CLINICAL STUDY PROTOCOL

Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Clinical Study Comparing the Efficacy and Safety of Tislelizumab (BGB-A317) plus Platinum and Fluoropyrimidine Versus Placebo plus Platinum and Fluoropyrimidine as First-Line Treatment in Patients with Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma
Protocol Identifier:	BGB-A317-305
Phase:	3
Investigational Medicinal Product(s):	Tislelizumab (BGB-A317)
Indication:	Advanced Gastric or Gastroesophageal Junction Adenocarcinoma
EudraCT Number:	2018-000312-24
Sponsor:	BeiGene, Ltd. c/o BeiGene USA, Inc. 1840 Gateway Drive, 3rd Floor San Mateo, California 94404, USA
Sponsor Medical Monitor:	[redacted]
Original Date:	12 February 2018
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NCT Number:	NCT03777657

FINAL PROTOCOL APPROVAL SHEET

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Clinical Study Comparing the Efficacy and Safety of Tislelizumab (BGB-A317) plus Platinum and Fluoropyrimidine Versus Placebo plus Platinum and Fluoropyrimidine as First-Line Treatment in Patients with Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma

BeiGene, Ltd. Approval:

[redacted]

INVESTIGATOR SIGNATURE PAGE

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Clinical Study Comparing the Efficacy and Safety of Tislelizumab (BGB-A317) plus Platinum and Fluoropyrimidine Versus Placebo plus Platinum and Fluoropyrimidine as First-Line Treatment in Patients with Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma

Protocol Identifier: BGB-A317-305

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 Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd or one of its affiliates.

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

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

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

_____

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SYNOPSIS

Name of Sponsor/Company: BeiGene, Ltd.

Investigational Medicinal Product: Tislelizumab

Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Clinical Study Comparing the Efficacy and Safety of Tislelizumab (BGB-A317) plus Platinum and Fluoropyrimidine Versus Placebo plus Platinum and Fluoropyrimidine as First-Line Treatment in Patients with Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma

Protocol Identifier: BGB-A317-305

Phase of Development: 3

Number of Patients: Approximately 980

Study Centers: Approximately 180 centers globally

Study Objectives:

Primary:

- To compare overall survival of tislelizumab plus chemotherapy versus placebo plus chemotherapy in the programmed cell death protein ligand-1 positive (PD-L1+) and intent-to-treat analysis sets

Secondary:

- To compare progression-free survival per Response Evaluation Criteria in Solid Tumors 1.1 as assessed by investigators of tislelizumab plus chemotherapy versus placebo plus chemotherapy in the programmed cell death protein ligand-1 positive and intent-to-treat analysis sets
- To evaluate overall response rate, and duration of response, per Response Evaluation Criteria in Solid Tumors 1.1 as assessed by investigators
- To evaluate European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Gastric Cancer Module QLQ-STO22 Score, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 Score, and European Quality of Life 5-Dimensions 5-Levels Health Questionnaire Score
- To evaluate the safety and tolerability profile of tislelizumab or placebo plus chemotherapy
- To evaluate disease control rate, clinical benefit rate, and time to response per Response Evaluation Criteria in Solid Tumors 1.1 as assessed by investigators

Exploratory:

- To evaluate progression-free survival after next line of treatment (PFS2)
- To characterize the pharmacokinetics of tislelizumab
- To determine host immunogenicity to tislelizumab

- To assess predictive, prognostic, exploratory biomarkers including but not limited to programmed cell death protein ligand-1 (PD-L1) expression, Epstein-Barr virus (EBV) infection, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) status, genomically stable (GS) or chromosomal instability (CIN), immune-related gene expression profiling, tumor infiltrated lymphocytes (TILs) and tumor mutation burden in tumor tissues and/or blood samples and the association with response to study treatment, mechanisms of resistance, and/or disease status

Study Endpoints:

Primary:

- Overall survival – defined as the time from the date of randomization to the date of death due to any cause

Secondary:

- Progression-free survival as assessed by investigators – defined as the time from the date of randomization to the date of the first objectively documented tumor progression, assessed by investigators per Response Evaluation Criteria in Solid Tumors v1.1, or death, whichever occurs first
- Overall response rate as assessed by investigators – defined as the proportion of patients whose best overall response is complete response or partial response per Response Evaluation Criteria in Solid Tumors v1.1
- Duration of response as assessed by investigators – defined as the time from the first determination of an objective response per Response Evaluation Criteria in Solid Tumors v1.1, until the first documentation of progression or death, whichever occurs first
- Change from baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Gastric Cancer Module QLQ-STO22 Score and change from baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 Score and European Quality of Life 5-Dimensions 5-Levels Health Questionnaire Score
- The incidence and severity of adverse events according to National Cancer Institute Common Terminology Criteria for Adverse Events v5.0
- Disease control rate (ie, proportion of complete response + partial response + stable disease), clinical benefit rate (ie, proportion of complete response + partial response + durable stable disease), and time to response (ie, time from randomization to the first determination of an objective response) per Response Evaluation Criteria in Solid Tumors 1.1 as assessed by investigators

Exploratory:

- Progression-free survival after next line of treatment (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
- Summary of serum concentration of tislelizumab
- Assessments of immunogenicity of tislelizumab by determining the incidence of antidrug antibodies
- Status of programmed cell death protein ligand-1 (PD-L1) expression, immune or

gastric-related, and other exploratory biomarkers including but not limited to Epstein-Barr virus (EBV) infection, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), genomically stable (GS) or chromosomal instability (CIN), immune-related gene expression profiling, tumor infiltrated lymphocytes (TILs) and tumor mutation burden in tumor tissues and/or blood samples obtained before treatment with tislelizumab and/or at progression, and the association with disease status and/or response to tislelizumab in combination with chemotherapy or chemotherapy alone

Study Design:

This is a randomized (1:1), double-blind, placebo-controlled, Phase 3 study designed to compare the efficacy and safety of tislelizumab or placebo plus chemotherapy as first-line (1L) therapy for locally advanced unresectable or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma.

After providing written informed consent, completing all screening assessments, and being confirmed as eligible for study participation, approximately 980 patients will be randomized 1:1 to receive either tislelizumab plus chemotherapy or placebo plus chemotherapy.

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

- Regions of enrollment: China (including Taiwan) vs. Japan and S. Korea vs. US and Europe and other regions. NOTE: other regions include other western countries/populations.
- Programmed cell death protein ligand-1 (PD-L1) expression (positive or negative): PD-L1+ patients are patients with tumor and immune cell score (TIC score) ≥ 5% using VENTANA PD-L1 (SP263) Cdx Assay*. TIC score is the total percentage of the tumor area covered by tumor cells with PD-L1 membrane staining and tumor-associated immune cells with PD-L1 staining at any intensity.
- *During enrollment, the proportion of patients of multiple PD-L1 expression levels will be monitored. Hence, study assumptions could be adjusted accordingly if it is deemed appropriate.
- Presence of peritoneal metastasis (yes or no)
- Investigator's choice of chemotherapy (oxaliplatin + capecitabine versus cisplatin + 5-fluorouracil [5-FU])

After randomization, patients will be treated on the following arms. Cross-over between the treatment arms will not be allowed.

- Arm A: Tislelizumab 200 mg intravenously once every 3 weeks (Q3W) + chemotherapy
- Arm B: Placebo intravenously Q3W + chemotherapy

Oxaliplatin + capecitabine or cisplatin + 5-FU regimens are used as the backbone chemotherapy. The chemotherapy backbone regimen needs to be decided on an individual patient basis before randomization. There is no switching between regimens throughout the entire course of the study.

Oxaliplatin + Capecitabine	**Day 1:** Oxaliplatin 130 mg/m² intravenously **Day 1 (evening) – Day 15 (morning) or Day 1 (morning) – Day 14 (evening):** capecitabine 1000 mg/m^2 orally twice daily Every 3 weeks as a cycle
Cisplatin + 5-FU	**Day 1:** Cisplatin 80 mg/m² IV **Days 1–5:** 5-FU 800 mg/m^2/day intravenous continuous infusion over 24 hours daily Every 3 weeks as a cycle

The oxaliplatin + capecitabine or cisplatin + 5-FU doublet regimen is administered up to 6 cycles. Capecitabine as maintenance therapy is optional only for those patients who received capecitabine and oxaliplatin and may be administered until disease progression, intolerable toxicity, withdrawal of consent, or another treatment discontinuation criterion is met. Tislelizumab (or placebo) will be administered until disease progression, intolerable toxicity, withdrawal of consent, or another treatment discontinuation criterion is met. Treatment beyond initial investigator-assessed Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 defined progression will be permitted provided that the patient has investigator-assessed clinical benefit and is tolerating study drug. The following criteria must be met to treat patients after initial evidence of radiological disease progression: absence of clinical symptoms and signs of disease progression; stable Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤ 1; absence of rapid progression of disease or progressive tumor at critical anatomical sites that require urgent alternative medical intervention; and additional written informed consent. The medical monitor must agree, in writing, with the investigator's decision to continue study drugs beyond initial investigator-assessed progression, and the decision must be documented in the study records.

Study Assessments:

Tumor assessments will be performed by investigator using RECIST v1.1 criteria (Eisenhauer EA 2009). Tumor imaging (computed tomography [CT] with or without contrast or magnetic resonance imaging [MRI]) must be performed within 28 days prior to randomization. On-study tumor assessments will occur every 6 weeks (± 7 days) during the first 48 weeks and every 9 weeks (± 7 days) thereafter until disease progression. If a patient discontinues study treatment due to any reasons other than disease progression, tumor assessments will continue to be performed as scheduled until disease progression, loss to follow up, withdrawal of consent, death, or until the study terminates, whichever occurs first.

Patient reported outcomes will be collected using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Gastric Cancer Module QLQ-STO22 (EORTC QLQ-STO22), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), and European Quality of Life 5-Dimensions 5-Levels Health Questionnaire (EQ-5D-5L) at screening or baseline, at every cycle through Cycle 6, then every other cycle thereafter until progressive disease (PD), and at the End of Treatment Visit.

Patients will be evaluated for any adverse events (AEs) and serious adverse events (SAEs) occurring up to 30 days after the last dose of study drug (all severity grades), per National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] v5.0 or until initiation of new anticancer therapy, whichever occurs first, and for immune-mediated AEs (imAEs) occurring up to 90 days after the last dose of tislelizumab or placebo regardless of whether or not the patient starts a new anticancer therapy. All SAEs considered related to the study drug(s) that are brought to the attention of the investigator should be reported regardless of time since the last dose of treatment until patient death, withdrawal of consent, or loss to follow-up, whichever occurs first. All study drug-related SAEs will be followed until they resolve to baseline or ≤ Grade 1, the investigator assesses the AE as stable and unlikely to improve, or the patient is lost to follow-up, whichever occurs first.

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

Duration of Patient Participation:

Approximately 48 months duration of study

Study Population:

Patients with locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma, and no prior systemic therapy for advanced disease.

Key Eligibility Criteria:

Adult patients (≥ 18 years of age or acceptable age according to local regulations, whichever is older) at the time of voluntarily signing informed consent with histologically confirmed diagnosis of gastric or GEJ adenocarcinoma who have not received previous systemic therapy for locally advanced unresectable or metastatic gastric/GEJ cancer. All patients are also required to have ≥ 1 measurable or non-measurable lesion per RECIST v1.1, an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of ≤ 1, and adequate organ function.

Investigational Medicinal Product, Dose, and Mode of Administration:

Tislelizumab will be administered at a dose of 200 mg intravenously on Day 1, given every 3 weeks.

Reference Therapy, Dose, and Mode of Administration:

Please refer to Study Design above.

Statistical Methods:

Overall survival (OS) within the 2 primary analysis sets (ie, PD L1+ and intent-to-treat [ITT]) of the study are 2 primary endpoints of the study. The type I error is strongly controlled at 0.025 in the 2 primary hypotheses. A hierarchical testing procedure will be adopted in this study and the OS analysis in ITT analysis set will be performed only if the OS analysis in the PD-L1+ analysis set is statistically significant favoring tislelizumab + chemotherapies.

Hypothesis testing of PFS in the PD-L1+ and ITT analysis sets will be performed at the same time as the interim analysis of OS if OS analyses are significant in both PD-L1+ and ITT analysis sets. Only when the superiority of both PFS and ORR in PD-L1+ are demonstrated, its alpha will be shifted to the hypothesis testing of the secondary endpoints PFS, overall response rate (ORR) in the ITT analysis set. The inferential test will be stopped at the first non-significant endpoint. Nominal p-values may be computed for other efficacy analysis but should be interpreted with caution.

Analysis Sets:

- ITT analysis set – Includes all randomized patients. Patients will be analyzed according to their randomized treatment arm. This will be the dual primary analysis set for efficacy analyses.
- PD-L1+ analysis set (≥ 5% of area with PD-L1 staining cells [including tumor cells and tumor-associated immune cells]/total tumor area) – Includes all randomized patients whose tumors were PD-L1+. Patients will be analyzed according to their randomized treatment arms. This will be the dual primary analysis set for efficacy analyses.
- Per-Protocol (PP) analysis set – Includes all randomized patients who received at least 1 dose of the assigned study drug and had no major protocol deviations. Major protocol deviations will be determined and documented before the database lock for the primary analyses.
- Safety analysis set – Includes all patients who received at least 1 dose of study drugs. This will be the analysis set for the safety analyses.

Primary Efficacy Endpoint Analysis:

OS in the PD-L1+ 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 once the targeted number of death events is 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 cutoff, whichever comes earlier.

OS will be compared between Arm A and Arm B using stratified log-rank test at 1-sided 0.025 level of significance stratified by pooled stratification factors of regions of enrollment (east Asia versus rest of the world [ROW]) and presence of peritoneal metastasis.

The median OS and the cumulative probability of OS at every 6 months 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 12 and 24 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 factor and region of enrollment (east Asia versus ROW) and presence of peritoneal metastasis as strata. From this model, the hazard ratio (HR) of OS will be estimated and presented with a 2-sided 95% CI.

These analyses will be performed in the PD-L1+ analysis set as the primary analysis. Outcomes in the Per Protocol analysis set will be evaluated as a sensitivity analysis.

OS in the ITT analysis set:

Analysis of OS in the ITT analysis set will be performed only if superiority of OS favoring tislelizumab + chemotherapy is demonstrated in the PD-L1+ analysis set. The hypothesis testing of OS in the ITT analysis set will be carried out similarly at a significance level of 0.025 (1-sided in the stratified analysis [ie log-rank and Cox regression]), stratified by pooled stratification factors of regions of enrollment (east Asia versus ROW), PD-L1 expression and presence of peritoneal metastasis.

There will be one interim analysis of OS using the O'Brien-Fleming boundary approximated by Hwang-Shih-DeCani spending function with the gamma parameter set at -4. The non-binding lower (futility) boundary is defined by Hwang-Shih-DeCani spending function with the gamma parameter set at -12. The interim analysis of OS will be performed when approximately 269 deaths in the PD-L1+ analysis set and 538 deaths in the ITT analysis set (70% of the target number of OS events in each analysis set) among the 2 treatment arms have been observed which is estimated to occur approximately 30 months after the first patient is randomized. The final analysis of OS will take place after approximately 384 and 768 death events have been observed in the 2 analysis sets, respectively, which is estimated as 48 months after the first patient is randomized. Stopping boundaries in p-value and Z score for primary analyses of OS are shown in Table a. The boundaries will be updated according to the actual numbers of events in the interim and final analyses, using the above pre-specified alpha spending function.

Table a: Stopping Boundaries (in p-value and Z score) of Primary Analysis of OS

Analysis Set	Analysis	Time (m)	# Events	p-value [a] (Z score) for Efficacy	p-value [a] (Z score) for Interim Futility	Approximate HR Threshold	Cumulative Prob of Crossing Under H_1
PD-L1+[b]	Interim analysis	30	269	< 0.0072 (> 2.45)	> 0.5731 (< -0.18)	0.742	0.47
	Final analysis	48	384	< 0.0228 (> 2.00)	-	0.815	0.80
ITT	Interim analysis	30	538	< 0.0072 (> 2.45)	> 0.5384 (<-0.1)	0.810	0.56
	Final analysis	48	768	< 0.0228 (> 2.00)	-	0.866	0.87

a: 1-sided, b: PD-L1+ is 50% of the ITT

Secondary Efficacy Endpoint Analyses:

The distribution of PFS as determined by investigators will be estimated using the Kaplan-Meier (KM) method; the median PFS along with 95% confidence intervals (CIs) will be presented by treatment arm; the comparison of the distribution of PFS between treatment groups will be performed using a stratified log-rank test; A Cox regression stratified by the factors same as the ones used in the OS analyses will be used to estimate the hazard ratio (HR) of PFS, along with 95% CI.

The null hypotheses of no difference in ORR per RECIST 1.1 assessed by investigators will be tested in a Cochran-Mantel-Haenszel (CMH) test adjusting for pooled stratification factors in the ITT and PD-L1+ analysis sets. 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, as well as Clopper-Pearson 95% CIs of ORR for each treatment arm.

Duration of response (DOR) assessed by investigators will be analyzed similarly to PFS in the responders.

Change from baseline of EORTC QLQ-STO22, EORTC QLQ-C30, and EQ-5D-5L will be compared between Arms A and B.

Both EORTC scales and single items will be scored on a categorical scale and transformed to a 0-100 scale. In addition to change from baseline scores, minimal important differences defined as 10-point change from baseline will be used to calculate the proportion of patients with clinically meaningful deterioration over time. Descriptive statistics will be used to show the changes from baseline and percentage of patients with deterioration at each time point in each arm, unless otherwise specified.

Best overall response (BOR) is defined as the best response per RECIST v1.1 recorded from randomization till data cut, progressive disease or start of new anticancer treatment. The proportion and its corresponding Clopper-Pearson 95% CI for each of the response categories (complete response [CR], partial response [PR], stable disease [SD] and PD) will be presented by treatment arm. Time to response will be summarized using descriptive statistics, such as mean, median, and standard deviation. Only patients who have achieved an objective response will be included in the analysis of time to response.

Disease control rate (DCR) and clinical benefit rate (CBR) assessed by investigators will be analyzed similarly to ORR in the ITT and PD-L1+ analysis sets.

Exploratory Efficacy Analyses:

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 (KM) method as described in the PFS and OS analyses will be used in the analysis of PFS2.

Safety Analyses:

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 v5.0. 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 and up to 30 days following study drug discontinuation or initiation of new anticancer 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 or not the patient starts a new anticancer therapy. SAEs, deaths, TEAEs with Grade 3 or above, treatment-related TEAEs, TEAEs that led to treatment discontinuation, dose reduction, dose interruption or dose delay, and imAEs will be summarized.

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

Pharmacokinetic Analysis:

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

Tislelizumab serum concentration data, including but not limited to trough serum concentration (C_{trough}), will be tabulated and summarized by visit/cycle at which these concentrations are collected. Descriptive statistics will include means, medians, ranges, and standard deviations, as appropriate. Additional PK analyses may be conducted, as appropriate. Exposure-response (efficacy or safety endpoints) analysis may be carried out if supported by data.

Immunogenicity Analysis:

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

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

Sample Size Considerations:

The sample size calculation is based on the primary efficacy analyses of OS in the comparison between Arms A and B in the PD-L1+ and ITT analysis sets. The number of events needed is based on the assumption of an exponential distribution. The 1-sided overall type I error in the study is set at 0.025. Table b summarizes the statistical assumption and power in the sample size calculation. Assuming a 50% PD-L1+ prevalence rate, a total of 928 patients including approximately 464 (ie, 50%) in the PD-L1+ subset will be enrolled in a 1:1 randomization to observe targeted OS events at the defined time periods as shown in Table a. Assuming a roughly 5% dropout rate, approximately 980 patients will be enrolled over 24 months at enrollment rates of 17 patients/month in the first 2 months, 34 patients/month in the next 2 months, and 44 patients/month in the last 20 months. The enrollment assumptions, including percentage of PD-L1+ patients, will be monitored during the enrollment; therefore, the sample size and timeline could be adjusted accordingly. Enrollment of patients whose tumors are PD-L1- might be stopped if necessary, to ensure that the percentage of PD-L1+ is no less than 50% of the ITT analysis set. The primary analyses will be performed when the target number of

events is observed. An interim analysis of OS (see Table a) is planned after approximately 70% of the total planned death events have occurred in both ITT and PD-L1+ analysis sets.

Table b: Hazard ratio and median OS assumption, number of events, alpha and power in the primary hypothesis tests

Analysis Set	HR	Median in Arm A (in months)	Median in Arm B (in months)	# Events	Alpha	Power
PD-L1+	0.75	15.3	11.5	384	0.025	80%
ITT	0.8	14.4	11.5	768	0.025	87%

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
ADA	antidrug antibody
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma or serum concentration-time curve
CI	confidence interval
C_{max}	maximum observed plasma concentration
CPS	combined positive score
CR	complete response
CT	computed tomography
C_{trough}	trough serum concentration
DCR	disease control rate
dMMR	mismatch repair deficient
DOR	duration of response
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
ESMO	European Society for Medical Oncology
EORTC QLQ-STO22	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Gastric Cancer Module QLQ-STO22
EOT	end of treatment
EQ-5D-5L	European Quality of Life 5-Dimensions 5-Levels Health Questionnaire
Fc	fragment crystallizable region (typically, of immunoglobulin G)
FcγR	gamma Fc receptor (eg, Fcγ-RI, Fcγ-RIII)
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FFPE	Formalin-fixed paraffin-embedded
GC	Gastric cancer
GEJ	gastroesophageal junction

Abbreviation	Definition
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
ICF	informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IgG	immunoglobulin G (eg, IgG1, IgG2, IgG3, IgG4); other types of immunoglobulins include IgD and IgM
INR	international normalized ratio
imAE	immune-mediated adverse event
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-treat
K_D	dissociation constant
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MSI	microsatellite instability-high
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	overall response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein-1
PD-L1	programmed cell death protein ligand-1
PD-L2	programmed cell death protein ligand-2
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
Q3W	once every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
ROW	Rest of the world

Abbreviation	Definition
SAE	serious adverse event
SD	stable disease
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
Tislelizumab	BGB-A317
TTR	time to response
ULN	upper limit of normal
V_d	volume of distribution
1L	first-line
5-FU	5-fluorouracil

1. INTRODUCTION

1.1. Advanced and Metastatic Gastric Cancer

There were an estimated 17.5 million cancer cases and 8.7 million cancer deaths in 2015 worldwide. Gastric cancer (GC) alone contributed about 1.3 million cases with 800,000 deaths. It is the fifth most common cancer worldwide and the second leading cause of cancer death together with colorectal and liver cancer (Global Burden of Disease Cancer Collaboration 2017). More than half of gastric cancer cases and deaths are estimated to occur in China, with approximately 680,000 cases and approximately 500,000 deaths in 2015 (Chen et al 2016a). Predicted GC deaths for the European Union in 2017 are approximately 55,000 (Malvezzi et al 2017). For the United States (US), estimates for GC in 2017 are approximately 28,000 cases with 11,000 deaths (Stomach Cancer: Statistics 2017).

Adenocarcinoma is the major histologic subtype representing approximately 90% of GC (Smyth et al 2016). About two-thirds are true GCs (non-cardia) and the remainder are gastroesophageal junction (GEJ) cancers (cardia) (Colquhoun et al 2015). The most common anatomical subsites differ in world regions due to differences in risk factors. Distal and antral GCs are more common in East Asia and tumors of the proximal stomach or GEJ are more common in non-Asian countries (Forman and Burley 2006; World Cancer Research Fund International/American Institute for Cancer Research 2017).

