospital and follow procedures of admitting institution. Refer to endocrinologist for further diabetic management.	Hold study treatment until blood glucose stabilized at baseline.
Ocular Toxicity	**1** Asymptomatic eye exam/test abnormality	Consider alternative causes and prescribe topical treatment as required.	Continue study treatment.
	2 Anterior uveitis or mild symptoms	Refer patient to an ophthalmologist for assessment and topical corticosteroid treatment. Consider a course of oral steroids.	Continue study treatment or hold treatment if symptoms worsen or if there are symptoms of visual disturbance.
	3 Posterior uveitis/ panuveitis or significant symptoms	Refer patient urgently to an ophthalmologist. Initiate oral prednisolone 1-2 mg/kg and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1; reintroduce only after discussion with the study medical monitor.
	4 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.	Hold study treatment; reintroduce only after discussion with the study medical monitor.
	4 Acute abdominal pain, surgical emergency	Admit to hospital for emergency management and appropriate referral.	Discontinue study treatment.
Arthritis	**1** Mild pain with inflammation, swelling	Management per local guideline.	Continue study treatment.
	2 Moderate pain with inflammation, swelling, limited instrumental (fine motor) activities	Management as per local guideline. Consider referring patient to a rheumatologist. If symptoms worsen on treatment manage as a Grade 3 event.	Continue treatment or, if symptoms continue worsens, hold study treatment until symptoms improve to baseline or Grade 0-1.

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.
Mucositis/ stomatitis	**1** Test findings only or minimal symptoms	Consider topical treatment or analgesia as per local guideline.	Continue study treatment.
	2 Moderate pain, reduced oral intake, limited instrumental activities	As per local guidelines, treat with analgesics, topical treatments and oral hygiene care. Ensure adequate hydration. If symptoms worsen or there is sepsis or bleeding, manage as a Grade 3 event.	Continue study treatment.
	3 Severe pain, limited food and fluid intake, daily living activity limited	Admit to hospital for appropriate management. Initiate IV (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when symptoms improved to Grade 2 and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1.
	4 Life-threatening complications or dehydration	Admit to hospital for emergency care. Consider IV corticosteroids if not contraindicated by infection.	Discontinue study treatment.
Myositis/ Rhabdomyolysis	**1** Mild weakness with/without pain	Prescribe analgesics. If CK is significantly elevated and patient has symptoms, consider oral steroids and treat as Grade 2.	Continue study treatment.
	2 Moderate weakness with/without pain	If CK is 3X ULN or worse, initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1.
	3-4 Severe weakness, limiting self-care	Admit to hospital and initiate oral prednisolone 1 mg/kg. Consider bolus IV (methyl)prednisolone and 1-2 mg/kg/day maintenance for severe activity restriction or dysphagia. If symptoms do not improve add immunosuppressant therapy. Taper oral steroids over at least 4 weeks.	Hold study treatment until improved to Grade 0-1. Discontinue if any evidence of myocardial involvement.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Myocarditis	**< 2** Asymptomatic but significantly increased CK-MB or increased troponin OR clinically significant intraventricular conduction delay	Initiate cardiac evaluation under close monitoring with repeat serum testing; consider referral to a cardiologist. If diagnosis of myocarditis is confirmed, treat as Grade 2.	Hold study treatment. If a diagnosis of myocarditis is confirmed, permanently discontinue study treatment in patients with moderate or severe symptoms. Patients with no symptoms or mild symptoms may not restart tislelizumab unless cardiac parameters have returned to baseline and after discussion with the study medical monitor.
	2 Symptoms on mild-moderate exertion	Admit to hospital and initiate oral prednisolone or IV (methyl)prednisolone at 1-2 mg/kg/day. Consult with a cardiologist and manage symptoms of cardiac failure according to local guidelines. If no immediate response change to pulsed doses of (methyl)prednisolone 1g/day and add MMF, infliximab or anti-thymocyte globulin.	
	3 Severe symptoms with mild exertion		
	4 Life-threatening		

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; CHF, congestive heart failure; CK, creatine kinase; CK-MB, creatine kinase cardiac isoenzyme; INR, international normalized ratio; IV, intravenous; LFT, liver function test; MMF, mycophenolate mofetil; N/A, not applicable; NYHA, New York Heart Association; T4, thyroxine; TB, tuberculosis; TFT, thyroid function test; TSH, thyroid-stimulating hormone; U&E, urea and electrolytes; ULN, upper limit of normal.

APPENDIX 8. CHRONIC KIDNEY DISEASE EPIDEMIOLOGY COLLABORATION (CKD-EPI) EQUATION

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

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

GFR = 141 × min (Scr /κ, 1) α × max (Scr /κ, 1)-1.209 × 0.993Age × 1.018 [if female] × 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.