Patients with newly diagnosed, inoperable, locally advanced or metastatic disease generally receive chemotherapy regimens containing a platinum and a fluoropyrimidine (Smyth et al 2016; NCCN 2017). Triplet regimens may provide additional clinical benefit, as suggested in a meta-analysis for the addition of an anthracycline (Okines et al 2009). Because of their added toxicities, however, they have not been uniformly adopted and are recommended only for medically fit patients with good performance status and access to frequent toxicity evaluations. Response rates for first-line (1L) chemotherapy regimens are around 30% to 50% with median progression-free survival (PFS) ranging from 5 to 7 months. Median overall survival (OS) is less than 12 months, and less than 10% of patients are still alive after 5 years (Chau et al 2004; Cunningham et al 2008; Kang et al 2009; Van Cutsem et al 2006; Wagner et al 2006). Approximately 12% to 20% of gastric adenocarcinomas are HER2-positive (Van Cutsem et al 2015). For these patients, a unique treatment paradigm has been established that combines 1L platinum- and fluoropyrimidine-based chemotherapy with the anti-HER2 antibody trastuzumab (Bang et al 2010). The reference chemotherapy regimen for 1L treatment of HER2 negative metastatic gastric and GEJ adenocarcinoma is a fluoropyrimidine (5-fluorouracil [5-FU] or capecitabine) in combination with a platinum.

1.2. Immunotherapy of Gastric Cancer

The presence of tumor infiltrating lymphocytes (TILs) has been associated with an improved prognosis for different tumor types, including GC (Fridman 2012). On the contrary, high programmed cell death protein ligand-1 (PD-L1) expression plays a leading role as immune inhibitory mechanism and has been identified as a negative prognostic marker in GC (Zheng et al 2014). Nevertheless, more studies are needed to improve the understanding of the prognostic role of PD-L1 expression and immune cell activity. Interesting recent data from a small cohort of resected GCs showed that patients with higher CD8+ T-cell density have higher PD-L1

expression and worse outcome (Thompson et al 2016). Categorization of tumor according to the mechanism of immune-surveillance escape includes type I (high PD-L1 with TILs driving adaptive immune resistance), type II (low PD-L1 with no TIL, indicating immune ignorance), type III (high PD-L1 with no TIL, indicating intrinsic induction), and type IV (low PD-L1 with TIL, indicating the role of other suppressor(s) in promoting immune tolerance). While the predictive role of PD-L1 expression is still controversial in the clinic, the tumor stratification based on the presence of T cells and PD-L1 might be a promising predictive tool to define optimal therapy for patients with advanced cancer (Teng et al 2015). Indeed, interest in characteristics of tumor environment is not only in prognostic terms but also in predicting response to immune checkpoint inhibition. In GC, it seems that infiltration of CD8+ T-cells is associated with high expression of PD-L1 (adaptive immune resistance type mechanism), suggesting potential efficacy of anti-PD-1/PD-L1. Of note, CTLA-4 is only expressed by a small subset of patients with GC, whereas programmed cell death protein-1 (PD-1) as well as PD-L1 are expressed by approximately 50% of tumor-infiltrating lymphocytes (Schlößer et al 2016).

1.2.1. Pembrolizumab

Pembrolizumab is a selective humanized monoclonal antibody that was designed to directly block the interaction between PD-1 and PD-L1 or programmed cell death protein ligand-2 (PD-L2). The safety and efficacy of pembrolizumab alone or in combination with chemotherapy in patients with GCs have been evaluated in the following studies.

KEYNOTE-012 study (ClinicalTrials.gov ID: NCT01848834) is a multicenter open-label Phase 1b study, in which pembrolizumab was administered to patients with advanced GC, urothelial cancer, triple-negative breast cancer, and head and neck cancer, have recently become available. To be eligible, patients needed at least 1% PD-L1 expression in tumor cells, immune cells, or both cell types. Thirty-nine patients were enrolled in the GC Cohort. In this cohort, partial responses (PRs) were observed in 22% of cases (according to central review) and disease stabilization in 14% (according to central review). Of note, median overall survival (OS) was 11 months in a population in which most of the patients had received 2 or more previous lines of therapy. The overall response rate (ORR) was very similar across the countries, regardless of the Asian ethnicity (ORR 24% in Asian patients and 21% in non-Asian patients) (Muro et al 2016).

KEYNOTE-059 study (ClinicalTrials.gov ID: NCT02335411) is a Phase 2 study evaluating the efficacy and safety of pembrolizumab alone or in combination with chemotherapy in patients with advanced GC and GEJ cancer (Wainberg et al 2017). In Cohort 1 of this study, patients with ≥ 2 prior lines of chemotherapy were treated with pembrolizumab (200 mg once every 3 weeks [Q3W]). The preliminary efficacy data for Cohort 1 are summarized in Table 1.

Based on the efficacy (tumor response rate and durability of response) and safety data from this cohort, the FDA (Food and Drug Administration) has approved pembrolizumab for the treatment of patients with PD-L1+ recurrent or advanced gastric or GEJ adenocarcinoma who have received 2 or more lines of chemotherapy, including fluoropyrimidine- and platinum-containing chemotherapy, and, if appropriate, HER2/neu-targeted therapy.

In Cohort 3 of KEYNOTE-059 (ClinicalTrials.gov ID: NCT02335411), PD-L1+ patients without prior therapy were treated with pembrolizumab alone. The preliminary efficacy data for Cohort 3 are also summarized in Table 1.

Table 1: KEYNOTE-059 Study Cohort 1 and Cohort 3: Pembrolizumab Alone

Parameter	Cohort 1 (≥ 2L prior treatment)			Cohort 3 (1L GC)
–	All patients (n=259)	PD-L1+ (n=148)	PD-L1- (n=109)	PD-L1+ (n=31)
ORR (95% CI), %	12 (8-17)	16 (11-23)	6 (3-13)	26 (12-45)
mPFS (95% CI), mo	2.0 (2.0-2.1)	2.1 (2.0-2.1)	2.0 (1.9-2.0)	3.3 (2.0-6.0)
6-mo PFS Rate	14.6%	18.2%	9.9%	34.9%
mOS (95% CI)	5.5 (4.2-6.5)	5.8 (4.4-7.8)	4.6 (3.2-6.5)	20.7 (9.2-20.7)
6-mo OS Rate	45.7%	48.4%	42.9%	72.9%

In Cohort 2 of KEYNOTE-059, patients without any prior therapy was treated with pembrolizumab in combination with chemotherapy (cisplatin + 5-FU or capecitabine, Q3W). The preliminary efficacy data are summarized in Table 2.

Table 2: KEYNOTE-059 Study Cohort 2

Parameter	All patients (n=25)	PD-L1+ (n=16)	PD-L1- (n=8)
ORR (95% CI), %	60 (39-79)	69 (41-89)	38 (9-76)
mPFS (95% CI), mo	6.6 (5.9-10.6)	-	-
6-mo PFS Rate	68.0%	-	-
mOS (95% CI)	13.8 (8.6-NR)	-	-
6-mo OS Rate	76.0%	-	-

Two Phase 3 studies (KEYNOTE-062 [ClinicalTrials.gov ID: NCT02494583] and KEYNOTE-063 [ClinicalTrials.gov ID: NCT03019588]) (www.clinicaltrials.gov) are on-going to evaluate pembrolizumab alone or in combination with chemotherapy in patients with PD-L1(+) GC in various geographic regions.

KEYNOTE-061 is a randomized, open-label, Phase 3 study to compare pembrolizumab with paclitaxel as second-line treatment in patients with advanced GC or GEJC that progressed on 1L chemotherapy with a platinum and fluoropyrimidine. Eligible patients were randomized (1:1) in blocks of 4 per stratum to receive either pembrolizumab 200 mg every 3 weeks for up to 2 years or standard-dose paclitaxel. As of Oct 26, 2017, 326 patients in the population with combined positive score (CPS) of 1 or higher had died (151 [77%] of 196 patients in the pembrolizumab group and 175 [88%] of 199 patients in the paclitaxel group). Median overall survival was 9.1 months (95% confidence interval [CI] 6.2-10.7) with pembrolizumab and 8.3 months (7.6-9.0) with paclitaxel (hazard ratio [HR] 0.82, 95% CI 0.66-1.03; 1-sided p=0.0421). Median progression-free survival was 1.5 months (95% CI 1.4-2.0) with pembrolizumab and 4.1 months (3.1-4.2) with paclitaxel (HR 1.27, 95% CI 1.03-1.57). In the total population, Grade 3-5 treatment-related adverse events (AEs) occurred in 42 (14%) of the 294 patients treated with pembrolizumab and 96 (35%) of the 276 patients treated with paclitaxel. In summary, Pembrolizumab did not significantly improve overall survival compared with paclitaxel as

second-line therapy for advanced gastric or gastro-esophageal junction cancer with PD-L1 CPS of 1 or higher. Pembrolizumab had a better safety profile than paclitaxel. However, protocol-specified and post-hoc exploratory subgroup analyses suggest that the treatment effect of pembrolizumab might be more pronounced in patients with a better performance status, greater levels of PD-L1 expression (CPS ≥ 10, HR = 0.64), and tumors with high levels of microsatellite instability. These data support further exploration to identify patients who are likely to benefit from pembrolizumab monotherapy and the ongoing development of pembrolizumab as part of combination therapy regimens (Shitara et al 2018).

KEYNOTE-062 is a randomized, active-controlled, partially blinded, phase 3, 1L treatment study patients with advanced GC or GEJC. Eligible patients were randomized (1:1:1) to pembrolizumab 200 mg every 3 weeks for up to 2 years, or pembrolizumab + chemotherapy (cisplatin 80 mg/m^2 once every 3 weeks + 5-FU 800 mg/m^2 on Day 1 to Day 5 of each cycle), or placebo once every 3 weeks + chemotherapy (cisplatin + 5-FU); 5-FU may be replaced by capecitabine 1000 mg/m^2 twice a day on Day 1 to Day14 of each cycle per local guideline. As of cutoff date 26 March 2019, 763 patients (281 patients with CPS ≥ 10) were randomized to receive pembrolizumab + chemotherapy (257 patients), pembrolizumab (256 patients), or placebo + chemotherapy (250 patients). Median follow-up was 11.3 months. Pembrolizumab prolonged OS in CPS ≥ 10 compared with chemotherapy (median 17.4 versus 10.8 months; HR 0.69; 95% CI 0.49-0.97). Pembrolizumab + chemotherapy was not superior to chemotherapy for OS (12.5 versus 11.1 months; HR 0.85; 95% CI 0.70-1.03) and PFS (6.9 versus 6.4 months; HR 0.84; 95% CI 0.70-1.02) in CPS ≥ 1 or OS (12.3 versus 10.8 months; HR 0.85; 95% CI 0.62-1.17) in CPS ≥ 10. ORR was higher in pembrolizumab + chemotherapy group than placebo + chemotherapy group in CPS ≥ 1 (48.6% versus 37.2%) and CPS ≥ 10 (52.5% versus 37.8%). Grade 3-5 drug-related AE rates were 17% in pembrolizumab group, 73% in pembrolizumab + chemotherapy group, and 69% in placebo + chemotherapy group. These data support further exploration to identify patients who are likely to benefit from pembrolizumab + chemotherapy (Shitara et al 2019).

1.2.2. Nivolumab

Nivolumab is a fully human immunoglobulin (Ig) G4 monoclonal antibody directed against the negative immunoregulatory human cell surface receptor programmed death-1 (PD-1). The safety and efficacy of nivolumab alone or in combination with chemotherapy in patients with GC have been evaluated in the following studies.

CheckMate-032 evaluated the efficacy and safety of nivolumab in patients with advanced chemotherapy-refractory esophago-gastric cancer according to microsatellite instability status (Ott et al 2017). The preliminary efficacy results are summarized in Table 3. The authors concluded that nivolumab alone demonstrated clinical activity in chemotherapy-refractory patients. Numerically higher response rates were observed in microsatellite instability-high patients.

Table 3: CheckMate-032: Nivolumab Alone

	All patients (n=59)	**MSI-H (n=7)**	**Non-MSI-H (n=18)**	**MSI-U (n=34)**
ORR (95% CI), %	12 (5-23)	29 (4-71)	11 (1-35)	9 (2-24)

mOS (95% CI)	6.2 (3.4-12.4)	15 (2-NE)	6 (3-12)	5 (3-16)
12-mo OS Rate	39%	57% (17-84)	33 (14-55)	39 (22-56)

ATTRACTION-2 is a randomized, double-blind, placebo-controlled, Phase 3 study conducted in Japan, South Korea, and Taiwan to evaluate safety and efficacy of nivolumab in patients with advanced gastric or gastro-esophageal junction cancer refractory to, or intolerant of, at least 2 previous chemotherapy regimens (ONO-4538-12) (Kang et al 2017a). The study met its primary endpoint: median OS was 5.26 months (95% CI 4.60–6.37) in the nivolumab group and 4.14 months (3.42–4.86) in the placebo group (hazard ratio 0.63, 95% confidence interval [CI] 0.51–0.78; $p < 0.0001$). Twelve-month OS rates were 26.2% (95% CI 20.7–32.0) with nivolumab and 10.9% (6.2–17.0) with placebo. No new safety signals were observed.

Checkmate 649 (ClinicalTrials.gov ID: NCT02872116) (www.clinicaltrials.gov) is a randomized, multicenter, open-label, Phase 3 study of nivolumab plus ipilimumab or nivolumab in combination with oxaliplatin plus fluoropyrimidine versus oxaliplatin plus fluoropyrimidine in patients with previously untreated advanced or metastatic gastric (G) or GEJ cancer. In this study, of 2687 patients assessed for eligibility, 1581 patients are randomized to treatment (nivolumab plus chemotherapy [n = 789, 50%] or chemotherapy alone [n = 792, 50%]). The median follow-up for OS was 13.1 months (interquartile range [IQR]: 6.7 to 19.1) for nivolumab plus chemotherapy and 11.1 months (IQR: 5.8 to 16.1) for chemotherapy alone. Nivolumab plus chemotherapy resulted in significant improvements in OS (hazard ratio [HR]: 0.71 [98.4% CI: 0.59 to 0.86]; $p < 0.0001$) and PFS (HR: 0.68 [98 % CI: 0.56 to 0.81]; $p < 0.0001$) versus chemotherapy alone in patients with a PD-L1 CPS ≥ 5 (minimum follow-up time of 12.1 months). Additional results showed significant improvement in OS, along with PFS benefit, in patients with a PD-L1 CPS ≥ 1 and all randomly assigned patients. Among all treated patients, 462 of 782 patients (59%) in the nivolumab plus chemotherapy group and 341 of 767 patients (44%) in the chemotherapy alone group had Grade 3 or 4 treatment-related adverse events. The most common (≥ 25%) treatment-related adverse events were nausea, diarrhoea, and peripheral neuropathy across both groups. Sixteen deaths (2%) in the nivolumab plus chemotherapy group and 4 deaths (1%) in the chemotherapy alone group were considered to be treatment-related. No new safety signals were identified. (Janjigian et al 2021).

1.2.3. Avelumab

Avelumab, a fully human anti-PD-L1 immunoglobulin G (IgG)1 antibody (MSB0010718C), showed an acceptable safety profile and clinical activity in GC patients. The safety and efficacy of avelumab in patients with GC have been evaluated in the following studies.

The Phase 1b JAVELIN study enrolled 2 cohorts of patients: the first encompassing 62 patients who had progressed on prior therapy (second-line group) and a second with 89 patients who had previously received chemotherapy without disease progression (maintenance group) (Chung et al 2016). Objective responses and disease stabilization were observed in both groups. PD-L1 expression was evaluable in 74 patients; the cutoff for defining positivity was ≥ 1%. In the maintenance cohort, median PFS was 17.6 weeks for PD-L1(+) and 11.6 weeks for PD-L1(−). In the second-line cohort, median PFS was longer for PD-L1(−) (10.4 vs. 6.3 weeks).

The JAVELIN Gastric 100 trial is Phase 3 open-label study of maintenance therapy with avelumab (MSB0010718C) vs. continuation of 1L chemotherapy in patients with unresectable, locally advanced or metastatic, adenocarcinoma of the stomach, or of GEJ (Moehler et al 2016).

The JAVELIN Gastric 300 trial is a Phase 3 study in patients with GC or GEJ adenocarcinoma who have been previously treated with 1L combination chemotherapy and second-line ramucirumab, alone or in combination. The primary endpoint is best overall response (according to Response Evaluation Criteria in Solid Tumors [RECIST] 1.1 criteria). Secondary objectives include assessment of PFS, OS, and immune-related efficacy evaluations. Association between tumor PD-L1 expression and efficacy will be also evaluated (Oh et al 2016). In November 2017, Merck KGaA/Pfizer announced that the Phase 3 JAVELIN Gastric 300 trial did not meet its primary endpoint of superior OS with avelumab vs. physician's choice of chemotherapy (paclitaxel or irinotecan monotherapy) (Avelumab Nov 2017).

1.2.4. Summary of Immuno-Oncology in Gastric Cancer

Gastric (including GEJ) cancer is a very aggressive tumor and the second leading cause of cancer death together with colorectal and liver cancer worldwide (Global Burden of Disease Cancer Collaboration 2017). Radical surgery remains the first curative choice, while perioperative chemotherapy is a standard treatment in early GC (Waddell et al 2013; Shen et al 2013). However, 50% of advanced GC patients suffer from local or systemic recurrence even after standard adjuvant treatment, and only 10–15% of all GC patients achieve 5-year OS (Chen et al, 2016b; Choi et al 2015). Today, immunotherapy has important clinical applications with potential favorable outcomes.

GC cells acquire the ability to elude the host immune responses by several mechanisms such as the loss of antigen presentation and by recruitment of immune suppressive cells (eg, up-regulation of PD-L1). GC microenvironment is infiltrated with tumor infiltrating lymphocytes (TILs), which have a more pronounced cytolytic activity than stromal T-cells in chronic gastritis, and the high levels of TILs could be considered a good prognostic factor (Amedeo et al 2011). Thus, PD-1/PD-L1 inhibitors are showing very promising results in GC.

In GC patients, tumors with PD-L1 expression have been reported to be positively associated with depth of muscle invasion, tumor size, and lymph node metastasis. The survival of patients with PD-L1 or PD-L2 expressing tumors is significantly worse than for those patients without PD-L1/PD-L2 expressing tumors. PD-L1 or PD-L2 expressing tumors have been reported in approximately 22% to 40% of GC and PD-L1 expression has been suggested as a prognostic marker (Wu et al 2006; Ohigashi et al 2005). Thus, blockage of PD-1/PD-L1/PD-L2 might improve the survival of GC patients. Anti PD-1 and PD-L1 inhibitors (eg, nivolumab, pembrolizumab, and avelumab) have been investigated in GC treatment and have demonstrated anti-tumor activity (Le et al 2016; Muro et al 2015; Chung et al 2015).

Treatment with pembrolizumab achieved a 33% ORR by investigator assessment and 22% by central data review in advanced GC patients with PD-L1 expressing tumors. The 6-month PFS rate was 26% and median PFS was 1.9 months (95% CI: 1.8, 3.5). The 6-month OS rate was 66% and mOS was 11.4 months (95% CI: 5.7, NR). PD-L1 expressing tumors (cutoff 1%) were reported in 40% of GC patients in this study, which is consistent with previous reports (Muro et al 2015).

Preliminary data for second-line use of pembrolizumab in advanced GC have been reported in the KEYNOTE-061 study. Although pembrolizumab did not significantly improve overall survival compared with paclitaxel in PD-L1 CPS ≥ 1 GC patients, protocol-specified and post-hoc exploratory subgroup analyses suggest that the treatment effect of pembrolizumab might be more pronounced in patients with a better performance status, greater levels of PD-L1 expression (CPS ≥ 10, HR=0.64), and tumors with high levels of microsatellite instability. The KEYNOTE-062 trial showed that pembrolizumab plus chemotherapy as first-line treatment achieved a higher ORR than the chemotherapy group in CPS ≥ 1 (48.6% versus 37.2%) and CPS ≥ 10 (52.5% versus 37.8%).

Preliminary data for second line (2L) and switch maintenance use of avelumab in advanced GC have been recently reported. The ORRs were 15% and 7.3%, the 6-month PFS rates were 19% and 34%, and the median PFS were 2.9 months and 3.5 months, respectively (Chung et al 2015).

The preliminary safety data of pembrolizumab plus 5-FU and cisplatin in chemotherapy treatment-naive patients with advanced GC has been reported recently (Wainberg et al 2017). The safety profile reflected additive toxicity of the individual agents with 72% experiencing Grade 3/4 treatment-related AEs and was considered manageable using established safety guidelines. No treatment-related discontinuation attributed to pembrolizumab nor treatment-related deaths were reported. A study of nivolumab in combination with oxaliplatin and fluoropyrimidine in chemotherapy-naive GC or GEJ in an Asian population is ongoing (Kang et al 2017b).

As of May 2020, the Phase 3 CheckMate-649 study reported superior OS, along with PFS benefit and an acceptable safety profile of nivolumab in combination with chemotherapy versus chemotherapy alone, in previously untreated patients with gastric or gastroesophageal junction or esophageal adenocarcinoma (Janjigian et al 2021).

Cancer therapeutics such as chemotherapy may modulate tumor/immune-system interactions in favor of the immune system. Chemotherapy can result in tumor cell death with a resultant increase in tumor antigen delivery to antigen-presenting cells. Tumor cell death may also lead to a reduction in soluble and membrane-bound factors inhibiting tumor-infiltrating T-cells. Chemotherapy may also disrupt immune system regulatory networks by decreasing numbers of T-regulatory cells. Immunogenic chemotherapy such as oxaliplatin in combination with an immune checkpoint inhibitor can: trigger T-cell infiltration into tumor; provide additive or synergistic anti-tumor activity in-vivo; and may be expected to contribute to durable anti-tumor responses (Pfirschke and Engblom 2016).

In summary, PD-1/PD-L1 inhibitors combined with chemotherapy provide a basis for potential beneficial immunologic effects, which include inhibition of suppressive immune cells, induction of immunogenic cell death, enhanced presentation of tumor antigens, induction of maturation/ activation of dendritic cells, and enhancement of effector T-cell function. Moreover, chemotherapy can induce PD-L1 expression on tumor cells, providing a strong rationale for specific use in combination with a PD-1 inhibitor (Emens and Middleton 2015).

Thus, preclinical and clinical data suggest that tislelizumab in combination with platinum and fluoropyrimidine may be expected to bring clinical benefits to advanced GC/GEJ patients with a manageable safety profile.

1.3. Background Information on Tislelizumab

Refer to the most recent edition of the Tislelizumab Investigator's Brochure for additional background on tislelizumab.

1.3.1. Pharmacology

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

Tislelizumab acts by binding to the extracellular domain of human PD-1 with high specificity as well as high affinity (dissociation constant [K_D]=0.15 nM). It competitively blocks binding efforts by both PD-L1 and 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 in vivo antitumor activity in several allogeneic xenograft models, in which peripheral blood mononuclear cells were co-injected with human cancer cells (A431 [epidermoid carcinoma]) or tumor fragments (BCCO-028 [colon cancer]) into immunocompromised mice.

In addition, tislelizumab is an IgG4-variant antibody to gamma fragment crystallizable region (Fc) receptors (FcγR) such as FcγRI and FcγRIIIA and it has very low binding affinity to complement 1q (C1q), a subunit of complement 1. In vitro assays with tislelizumab suggest either low or no antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), or complement-dependent cytotoxicity (CDC) effects in humans (Zhang et al 2018). Tislelizumab was specifically engineered to minimize these potential mechanisms of T-cell clearance. Preserving T cells may slow tumor resistance to anti-PD-1 therapy.

1.3.2. Toxicology

The nonclinical toxicity and toxicokinetic profile of tislelizumab was characterized in single-dose studies in mice and cynomolgus monkeys and in a repeated-dose study in cynomolgus monkeys dosed once every 2 weeks for 13 weeks. Tissue cross-reactivity in normal human and cynomolgus monkey frozen tissues was also evaluated. In addition, the potential off-target binding of tislelizumab was screened using the Retrogenix microarray assay. The single-dose regimens spanned from the intended human dose to 10-fold higher than the maximum of the intended human dose, and the repeated-dose regimens spanned to 3-fold higher than the maximum of the intended human dose. Cynomolgus monkey was the only relevant species based on the target sequence homology and binding activity.

Overall, no apparent toxicity was noted in mice or monkey toxicity studies. No tissue cross-reactivity was found in either human or monkey tissues, nor was any effect on cytokine release observed in human whole blood assay. Based on the Retrogenix cell microarray screening of more than 6400 different proteins, tislelizumab clearly exhibited relatively high selective binding to the intended target, PD-1 protein, and had weakly binding to only one off-target protein. The toxicokinetic profile was well characterized with dose proportional increases in systemic exposure without apparent accumulation or sex difference. Immunogenicity was observed without apparent immunotoxicity or effect on the systemic

exposure. The no observed adverse effect level of tislelizumab in the 13-week monkey toxicity study was considered to be 30 mg/kg. The toxicity profile of tislelizumab is considered adequate to support the current study BGB-A317-305.

Refer to the Tislelizumab Investigator's Brochure for detailed information regarding toxicology studies.

1.3.3. Clinical Pharmacology

Tislelizumab exhibited a dose-proportional increase in exposure over the entire dose range (0.5 to 10 mg/kg) tested in study BGB-A317-001. A population PK analysis was performed based on pooled data (PK, dosing information, demographics, and patient or disease characteristics) from 2596 patients across 12 clinical studies. The PK of tislelizumab was best characterized using a 3-compartmental model with linear clearance mechanism. No time-varying clearance was observed in tislelizumab PK. The typical estimates of clearance (CL), central volume of distribution (V_c), and peripheral volumes 2 and 3 (V_2 and V_3, respectively), were 0.153 L/day, 3.05 L, 1.27 L, and 2.10 L, respectively, with interindividual variability in CL (26.3%), V_c (16.7%), V_2 (74.7%), and V_3 (99.9%). The terminal half-life ($t_{1/2}$) was estimated to be approximately 23.8 days. The accumulation ratios are estimated to be 2.14 and 2.49 for area under the serum concentration-time curve at steady state (AUC_{ss}) and minimum concentration at steady-state ($C_{min,ss}$), respectively. Steady state is expected to be reached in approximately 12 weeks.

The population PK analyses demonstrated that race, baseline aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, lactate dehydrogenase, estimated glomerular filtration rate, Eastern Cooperative Oncology Group Performance Status (ECOG PS), and sum of products of perpendicular diameters of classical Hodgkin lymphoma did not have statistically significant influences on tislelizumab PK. Baseline body weight, tumor size of solid tumors, albumin level, age, sex, immunogenicity, and tumor type were found to be statistically significant covariates on the PK of tislelizumab; however, the exposure changes by these covariates were relatively small compared to the overall range estimated for the PK exposures, and hence are not considered clinically meaningful.

1.3.4. Prior Clinical Experience of Tislelizumab

The overall safety experience with tislelizumab, as a monotherapy or in combination with chemotherapy, is based on experience in 3220 patients (2173 patients treated with monotherapy and 1047 patients treated with chemotherapy) in clinical studies as of the cutoff date 20 July 2022.

For more detailed information on the safety and efficacy of tislelizumab when given as monotherapy or in combination with chemotherapy, refer to the most recent edition of the Tislelizumab Investigator's Brochure.

1.3.4.1. Pooled Safety Assessment of Monotherapy Studies

A pooled analysis of 7 monotherapy studies was conducted to provide a comprehensive safety assessment separate from the combination therapy. Data from patients with solid tumors were analyzed separately from patients with hematologic malignancies.

Data are available from 1992 patients treated in 7 pooled solid tumor monotherapy studies. The median treatment exposure duration was 4.07 months (range: 0.10 to 55.46) and median study follow-up duration was 11.65 months (range: 0.07 to 58.91). The median age of these patients was 60 years, and 72.1% were men.

Of the 1992 patients in the solid tumor monotherapy pool, 1925 (96.6%) experienced ≥ 1 TEAE. The most commonly occurring TEAEs were Anaemia (25.3%), Aspartate aminotransferase increased (18.4%), Alanine aminotransferase increased (17.1%), Decreased appetite (16.7%), and Cough (15.3%). Of the 1992 patients, 712 patients (35.7%) experienced at least 1 treatment-emergent SAE. The most commonly occurring SAEs were Pneumonia (4.8%), Pneumonitis (1.4%), Dysphagia (1.2%), Pyrexia (1.1%), and Pleural effusion (1.0%).

Of the 1992 patients in the solid tumor monotherapy pool, 55 (2.8%) experienced ≥ 1 infusion-related reaction of any grade.

Of the 1992 patients in the adjudicated solid tumor group the pooled monotherapy studies, 312 (16.3%) experienced at least 1 imAE of any grade. The most commonly occurring imAEs of any grade were Hypothyroidism (6.3%), Pneumonitis (2.1%), Hyperthyroidism (0.9%), Rash (0.9%), Alanine aminotransferase increased (0.7%), and Immune-mediated lung disease (0.7%). Within the solid tumor group, imAEs ≥ Grade 3 in severity were reported in 83 patients (4.3%). The most commonly occurring ≥ Grade 3 imAEs were Pneumonitis (0.8%), Interstitial lung disease (0.4%), Alanine aminotransferase increased (0.4%), Aspartate aminotransferase increased (0.3%), and Hepatitis (0.3%).

For more detailed information on the safety of tislelizumab when given as monotherapy, refer to the most recent edition of the Tislelizumab Investigator's Brochure.

1.3.4.2. Efficacy Assessment of Tislelizumab

Efficacy data from 2 monotherapy studies (BGB-A317_Study_001 and BGB-A317-102) and 1 combination therapy study (BGB-A317-205) in solid tumors are available and are summarized below.

1.3.4.2.1. Study BGB-A317_Study_001

Study BGB-A317_Study_001 is a 2-stage study consisting of a Phase 1a dose-escalation (0.5-10 mg/kg) and dose-finding component with 3 parts (2 and 5 mg/kg given either once every 2 or 3 weeks, and a fixed dose of 200 mg given once every 3 weeks) to establish the maximum tolerated dose (MTD), if any, a recommended Phase 2 dose (RP2D), and followed by a Phase 1b component to investigate efficacy in select tumor types at the RP2D to further evaluate safety and tolerability of tislelizumab. Indication specific cohorts included esophageal (EC), gastric (GC), hepatocellular (HCC), and non-small cell lung (NSCLC) cancer.

Responses were assessed by the investigator per the RECIST v1.1 criteria.

There were 451 patients treated in the study and 441 patients were included in the efficacy evaluable set. The Efficacy Evaluable Analysis Set includes all treated patients who had at least 1 measurable baseline target lesion and had at least 1 evaluable post-baseline tumor assessment. This set included 52 patients in the gastric cancer (GC) cohort.

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

Of the 52 patients in the GC cohort, no patients (0%) had a CR. A total of 7 patients (13.5%) had a confirmed PR. Additionally, there were 9 patients (17.3%) with a best overall response of stable disease (SD). A total of 31 patients (59.6%) had a best response of PD in this cohort, and the assessment for 5 patients (9.6%) were missing.

1.3.4.2.2. Study BGB-A317-102

Study BGB-A317-102 is a non-randomized, Phase 1/2 study of tislelizumab monotherapy in Chinese patients with advanced solid tumors. Phase 1 includes a dose verification substudy and a substudy of PK evaluation of the products derived from 2 manufacturing processes and scales. Phase 2 evaluates the activity and safety of tislelizumab at its recommended Phase 2 dose of 200 mg given once every 3 weeks in indication specific expansion cohorts.

Responses were assessed by the Investigator per the RECIST v1.1 criteria.

Overall, of the 300 patients treated in Study BGB-A317-102, 249 patients were included in the Efficacy Evaluable Analysis Set as of the data cutoff date of 31 May 2020. The Efficacy Evaluable Analysis Set includes all treated patients who had at least 1 measurable baseline target lesion and had at least 1 evaluable post-baseline tumor assessment. This set included 16 patients in the GC cohort.

The tumor responses in the efficacy evaluable analysis set of Study BGB-A317-102 across all disease cohorts and study phases was 1 patient (0.4%) with a CR and 50 patients (20.1%) with confirmed PR. The resulting objective response rate was 20.5%. Additionally, there were 83 patients (33.3%) with a best overall response of stable disease. A total of 115 patients (46.2%) had a best response of PD in this study.

The tumor responses in the Efficacy Evaluable Analysis Set of Study BGB-A317-102 in the GC cohort (16 patients) was no patients (0%) had a CR and 4 patients (25.0%) had a confirmed PR. Additionally, there were 2 patients (12.5%) with a best overall response of SD. A total of 10 patients (62.5%) had a best response of PD in this cohort.

1.3.4.3. Safety and Efficacy Assessment of Study BGB-A317-205 (Combination therapy)

Study BGB-A317-205 is a multi-cohort, Phase 2 study of tislelizumab in combination with standard chemotherapy (cisplatin/5-fluorouracil or oxaliplatin/capecitabine) as first-line treatment in esophageal squamous cell carcinoma (ESCC) and GC/GEJ conducted in Chinese patients.

As of 31 March 2019, of the 30 patients treated (15 patients each from the ESCC and GC/GEJ adenocarcinoma, respectively), 7 (46.7%) patients in each cohort remained on study; 4 patients (26.7%) in each cohort were still receiving tislelizumab treatment. In the GC/GEJ adenocarcinoma cohort, the median duration was 26.1 weeks (range: 3 to 75 weeks) for treatment with tislelizumab.

All 15 patients (100.0%) treated in GC/GEJ cohort experienced at least 1 TEAE. For the GC/GEJ adenocarcinoma cohort, TEAEs reported in at least 30% of patients included aspartate aminotransferase increased, asthenia (9 patients each, 60.0%), platelet count decreased (8 patients, 53.3%), alanine aminotransferase increased, blood bilirubin increased, nausea, vomiting (7 patients each, 46.7%), anaemia, decreased appetite, neutrophil count decreased (6 patients each, 40.0%), diarrhoea, hypoalbuminaemia, leukopenia, and pyrexia (5 patients each, 33.3%).

Serious TEAEs were reported in 5 patients (33.3%). All these serious TEAEs were considered both tislelizumab-related and chemotherapy-related.

Tislelizumab-related TEAEs were reported for all 15 (100%) patients in the GC/GEJ adenocarcinoma cohort. For the GC/GEJ adenocarcinoma cohort, treatment-related TEAEs reported in at least 30% of patients included aspartate aminotransferase increased, asthenia (9 patients each, 60.0%), platelet count decreased (8 patients, 53.3%), alanine aminotransferase increased, blood bilirubin increased, nausea, vomiting (7 patients each, 46.7%), anaemia, decreased appetite, neutrophil count decreased (6 patients each, 40.0%), diarrhoea, pyrexia, hypoalbuminaemia, and leukopenia (5 patients each, 33.3%). Ten patients (66.7%) experienced a severe (≥ Grade 3) tislelizumab-related TEAE. In the GC/GEJ adenocarcinoma cohort, 10 patients (66.7%) experienced at least 1 TEAE of Grade 3 or 4; all the events were reported for single patients by Preferred Term.

In the GC/GEJ adenocarcinoma cohort, 11 patients (73.3%) experienced at least 1 immune-mediated TEAE. The most frequently reported categories of immune-mediated TEAE were immune-mediated endocrinopathies and immune-mediated hepatitis (4 patients each, 26.7%), followed by immune-mediated colitis and immune-mediated pneumonitis (3 patients each, 20.0%), and other immune-mediated reactions (2 patients, 13.3%). Grade 3 or 4 immune-mediated TEAEs were reported in 7 patients (46.7%).

No patient experienced infusion-related reactions due to tislelizumab infusion.

In the GC/GEJ adenocarcinoma cohort, TEAEs leading to tislelizumab treatment discontinuation were reported in 3 patients (20.0%). All TEAEs that led to tislelizumab treatment discontinuation were assessed as ≥ Grade 3 and were reported in single patients.

In the GC/GEJ adenocarcinoma cohort, 6 patients (40.0%) died during the study. Five deaths occurred > 30 days after the last dose of study drugs and one death occurred within 30 days of receiving the last dose of study drugs. The cause of all deaths was disease progression.

The Efficacy Evaluable Analysis Set includes all the GC/GEJ patients who have received at least 1 dose of the study drug, had measurable or evaluable disease at baseline according to RECIST v1.1, and had at least 1 post baseline tumor response assessment unless any clinical PD or death occurred within 10 weeks after the first dose. The tumor responses in the efficacy evaluable analysis set of GC/GEJ patients (13 patients) was no patients (0%) with a CR and 7 patients (53.8%) with confirmed PR. Additionally, there were 3 patients (23.1%) with a best overall response of SD. Only 1 patient (7.7%) had a best response of PD.

1.4. Study Rationales

1.4.1. Rationale for Tislelizumab in the Treatment of Gastric Cancer

Immunotherapeutic approaches with anti-PD-1 have demonstrated clinical efficacy in several advanced cancer types, including melanoma (Weber et al 2015), non-small cell lung cancer (NSCLC) (Borghaei et al 2015), and renal cell carcinoma (RCC) (Motzer et al 2015) and have been approved in the US, Europe, Japan and other countries (Raedler 2015; Kazandjian et al 2016; Xu et al 2017; News of Nivolumab on AJMC 2014; News of Nivolumab on Targeted Oncology 2017).

Preclinical data indicate that PD-1 targeted therapies may improve antitumor activity and increased IFN-gamma production levels as well as increased proportion of PD-1-expressing CD4/CD8 tumor-infiltrating T-effector cells (Curran et al 2010).

In addition, high levels of FcγR-expressing myeloid derived cells (eg, M2 macrophage, MDSC) in tumor tissues predict a poor survival of tumor-bearing animals after anti-PD-1 monoclonal antibody treatment; this is possibly due to Fc-FcγR-mediated ADCC or antibody-dependent cellular phagocytosis (ADCP) depletion of effector T-cells (Gül et al 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 theoretically may show superior efficacy and lower toxicity in GC.

Available data from clinical trials with other anti-PD-1 monoclonal antibodies, such as pembrolizumab and nivolumab, have shown that anti-PD-1 antibodies have both manageable safety profile and promising antitumor activity in patients with unresectable GC/GEJ (Section 1.2).

Data for a GC Cohort of tislelizumab treated patients was presented at European Society for Medical Oncology (ESMO) in 2017 (Desai et al 2017). As of 8 Jun 2017, 46 patients with heavily pretreated GC have been enrolled in BGB-A317_Study_001 Phase 1a/1b totally. A total of 34 GC patients were evaluable. Four patients achieved a confirmed PR, and 3 patients achieved a best overall response of SD. The disease control rate (DCR) was 21%. Treatment-related adverse events (TRAEs) occurred in 15 patients. Decreased appetite (n=4, 27%), abdominal pain (4, 27%), fatigue (3, 20%) and nausea (n=3, 20%) were the most commonly reported TRAEs. The majority of these TRAEs were ≤ Grade 2 in severity. One patient experienced proteinuria that was ≥ Grade 3. Treatment with tislelizumab was generally well tolerated in pretreated patients with advanced GC. Adverse events reported were consistent with the overall safety profile observed in the BGB-A317_Study_001 Phase 1a/1b study, and were generally of low severity, manageable and reversible. The preliminary safety profile and antitumor activity support continued development of tislelizumab in patients with advanced/metastatic GC.

The BGB-A317-205 Phase 2, single arm study is investigating the safety, pharmacokinetics and preliminary antitumor activity of the anti-PD-1 monoclonal antibody tislelizumab in combination with chemotherapy as 1L treatment in adults with inoperable, locally advanced or metastatic esophageal, gastric, or gastroesophageal junction carcinoma. The first Safety Monitoring Committee (SMC) evaluation demonstrated that tislelizumab + oxaliplatin and capecitabine has a

manageable safety profile. The safety data summary will be available before the study initiation of BGB-A317-305.

Finally, according to the latest data collected from the Phase 1 study BGB-A317_Study_001, tislelizumab monotherapy has established a manageable safety profile, with the most common side effects consistent with known class effects of other anti-PD-1 antibodies (Section 1.3.4).

This is a randomized (1:1), double-blind, placebo-controlled, Phase 3 study of tislelizumab plus chemotherapy verses placebo plus chemotherapy as 1L treatment in patients with locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma, based on the research hypothesis that tislelizumab given in addition to SOC chemotherapy will have superior efficacy as demonstrated by PFS and/or OS and acceptable tolerability profile as compared with chemotherapy alone and the PD-L1+ patients will be enriched for responsive to tislelizumab plus chemotherapy.

1.4.2. Rationale for Selection of Tislelizumab Dose

The dosage of 200 mg intravenously once every 3 weeks was selected based on safety, efficacy, and PK assessments in the first-in-human study BGB A317_Study_001. A wide range of dosages were investigated in this study, including 2 mg/kg or 5 mg/kg on schedules of once every 2 weeks or once every 3 weeks. For the once every 3 weeks schedule, a fixed dose of 200mg was also investigated, and was ultimately selected for the following reasons:

- All dosages tested, including 200 mg once every 3 weeks, were tolerated. The maximum tolerated dose was not reached with dosages up to 10 mg/kg once every 2 weeks. The observed serum concentration after 200 mg dosing was within the range seen after 2 mg/kg and 5 mg/kg dosing.
- Preliminary clinical activity was observed at this dosage.
- Exposure-response relationships were flat for ORR and safety endpoints across a variety of tumor types (data from studies BGB A317_Study_001, BGB A317 102, and BGB A317 203). In addition, no clinically significant covariates were identified in population PK analysis.
- Compared with doses based on patient weight, a fixed dose simplifies dose administration and reduces the chance of medical errors.
- Compared with a once every 2 weeks schedule, a once every 3 weeks schedule allows for more convenient integration with common chemotherapeutic regimens and increases patient convenience.

1.4.3. Rationale for Selection of Chemotherapies

Platinum compounds and fluoropyrimidines are generally considered as 1L, standard-of-care treatment options in metastatic GC and GEJ cancer across geographic regions. In Western countries and Asia, the reference chemotherapy regimen for 1L treatment of metastatic gastric and GEJ adenocarcinoma is a fluoropyrimidine (5-FU or capecitabine) in combination with a platinum agent (cisplatin or oxaliplatin) with or without a third cytotoxic drug (usually epirubicin or docetaxel) (Van Cutsem et al 2011).

National Comprehensive Cancer Network (NCCN) guideline suggests the 2-drug chemotherapy as the preferred regimen in the 1L setting; the 3-drug regimen, due to its toxicity profile, should be considered only for use in patients with good performance status. In addition, the triplet regimen is not common in Asia due to its high toxicity profile (NCCN guideline v3 2016; Japanese gastric cancer treatment guidelines v4 2014).

The comparator selected in this study is a platinum doublet regimen (ie oxaliplatin plus capecitabine and cisplatin plus 5-FU).

Several Phase 3 studies and meta-analyses, oxaliplatin and capecitabine have both been shown to be non-inferior to cisplatin and 5-FU, respectively with a favorable safety profile (Wagner et al 2010; Al-Batran et al 2008; Cunningham et al 2010).

Based on these observations, platinum- and fluoropyrimidine-based doublet regimens, oxaliplatin + capecitabine and cisplatin + 5-FU (Ajani et al 2017; Kang et al 2009; Dank et al 2008; Van Cutsem et al 2006) are considered to be reasonable comparators in this Phase 3 study, and the investigators can choose either regimen per their local standard. The dose level used in this Phase 3 study is also consistent with prevailing clinical practice.

Maintenance chemotherapy is an evolving concept in medical oncology. The role of maintenance therapy has been demonstrated in non–small-cell lung cancer and colorectal cancer (Luis et al 2013; Aprile et al 2016). Although data are limited, it has been shown that capecitabine maintenance may be feasible in treatment of advanced/metastatic GC and GEJ cancer (Eren et al 2016; Qiu et al 2014). The efficacy and safety of capecitabine as maintenance treatment after 1L chemotherapy in GC has been evaluated in 287 Chinese patients who had previously received 6 cycles of oxaliplatin and capecitabine as 1L chemotherapy, without disease progression but with documented Grade 2 or higher neuropathy.

Overall, 222 patients interrupted the treatment and 64 patients received capecitabine as maintenance. The median PFS was 11.4 months (95% CI 10.2-12-2 months) for patients who received maintenance therapy versus 7.1 months (95%CI 6.1-8.0 months) for those in the control group ($p < 0.001$). A multivariate analysis showed that the maintenance treatment was an independent prognostic factor. Moreover, the safety profile was consistently mild in the phase of maintenance treatment (Qiu et al 2014). Capecitabine may be a viable option as maintenance treatment of GC and GEJ cancer if no progression occurs after a predefined number of cycles of chemotherapy. In the present study, those patients receiving oxaliplatin + capecitabine regimen who experience a complete response, partial response, or stable disease have the option to continue with capecitabine as maintenance therapy.

1.5. Benefit-Risk Assessment

Available data from clinical trials of other anti-PD-1 antibodies, such as nivolumab and pembrolizumab, have demonstrated favorable efficacy in metastatic or unresectable GC and GEJ adenocarcinoma patients previously treated with 2 or more prior chemotherapy regimens. Available data has also indicated that combined treatment of chemotherapy and anti-PD-1 antibodies has a manageable safety profile when administered as 1L therapy in patients with advanced gastrointestinal malignancies.

According to the latest data collected from the Phase 1 studies of BGB-A317_Study_001 and BGB-A317-102, tislelizumab has demonstrated a favorable safety profile that is consistent with

known class effects. Anti-tumor activity with tislelizumab has been demonstrated in patients with esophageal squamous cell carcinoma (ESCC) and GC.

As noted in Section 1.3.4.3, the incidence and type of treatment-related AEs of patients from Phase 2 BGB-A317-205 study were similar to the AEs known to be associated with chemotherapy regimens combined with other PD-1 products. Tislelizumab in combination with oxaliplatin + capecitabine demonstrated manageable safety profiles.

Given the unmet medical need and limited treatment options for these patients, the benefit/risk assessment of BGB-A317-305 is considered favorable based on available data from tislelizumab Phase 1 studies data (BGB-A317_Study_001 and BGB-A317-102), Phase 2 study in GC (BGB-A317-205), and the primary efficacy by anti-PD-1 antibodies in GC and GEJ adenocarcinoma.