Sites may use a different equation than the one listed above if consistent with local guidance.

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

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

Contraception Guidelines

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

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

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

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

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

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

- Surgically sterile (ie, through bilateral salpingectomy, bilateral oophorectomy, or hysterectomy)
- Postmenopausal, defined as:

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

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

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

APPENDIX 10. 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 11. 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 12. 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

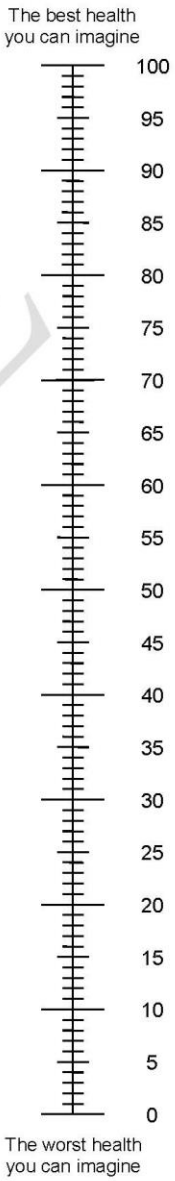
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

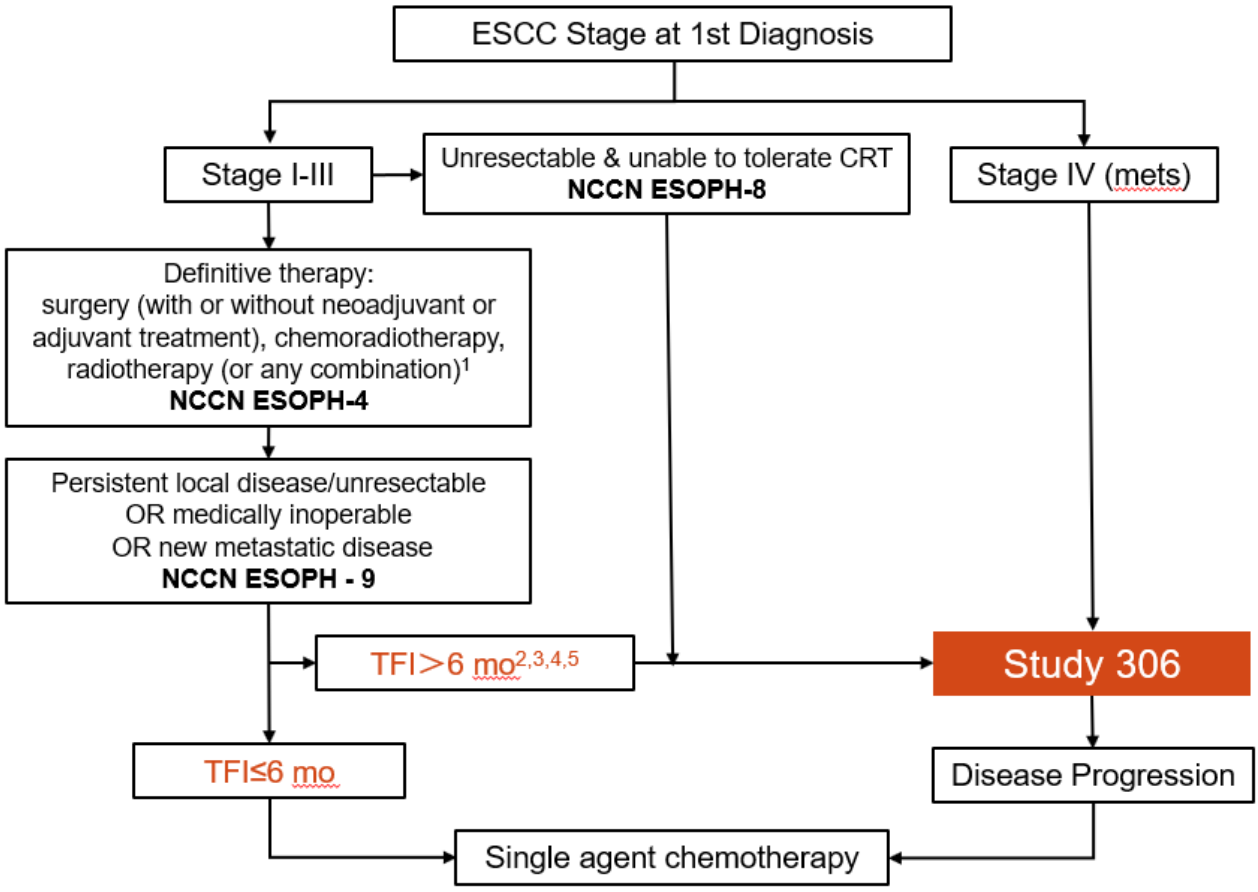
I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- 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 13. FLOW CHART