An Independent Data Monitoring Committee (IDMC) will be established to regularly monitor the safety of patients in this study. 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 compare overall survival of tislelizumab plus chemotherapy versus placebo plus chemotherapy in the programmed cell death protein ligand-1 positive and intent-to-treat analysis sets

2.1.2. Secondary Objectives

- To compare progression-free survival per Response Evaluation Criteria in Solid Tumors 1.1 as assessed by investigators of tislelizumab plus chemotherapy versus placebo plus chemotherapy in the programmed cell death protein ligand-1 positive and intent-to-treat analysis sets
- To evaluate overall response rate, and duration of response, per Response Evaluation Criteria in Solid Tumors 1.1 as assessed by investigators
- To evaluate European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Gastric Cancer Module QLQ-STO22 Score, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 Score and European Quality of Life 5-Dimensions 5-Levels Health Questionnaire Score
- To evaluate the safety and tolerability profile of tislelizumab or placebo plus chemotherapy
- To evaluate disease control rate, clinical benefit rate, and time to response per Response Evaluation Criteria in Solid Tumors 1.1 as assessed by investigators

2.1.3. Exploratory Objectives

- To evaluate progression-free survival after next line of treatment (PFS2)
- To characterize the pharmacokinetics of tislelizumab
- To determine host immunogenicity to tislelizumab
- To assess predictive, prognostic, exploratory biomarkers including but not limited to programmed cell death protein ligand-1 (PD-L1) expression, Epstein-Barr virus (EBV) infection, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) status, genomically stable (GS) or chromosomal instability (CIN), immune-related gene expression profiling, tumor infiltrated lymphocytes (TILs) and tumor mutation burden in tumor tissues and/or blood samples and the association with response to study treatment, mechanisms of resistance, and/or disease status

2.2. Study Endpoints

2.2.1. Primary Endpoint

- Overall survival – defined as the time from the date of randomization to the date of death due to any cause

2.2.2. Secondary Endpoints

- Progression-free survival as assessed by investigators – defined as the time from the date of randomization to the date of the first objectively documented tumor progression, assessed by investigators per Response Evaluation Criteria in Solid Tumors v1.1, or death, whichever occurs first
- Overall response rate as assessed by investigators – defined as the proportion of patients whose best overall response is complete response or partial response per Response Evaluation Criteria in Solid Tumors v1.1
- Duration of response (DOR) as assessed by investigators – defined as the time from the first determination of an objective response per Response Evaluation Criteria in Solid Tumors v1.1, until the first documentation of progression or death, whichever occurs first
- Change from baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Gastric Cancer Module QLQ-STO22 Score and change from baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 Score and European Quality of Life 5-Dimensions 5-Levels Health Questionnaire Score
- The incidence and severity of adverse events according to National Cancer Institute Common Terminology Criteria for Adverse Events v5.0
- Disease control rate (ie, proportion of complete response + partial response + stable disease), clinical benefit rate (ie, proportion of complete response + partial response + durable stable disease), and time to response (ie, time from randomization to the first determination of an objective response) per Response Evaluation Criteria in Solid Tumors 1.1 as assessed by investigators

2.2.3. Exploratory Endpoints

- Progression-free survival after next line of treatment (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
- Summary of serum concentration of tislelizumab
- Assessments of immunogenicity of tislelizumab by determining the incidence of antidrug antibodies (ADAs)
- Status of programmed cell death protein ligand-1 (PD-L1) expression, immune or gastric-related, and other exploratory biomarkers including but not limited to Epstein-Barr virus (EBV) infection, microsatellite instability-high (MSI-H) or mismatch

repair deficient (dMMR), genomically stable (GS) or chromosomal instability (CIN), immune-related gene expression profiling, tumor infiltrated lymphocytes (TILs) and tumor mutation burden in tumor tissues and/or blood samples obtained before treatment with tislelizumab and/or at progression, and the association with disease status and/or response to tislelizumab in combination with chemotherapy or chemotherapy alone

3. STUDY DESIGN

3.1. Summary of Study Design

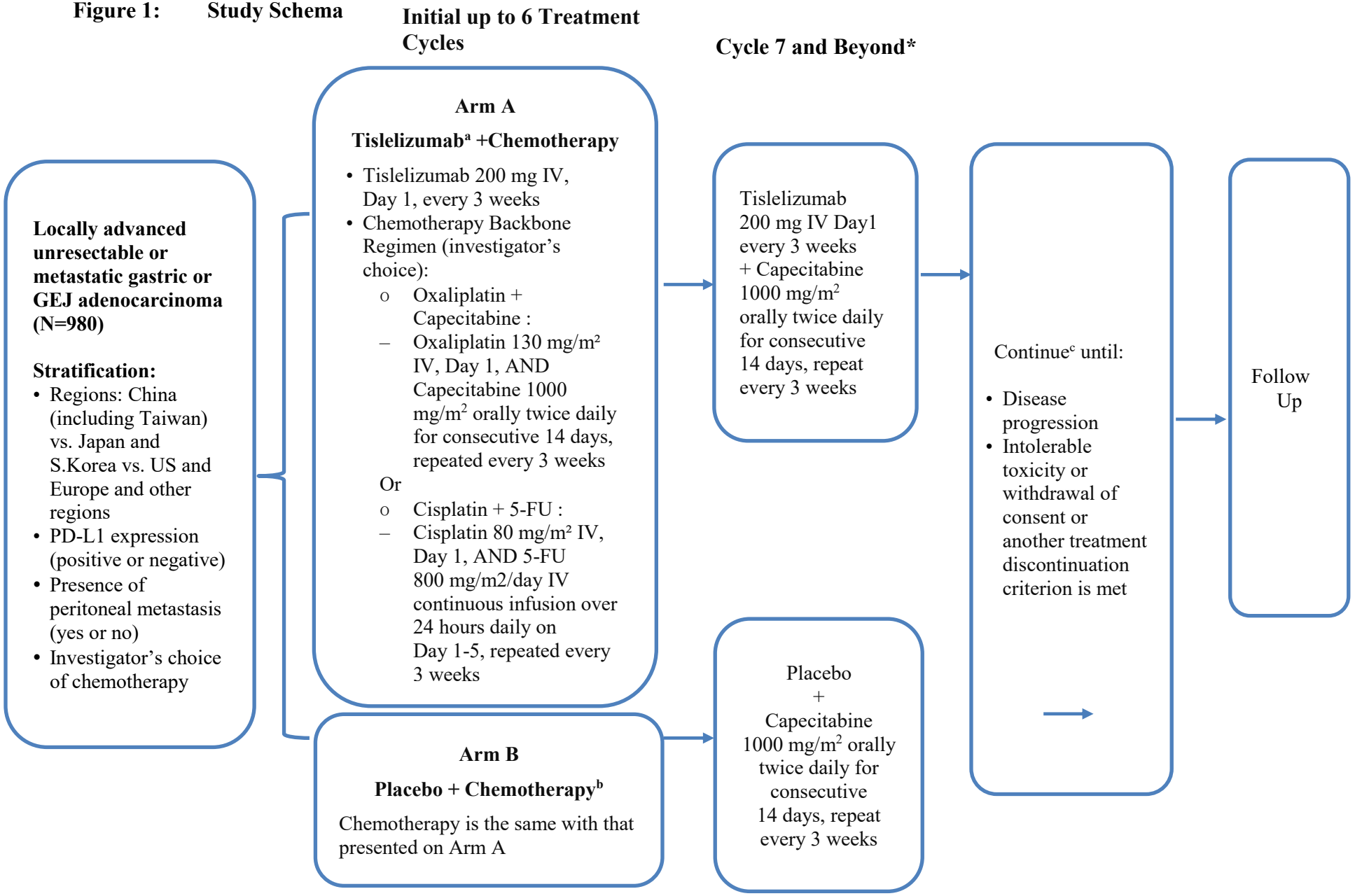
This is a randomized (1:1), double-blind, placebo-controlled, Phase 3 study of tislelizumab plus platinum and fluoropyrimidine versus placebo plus platinum and fluoropyrimidine in patients with locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma. Patients must have not received previous systemic therapy for locally advanced unresectable or metastatic gastric/GEJ cancer. All patients are also required to have ≥ 1 measurable or non-measurable lesion per RECIST v1.1, an ECOG PS score of ≤ 1, and adequate organ function.

The study procedures will occur over a Screening Phase (up to 28 days); Treatment Phase (until the investigator determines that study drugs will no longer be used); Safety Follow-up Phase (30 days [± 7 days] after the last dose of study drugs, or before the initiation of a new anticancer treatment, whichever occurs first); and a Survival Follow-up Phase (continuing until death, loss to follow-up, withdrawal of consent, or study termination by sponsor).

In addition, immune-mediated adverse events (imAEs) will be recorded up to 90 days after the last dose of tislelizumab or placebo, regardless of whether or not the patient starts a new anticancer therapy.

The study design schematic is presented in Figure 1.

Figure 1: Study Schema



* Capecitabine as maintenance therapy is optional and only for oxaliplatin + capecitabine regimen
Abbreviations: GEJ, gastroesophageal junction; IV, intravenously; 5-FU, 5-fluorouracil; vs, versus

a. The initial infusion (Cycle 1, Day 1) will be administered over a period of 60 minutes. If this infusion is well tolerated, subsequent infusions may be administered over 30 minutes. After tislelizumab or placebo infusion, patients will be further monitored for a period of 1 hour during Cycles 1 and 2. From Cycle 3 onward, a post-infusion monitoring period of at least 30 minutes will be required.
b. The oxaliplatin + capecitabine or cisplatin + 5-FU doublet regimen is administered up to 6 cycles, capecitabine as optional maintenance therapy only for oxaliplatin + capecitabine regimen may be administered until disease progression, intolerable toxicity, withdrawal of consent, or another treatment discontinuation criterion is met. Tislelizumab (or placebo) will be administered until disease progression, intolerable toxicity, withdrawal of consent, or another treatment discontinuation criterion is met.
c. Treatment beyond initial investigator-assessed RECIST v1.1 defined progression will be permitted provided that the patient has investigator-assessed clinical benefit and is tolerating the study drug. The following criteria must be met to treat patients after initial evidence of radiological disease progression: absence of clinical symptoms and signs of disease progression; stable ECOG PS ≤ 1; absence of rapid progression of disease or progressive tumor at critical anatomical sites that require urgent alternative medical intervention; and additional written informed consent. The medical monitor must agree, in writing, with the investigator's decision to continue study drugs beyond initial investigator-assessed progression, and the decision must be documented in the study records.

For all study procedures see Section 7 and Appendix 1.

3.2. Screening Period

Screening evaluations will be performed within 28 days prior to randomization. Patients who agree to participate in this study will sign the informed consent form (ICF) prior to undergoing any study-specific screening procedure. Patients who are suspected to have serious respiratory concurrent illness or exhibit significant respiratory symptoms unrelated to underlying cancer will also take a pulmonary function test (refer to Section 7.1 and Appendix 1 for details). Screening evaluations may be repeated as needed within the screening period; the investigator is to assess preliminary patient eligibility according to the latest screening assessment results.

Tumor tissues must be collected for the purpose of PD-L1 assessment and other biomarker analyses. A fresh biopsy sample is highly preferred if feasible in clinic. If no archival samples are available, a fresh tumor biopsy at baseline is mandatorily required. For patients with unavailable MSI/MMR status, an MSI or MMR assessment will be performed in investigational sites, third-party local lab or designated central laboratory. For MMR testing, 5 formalin-fixed paraffin-embedded [FFPE] slides required; for MSI testing, 5 FFPE slides and approximately 2 mL blood samples will be collected. Patients with unknown HER2 status must undergo an HER2 test at the investigational sites, third-party local lab or designated central laboratory prior to enrollment. Refer to Section 7.7 for details.

3.3. Treatment Period

After completing all screening activities, patients confirmed to be eligible by the investigator will be randomized in a 1:1 ratio to receive either tislelizumab or placebo plus chemotherapy treatment. The choice of chemotherapy regimen must be decided prior to randomization and the interchange of chemotherapy regimen is not permitted during the study period.

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

- Regions of enrollment: China (including Taiwan) vs. Japan and S. Korea vs. US and Europe and other regions. NOTE: other regions include other western countries/populations.
- PD-L1 expression (positive or negative): PD-L1+ patients are patients with tumor and immune cell score (TIC score) ≥ 5% using VENTANA PD-L1 (SP263) Cdx Assay*. TIC score is the total percentage of the tumor area covered by tumor cells with PD-L1 membrane staining and tumor-associated immune cells with PD-L1 staining at any intensity.

  *During enrollment, the proportion of patients of multiple PD-L1 expression levels will be monitored. Hence, study assumptions (see Section 9.6) could be adjusted accordingly if it is deemed appropriate.
- Presence of peritoneal metastasis (yes or no)
- Investigator's choice of chemotherapy (oxaliplatin + capecitabine versus cisplatin + 5-FU)

After randomization, patients will be treated on the following arms. Cross-over between the treatment arms will not be allowed.

- Arm A: Tislelizumab 200 mg intravenously Q3W + chemotherapy
- Arm B: Placebo intravenously Q3W + chemotherapy

Oxaliplatin + capecitabine or cisplatin + 5-FU regimens are used as the backbone chemotherapy. The chemotherapy backbone regimen needs to be decided on an individual patient basis before randomization. There is no switching between regimens throughout the entire course of the study.

Oxaliplatin + Capecitabine	**Day 1:** Oxaliplatin 130 mg/m² intravenously **Day 1 (evening) – Day 15 (morning) or Day 1 (morning) – Day 14 (evening):** Capecitabine 1000 mg/m^2 orally twice daily Every 3 weeks as a cycle
Cisplatin + 5-FU	**Day 1:** Cisplatin 80mg/m² intravenously **Days 1–5:** 5-FU 800mg/m^2/day intravenously continuous infusion over 24 hours daily Every 3 weeks as a cycle

The oxaliplatin + capecitabine or cisplatin + 5-FU doublet regimen is administered up to 6 cycles. Capecitabine as maintenance therapy is optional only for the oxaliplatin + capecitabine regimen and may be administered until disease progression, intolerable toxicity, withdrawal of consent, or another treatment discontinuation criterion is met (whichever occurs first; see Section 3.6.1). Tislelizumab (or placebo) will be administered until disease progression, intolerable toxicity, withdrawal of consent, or another treatment discontinuation criterion is met (whichever occurs first; see Section 3.6.1).

In both arms, treatment beyond the initial investigator-assessed RECIST v1.1-defined progression is permitted provided that the patient has investigator-assessed clinical benefit and is tolerating study drug.

Specific requirements for post-progression continuation of patients treated with tislelizumab or placebo and capecitabine are described in Section 3.6.1.

Radiological assessment of tumor-response status will be performed approximately every 6 weeks (± 7 days) for the first 48 weeks and every 9 weeks (± 7 days) after 48 weeks based on RECIST v1.1 from randomization. Tumor response will be assessed 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] v5.0), and laboratory results. Vital signs, physical examinations, ECOG PS 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 2 years of treatment (as measured from Cycle 1 Day 1):

- Patients may continue on 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 must be explicitly approved by the sponsor and will be contingent on the continued availability of tislelizumab. The study assessment and procedure schedule will remain the same.

- Patients with confirmed CR, PR, or SD may stop treatment after 2 years 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. The investigator should notify the sponsor that treatment will be stopped prior to stopping the treatment. In these cases, 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. If new information becomes available indicating the patient should restart treatment, the patient must sign a new ICF, meet (continued) treatment eligibility, and the investigator must receive approval before the patient can restart treatment.
  - If a patient has evidence of PD within 1 year of treatment interruption, the investigator can consider restarting tislelizumab therapy after discussion with the sponsor, contingent on the continued availability of tislelizumab.

Optional blood samples of approximately 10 mL will be taken at baseline (predose at Day 1 of Cycle 1), at the time of first tumor response (predose at Day1 of the following Cycle) and at end of treatment (EOT) after disease progression (10 mL each timepoint) for all randomized patients to explore the association of blood-based biomarkers with response, prognosis and resistance to tislelizumab in combination with chemotherapy or chemotherapy alone. Written informed consent is required for blood sample collections.

3.4. Safety Follow-up

Patients who discontinue treatment for any reason will be asked to return to the clinic for the Safety Follow-up Visit (to occur on 30 days [± 7 days] after the last dose of study drugs, or before the initiation of a new anticancer treatment, whichever occurs first). (N.B. a patient may unintentionally miss the Safety Follow-up Visit window if the decision of discontinuation is made more than 30 days [± 7days] after the actual last dose date. In this scenario, it will not be regarded as a protocol deviation and the EOT visit can be used as Safety Follow-up.)

In addition, telephone contacts with patients should be conducted to assess imAEs and concomitant medications (if appropriate, ie, associated with an imAE or is a new anticancer therapy) at 60 days (± 14 days) and 90 days (± 14 days) after the last dose of tislelizumab or placebo, regardless of whether or not the patient starts a new anticancer therapy. If patients report a suspected imAE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated.

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

The EOT visit at which a response assessment showed progressive disease, resulting in patient discontinuation, may be used as the Safety Follow-up visit, provided that it occurred approximately 30 days (± 7 days) after the last study treatment. Patients who discontinue study treatment prior to disease progression will have their tumors assessed as outlined in Section 7.5.

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

3.5. Survival Follow-up

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

Patients will be followed for survival and to obtain information on subsequent anticancer therapy after discontinuation of study treatment via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (± 14 days) after the EOT/Safety Follow-up visit or as directed by the sponsor until death, loss to follow-up, withdrawal of consent, or the end of the study (see Section 3.6.5).

3.6. Patient, Treatment, Study, and Site Discontinuation

Patients who discontinue study treatment early should be followed for assessments of antitumor activity (Section 7.5), safety (Section 7.4) and survival (Section 3.5), if possible.

3.6.1. Discontinuation from Study Treatment

Patients have the right to voluntarily withdraw from the study or discontinue study treatment at any time for any reason. In addition, the investigator has the right to discontinue a patient from the study treatment at any time. Patients who discontinue study treatment early should be followed for assessments of antitumor activity, safety, and survival, if possible.

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

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

- Patient withdrawal of consent
- Pregnancy
- Any medical condition that the investigator or sponsor determines may jeopardize the patient's safety, if he or she were to continue the study treatment
- Use of any 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. Investigative site staff should first counsel patients who are significantly noncompliant (eg, missing 2 treatment cycles) on the importance of study drug compliance and drug accountability. The investigator may, in consultation with the medical monitor, discontinue patients from treatment who are consistently noncompliant.

Patients in both treatment arms will be permitted to continue study drugs beyond initial investigator-assessed RECIST v1.1-defined progression provided that the patient has

investigator-assessed clinical benefit and is tolerating study drug. The following criteria must be met to treat patients after initial evidence of radiological disease progression:

- Absence of clinical symptoms and signs of disease progression (including clinically significant worsening of laboratory values)
- Stable ECOG PS ≤ 1
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, spinal cord compression) that requires urgent alternative medical intervention
- The investigator must obtain written informed consent for treatment beyond radiologic disease progression and inform patients that this practice is not considered standard in the treatment of cancer. Patients must be informed that by continuing treatment beyond progression they may be forgoing other treatment that has shown benefit.
- The medical monitor must agree, in writing, with the investigator's decision to continue study drugs beyond initial investigator-assessed progression, and the decision must be documented in the study records.

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

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

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

3.6.3. Withdrawal of Consent

Patients who request to discontinue study drug will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a patient specifically withdraws consent for any further contact with him/her or persons previously authorized by patient to provide this information. Patients should notify the investigator of the decision to withdraw consent from future follow-up verbally or in writing. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up and entered on the appropriate CRF page. In the event that survival status (whether the patient is alive or dead) is being measured, publicly available information should be used to determine survival status only as appropriately directed in accordance with local law.

3.6.4. Lost to Follow-Up

All reasonable efforts must be made to locate patients to determine and report their ongoing status. This includes follow-up with persons authorized by the patient as noted above. Lost to follow-up is defined by the inability to reach the patient after a minimum of three documented phone calls, faxes, or emails as well as lack of response by patient to one registered mail letter.

All attempts should be documented in the patient's medical records. If it is determined that the patient has died, the site will use permissible local methods to obtain the date and cause of death. If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the patient's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining patient's contact information or other public survival status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If the patient's survival status is determined, the survival status will be documented, and the patient will not be considered lost to follow-up. If after all attempts, the patient remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the patient's medical records.

3.6.5. End of Study

The end of the study is defined as the timepoint when the final data point is collected from the last patient in the study. The primary analyses will be conducted when the predefined death events have been observed (see Section 9.2.1) for the efficacy and safety evaluation. The study will continue until the last patient dies, is lost to follow-up, or withdraws consent.

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

- The incidence or severity of adverse events 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 visit/Safety Follow-up Visit.

At the end of study, any patients 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 until it is commercially available or post-study drug supply program 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 investigators 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

- Good Clinical Practice (GCP) noncompliance
- Study activity is completed (ie, all patients have completed, and all obligations have been fulfilled)

4. STUDY POPULATION

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

4.1. Inclusion Criteria

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

1. Able to provide written informed consent and can understand and comply with the requirements of the study
2. Adult patients (≥ 18 years of age or acceptable age according to local regulations, whichever is older) at the time of voluntarily signing informed consent
3. Locally advanced unresectable or metastatic GC or GEJ carcinoma and have histologically confirmed adenocarcinoma
4. At least 1 measurable or non-measurable lesion per RECIST v1.1 as determined by investigator assessment.
5. No previous systemic therapy for locally advanced unresectable or metastatic gastric/GEJ cancer. NOTE: Patients may have received prior neoadjuvant or adjuvant therapy as long as it was completed and have no recurrence or disease progression for at least 6 months.
6. Patients must be able to provide tumor tissues (FFPE blocks or approximately 15 [≥ 7 if MSI/MMR and HER2 results are available] freshly cut unstained FFPE slides) with an associated pathological report. A fresh biopsy sample is highly preferred if feasible in clinic. If no archival samples are available, a fresh tumor biopsy at baseline is mandatorily required and slides requirement is the same with that in archival tumor tissues. PD-L1 expression will be assessed centrally, and patients who have evaluable PD-L1 results are eligible.
7. ECOG PS ≤ 1 within 7 days prior to randomization
8. Adequate organ function as indicated by the following laboratory values ≤ 7 days prior to randomization:
    a. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L, platelets ≥ 100 x 10^9/L, hemoglobin ≥ 90 g/L. NOTE: Patients must not have required a blood transfusion or growth factor support ≤ 14 days before sample collection
    b. Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or estimated Glomerular Filtration Rate ≥ 60 mL/min/1.73 m^2. (Appendix 8)
    c. Aspartate transaminase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN
    d. Serum total bilirubin ≤ 1.5 x ULN (total bilirubin must be < 3 x ULN for patients with Gilberts syndrome)
    e. International normalized ratio (INR) or prothrombin time (PT) (or prothrombin time ratio) ≤ 1.5 x ULN unless patient is receiving anticoagulant therapy and PT values are within the intended therapeutic range of the anticoagulant
    f. Activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN
    g. Albumin ≥ 3.0 g/dL or 30 g/liter

9. Patients with inactive/asymptomatic carrier, chronic, or active HBV infection must meet the following criteria: HBV deoxyribonucleic acid (DNA) < 500 IU/mL (or 2500 copies/mL) at screening. Patients with cured hepatitis C virus (HCV) infection at screening can be enrolled.

	Eligible
HBV	HB sAg (-)
	HB sAg (+) and HBV DNA < 500 IU/mL (or 2500 copies/mL)
HCV	HCV Ab (-)
	HCV Ab (+) and HCV RNA (-)

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

4.2. Exclusion Criteria

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

1. Patient has squamous cell or undifferentiated or other histological type GC
2. Active leptomeningeal disease or uncontrolled brain metastasis. Patients with equivocal findings or with confirmed brain metastases are eligible for enrollment provided that they are asymptomatic and radiologically stable without the need for corticosteroid treatment for ≥ 4 weeks before randomization.
3. Active autoimmune diseases or history of autoimmune diseases that may relapse (Appendix 5).

   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
4. Any active malignancy ≤ 2 years before randomization, with the exception of the specific cancer under investigation in this study and any locally recurring cancer that has been

treated curatively (eg, resected basal or squamous cell skin cancer, superficial bladder cancer, carcinoma *in situ* of the cervix or breast).

5. Uncontrollable pleural effusion, pericardial effusion, or ascites requiring frequent drainage (at least once a week) and/or diuretics within 7 days prior to randomization (the cytological confirmation of any effusion is permitted).
6. Have clinically significant bleeding (CTCAE ≥ Grade 2) from the gastrointestinal (GI) tract within 1 month prior to randomization
7. Have a history of ≥ Grade 2 (CTCAE) GI perforation and/or fistulae (including prior gastric fistula operation) within 6 months prior to randomization
8. Have a clinically significant bowel obstruction (CTCAE ≥ Grade 2)
9. Diagnosed with gastric or GEJ adenocarcinoma with positive HER2
10. Any condition that requires systemic treatment with either corticosteroids (> 10 mg daily of prednisone or equivalent) or other immunosuppressive medication ≤ 14 days before randomization

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

    a. Adrenal replacement steroid (dose ≤ 10 mg daily of prednisone or equivalent)
    b. Topical, ocular, intra-articular, intranasal, or inhalational corticosteroid with minimal systemic absorption
    c. Short course (≤ 7 days) of corticosteroid prescribed prophylactically (eg, for contrast dye allergy or antiemetic therapy for specific chemotherapy) or for the treatment of a non-autoimmune condition (eg, delayed-type hypersensitivity reaction caused by contact allergen)
11. With history of interstitial lung disease, non-infectious pneumonitis or uncontrolled systemic diseases, including diabetes, hypertension, pulmonary fibrosis, acute lung diseases, etc.

    NOTE: Patients with radiation pneumonitis may be randomized if the radiation pneumonitis has been confirmed as stable (beyond acute phase) without any concerns about recurrence. Patients with severe but stable radiation-induced pneumonitis may be required to undergo routine pulmonary function studies
12. With severe chronic or active infections requiring systemic antibacterial, antifungal or antiviral therapy, including tuberculosis infection, etc.
13. A known history of HIV infection
14. Any of the following cardiovascular risk factors:

    a. Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living, ≤ 28 days before randomization
    b. Symptomatic pulmonary embolism ≤ 28 days before randomization
    c. Any history of acute myocardial infarction ≤ 6 months before randomization
    d. Any history of heart failure meeting New York Heart Association Classification III or IV (Appendix 6) ≤ 6 months before randomization

e. Any event of ventricular arrhythmia ≥ Grade 2 in severity ≤ 6 months before randomization
f. Any history of cerebrovascular accident ≤ 6 months before randomization

15. Patients with weight loss ≥ 20% within 2 months prior to randomization and/or CTCAE ≥ Grade 2 anorexia within 7 days prior to randomization
16. Within 28 days or 5 half-lives (whichever is shorter but at least 14 days) prior to randomization: any immunotherapy (eg, interleukin, interferon, thymoxin, etc) or any investigational therapies; Within 28 days prior to randomization for investigational devices.
17. Within 14 days prior to randomization: any Chinese herbal medicine or Chinese patent medicines used to control cancer or boost immunity
18. Palliative radiation treatment within 14 days prior to randomization
19. Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2 or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways
20. Have undergone major surgery within 28 days prior to randomization, except if the procedure is minimally invasive (for example, introduction of peripherally inserted central catheter [PICC])
21. Prior allogeneic stem cell transplantation or organ transplantation
22. A history of severe hypersensitivity reactions to other monoclonal antibodies or any components of study treatment
23. Known dihydropyrimidine dehydrogenase (DPD) deficiency
24. 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, specific laboratory abnormalities)
25. Administered a live vaccine within 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.
26. Underlying medical conditions or alcohol or drug abuse or dependence that, in the investigator's opinion, will be unfavorable for the administration of study drug or affect the explanation of drug toxicity or adverse events; or insufficient compliance during the study according to investigator's judgement.
27. Have an estimated life expectancy < 3 months, in the judgment of the investigator.

5. STUDY TREATMENT

5.1. Formulation, Packaging, and Handling

5.1.1. Tislelizumab and Placebo

5.1.1.1. Tislelizumab

Tislelizumab is a monoclonal antibody formulated for intravenous infusion 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 rubber stopper and capped by an aluminum flip-off seal cap. Each vial is packaged into a single carton box.

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

The study drug must be kept at the temperature and light conditions as specified on the label and in the Pharmacy Manual.

Refer to the Pharmacy Manual for details regarding reconstitution, intravenous administration, accountability, and disposal. Refer to the Tislelizumab Investigator's Brochure for other details regarding tislelizumab.

5.1.1.2. Placebo

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

As with tislelizumab, the contents of the label will be in accordance with all applicable local regulatory requirements.

The study drug must be kept at the temperature and light conditions as specified on the label and in the Pharmacy Manual.

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

5.1.2. Chemotherapy

Management (ie, handling, storage, administration, and disposal) of cisplatin, 5-FU, capecitabine and oxaliplatin will be in accordance with relevant local guidelines and/or prescribing information. For sites where the sponsor is required to provide all study drugs including standard of care drugs: cisplatin, 5-FU, capecitabine, and oxaliplatin will either be supplied or reimbursed by the sponsor or designee.

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

5.2. Dosage, Administration, and Compliance

Dosing schedules for tislelizumab or placebo and chemotherapy are provided in Table 4 and Table 5. 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, as described in Section 5.5.

Table 4: Selection and Timing of Dose Administration of Tislelizumab or Placebo in Combination with Oxaliplatin and Capecitabine

Order of Administration on Day 1	Study Drug[a]	Dose (Route)	Initial 6 Treatment Cycles[b]	Cycle 7 and Beyond
First	Tislelizumab or placebo	200 mg (IV)	Day 1 of each 21-day cycle: Cycle 1: infuse over 60 minutes (wait 1 hour before chemotherapy) Cycles 2 to 6: infuse over 30 minutes (wait 1 hour before chemotherapy at cycle 2 and thereafter wait 30 minutes before chemotherapy)	Day 1 of each 21-day cycle, infusion over 30 minutes (wait 30 minutes before chemotherapy, if applicable)
Second	Oxaliplatin	130 mg/m^2 (IV)	Day 1 of each 21-day cycle	Discontinue treatment
Third	Capecitabine	1000 mg/m^2 (Oral)	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	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 during each 21-day cycle (Optional)

Abbreviations: IV, intravenous.

a. These products may be obtained by the investigational sites as local commercial products in certain countries if allowed by local regulations. These products should be prepared/stored/administered in accordance with the package inserts or summaries of product characteristics (SmPCs) or Pharmacy Manual.

b. Reduction of tislelizumab infusion time from 60 minutes to 30 minutes is based on the 60-minute infusion time being well tolerated.

Table 5: Selection and Timing of Dose Administration of Tislelizumab or Placebo in Combination with Cisplatin and 5-FU

Order of Administration on Day 1	Study Drug[a]	Dose (Route)	Initial 6 Treatment Cycles[b]	Cycle 7 and Beyond
First	Tislelizumab or placebo	200 mg (IV)	Day 1 of each 21-day cycle: Cycle 1: infuse over 60 minutes (wait 1 hour before chemotherapy) Cycles 2 to 6: infuse over 30 minutes (wait 1 hour before chemotherapy at cycle 2 and thereafter wait 30 minutes before chemotherapy)	Day 1 of each 21-day cycle, infusion over 30 minutes
Second	Cisplatin	80 mg/m² (IV)	Day 1 of each 21-day cycle	Discontinue treatment
Third	5-FU	800 mg/m^2/day (IV, using continuous pumping system)	Day 1 through Day 5 of each 21-day cycle	Discontinue treatment

Abbreviations: 5-FU, 5-fluorouracil; IV, intravenous.

a. These products may be obtained by the investigational sites as local commercial products in certain countries if allowed by local regulations. These products should be prepared/stored/administered in accordance with the package inserts or summaries of product characteristics (SmPCs) or Pharmacy Manual.

b. Reduction of tislelizumab infusion time from 60 minutes to 30 minutes is based on the 60-minute infusion time being well tolerated in previous cycles.

5.2.1. Tislelizumab or Placebo

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

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

As a routine precaution, after infusion of tislelizumab or placebo 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 before chemotherapy. From Cycle 3 onward, at least a 30-minute monitoring period is required in an area with resuscitation equipment and emergency agents before chemotherapy.

The initial infusion (Cycle 1, Day 1) will be delivered 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 or placebo 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 5.5.2, Section 8.7, and Appendix 7.

Details of tislelizumab or placebo and chemotherapy dose administration are summarized in Table 4 and Table 5.

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

5.2.2. Chemotherapy

When the oxaliplatin and capecitabine regimen is used as chemotherapy, patients will be treated with tislelizumab 200 mg or placebo intravenously on Day 1, followed by oxaliplatin 130 mg/m² intravenously on Day 1, and capecitabine 1000 mg/m² orally twice daily for 14 consecutive days from Day 1 during each 21-day cycle (Q3W). Oxaliplatin will be administered for up to 6 cycles and capecitabine as maintenance therapy may be administered until disease progression, intolerable toxicity, or another treatment discontinuation criterion is met. Tislelizumab (or placebo) will be administered until disease progression, intolerable toxicity, or treatment discontinuation for another reason.

NOTE: The capecitabine can be dosed either 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 cycle.

When the cisplatin and 5-FU regimen is used as chemotherapy, patients will be treated with tislelizumab 200 mg or placebo intravenously on Day 1, followed by cisplatin 80 mg/m² intravenously on Day 1, and 5-FU 800 mg/m²/day intravenously continuous infusion using pumping system over 24 hours daily on Day 1 through Day 5 during each 21-day cycle (Q3W). Cisplatin and 5-FU will be given for up to 6 cycles, and tislelizumab or placebo will be administered until disease progression, intolerable toxicity, or treatment discontinuation for another reason.

Each drug in the regimen should be administered sequentially. Details of tislelizumab or placebo and chemotherapy dose administration, including order of dosing and time between doses, are summarized in Table 4 and Table 5.

If the patient is unable to resume chemotherapy treatment within 6 weeks after the last dose of chemotherapy, then the patient should be discontinued from treatment. If the patient is not able to resume chemotherapy within 6 weeks after the last dose for unforeseen non-drug-related reasons, continued treatment may be allowed if approved by the medical monitor.

All subsequent chemotherapy doses must be rescheduled according to the last chemotherapy dose administration date.

Recommended guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.5.3 and Appendix 10. For commercially available drugs, please refer to SmPC or Pharmacy Manual as a resource. If there is a significant difference between the

protocol specified-guidelines and institutional standards of care, the investigator or designee should discuss this with the sponsor's medical monitor or its designee.

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

5.2.3. Supportive Care

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

5.3. Overdose or Incorrect Administration

Any overdose (defined as ≥ 600 mg of tislelizumab or placebo in a 24-hour period) or incorrect administration of study drug (for chemotherapy, doses > 120% of targeted total dose specified in this protocol represent an incorrect administration) should be noted in the patient's chart and on the appropriate eCRF. AEs associated with an overdose or incorrect administration of study drug will be recorded on the adverse event 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 and placebo) will be provided by the sponsor, as required by local or country-specific guidance. The investigational site will acknowledge receipt of tislelizumab and placebo. Any damaged shipments will be replaced, as appropriate.

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 Modification

Every effort should be made to administer the study drugs according to the planned dose and schedule. In the event of significant toxicities or logistical reasons not related to study therapy, dosing may be delayed and/or reduced based on the guidelines provided below. Reasons for dose reductions 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 reduce doses for other reasons (eg, AEs or laboratory findings) as appropriate.

5.5.1. General Guidance Regarding Dose Modifications

Reasons for dose modifications or delays, the supportive measures taken, and the outcome will be documented in the patient's chart and recorded in the eCRF. The severity of adverse events will be graded according to the NCI-CTCAE v5.0 grading system.

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

- Baseline body weight is used to calculate the required chemotherapy doses. The Mosteller formula is recommended for BSA calculation.

$$\text{BSA } (m^2) = \sqrt{\frac{hight\ (cm) \times weight\ (kg)}{3600}} \textbf{ OR } \text{BSA } (m^2) = \sqrt{\frac{hight\ (in) \times weight\ (lbs)}{3131}}$$

- Dose modifications are required if the patient's body weight changes by ≥ 10% from baseline (or the newly referred body weight). Chemotherapy doses should not be modified for any body weight change of less than 10%, unless there is an ongoing toxicity requiring dose modification. When several toxicities with different grades of severity occur at the same time, the dose modifications should be according to the highest grade observed.
- If any component of chemotherapy is temporarily interrupted, both chemotherapeutic agents will be delayed until doublet chemotherapy can be given as planned.
- In case of chemotherapy-related toxicity, chemotherapy will be delayed until it was resolved to baseline or ≤ Grade 1 prior to administering the next dose of chemotherapy, with the exception of alopecia, Grade 2 fatigue, or other AEs, which, in the opinion of the investigator, would not affect the safety evaluation of the study drugs. Tislelizumab or placebo should continue as scheduled. If the AE is resolved to baseline or ≤ Grade 1 within 10 days, chemotherapy will be administrated. The administration of chemotherapy and tislelizumab or placebo will be resynchronized at the subsequent cycle, which will be rescheduled according to the chemotherapy dose administration date. If the AE is not resolved within 10 days, chemotherapy will be omitted. If AE is resolved to baseline or ≤ Grade 1 within 21 days, chemotherapy and tislelizumab or placebo will be administered on Day 1 of the next planned cycle.
- In case of tislelizumab or placebo related toxicity, tislelizumab or placebo will be delayed until it resolves to baseline or ≤ Grade 1 prior to administering the next dose of tislelizumab or placebo, with the exception of alopecia, Grade 2 fatigue, or other AEs, which, in the opinion of the investigator, would not affect the safety evaluation of the study drugs. Chemotherapy should continue as scheduled. If the AE is resolved to baseline or ≤ Grade 1 within 10 days, tislelizumab or placebo will be administrated. 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 is not resolved within 10 days, tislelizumab or placebo will be omitted. If AE is resolved to baseline or ≤ Grade 1 within 21 days, tislelizumab or placebo and chemotherapy will be administered on Day 1 of the next planned cycle.

- The tumor assessment schedule will not be altered if chemotherapy and/or tislelizumab or placebo are delayed or discontinued.
- Every effort should be made to continue treatments in combination when patient's condition allows, also taking into consideration patient's convenience for the treatment schedule.
- Following either completion of or discontinuation from chemotherapy, tislelizumab or placebo should be continued as scheduled, if clinically appropriate. Capecitabine maintenance after completion of oxaliplatin + capecitabine doublet chemotherapy is also permitted.
- Reasons for dose modifications or delays, the supportive measures taken, and the outcomes will be documented in the patient's chart and recorded on the eCRF. The severity of adverse events will be graded according to the NCI-CTCAE v5.0 grading system.
- If one component of chemotherapy is discontinued permanently during the initial 6 cycles of treatment for reasons other than progressive disease (PD), the other component of chemotherapy could be continued per the study protocol or local practice.
- If tislelizumab or placebo is discontinued permanently during the initial 6 cycles of treatment, the patient may continue the chemotherapy per the study protocol or local practice.

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

5.5.2. Dose Modification for Tislelizumab or Placebo

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

Patients may temporarily suspend study treatment if they experience toxicity that is considered related to tislelizumab or placebo that requires a dose to be withheld, or if they have logistical reasons not related to study therapy. If a dose of tislelizumab or placebo is delayed for ≤ 10 days for a planned dosing cycle (eg, Cycle 3, Day 1), tislelizumab or placebo should be administered in the current cycle. If the delay is more than 10 days, patients should skip the tislelizumab or placebo dose at this cycle and will be dosed at the start of the next planned cycle (see Section 5.5.1).

The patients should resume tislelizumab or placebo treatment as soon as possible after the AEs recover to baseline or Grade 1 (whichever is more severe) within 12 weeks after last dose of tislelizumab or placebo. If the patient is unable to resume tislelizumab or placebo within 12 weeks after the last dose of tislelizumab or placebo, then the patient should be discontinued from treatment.

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

If a scheduled dose coincides with logistical reasons not related to study therapy (eg, elective surgery, unrelated medical events, patient vacation, and holidays) that precludes dosing, dosing should commence on the nearest following date and subsequent dosing can continue on a new 21-day schedule based on the infusion date.

If tislelizumab or placebo is discontinued because of tolerability concerns during the first 6 cycles of treatment, the patient may continue on the chemotherapy regimen (cisplatin + 5-FU or oxaliplatin + capecitabine) or 1 component of these regimens if agreed upon by the investigator and patient.

Patients who discontinue treatment for tislelizumab (or placebo) and/or chemotherapy toxicity in the absence of disease progression should continue on tumor assessment until an objective disease progression event occurs.

Specific treatment modifications to manage tislelizumab-related toxicities, such as imAEs and infusion-related reactions, are described Appendix 7 and Section 8.7.1, respectively.

5.5.3. Dose Modifications of Chemotherapy

Toxicities related to chemotherapy must be resolved to baseline or ≤ Grade 1 prior to administering the next dose of chemotherapy, with the exception of alopecia, Grade 2 fatigue, or other AEs, which, in the opinion of the investigator, would not affect the safety evaluation of the study drugs. A maximum of 2 dose reductions per 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.

If the patient is unable to resume chemotherapy treatment within 6 weeks after the last dose of chemotherapy, then the patient should be discontinued from treatment. If the patient is not able to resume chemotherapy within 6 weeks after the last dose for unforeseen non-drug-related reasons continued treatment may be allowed if approved by the medical monitor.

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (eg, elective surgery, unrelated medical events, patient vacation, and holidays). Patients should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the sponsor. The reason for interruption should be documented in the patient's study record.

Patients may also discontinue chemotherapy following multiple cycles if, in the investigator's judgment, cumulative toxicity is likely to increase over time and become problematic. Recommended guidance regarding dose modifications of chemotherapy for certain toxicities is presented in Appendix 10. For toxicities not listed, dose modifications are permitted per local standards.

5.5.4. Blinding

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

- Emergency unblinding

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

  All AEs should be evaluated and determined whether they are related to tizlelizumab plus chemotherapy or chemotherapy alone and treatment provided accordingly. Therefore, emergency unblinding should not be required to manage the patient's care. If knowledge of the investigational medicinal product is critical to the patient's management and the investigator decides that unblinding is required to manage an adverse reaction (eg, some ≥ Grade 3 imAEs or the event of a medical emergency or pregnancy), the investigator should make every effort to contact the sponsor medical monitor prior to unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient. If a patient's treatment assignment is unblinded due to an emergency treatment, the sponsor must be notified immediately.

- Inadvertent unblinding

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

- Unblinding for serious adverse reaction reporting

  The sponsor will unblind patients who experience an unexpected serious adverse reaction, for the purpose of reporting to the regulatory authorities. In such a case, the medical monitors will not be informed of the treatment allocation, according to the sponsor's standard procedures.

- Unblinding after final analysis

  Investigators, site personnel, and patients will be unblinded to treatment arms and PD-L1 result at the time of final analysis. Placebo administration will be discontinued after the unblinding. Crossover between the treatment arms will not be allowed.

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.

6. PRIOR AND CONCOMITANT THERAPY

6.1. Concomitant Therapy

6.1.1. Permitted Concomitant Medications/Procedures

All treatments that the investigator considers necessary for a patient's health and safety may be administered at the discretion of the investigator in keeping with the local standards of medical care. All concomitant medication, including all prescription and over-the-counter medications, herbal supplements and remedies, and intravenous medications and fluids, will be recorded on the eCRF. Patients may continue to receive hormone replacement if it was initiated prior to enrollment. Bisphosphonates and RANK-L inhibitors, if initiated prior to enrollment, are allowed for bone metastases.

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

Systemic corticosteroids required for the control of imAEs are suggested to be tapered over at least 1 month and be at non-immunosuppressive doses (≤ 10 mg/day of prednisone or equivalent) before the next study drug administration. The use of steroids as prophylactic treatment for patients with contrast allergies to diagnostic imaging contrast dyes or antiemetic therapy for specific chemotherapy is permitted.

Patients with active hepatitis B, defined as either detectable HBsAg or HBV DNA at baseline must initiate treatment 2 weeks prior to randomization or the first dose of study drug, and continue until 6 months after the last dose of study drug or per local guideline (eg, AASLD guidelines). Patients should continue effective antiviral treatment during the study to decrease potential viral re-activation risk. Tenofovir and entecavir are recommended in the American Association for the Study of Liver Disease (AASLD) guideline because they lack resistance with long-term use (Terrault et al, 2016; AASLD/IDSA HCV Guidance Panel, 2015). The investigator might use other antiviral agents, if appropriate, following local guidelines. Management of antiviral therapy is at the discretion of the investigator; however, reason(s) must be provided in the CRF if a patient with active hepatitis B is not treated with antiviral prophylaxis.

However, interferon-based therapy for HBV or HCV is not permitted on study.

Hematopoietic growth factors (ie, G-CSF or GM-CSF) may be used according to institutional or other specific guidelines (eg, country or regional guidelines or guidelines of oncology organizations, such as the American Society of Clinical Oncology [ASCO]) to treat febrile neutropenia but should not be used as primary prophylaxis. The use of any growth factor support must be documented in the patient's record and eCRF. Growth factors must be discontinued at least 48 hours prior to initiation of the next cycle of chemotherapy.

According to NCCN 2014 guidelines (https://www.nccn.org/), erythropoiesis-stimulating agents (ESAs) may be considered for the treatment of cancer-related anemia in patients undergoing palliative treatment. Erythropoietic therapy may be considered for treatment of chemotherapy-induced anemia in cases where hemoglobin is < 11 g/dL or a decrease of ≥ 2 g/dL from baseline, but only after the patient has been counseled about the risks and benefits of ESA use.

The use of prophylactic medication such as magnesium/calcium infusions or others for prevention of oxaliplatin-induced neuropathy is at the discretion of the investigator; however, these treatments are not recommended for use in this study, as their benefits have not been clearly established.

Whole brain radiation therapy (WBRT) and stereotactic radiosurgery (SRS) are permitted for patients with progressive central nervous system metastasis. Patients with symptomatic brain metastases are not eligible for participation in the study (refer to Section 4). Palliative (limited-field) radiation therapy is permitted, but only for pain control to sites of bone disease present at baseline provided that 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 sponsor's medical monitor, and the medical monitor agrees that the conditions required to receive palliative radiation have been met

Additionally, palliative radiation or other focally ablative therapy for other nontarget sites of the disease is permitted if the investigator determines that it is clinically indicated. These patients should have a tumor assessment of the lesion(s) before receiving the radiotherapy in order to rule out progression of disease.

6.1.2. Prohibited or Restricted Concomitant Medications

The following medications are prohibited or restricted at screening and during the study:

- Immunosuppressive agents (except to treat a drug-related AE) are restricted
- 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 (eg, antiemetic therapy for specific chemotherapy) are restricted
- Any concurrent systemic anticancer therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents [including Chinese herbal medicine and Chinese patent medicines] for the treatment of cancer) is not allowed
- Radiation therapy is not allowed, except for palliative radiation therapy described in Section 6.1.1.
- Live vaccines within 28 days before the first dose of study drugs and 60 days following the last dose of study drugs are prohibited. (NOTE: seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed.)
- Concomitant use of drugs with a potential ototoxic or nephrotoxic effect (eg, aminoglycosides, cefalotine, furosemide, amphotericin B) should be avoided or adequately monitored
- Allopurinol use in patients administered 5-FU should be avoided. Interactions with allopurinol have been observed with 5-FU that possible decrease efficacy of 5-FU.