Abbreviations: ESCC, esophageal squamous cell carcinoma; mets, metastasis; NCCN, National Comprehensive Cancer Network; TFI, treatment-free interval

1. Combinations include any combination of surgery, chemotherapy and radiotherapy.
2. TFI: treatment-free interval. Duration from the last day of prior treatment therapy.
3. Patients who had surgery or radio therapy alone, local chemotherapy (e.g., intrathoracic chemotherapy), or any systemic chemotherapy (neoadjuvant, concurrent, or adjuvant) with a nonplatinum-based regimen (except for paclitaxel monotherapy), even if the TFI was ≤ 6 months, are eligible for platinum-based chemotherapy doublet and are appropriate for this study.
4. Patients who had progression after receiving ≥ 2 definitive therapies are also allowed into this study as long as TFI > 6 mo. Patients with TFI ≤ 6 months with no prior platinum-based chemotherapy are also eligible.
5. The chemotherapy in concurrent chemoradiotherapy is usually deemed as a chemosensitizer. In this case, patients may be enrolled into the study, even if the TFI is ≤ 6 months.

APPENDIX 14. AMERICAN JOINT COMMITTEE ON CANCER TNM CLASSIFICATION OF CARCINOMA OF THE ESOPHAGUS AND ESOPAGOGASTRIC JUNCTION (7TH ED, 2010)

T classification

Tis is redefined and T4 is subclassified

Tis	High-grade dysplasia
T4a	Resectable cancer invades adjacent structures such as pleura, pericardium, diaphragm
T4b	Unresectable cancer invades adjacent structures such as aorta, vertebral body, trachea

N classification

Regional lymph node is redefined

Any periesophageal lymph node from cervical nodes to celiac nodes

N is subclassified

N0	No regional lymph node metastases
N1	1 to 2 positive regional lymph nodes
N2	3 to 6 positive regional lymph nodes
N3	≥7 positive regional lymph nodes

M classification

M is redefined

M0	No distant metastases
M1	Distant metastases

Additions of nonanatomic cancer characteristics

Histopathologic cell type

Adenocarcinoma

Squamous-cell carcinoma

Histologic grade

G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

Cancer location

Upper thoracic	20–25 cm from incisors
Middle thoracic	>25 to 30 cm from incisors
Lower thoracic	>30 to 40 cm from incisors
Esophagogastric junction	Includes cancers whose epicenter is in the distal thoracic esophagus, esophagogastric junction, or within the proximal 5 cm of the stomach (cardia) that extend into the esophagogastric junction or distal thoracic esophagus (Siewert III). These stomach cancers are stage grouped similarly to adenocarcinoma of the esophagus

Squamous-cell carcinoma stage groupings

Stage	T	N	M	G	Location
0	is (HGD)	0	0	1	Any
IA	1	0	0	1	Any
IB	1	0	0	2–3	Any
	2–3	0	0	1	Lower
IIA	2–3	0	0	1	Upper, middle
	2–3	0	0	2–3	Lower
IIB	2–3	0	0	2–3	Upper, middle
	1–2	1	0	Any	Any
IIIA	1–2	2	0	Any	Any
	3	1	0	Any	Any
	4a	0	0	Any	Any
IIIB	3	2	0	Any	Any
IIIC	4a	1–2	0	Any	Any
	4b	Any	0	Any	Any
	Any	N3	0	Any	Any
IV	Any	Any	1	Any	Any

APPENDIX 15. NUTRITIONAL RISK INDEX

Recent weight loss history of the patient may not always be known and the body weight loss does not take the albumin level into consideration, so the Nutritional Risk Index (NRI) is referenced as an alternative per investigator's choice to assess the patient's nutritional status for the purpose of eligibility. The formula is provided below (Shirasu et al 2018):

NRI = (1.489 × serum albumin) + (41.7 × present body weight / ideal body weight)

The Ideal Body Weight (IBW) formula is based on the Peterson formula (Peterson, 2016):

IBW (kg) = 2.2 x Target BMI + [3.5 x Target BMI x (Height (m) - 1.5 m)]. For the purpose of this study, we will use a Target BMI of 22, so the formula becomes:

IBW (kg) = 48.4 + [77 x (Height (m) - 1.5 m)]

Or you can use below online calculator to calculate the IBW, and please choose the calculation results of the Peterson formula:

https://www.gigacalculator.com/calculators/ideal-weight-calculator.php

Signature Page

Approval with eSignature	[redacted] Development 13-Mar-2024 14:18:12 GMT+0000

Approved Date 3/13/2024