- Antivirals and antiprotozoals: 5-FU should not be administered together with the antiviral drug sorivudine or its chemically related analogues, such as brivudine. A clinically significant drug-drug interaction between sorivudine and 5-FU, resulting from the inhibition of dihydropyrimidine dehydrogenase (DPD) by sorivudine, has been described in the literature (Diasio, 1998). This interaction, which leads to increased fluoropyrimidine toxicity, is potentially fatal.
- Metronidazole has been shown to increase the toxicity of 5-FU in patients with colorectal cancer, apparently by reducing the clearance of the antineoplastic (Bardakji, 1986). As it has been described in the literature, caution should be exercised in the cancer populations participating in this study.
- Phenytoin has been observed to have toxicity associated with elevated phenytoin concentrations in patients concomitantly taking capecitabine. Concentrations of phenytoin should be carefully monitored in patients taking capecitabine and phenytoin.
- Altered coagulation parameters and/or bleeding have been reported in patients taking capecitabine concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. Caution should be exercised with use of coumarin-derivative anticoagulants in the cancer populations participating in this study.
- Refer to the approved product labeling complete information regarding drug-drug interactions

The following are also prohibited during the study:

- Herbal remedies with immune-stimulating properties (eg, mistletoe extract) or known to potentially interfere with liver or other major organ function (eg, hypericin)
- Herbal remedies for the treatment of cancer or Chinese patent medicines with approval from the China NMPA for use as an anticancer treatment (regardless of cancer type)
- Patients should not abuse alcohol or other drugs during the study

Patients must notify the investigator of all herbal remedies used during the study.

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.

Treatment assignment in IRT and 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.

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other events, the visit should be scheduled on the nearest feasible date (the visit window is provided in Appendix 1), with subsequent visits rescheduled accordingly.

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 unless otherwise specified. ICF signature alone does not define the start of the screening period, instead, date of the first study related procedure is to be used as date of screening visit. Patients who are suspected or known to have serious respiratory concurrent illness or exhibit significant respiratory symptoms unrelated to underlying cancer should take a pulmonary function test (refer to Appendix 1 for details). Screening evaluations may be repeated as needed within the screening period; the investigator is to assess patient eligibility according to the latest screening assessment results.

Results of standard of care tests or examinations performed prior to obtaining informed consent and ≤ 28 days prior to randomization may be used for the purposes of screening rather than repeating the standard of care tests unless otherwise indicated.

Procedures conducted during the Screening Visit only are described in this section. For the description of other assessments that are conducted during screening, as well as throughout the study, refer to Safety Assessments (Section 7.4), Tumor and Response Evaluations (Section 7.5) and Biomarkers (Section 7.7). The PK sampling schedule is shown in Appendix 1.

Rescreening under limited conditions may be allowed after consultation with BeiGene. Rescreening is allowed only once. If the patient was rescreened, the patient must be re-consented. Any new result will override the previous one (ie, the most recent result prior to randomization) and is the value by which study inclusion will be assessed, as it represents the patient's most current clinical state.

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 related symptoms or signs; 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 the first dose of study drugs.

If appropriate, clinically significant disease should be graded according to NCI-CTCAE v5.0 and reported in the Medical History eCRF.

Cancer history will include pathologic diagnosis, stage at screening, tumor location, location of metastatic disease at study baseline, an assessment of prior surgery, prior radiotherapy, prior drug therapy, including start and stop dates, best response and reason for discontinuation. Radiographic studies performed prior to study entry may be collected for review by the investigator.

7.1.2. Females of Childbearing Potential and Contraception

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

7.1.3. Informed Consent and Screening Log

Voluntary, written informed consent for participation in the study must be obtained before performing any study-specific procedures unless otherwise specified. ICF signature alone does not define the start of the screening period, instead, date of the first study related procedure is to be used as date of screening visit. 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 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 approve the enrollment. Study site personnel should ensure that a medical monitor-approved Eligibility Authorization Packet is received before randomization.

Once enrolled in the IRT, patients that have met all eligibility criteria will be ready to be randomized through the IRT. The following information is required for patient randomization:

- Patient number
- Year of birth
- Gender: male versus female
- Region: China (including Taiwan) vs. Japan and S. Korea vs. US and Europe and other regions. NOTE: other regions include other western countries/populations.
- PD-L1 expression (positive or negative): PD-L1+ patients are patients with tumor and immune cell score (TIC score) ≥ 5% using VENTANA PD-L1 (SP263) Cdx Assay. TIC score is the total percentage of the tumor area covered by tumor cells with PD-L1 membrane staining and tumor-associated immune cells with PD-L1 staining at any intensity.
- Presence of peritoneal metastasis (yes or no)
- Investigator's choice of chemotherapy

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 assign study drugs which is supplied centrally by sponsor. The choice of chemotherapy regimen must be decided prior to randomization and the interchange of chemotherapy regimen is not permitted during study period. Study treatment must commence within 3 days after randomization/treatment assignment.

7.3. Tislelizumab, Placebo and Chemotherapy Dispensing

Tislelizumab or placebo and chemotherapy 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 pulse rate, and blood pressure (systolic and diastolic) while the patient is in a seated position after resting for 10 minutes, and body temperature (˚C).

For the first infusion of tislelizumab or placebo, the patient's vital signs are required to be recorded within 60 minutes before, during, and within 30 minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before infusion and, if clinically indicated, during and within 30 minutes after the infusion. Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms. Refer to Section 5.2.1 regarding precautionary monitoring of patients post infusion of tislelizumab or placebo.

7.4.2. Physical Examinations

A complete physical examination including an evaluation of 1) head, eyes, ears, nose, throat, 2) cardiovascular, 3) dermatological, 4) musculoskeletal, 5) respiratory, 6) gastrointestinal, and 7) neurological systems is required to be performed at screening. Any abnormality identified at baseline will be graded according to NCI-CTCAE v5.0 and recorded on the Medical History eCRF with appropriate disease/condition terms.

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

7.4.3. Eastern Cooperative Oncology Group Performance Status

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

7.4.4. Laboratory Safety Tests

Local and/or central laboratory assessments on serum chemistry, hematology, thyroid function, coagulation, and urinalysis will be conducted, of which certain elements will be collected as specified in Appendix 2. If serum chemistry, hematology, coagulation, or urinalysis at screening are not performed within 7 days prior to the administration of study drugs on Cycle 1 Day 1, these tests should be repeated and reviewed before study drugs 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 each subsequent cycle. After Cycle 1, results are to be reviewed within 72 hours before study drug administration.

If a patient experiences elevated ALT/AST ≥ 5 x ULN and/or elevated total bilirubin ≥ 3 x ULN, the sponsor should be notified as soon as possible. Clinical and laboratory monitoring should be initiated by the investigator.

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.

7.4.4.1. 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) is 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 CK-MB fractionation is not available.

7.4.5. Electrocardiograms

A 12-lead ECG is required at screening, safety follow-up, and as clinically indicated. ECGs should be obtained on the same machine for all study assessments, if possible. Lead placement should be as consistent as possible. The ECG recordings should be performed after the patient has been resting for at least 10 minutes.

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

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

7.4.6. Adverse Events

Adverse events will be graded and recorded throughout the study according to NCI-CTCAE, version 5.0 (NCI-CTCAE). Characterization of toxicities will include severity, duration, and time to onset.

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

7.4.7. Ophthalmologic Examination

Eye exam, visual acuity test, and optical coherence tomography (or equivalent diagnostic test) will be assessed by an appropriate specialist at the Screening Visit for all patients. 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. Patients will undergo repeat assessments by an appropriate specialist approximately every 15 weeks (± 7 days) during study treatment and at either the EOT or during safety follow-up.

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

7.4.8. Hepatitis B and C Testing

Testing will be performed by local and/or central laboratory at Screening and will include HBV/hepatitis C virus (HCV) serology (HB sAg, HB sAb, hepatitis B core antibody [HB cAb], and HCV antibody) and viral load assessment (HBV and HCV) will be required if clinically indicated.

Patients who have detectable HBV DNA at screening will perform a viral load test at least every 4 cycles (ie, Day 1 of Cycle 5, 9 and 13, etc).

7.5. Tumor and Response Evaluations

Tumor imaging will be performed within 28 days prior to randomization. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and ≤ 28 days prior to randomization may be used for the purposes of screening rather than repeating the standard-of-care tests. During the study, tumor imaging will be performed approximately every 6 weeks (± 7 days) during the first 48 weeks and thereafter approximately every 9 weeks (± 7 days).

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

Tumor assessments must include CT scans (with oral/intravenous contrast, unless contraindicated) or MRI, with preference for CT, of the chest, abdomen, and pelvis. 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 as used to assess disease sites at screening is required to be used throughout the study (eg, the same contrast protocol for CT scans).

- An MRI (or CT scan if MRI is contraindicated or not readily available) of the brain may be required at screening based on clinical judgement.
- If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the study, a non-contrast CT of the chest plus a contrast-enhanced MRI (if possible) of abdomen and pelvis should be performed.
- If a CT scan for tumor assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan.
- Bone scans (technetium-99m [TC-99m]) or 18F-sodium fluoride (NaF) positron-emission tomography (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 18F-NaF PET bone scans should be conducted when a CR is suspected. In addition, TC-99m or 18F-NaF PET bone scans may be conducted when progression in bone is suspected.
- CT scans of the neck or extremities should also be performed if clinically indicated and followed throughout the study, if there is evidence of metastatic disease in these regions at Screening. At the investigator's discretion, other methods of assessment of target lesion and nontarget lesions per RECIST v1.1 may be used.

Response will be assessed by the investigator using RECIST v1.1 (see Appendix 4).

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 disease progression (eg, toxicity) will continue to undergo tumor assessments following the original plan until the patient begins a subsequent anticancer treatment, experiences disease progression, withdraws consent, is lost to follow-up, 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 Antidrug Antibody Testing

Pharmacokinetic samples will be collected in patients randomized to receive tislelizumab or placebo at the time points presented in Appendix 1. Procedures for collection of PK samples are described in the Laboratory Manual.

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.

The following assessments will be performed at a central laboratory:

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

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

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

7.7. Biomarkers

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

7.7.1. Tissue Biomarkers

See Appendix 1 for the tissue biomarker sample collection schedule.

Tumor tissues (FFPE blocks or approximately 15 [≥ 7 if MSI/MMR and HER2 results are available; additional 5 if MSI/MMR result is not available; and additional 3 to 6 if HER2 status is not identified] freshly cut unstained FFPE slides) need to be sent to investigational site or central laboratory for biomarker analysis, including central immunohistochemistry assay of PD-L1 status. For patients with unavailable MSI/MMR status, an MSI or MMR assessment will be performed in investigational sites, third-party local lab or designated central laboratory. For MMR testing, 5 FFPE slides required; for MSI testing, 5 FFPE slides and approximately 2 mL blood samples will be collected. Patients with unknown HER2 status must undergo a HER2 test at the investigational sites (or other designated sites), third-party local lab or sponsor designated central laboratory prior to enrollment. Refer to Section 4.1 for inclusion criteria and Appendix 14 for HER2 pathological review guideline.

In addition to PD-L1 expression, MSI/MMR and HER2 status, status of EBV infection, GS, and CIN will be collected if available. Other exploratory predictive biomarkers, such as gene

expression profiling (GEP), tumor infiltrating lymphocytes (TILs), and tumor mutation burden (TMB) that are related to response or clinical benefit of tislelizumab may also be evaluated from remaining tumor tissue obtained at baseline. A fresh biopsy sample is highly preferred if feasible in clinic. If no archival samples are available, a fresh tumor biopsy at baseline is mandatorily required. Acceptable fresh biopsy samples include core needle biopsies for deep tumor tissue or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.

Optional biopsy will also be taken at the EOT visit for the patients who have confirmed disease progression during the study from accessible tumor sites to obtain samples, which could be used for exploratory study including but not limited to the resistance mechanism. If feasible, any follow up biopsy should be ideally taken from the same tumor lesion as the baseline biopsy. Written informed consent is required for fresh tumor biopsies at EOT.

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

7.7.2. Blood Biomarkers

See Appendix 1 for the blood biomarkers sample collection schedule.

Optional blood samples of approximately 10 mL will be taken at baseline (predose at Day 1 of Cycle 1), at the time of first tumor response (predose at Day 1 of the following Cycle) and at EOT after disease progression (10 mL each timepoint) for all randomized patients to explore the association of blood-based biomarkers with response, prognosis and resistance to tislelizumab in combination with chemotherapy or chemotherapy alone. Written informed consent is required for optional blood sample collection.

7.8. Patient-reported Outcomes

Patients will be asked to complete the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30) (Appendix 11), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Gastric Cancer Module QLQ-STO22 (EORTC QLQ-STO22) (Appendix 12), and European Quality of Life 5-Dimensions 5-Levels Health Questionnaire (EQ-5D-5L) (Appendix 13) questionnaires before any clinical activities are performed during on-study clinic visits apart from blood draw according to the schedule in Appendix 1. The questionnaires will be provided in the patient's preferred language.

7.9. Visit Windows

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

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other events, the visit should be scheduled on the nearest feasible date (the visit window is provided in

Appendix 1), with subsequent visits conducted according to a new 21-day schedule based on the date of the patient's last study treatment.

7.10. Unscheduled Visits

Unscheduled visits may be performed at any time at the patient's or 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 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 Tislelizumab and Chemotherapy

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 8.7.2.

An imAE may occur at any time during or after treatment. Often, the etiology of imAEs is not clear, and other causes should be ruled out. This may require diagnostic testing and consultation with a specialist. Suggested evaluation and management guidelines for suspected imAEs are provided in Appendix 7.

8.1.2. Risks Associated with Platinum and Fluoropyrimidine

Refer to the most recent, locally approved package insert for information on the risk associated with a particular platinum- or fluoropyrimidine-based chemotherapy.

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 taken into account. Specifically, patients at risk for study-emergent active autoimmune diseases, or with a history of autoimmune diseases that may relapse, patients who have undergone allogenic stem cell or organ transplantation and patients who have received a live viral vaccine within 28 days before randomization are excluded from the study. Patients with contraindications for chemotherapy treatment are also excluded from the study (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 adverse events, defined and graded according to NCI-CTCAE v5.0 (except as noted in Section 8.6.4). Patients will be assessed for safety (including laboratory values) according to the schedule in Appendix 1. Clinical laboratory results must be reviewed prior to the start of each cycle.

In this study, all enrolled patients will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of AEs, physical examinations, laboratory

measurements (hematology, chemistry, etc.), imaging, consultations (as needed), and other assessments including those listed in Appendix 1. In addition, patients will be closely monitored for the development of any signs or symptoms of autoimmune conditions and infections.

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

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

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

8.3. Adverse Events

8.3.1. Definitions and Reporting

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

Examples of AEs include:

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

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

8.3.2. Assessment of Severity

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

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

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

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

NOTE: The terms "severe" and "serious" are not synonymous. Severity is a measure of intensity (for example, grade of a specific AE, mild [Grade 1], moderate [Grade 2], severe [Grade 3], or life-threatening [Grade 4]), whereas seriousness is classified by the criteria based on the regulatory definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the sponsor to applicable regulatory authorities as described in Section 8.6.2.3.

8.3.3. Assessment of Causality

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

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

The causality of each AE should be assessed and classified by the investigator as "related" or "not related". An AE is considered related if there is "a reasonable possibility" that the AE may have been caused by the study 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 postmortem findings, including histopathology.

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

8.3.5. Laboratory Test Abnormalities

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
- require 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 (or mmol/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, meet any of the following criteria:

- Results in death
- Is life-threatening

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

- Requires hospitalization or prolongation of existing hospitalization

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

- Results in disability/incapacity

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

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

The following are NOT considered SAEs:

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

8.5. Suspected Unexpected Serious Adverse Reaction

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

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

8.6.1. Adverse Event Reporting Period

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

After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until either 30 days after last dose of study drugs or initiation of new anticancer therapy, whichever occurs first. Immune-mediated AEs (serious or non-serious) should be reported until 90 days after the last dose of tislelizumab or placebo, regardless of whether or not the patient starts a new anticancer therapy. All SAEs considered related to the study drug(s) that are brought to the attention of the investigator should be reported regardless of time since the last dose of treatment.

AEs and SAEs should be recorded according to the details in Table 6. For the follow-up period for AEs, see Section 8.3.4. For the definition of TEAEs, see Section 9.3.2.

Table 6: 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 (not treatment-related)	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
Treatment-related SAEs	Signing of informed consent	Patient 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)	
Nonserious AEs other than 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

Event type	Record new or worsening events that occur during this period	
	Begin	**End**
Immune-mediated AEs (serious or nonserious)	First dose of study drug	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.

8.6.2. Reporting Serious Adverse Events

8.6.2.1. Prompt Reporting of Serious Adverse Events

As soon as the investigator determines that an AE meets the protocol definition of an SAE, the event must be reported promptly (within 24 hours) to the sponsor or designee as described in Table 7.

Table 7: Timeframes and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

	Timeframe for Sending Initial Report	Documentation Method	Timeframe for Making Follow-up Report	Documentation Method	Reporting Method
All SAEs	Within 24 h of first knowledge of the SAE	SAE Report	As expeditiously as possible	SAE Report	Electronic submission of SAE form to portal [a]

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

[a] SAE reports should be submitted to the sponsor safety database electronically from within the electronic data capture system. If the electronic submission is not available for any reason, a paper SAE form should be submitted by email or fax.

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. Treatment assignment revealed through unblinding (see Section 5.5.4) must not be included in the SAE report.

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

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

8.6.3. Eliciting Adverse Events

The investigator or designee will ask 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 as to whether a nonserious AE is due to disease progression, it should be recorded as an AE. All SAEs and deaths regardless of relatedness to disease progression should be recorded and reported (see Section 8.6.2.1).

8.6.5. Deaths

When a patient dies, if the only information available is death and the cause of death is unknown, then the death is reported as an AE, eg, "death NOS". In all other cases, death is captured as an outcome.

8.6.6. Pregnancies

If a female patient or the partner of a male patient becomes pregnant while receiving investigational therapy or within 120 days after the last dose of tislelizumab or placebo or within 180 days after the last dose of chemotherapy, a pregnancy report form is required to be submitted to the sponsor. The pregnancy report must follow the same prompt reporting guidelines

described in Section 8.6.2.1. The outcome of the pregnancy, including any premature termination of the pregnancy must also be reported to the sponsor.

While pregnancy itself is not considered to be an adverse event, 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.

Patients who become pregnant must immediately discontinue treatment (see Section 3.6.1). For patients who are no longer pregnant, resumption of treatment may be discussed with the medical monitor.

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
- The prescribing information of chemotherapy

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 8.7.2) should be classified as imAEs and identified as such in the eCRF AE page.

8.6.9. Recording Infusion-Related Reactions

The signs and symptoms of an infusion-related reaction should be recorded as the adverse terms for those individual signs and symptoms. In assessing whether an adverse event is infusion related, note that 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.

8.7. Management of AE of Special Interest

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

8.7.1. Infusion-Related Reactions and Hypersensitivity Reactions

Patients should be closely monitored during and after study drug administration for infusion-related reactions and hypersensitivity reactions. See Section 5.2.1 for the monitoring periods required. Immediate access to an Intensive Care Unit (ICU) or equivalent environment and appropriate medical therapy (including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen) must be available to treat infusion-related reactions.

See Appendix 7 for management of infusion-related reactions and hypersensitivity reactions as well as treatment modifications.

8.7.2. Immune-Mediated Adverse Events

In this study, imAEs are of special interest. Potential imAEs are listed in Table 8 below. All AEs similar to those listed in the table should be evaluated in patients receiving tislelizumab or placebo to determine whether the AE is immune-mediated. The investigator should exclude alternative explanations (eg, combination drugs, infectious disease, metabolic causes, toxins, disease progression, or other neoplastic causes) with appropriate diagnostic tests that may include but are not limited to serologic, immunologic, and histologic (biopsy) data (see Appendix 7). If alternative causes have been ruled out and the AE required the use of systemic steroids, other immunosuppressants, or endocrine therapy, and it is consistent with an immune-mediated mechanism of action, the imAE indicator in the eCRF AE page should be checked.

Recommendations for managing imAEs are detailed in Appendix 7.

Table 8: Examples of 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
Musculoskeletal	arthritis; arthralgia; myalgia; myasthenic syndrome/myasthenia gravis, myositis
Blood	anemia; leukopenia; thrombocytopenia
Renal	interstitial nephritis; glomerulonephritis; acute renal failure
Cardiac	pericarditis; myocarditis; heart failure
Neurologic	encephalitis; Guillain-Barre syndrome; meningitis; meningoradiculitis; meningoencephalitis; neuropathy

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

9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

The statistical analyses will be performed by the sponsor or designee after data collection 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.

The stratified randomization will be produced, reviewed, and approved by an independent statistician.

9.1.2. Analysis Sets

Intent-to-Treat (ITT) analysis set – Includes all randomized patients. Patients will be analyzed according to their randomized treatment arm. This will be the dual primary analysis set for all efficacy analyses.

PD-L1+ analysis set (with tumor and immune cell score [TIC score] ≥ 5% using VENTANA PD-L1 [SP263] Cdx Assay. TIC score is the total percentage of the tumor area covered by tumor cells with PD-L1 membrane staining and tumor-associated immune cells with PD-L1 staining at any intensity) – Includes all randomized patients whose tumors were PD-L1+. Patients will be analyzed according to their randomized treatment arms. This will be the dual primary analysis set for efficacy analyses.

Per-Protocol (PP) analysis set – Includes all randomized patients who received at least 1 dose of the assigned study drug and had no major protocol deviations. Major protocol deviations will be determined and documented before the database lock for the primary analyses.

Safety analysis set – Includes all patients who received at least 1 dose of study drugs. This will be the analysis set for the safety analyses.

9.1.3. Patient Disposition

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

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

9.1.4. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized in the ITT analysis set using descriptive statistics. Continuous variables include age, weight, vital signs, time since initial cancer diagnosis, and time since advanced/metastatic disease diagnosis; categorical variables

include, PD-L1 expression, gender, ECOG, geographical region, race, tumor staging, number of metastatic sites, metastatic site (eg liver, peritoneal, lung bone, etc.), previous gastrectomy, weight loss (< 10% versus ≥ 10%), age (< 65 years versus ≥ 65 years), primary tumor location (GEJ vs. gastric), histologic type (well differentiated, moderately differentiated, poorly differentiated, unknown differentiated). The histologic type (Lauren Classification) including the diffuse-type, intestinal-type, mixed type and unknown status are also collected if available.

9.1.5. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHO Drug Dictionary drug codes. Prior and 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). A listing of prior and concomitant medications will be included in the CSR for this protocol.

9.2. Efficacy Analyses

The type I error will be strongly controlled at 0.025 (1-sided) in the primary analysis of OS in PD-L1+ and ITT analysis sets using sequential testing method. OS analysis in ITT analysis set will be performed only if the OS analysis in the PD-L1+ analysis set is statistically significant favoring tislelizumab + chemotherapy.

Hypothesis testing of the secondary endpoints PFS and ORR in the PD-L1+ and ITT analysis sets will be performed at the same time as the interim analysis of OS. Only when the superiority of OS in both PD-L1+ and ITT analysis sets have been demonstrated, its alpha of 0.025 (1-sided) will be shifted sequentially to the hypothesis testing of the secondary endpoints in order of PFS in PD-L1+, ORR in the PD-L1+ analysis set, followed by PFS and ORR in ITT analysis set. The inferential test will be stopped at the first non-significant endpoint. Nominal p-values may be computed for other efficacy analysis but should be interpreted with caution.

9.2.1. Primary Efficacy Analysis

<u>OS in the PD-L1+ analysis set:</u>

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 once the targeted number of death events is 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 cutoff, whichever comes earlier.

OS will be compared between Arm A and Arm B using stratified log-rank test at 1-sided 0.025 level of significance, stratified by pooled stratification factors of regions of enrollment (east Asia versus rest of the world [ROW]), and presence of peritoneal metastasis.

The median OS and the cumulative probability of OS at every 6 months 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 12 and 24 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 factor and region of enrollment (east Asia versus ROW) and presence of peritoneal metastasis as strata. From this model, the hazard ratio (HR) of OS will be estimated and presented with a 2-sided 95% CI.

These analyses will be performed in the PD-L1+ analysis set as the primary analysis. Outcomes in the Per Protocol analysis set will be evaluated as a sensitivity analysis.

OS in the ITT analysis set:

Analysis of OS in the ITT analysis set will be performed only if superiority of OS favoring tislelizumab + chemotherapy is demonstrated in the PD-L1+ analysis set.

The hypothesis testing of OS in the ITT analysis set will be carried out similarly at a significance level of 0.025 (1-sided) in the stratified analysis (ie, log-rank and Cox regression) stratified by pooled stratification factors of regions of enrollment (east Asia versus ROW), PD-L1 expression, and presence of peritoneal metastasis. There will be one interim analysis of OS using the O'Brien-Fleming boundary approximated by Hwang-Shih-DeCani spending function with the gamma parameter set at -4. The non-binding lower (futility) boundary is defined by Hwang-Shih-DeCani spending function with the gamma parameter set at -12. The interim analysis of OS will be performed when approximately 269 deaths in the PD-L1+ analysis set and 538 deaths in the ITT analysis set (70% of the target number of OS events in each analysis set) among the 2 treatment arms have been observed which is estimated to occur approximately 30 months after the first patient is randomized. The final analysis of OS will take place after approximately 384 and 768 death events have been observed in the 2 analysis sets, respectively, which is estimated as 48 months after the first patient is randomized. Stopping boundaries in p-value and Z score for primary analyses of OS are shown in Table 9. The boundaries will be updated according to the actual numbers of events in the interim and final analyses, using the above pre-specified alpha spending function.

Table 9: Stopping Boundaries (in p-value and Z score) of Primary Analysis of OS

Analysis Set	Analysis	Time (m)	# Events	p-value[a] (Z score) for Efficacy	p-value[a] (Z score) for Interim Futility	Approximate HR Threshold	Cumulative Prob of Crossing Under H_1
PD-L1+[b]	Interim analysis	30	269	< 0.0072 (>2.45)	> 0.5731 (< -0.18)	0.742	0.47
	Final analysis	48	384	< 0.0228 (> 2.00)	-	0.815	0.80
ITT	Interim analysis	30	538	< 0.0072 (>2.45)	> 0.5384 (< -0.1)	0.810	0.56
	Final analysis	48	768	< 0.0228 (> 2.00)	-	0.866	0.87

a. 1-sided
b. PD-L1+ is 50% of the ITT

9.2.2. Secondary Efficacy Analysis

PFS assessed by investigators per RECIST v1.1 will be estimated using the Kaplan-Meier (KM) method in the PD-L1+ and ITT analysis set. The PFS censoring rule will follow United States (US) FDA Guidance for Industry, Clinical Trial Endpoints for Approval of Cancer drugs and Biologics (2007) (FDA Guidance for Industry 2007). Data for patients without disease progression or death at the time of analysis will be censored at the time of the last adequate tumor assessment. Data for patients who are lost to follow-up prior to documented disease progression will be censored at the last adequate tumor assessment date when the patient is known to be progression free. Data for patients who start to receive new anticancer therapy will be censored at the last adequate tumor assessment date prior to the introduction of new therapy.

The median PFS and the cumulative probability of PFS at every 3 months including PFS-6m and PFS-12m 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.

The treatment effect will be estimated by fitting a Cox regression model to the PFS times including treatment arm as a factor and region of enrollment (east Asia versus ROW), PD-L1 expression (only when testing PFS in the ITT analysis set), and presence of peritoneal metastasis as strata. From this model, the hazard ratio (HR) of PFS will be estimated and presented with a 2-sided 95% CI.

The null hypotheses of no difference in ORR per RECIST 1.1 assessed by investigators will be tested in a Cochran-Mantel-Haenszel (CMH) test adjusting for pooled stratification factors in the ITT and PD-L1+ analysis sets. 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, as well as Clopper-Pearson 95% CIs of ORR for each treatment arm.

Duration of response (DOR) assessed by investigators will be analyzed similarly to PFS in the responders.

Change from baseline of EORTC QLQ-STO22, EORTC QLQ-C30 and EQ-5D-5L will be compared between Arms A and B.

Both EORTC scales and single items will be scored on a categorical scale and transformed to a 0-100 scale. In addition to change from baseline scores, minimal important differences defined as 10-point change from baseline will be used to calculate the proportion of patients with clinically meaningful deterioration over time. Descriptive statistics will be used to show the changes from baseline and percentage of patients with deterioration at each time point in each arm, unless otherwise specified.

BOR is defined as the best response per RECIST v1.1 recorded from randomization till data cut, progressive disease or start of new anticancer 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. Time to response (TTR) will be summarized using descriptive statistics, such as mean, median, and standard deviation. Only patients who have achieved an objective response will be included in the analysis of TTR.

DCR and clinical benefit rate (CBR) assessed by investigators will be analyzed similarly to ORR in the ITT and PD-L1+ analysis sets.

9.2.3. Exploratory Efficacy Analysis

To calculate progression-free survival after next line of treatment (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 (KM) method as described in the PFS and OS analyses will be used in the analysis of PFS2.

9.3. Safety Analyses

Safety will be assessed by the monitoring and recording of all AEs graded by NCI-CTCAE v5.0. 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 (investigator's description from the eCRF) will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to

MedDRA (Version 20.0 or higher) lower level term, preferred term and primary system organ class (SOC).

A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the date of first dose of study drug and up to 30 days following study drug discontinuation (Safety Follow-up visit) or initiation of new anticancer therapy, whichever comes first. The TEAE classification also applies to imAEs that are recorded up to 90 days after the last dose of tislelizumab or placebo, regardless of whether or not the patient starts a new anticancer therapy. Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in patient data listings.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by SOC and Preferred Term. A patient will be counted only once by the highest severity grade per NCI-CTCAE v5.0 within an SOC and Preferred Term, even if the patient experienced 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 a study drug or with missing assessment of the causal relationship. SAEs, deaths, TEAEs with ≥ Grade 3 severity, imAEs, 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 provided. 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 by NCI-CTCAE v5.0 will be summarized by NCI-CTCAE grade. In the summary of laboratory parameters by NCI-CTCAE grade, parameters with NCI-CTCAE grading in both high and low directions (eg, glucose, potassium, sodium) will be summarized separately.

9.3.4. Vital Signs

Descriptive statistics for vital sign parameters (systolic and diastolic blood pressure, heart rate, and 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.

9.3.6. Pulmonary Function Test

Pulmonary function test results will be listed by patient if available.

9.4. Pharmacokinetic Analysis

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

Additional PK analyses may be conducted as appropriate. Exposure-response (efficacy or safety endpoints) analysis such as population PK, PK/pharmacodynamic analyses may be carried out if supported by data. Any such analysis 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 sample size calculation is based on the primary efficacy analyses of OS in the comparison between Arms A and B in the ITT and PD-L1+ analysis sets. The number of events needed is based on the assumption of an exponential distribution. The 1-sided overall type I error in the study is set at 0.025. Table 10 summarizes the statistical assumption and power in the sample size calculation. Assuming a 50% PD-L1+ prevalence rate, a total of 928 patients including approximately 464 (ie, 50%) in the PD-L1+ subset is required in order to observe targeted numbers of OS events at the defined time periods as shown in Table 9 above. Assuming a roughly 5% dropout rate, approximately 980 patients will be enrolled in a 1:1 randomization ratio over 24 months period at enrollment rates of 17 patients/month in the first 2 months, 34 patients/month in the next 2 months and 44 patients/month in the last 20 months. The enrollment assumptions including percentage of PD-L1+ patients will be monitored during the enrollment; thus sample size and timeline could be adjusted accordingly. Enrollment of patients whose tumors are PD-L1- might be stopped if necessary, to ensure that the percentage of PD-L1+ is no less than 50% of the ITT analysis set. The primary analyses will be performed when the target number of events is observed. An interim analysis of OS (see Table 9) is planned after approximately 70% of the total planned death events have occurred in both ITT and PD-L1+ analysis sets.

Table 10: Hazard Ratio and Median OS Assumption, Number of Events, Alpha And Power in The Primary Hypothesis Tests

Analysis Set	HR	Median in Arm A (in months)	Median in Arm B (in months)	# Events	Alpha	Power
PD-L1+	0.75	15.3	11.5	384	0.025	80%
ITT	0.8	14.4	11.5	768	0.025	87%

9.7. Interim Analyses

This is a randomized, double-blind, placebo-controlled, Phase 3 clinical study. Data summary by actual treatment assignment and PD-L1 status will be limited and documented. Study team at the

sponsor will not have access to the summary or individual patient reports by actual treatment group during the study.

An interim analysis for OS superiority (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.

Safety monitoring will be conducted continuously through end of treatment visit.

10. STUDY COMMITTEES AND COMMUNICATION

10.1. Independent Data Monitoring Committee

Regular safety monitoring (at least every 6 months), and efficacy monitoring will be performed by an IDMC. The first IDMC safety review will occur after at least 50 patients have been randomized to study treatment (ie, approximately 25 patients per treatment arm) and have been on treatment for ≥1 month in order to determine if the proposed dosing schedule of tislelizumab or placebo plus chemotherapy is safe and tolerable. The IDMC will also be responsible for reviewing the unblinded results of interim analysis of OS and making recommendations for discontinuation or modification of the study. The function and membership of the IDMC will be described in the IDMC charter.

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

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

11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

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

11.1. Access to Information for Monitoring

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

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

11.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of the sponsor 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 the representatives of a regulatory agency or representatives of the sponsor with 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. Alternatively, the sponsor will 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 acknowledging the 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 the sponsor's designated depot or its designee and quantities dispensed to patients, including batch/lot number, date dispensed, patient identifier number, and the initials of the person dispensing the medication.

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

All drug supplies and associated documentation will be reviewed periodically 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 guidelines for Good Clinical Practice (ICH E6) 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 patient. The study will also comply with the Definitions and Standards for Expedited Reporting (ICH E2A).

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, reviewed, and approved by the IRB/IEC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/IEC. Copies of the IRB/IEC correspondence and approval of the amended ICF or other information and the approved amended ICF/other information must be forwarded to the sponsor promptly.

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 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 Long-term/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 Long-term/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' anonymity 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 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.

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

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

Investigator and site must use only the specific forms and clinical trial systems, (eg, the electronic data capture [EDC] system and any secure file transfer platforms [SFTPs]) designated by sponsor for sharing and transfers of personal and medical information.

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

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare for treatment purposes where allowed by local law or the patient's signed ICF.

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

The investigator agrees that all information received from the sponsor, including but not limited to the Investigator's Brochure, this protocol, eCRFs, the investigational drugs, and any other study information, are confidential and remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The investigator further agrees to take all

reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

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

Demographic factors such as age, gender, race, and ethnicity could influence the effects (safety and efficacy) of medicines and the risk/benefit assessment in different populations. Race and ethnicity data are collected in accordance with ICH guidance (ICH E5 1998, ICH E17 2017) adopted by the EMA and US FDA, to understand whether race/ethnicity could influence the PK, safety, and/or efficacy of the study drug. For example, population PK analysis is a well-established, quantitative method that can quantify and explain the variability in drug concentrations among patients. Such variability can be attributed to intrinsic factors (eg, body weight, age, gender, race/ethnicity), or to extrinsic factors (eg, concomitant medications), and can lead to clinically relevant changes in drug concentrations that require a change in the dose or dosing regimen. Results from race/ethnicity and other demographic analyses will be incorporated into drug product labeling to provide guidance on safety and efficacy variations (if any) linked to certain populations (eg, race or ethnic group) as well as any potential dose adjustment needed for those populations. Therefore, collecting race/ethnicity data in the study is essential to understand whether race/ethnicity could influence the PK, safety, and/or efficacy.

13.5. Financial Disclosure

Investigators (including any subinvestigators and coinvestigators) 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 the sponsor 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 Entry in the Electronic Case Report Form

All study-related data collected or received by the investigator or study team shall be promptly entered into the eCRFs. In no event should the entry of the study data into the eCRF be later than what is stipulated in the site contract after the data is collected or received by the investigator or study team without prior communication with and approval by the sponsor.

14.1.2. 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 e-signature of the investigator or designee must be provided in the EDC system to attest to its accuracy, authenticity, and completeness.

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

14.1.3. Data Management/Coding

All final patient data, both eCRF and external data (eg, laboratory data), collected according to the protocol, will be stored by the sponsor 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.

The AE verbatim descriptions (the investigator's description from the eCRF) will be coded using MedDRA. AEs will be coded to MedDRA by the lowest-level term, Preferred Term, and primary SOC. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. Concomitant diseases/medical history will be coded using MedDRA.

14.2. Data Integrity and In-house Blinding

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

PD-L1 status of each individual patient will be blinded to BeiGene study team in order to avoid unwanted bias. PD-L1 expression status in the IRT will not be accessible to anyone except for independent statistician, BeiGene IRT manager, and IDMC. PD-L1 expression status will not be included in the listings generated for data review either. Granted study teams from BeiGene and BeiGene's cooperator can only review the summarized proportions of patients with different PD-L1 expression levels in order to monitor PD-L1 prevalence in the study.

14.3. Study Records Retention

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

After 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 ensure that all reproductions are legible, are a true and accurate copy of the original, and meet accessibility and retrieval standards, including regenerating a hard copy, if required. Furthermore, the investigator must ensure that there is an acceptable backup of these reproductions and that an acceptable quality control process exists for making these reproductions.

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

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

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and the sponsor to store these in sealed containers away from 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 away from the site.

Subject to patient consent, or as otherwise allowed under applicable law, biological samples at the conclusion of this study may be retained ≤ 10 years or as allowed by your IRB/IEC, whichever is shorter.

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 that they will apply due diligence to avoid protocol deviations and shall report all protocol deviations to the sponsor.

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

14.5. Study Report and Publications

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

The results of this study will be published or presented at scientific meetings in a timely, objective, and clinically meaningful manner that is consistent with good science, industry and regulatory guidance, and the need to protect the intellectual property of 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 study 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
- Collection of all study documents for the trial master file filing according to GCP and local regulation
- Shipment of samples (including, but not limited to, those for PK, ADA, and biomarkers) to the assay laboratory for central laboratory analysis according to protocol and laboratory manual requirements

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 any reason. Potential reasons for suspension or discontinuation include but are not limited to, safety or ethical issues or noncompliance with this protocol, GCP, the sponsor's written instructions, the clinical study agreement, or applicable laws and regulations. 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 before it takes 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. The sponsor 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 IRB/IEC promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must still be provided 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 clinical study agreement established between the investigator and/or institutions 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 that 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 the following:

- 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 IRB/IEC 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 is executed and it includes provisions inconsistent with this statement, 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**	**8 (± 2)**	**15 (± 2)**	**1 (± 3)**	**0 to 7 Days**	**30 ± 7 Days After Last Dose**	**Every 3 Months ± 14 days**
Informed consent[1]	x							
Inclusion/exclusion criteria	x							
Randomization[5]	x							
Demographics/medical history/prior medications	x							
Cancer history[6]	x							
Vital signs/ height and weight[7]	x	x	x	x	x	x	x	
Physical examination[8]	x	x			x	x	x	
ECOG Performance Status	x	x			x	x	x	
12-lead ECG[9]	x	As clinically indicated					x	
Adverse events[10]	x	x	x	x	x	x	x	x
Concomitant medications	x	x	x	x	x	x	x	
Hematology[11]	x	x	x	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**	**8 (± 2)**	**15 (± 2)**	**1 (± 3)**	**0 to 7 Days**	**30 ± 7 Days After Last Dose**	**Every 3 Months ± 14 days**
Serum chemistry[11]	x	x	x	x	x	x	x	
Coagulation parameters [11,12]	x	x			x	x	x	
Urinalysis[11]	x	As clinically indicated						
Pregnancy test[13]	x	x			x			
Thyroid function[14]	x[1]				x[14]		x	
HBV/HCV tests[15]	x	Once at least every 4 cycles for patients who have detectable HBV DNA at Screening						
Pulmonary function tests[16]	x							
Optical coherence tomography (or equivalent diagnostic test) and visual acuity tests[17]	x				x	x[18]	x[18]	
Pharmacokinetics[19]		x			x		x	
Anti-tislelizumab antibodies[20]		x			x		x	
Tumor assessment[21]	x				x	x[2]		x
Archival tumor tissue[22]	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**	**8 (± 2)**	**15 (± 2)**	**1 (± 3)**	**0 to 7 Days**	**30 ± 7 Days After Last Dose**	**Every 3 Months ± 14 days**
Fresh tumor tissue [23]	x					x [23]		
Tislelizumab or placebo administration[24]		x			x			
Chemotherapy administration[25]		x			x			
EORTC-QLQ-C30[26] /EQ-5D-5L	x	x			x	x		
EORTC-QLQ-STO22[26]	x	x			x	x		
Survival status								x
Blood sample collection[27]	x	x	x			x		

Abbreviations: AE, adverse event; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-STO22, QLQ Module for Gastric Cancer; FFPE, formalin-fixed paraffin-embedded; HBcAb, hepatitis B core antibody; HB sAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HB sAb, hepatitis B surface antibody; imAE, immune-mediated adverse event; IRT, interactive response technology; IV, intravenous; MRI, magnetic resonance imaging; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PK, pharmacokinetic; PO, orally; Q3W, once every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; TSH, thyroid stimulating hormone; v, version.

1. Written informed consent is required prior to performing any study-specific tests or procedures. Informed consent may be obtained prior to the screening window allowing the acquisition of tumor biopsy sample and submission of fresh or archived tumor sample, which must be analyzed prior to randomization. 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. Please refer to Appendix 14 for HER2 assessment pathological review guideline.

2. The End of Treatment Visit is conducted when the investigator determines that study drug(s) will no longer be used. If routine laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the End of Treatment Visit, tests need not be repeated. Tumor assessment is not required at the End of Treatment Visit provided that fewer than 6 weeks have passed since the last assessment.
3. The Safety Follow-up Visit is required to be conducted 30 days (± 7 days) after the last dose of study drug(s), or before the initiation of a new anticancer treatment, whichever occurs first. In addition, telephone contacts with patients should be conducted to assess imAEs and concomitant medications (if appropriate, ie, associated with an imAE or is a new anticancer therapy) at 60 days (±14 days), and 90 days (±14 days) after the last dose of tislelizumab or placebo, regardless of whether or not the patient starts a new anticancer therapy. If patients report a suspected immune-related AE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated.
4. Survival Follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (± 14 days) 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 via IRT. All patients are required to receive study treatment within 3 days of randomization.
6. Include pathologic diagnosis, stage at screening, tumor location, location of metastatic disease at study baseline, an assessment of prior surgery, prior radiotherapy, prior drug therapy, including start and stop dates, best response and reason for discontinuation. Radiographic studies performed prior to study entry may be collected for review by the investigator.
7. Vital signs collected on study include temperature, pulse rate, and blood pressure. For the first infusion of tislelizumab or placebo, the patient's vital signs are required to be recorded within 60 minutes before, during, and within 30 minutes after the infusion of tislelizumab. For subsequent infusions, vital signs will be collected within 60 minutes before infusion and if clinically indicated, during and within 30 minutes after the infusion. The height is only measured at screening.
8. Physical examination: A complete physical examination should include an evaluation of the head, eyes, ears, nose, throat, cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems at screening. At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed.
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 for at least 10 minutes prior to each ECG collection.
10. The AEs and laboratory abnormalities will be graded per NCI-CTCAE v5.0. All AEs will also be evaluated for seriousness. After the informed consent form has been signed, but prior to the administration of study drug, only SAEs should be reported. After the first dose of study drug, all AEs and SAEs, regardless of their assessed relationship to study drug, are to be reported until either 30 days after the last dose of study treatment or the initiation of new anticancer therapy, whichever occurs first. All imAEs will be reported for 90 days after the last dose of tislelizumab or placebo, regardless of whether or not 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.
11. 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 prior to the administration of study drugs, these tests should be repeated and reviewed before study drugs administration. Hematology and serum chemistry (including liver function tests) will be performed weekly for the first 3 cycles and then at the beginning of each subsequent cycle (data collected as specified in Appendix 2). After Cycle 1, results are to be reviewed within 72 hours before study drug administration. Urinalysis is to be conducted during the treatment period and Safety Follow-up period as clinically indicated. Refer to Section 8.3.5 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.
12. Includes international normalized ratio, prothrombin time (or prothrombin time ratio), and activated partial thromboplastin time.
13. Urine pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 7 days prior to randomization. Urine pregnancy tests will be performed at each visit prior to dosing (exception for China but should be implemented if

clinically indicated, and at end of treatment or safety follow up visit). A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.

14. Analysis of FT3, FT4, and TSH will be performed by 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, etc), and at Safety Follow-up Visit.
15. Testing will be performed by local and/or central laboratory at Screening and will include HBV/HCV serology (HB sAg, HB sAb, HB cAb, and HCV antibody) and viral load assessment (HBV and HCV) will be required if clinically indicated. Patients who have detectable HBV DNA at Screening will perform a viral load test at least every 4 cycles (ie, Day 1 of Cycle 5, 9, 13, etc).
16. Patients who are suspected or known to have serious/severe respiratory conditions or exhibit significant respiratory symptoms unrelated to the underlying cancer will have pulmonary function testing which may include but is not limited to spirometry and assessment of diffusion capacity done during the Screening period to assist the determination of suitability on the study.
17. 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 rather than repeating tests. Eye exam, visual acuity test, and optical coherence tomography (or equivalent diagnostic test) will be assessed at the Screening Visit. Patients will undergo repeat assessments approximately every 15 weeks (± 7 days)
18. The ophthalmologic assessments including eye exam, visual acuity test, and OCT (or equivalent diagnostic test) should only be performed once at either the EOT or during safety follow-up.
19. 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 or placebo infusion) sample is required to be collected at Day 1 of Cycles 1 and 5. An additional PK sample is required to be collected at the Safety Follow-up. Should a patient present with any ≥ Grade 3 imAE, an additional blood PK sample may be taken to determine the serum concentration of tislelizumab or placebo. These tests are required when it is allowed by local regulations/IRBs/ECs. In the event of dose delay or dose discontinuation, please refer to the Laboratory Manual for PK/ADA sample collection.
20. Blood used to test for anti-tislelizumab antibodies should be collected within 60 minutes before beginning the Day 1 infusion of Cycles 1, 2, 5, 9, and 17 and at the mandatory Safety Follow-up Visit. All samples should be drawn at the same time as blood collection for predose PK analysis. These tests are required when it is allowed by local regulations/IRBs/ECs.
21. Radiological images captured as standard of care prior to obtaining written informed consent and within 28 days of randomization may be used rather than repeating tests. All measurable and evaluable lesions are required to be assessed and documented at the Screening Visit. An MRI (or CT scan if MRI is contraindicated or not readily available) of the head may be required at screening based on clinical judgement; bone scan or ^{18}F-NaF PET is required if clinically indicated. The same radiographic procedure must be used throughout the study for each patient.

    The investigator must review radiograph results before dosing at the next cycle. Patients will undergo tumor assessments approximately every 6 weeks (±7 days) during the first 48 weeks and every 9 weeks (±7 days) after 48 weeks (based on RECIST v1.1 assessment) from randomization. The investigator may perform additional scans or more frequent assessments if clinically indicated. See Section 7.5 for more information. Patients who discontinue study treatment early for reasons other than disease progression (eg, toxicity) will continue to undergo tumor assessments following the original plan until the patient experiences disease progression, withdraws consent, dies, is lost to follow-up, or until the study terminates, whichever occurs first. Treatment beyond initial investigator-assessed RECIST v1.1 defined progression (Section 3.6.1) will be permitted provided that the patient has investigator-assessed clinical benefit and is tolerating study drug. The following criteria must be met to treat patients after initial evidence of radiological disease progression: absence of clinical symptoms and signs of disease progression; stable ECOG PS ≤ 1; absence of rapid progression of disease or progressive tumor at critical anatomical sites that require urgent alternative medical intervention; and additional written informed consent. The medical monitor must agree, in writing, with the investigator's decision to continue study drugs beyond initial investigator-assessed progression, and the decision must be documented in the study records.

22. Patients are required to provide archival tumor tissues (FFPE blocks or approximately 15 unstained slides [≥ 7 if MSI/MMR and HER2 status are available, additional 5 if MSI/MMR status is not available, and additional 3 to 6 if HER2 status is not identified]) for biomarker analysis.
23. Fresh biopsy: A fresh biopsy sample is highly preferred if feasible in clinic. If no archival samples are available, a fresh tumor biopsy at baseline is mandatorily required. 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 mechanism (written informed consent is required prior to fresh tumor biopsies). See Section 7.7 for more information.
24. Tislelizumab or placebo will be given intravenously Q3W. The initial infusion (Cycle 1, Day 1) will be delivered over 60 minutes, and then can be administered over 30 minutes for subsequent infusions if well tolerated. Patients must be monitored for 1 hour after infusion of tislelizumab or placebo on Day 1 of Cycle 1 and Cycle 2, from Cycle 3 onward, at least a 30-minute monitoring period is required. The first dose will be given on C1D1 and subsequent dosing will continue at the scheduled 21-day intervals. Each cycle has a (±) 3-day window.
25. Chemotherapy will be dosed every 3 weeks. Each cycle has a (±) 3-day window.
26. EORTC QLQ-C30, EORTC QLQ-STO22 and EQ-5D-5L will be completed at Screening or baseline, at every cycle through Cycle 6, then every other cycle thereafter until PD, and at EOT. QoL will be completed prior to any clinical activities apart from blood draw during on-study site visits.
27. If MSI assessment is required, a blood sample of approximately 2 mL will be taken at screening. An optional blood sample of approximately 10 mL will be taken at baseline (predose, on Cycle 1 Day 1), at the time of first tumor response (predose at Day 1 of the following Cycle) and at EOT after disease progression (10 mL each timepoint) for all randomized patients to explore the association of blood-based biomarkers with response, prognosis, and resistance to tislelizumab in combination with chemotherapy or chemotherapy alone. Written informed consent is required for optional blood sample collection.

APPENDIX 2. CLINICAL LABORATORY ASSESSMENTS

Serum Chemistry	Hematology	Thyroid Function	Coagulation	Urinalysis
• Alkaline phosphatase • Alanine aminotransferase • Aspartate aminotransferase • Albumin • Total bilirubin • Direct bilirubin • Blood urea nitrogen or urea • Potassium • Sodium • Creatinine • Glucose • Lactate dehydrogenase • Total protein • Chloride • Creatine Kinase (CK) [a] • CK-MB [a]	• Hematocrit • Hemoglobin • Platelet counts • WBC count • Lymphocyte count • Neutrophil count	• Free triiodothyronine • Free thyroxine • Thyroid stimulating hormone	• Prothrombin time (or prothrombin time ratio) • Partial thromboplastin time or activated partial thromboplastin time • International normalized ratio	• Glucose • Protein • Blood • Ketones

Abbreviations: CK-MB, creatine kinase-cardiac muscle isoenzyme; pH, negative of the logarithm to base 10 of the activity of the (solvated) hydronium ion; WBC, white blood cell.

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

APPENDIX 3. ECOG PERFORMANCE STATUS

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

Source: Eisenhauer et al 2009.

Definitions

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

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

Measurable Disease

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

- 10 mm by computed tomography (CT) and magnetic resonance imaging (MRI) (no less than double the slice thickness and a minimum of 10 mm). Assumes a scan slice thickness no greater than 5 mm.
- 10 mm caliper measurement by clinical exam (when superficial)

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 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered nonmeasurable disease. Leptomeningeal disease, ascites, pleural, or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques are all nonmeasurable.

Bone lesions:

- Bone scan, positron-emission tomography (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 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 malignant lesions (neither measurable nor nonmeasurable) since they are, by definition, simple cysts
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- The concept of cystic metastases also applies to metastatic lesions with a necrotic component. Hence, measurable lesions with a necrotic component may be selected as target lesions. However, if non-necrotic lesions are present, these are preferred for selection as target lesions.

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. A maximum of 2 measurable lymph nodes, inclusive of all lymphatic chains involved, may be chosen as target lesions (ie, the lymphatic system is considered one organ). Target lesions should be selected based on size (lesions with the longest diameter), how representative they are of all involved organs, and whether they 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 perpendicular 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, but the axial plane is recommended for measurements). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm by 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 nontarget 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 nodes" or "multiple liver metastases"). If a nontarget lymph node normalizes (< 10 mm in short axis) after baseline, the respective evaluation should be "absent."

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 assessable by clinical examination.

- Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.
- Chest x-ray: Chest CT is preferred over chest x-ray, particularly when progression is an important endpoint, since CT is more sensitive than x-ray, particularly in identifying new lesions. However, lesions on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- CT, MRI: Target lesion measurements should be performed in the axial plane. 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). If there is a change from CT to MRI or the reverse, target lesions should continue to be measured provided the imaging parameters do not render measurements incomparable.
- Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in

the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

- Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in studies where recurrence after 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 studies in ovarian cancer.
- Cytology, histology: These techniques can be used to differentiate between partial response (PR) and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

Response Criteria

Evaluation of Target Lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes 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).
- Both PR and PD: If the change in sum of diameters is consistent with both PR and PD at a tumor assessment visit, PD should take precedence.
- 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 form may be designed to have target nodal lesions 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 electronic case report form (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 nonreproducible, 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 measurement 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 timepoints 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 one or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits
- When the patient also has measurable disease: In this setting, to achieve "unequivocal progression" on the basis of the nontarget disease, there must be an overall level of substantial worsening in nontarget disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of 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 studies when it is not a criterion of study 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 it 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 preexisting lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain scan ordered that reveals metastases. The patient's brain metastases are considered evidence of PD even if he or 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 preexisting site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- Timepoint Response: It is assumed that at each protocol specified timepoint, a response assessment occurs. The following table provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline:

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 patients have nonmeasurable (therefore nontarget) disease only, the following table is to be used:

Nontarget Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	SD (Non-CR/non-PD)

Nontarget Lesions	New Lesions	Overall Response
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

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

Evaluation of Best Overall Response

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

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

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 studies where confirmation of response is required, repeated "NE" (not evaluable) timepoint assessments may complicate best response determination. The analysis plan for the studies must address how missing data/assessments will be addressed in determination of response and progression. For example, in most studies it is reasonable to consider a patient with timepoint responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document objective progression

even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

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

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

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes, or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If progression is confirmed at the next scheduled assessment, the date of progression should be the earlier date when progression was suspected.

Confirmation of Measurement/Duration of Response

Confirmation

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

In the case of SD, measurements must have met the SD criteria at least once after 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 studies, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

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

Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity, and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between studies 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) neuropathy	Inflammatory bowel disease
Interstitial cystitis	Kawasaki's disease
Lambert-Eaton myasthenia syndrome	Lupus erythematosus
Lyme disease (chronic)	Mooren's ulcer
Morphea	Multiple sclerosis
Myasthenia gravis	Neuromyotonia
Opsoclonus myoclonus syndrome	Optic neuritis
Ord's thyroiditis	Pemphigus
Pernicious anemia	Polyarteritis nodusa
Polyarthritis	Polyglandular autoimmune syndrome
Primary biliary cirrhosis	Psoriasis
Reiter's syndrome	Rheumatoid arthritis
Sarcoidosis	Sjögren's syndrome
Stiff person syndrome	Takayasu's arteritis
Ulcerative colitis	Vogt-Kovangai-Harada disease

APPENDIX 6. NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

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

Adapted from Dolgin et al 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. INFUSION-RELATED REACTIONS, HYPERSENSITIVITY REACTIONS AND IMMUNE-MEDIATED ADVERSE EVENTS: EVALUATION AND MANAGEMENT

Management of Infusion-Related Reactions and Hypersensitivity Reactions

Management and treatment modifications for symptoms of infusion-related reactions associated with study drug(s) administration are provided in the table below.

If a hypersensitivity reaction occurs, the patient must be managed according to the best available medical practice, as described in the 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.

Treatment Modifications for Symptoms of Infusion-Related or Hypersensitivity Reactions Associated with Study Drug(s) Administration

NCI-CTCAE Grade	Treatment Modification for study drug(s)
Grade 1 - mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease infusion rate by 50%. Closely monitor for worsening signs or symptoms. Medical management as needed. Subsequent infusions should be given after appropriate premedication and at the reduced infusion rate.
Grade 2 - moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, corticosteroids, and/or intravenous fluids); prophylactic medications indicated for ≤ 24 hours.	Stop infusion. Infusion may be resumed at 50% of previous rate once infusion-related reaction has resolved or decreased to Grade 1 in severity. Closely monitor for worsening signs or symptoms. Appropriate 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 observation or clinical management.	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: NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Event.

If the infusion rate of study drug(s) has been decreased by 50% or suspended due to an infusion-related reaction, this decreased rate must be maintained for all subsequent infusions and be administered 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.

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

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), an antipyretic (eg, paracetamol), and if considered indicated, oral or intravenous glucocorticoids, epinephrine, bronchodilators, and oxygen. In subsequent cycles, the patient should receive oral premedication with an antihistamine (eg, diphenhydramine) and an antipyretic (eg, paracetamol), and 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 intravenous antihistamines, antipyretics, glucocorticoids, epinephrine, bronchodilators, and oxygen.

In the event of a systemic anaphylactic/anaphylactoid reaction the infusion must be stopped immediately, and the patient discontinued from study treatment. Systemic anaphylactic/anaphylactoid reactions typically manifest within minutes following administration of the drug/antigen and are 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 or without edema); and gastrointestinal manifestations such as nausea, vomiting, crampy abdominal pain, and diarrhea.

The patient will be administered epinephrine injection and dexamethasone infusion if severe hypersensitivity reaction is observed. The patient should be closely monitored, and ICU should be alerted for possible transfer as indicated.

Evaluation of Immune-Mediated Adverse Events

The recommendations below for the diagnosis and management of any immune-mediated AE (imAE) are intended as 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.

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

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 AE?
- 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 AE in the eCRF should be checked. If further diagnostic evaluations change the assessment, the eCRF should be updated accordingly.

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

Immune-mediated Toxicity	Diagnostic Evaluation Guideline
Thyroid Disorders	Scheduled and repeated 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 DLCO. 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, and cryptosporidia (drug-resistant organism).

Immune-mediated Toxicity	Diagnostic Evaluation Guideline
	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 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 to 4; every 2 to 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 a nephrologist for further management assistance.
Dermatology	Consider other causes by conducting a physical examination. Consider dermatology referral for skin biopsy
Joint or muscle inflammation	Conduct musculoskeletal history and perform complete musculoskeletal examination. Consider joint X-ray and other imaging as required to exclude metastatic disease. Perform autoimmune serology and refer to rheumatology for further management assistance. For suspected myositis/rhabdomyolysis/myasthenia include: CK, ESR, CRP, troponin and consider a muscle biopsy.
Myocarditis	Perform ECG, echocardiogram, CK/CK-MB, troponin (I and/or T), and refer to a cardiologist.

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

Management 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, 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

Management of Immune-Mediated Adverse Events

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

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3-4 Severe or life-threatening symptoms	Refer patient to an endocrinologist for assessment and treatment. Initiate pulse intravenous methylprednisolone 1 mg/kg for patients with headache/visual disturbance due to pituitary inflammation. Convert to oral prednisolone and taper over at least 1 month. Maintain hormone replacement according to endocrinologist's advice.	Hold study treatment for patients with headache/visual disturbance due to pituitary inflammation until resolved/improved to Grade 2 or less. Discontinuation is usually not necessary.
Pneumonitis	**1** Radiographic changes only	Monitor symptoms every 2-3 days. If appearance worsens, treat as Grade 2.	Consider holding study treatment until appearance improves and cause is determined.
	2 Symptomatic: exertional breathlessness	Commence antibiotics if infection suspected. Add oral prednisolone 1 mg/kg/day if symptoms/appearance persist for 48 hours or worsen. Consider Pneumocystis infection prophylaxis. Taper corticosteroids over at least 6 weeks. Consider prophylaxis for adverse steroid effects: eg, blood glucose monitoring, vitamin D/calcium supplement.	Hold study treatment. Retreatment is acceptable if symptoms resolve completely or are controlled on prednisolone ≤ 10 mg/day. Discontinue study treatment if symptoms persist with corticosteroid treatment.
	3-4 Severe or life-threatening symptoms Breathless at rest	Admit to a hospital and initiate treatment with intravenous methylprednisolone 2-4 mg/kg/day. If there is no improvement, or worsening after 48 hours, add infliximab 5 mg/kg (if no hepatic involvement). Convert to oral prednisolone and taper over at least 2 months. Cover with empiric antibiotics and consider prophylaxis for Pneumocystis infection and other adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement.	Discontinue study treatment.
Neurological Toxicity	**1** Mild symptoms	—	Continue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	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 symptoms	Initiate treatment with oral prednisolone or intravenous methylprednisolone 1-2 mg/kg/day, depending on symptoms. Taper corticosteroids over at least 4 weeks. Consider azathioprine, MMF, cyclosporine if no response within 72-96 hours.	Discontinue study treatment.
Colitis/Diarrhea	**1** Mild symptoms: < 4 liquid stools per day over baseline and feeling well	Symptomatic management: fluids, loperamide, avoid high fiber/lactose diet. If Grade 1 persists for > 14 days manage as a Grade 2 event	Continue study treatment.
	2 Moderate symptoms: 4-6 liquid stools per day over baseline, or abdominal pain, or blood in stool, or nausea, or nocturnal episodes	Oral prednisolone 0.5 mg/kg/day (non-enteric coated). Do not wait for any diagnostic tests to start treatment. Taper steroids over 2-4 weeks. Consider endoscopy if symptoms are recurring.	Hold study treatment; resume when resolved/improved to baseline grade.
	3 Severe symptoms: > 7 liquid stools per day over baseline, or if episodic within 1 hour of eating	Initiate intravenous methylprednisolone 1-2mg/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 Class 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.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	2 Rash covers 10%-30% of BSA	Avoid skin irritants and sun exposure; topical emollients recommended. Topical steroids (moderate strength cream once a day or potent cream twice a day) ± oral or topical antihistamines for itch. Consider a short course of oral steroids.	Continue study treatment.
	3 Rash covers > 30% BSA or Grade 2 with substantial symptoms	Avoid skin irritants and sun exposure; topical emollients recommended. Initiate steroids as follows based on clinical judgement: For moderate symptoms: oral prednisolone 0.5-1 mg/kg/day for 3 days then taper over 2-4 weeks. For severe symptoms: intravenous methylprednisolone 0.5-1 mg/kg/day; convert to oral prednisolone and taper over at least 4 weeks.	Hold study treatment. Re-treat when AE is resolved or improved to mild rash (Grade 1-2) after discussion with the study medical monitor.
	4 Skin sloughing > 30% BSA with associated symptoms (eg, erythema, purpura, epidermal detachment)	Initiate intravenous methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Admit to a hospital and seek urgent dermatology consultation.	Discontinue study treatment.
Hepatitis	**1** ALT or AST > ULN to 3 x ULN	Check LFTs within 1 week and before the next dose check LFTs to verify that there has been no worsening. If LFTs are worsening, recheck every 48-72 hours until improvement is seen.	Continue study treatment if LFTs are unchanged or improving. Hold study treatment if LFTs are worsening until improvement is seen.

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

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
		1 mg/kg and taper over at least 2 weeks. Repeat creatinine/U&E every 48-72 hours.	tapered to < 10 mg prednisolone.
	3 Creatinine > 3 x baseline or > 3-6 x ULN	Hospitalize patient for monitoring and fluid balance; repeat creatinine every 24 hours; refer to a nephrologist and discuss need for biopsy. If worsening, initiate intravenous (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 > 6 x ULN	As per Grade 3, patient should be managed in a hospital where renal replacement therapy is available.	Discontinue study treatment.
Diabetes/ Hyperglycemia*	**1** Fasting glucose value ULN to 160 mg/dL; ULN to 8.9 mmol/L	Monitor closely and treat according to local guideline. Check for C-peptide and antibodies against glutamic acid decarboxylase and islet cells are recommended	Continue study treatment.
	2 Fasting glucose value 160-250 mg/dL; 8.9-13.9 mmol/L	Obtain a repeat blood glucose level at least every week. Manage according to local guideline.	Continue study treatment or hold treatment if hyperglycemia is worsening. Resume treatment when blood glucose is stabilized at baseline or Grade 0-1.
	3 Fasting glucose value 250-500 mg/dL; 13.9-27.8 mmol/L	Admit patient to hospital and refer to a diabetologist for hyperglycemia management. Corticosteroids may exacerbate hyperglycemia and should be avoided.	Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1.
	4 Fasting glucose value > 500 mg/dL; > 27.8 mmol/L	Admit patient to hospital and institute local emergency diabetes management. Refer the patient to a diabetologist for insulin maintenance and monitoring.	
Ocular Toxicity	**1** Asymptomatic eye examination/test abnormality	Consider alternative causes and prescribe topical treatment as required.	Continue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	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 intravenous (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 intravenous (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when amylase/lipase improved to Grade 2, and taper over at least 4 weeks	Hold study treatment; reintroduce only after discussion with the study medical monitor.
	4 Acute abdominal pain, surgical emergency	Admit to hospital for emergency management and appropriate referral.	Discontinue study treatment.
Arthritis	**1** Mild pain with inflammation, swelling	Management per local guideline.	Continue study treatment.
	2 Moderate pain with inflammation, swelling, limited instrumental (fine motor) activities	Management as per local guideline. Consider referring patient to a rheumatologist. If symptoms worsen on treatment manage as a Grade 3 event.	Continue treatment or, if symptoms continue to worsen, hold study treatment until symptoms improve to baseline or Grade 0-1.
	3 Severe pain with inflammation or permanent joint damage, daily living activity	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

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	limited		study medical monitor.
Mucositis/ stomatitis	**1** Test findings only or minimal symptoms	Consider topical treatment or analgesia as per local guideline.	Continue study treatment.
	2 Moderate pain, reduced oral intake, limited instrumental activities	As per local guidelines, treat with analgesics, topical treatments and oral hygiene care. Ensure adequate hydration. If symptoms worsen or there is sepsis or bleeding, manage as a Grade 3 event.	Continue study treatment.
	3 Severe pain, limited food and fluid intake, daily living activity limited	Admit to hospital for appropriate management. Initiate intravenous (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when symptoms improve 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 intravenous 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 3 x ULN or worse, initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks	Hold study treatment until improved to Grade 0-1
	3-4 Severe weakness, limiting self-care	Admit to hospital and initiate oral prednisolone 1 mg/kg. Consider bolus intravenous (methyl)prednisolone and 1-2 mg/kg/day maintenance for severe activity restriction or dysphagia. If symptoms do not improve add immunosuppressant therapy. Taper oral steroids over at least 4 weeks	For Grade 3: Hold study treatment until improved to Grade 0-1. Discontinue upon any evidence of myocardial involvement
Myocarditis[a]	**< 2** Asymptomatic but significantly increased CK-MB or increased	Initiate cardiac evaluation under close monitoring with repeat serum testing and including ECG, cardiac echo/MUGA,	

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	troponin OR clinically significant intraventricular conduction delay	and/or other interventions per institutional guidelines; 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 and considered immune-mediated, permanently discontinue study treatment in patients with moderate or severe symptoms. Patients with no symptoms or mild symptoms may not restart tislelizumab unless cardiac parameters have returned to baseline and after discussion with the study medical monitor.
	2 Symptoms on mild-moderate exertion	Admit to hospital and initiate oral prednisolone or intravenous (methyl) prednisolone at 1-2 mg/kg/day. Consult with a cardiologist and manage symptoms of cardiac failure according to local guidelines. If no immediate response change to pulsed doses of (methyl)prednisolone 1 g/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; ECG, electrocardiogram; INR, international normalized ratio; LFT, liver function test; MMF, mycophenolate mofetil; MUGA, multigated acquisition scan; 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.
[a] If clinically significant cardiac enzyme abnormalities are detected during laboratory assessment and serial cardiac enzyme assessments pose logistical hardship for the patient, then patient hospitalization should strongly be considered until immune-mediated myocarditis has been ruled out.

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) equation1 and the Modification of Diet in Renal Disease (MDRD) Study equation. The National Kidney Disease Education Program (NKDEP) calculators rely on creatinine determinations which are isotope dilution mass spectrometry (IDMS) traceable. All laboratories should be using creatinine methods calibrated to be IDMS traceable. Read more about creatinine standardization.

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

GFR = 141 x min (Scr /κ, 1) α x max (Scr /κ, 1)-1.209 x 0.993Age x 1.018 [if female] x 1.159 [if black]

where:

Scr is serum creatinine in mg/dL,

κ is 0.7 for females and 0.9 for males,

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

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

max indicates the maximum of Scr /κ or 1.

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

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

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

Contraception Guidelines

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

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with the inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with the inhibition of ovulation (oral, injectable, or implantable)

  Note: Oral birth control pills are not considered a highly effective form of birth control, and if they are selected, they must be used with a second, barrier method of contraception such as condoms with or without spermicide.
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner

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

  – A sterile male is one for whom azoospermia, in a semen sample, has been demonstrated as definitive evidence of infertility.
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment).

  – NOTE: Total sexual abstinence should only be used as a contraceptive method if it is in line with the patients' usual and preferred lifestyle. Periodic abstinence (eg, calendar, ovulation, symptom-thermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable methods of contraception.

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

Definitions of "Women of Childbearing Potential" AND "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 the lack of spontaneous menses for ≥ 12 months have been ruled out, such as polycystic ovarian syndrome, hyperprolactinemia, etc.

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

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

APPENDIX 10. DOSE MODIFICATION OF CHEMOTHERAPY

Recommended Dose Modifications for Hematologic Toxicity of 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. Recommended dose modifications for hematologic and non-hematologic toxicity are provided in Table 2 and Table 3 as below. Toxicities related to chemotherapy must be resolved to baseline or ≤ Grade 1 prior to administering the next dose of chemotherapy, with the exception of alopecia, Grade 2 fatigue, or other AEs, which, in the opinion of the investigator, would not affect the safety evaluation of the study drugs.

Table 1 : BGB-A317-305 Dose Reduction Level of Chemotherapy

Drug Dose	Standard Level (Every 3 weeks as a cycle)	1st Level	2nd Level
Capecitabine	1000 mg/m^2, BID (total 14 days)	Reduce dose to 75%	Reduce dose to 50%
Oxaliplatin	130 mg/m^2 (Day 1)	Reduce dose to 100 mg/m^2	Reduce dose to 80 mg/m^2
5-FU	800 mg/m^2(Day 1 to Day 5)	Reduce dose to 75%	Reduce dose to 50%
Cisplatin	80 mg/m^2 (Day 1)	Reduce dose to 75%	Reduce dose to 50%

Table 2: BGB-A317-305 Dose Modifications for Hematologic Toxicities of Chemotherapy

AE	Grade	Dose Modifications
Febrile Neutropenia	3	1st occurrence: 1st reduced dose level 2nd occurrence: Stop treatment permanently unless it is in the best interest of the patient to treat with 2nd reduced dose level
	4	1st occurrence: Stop treatment permanently unless it is in the best interest of the patient to treat with 2nd reduced dose level 2nd occurrence: Stop treatment permanently
Neutrophil count decreased	1/2	Maintain dose level
	3/4	1st occurrence: 1st reduced dose level 2nd occurrence: 2nd reduced dose level 3rd occurrence: Stop treatment permanently
Platelet count decreased	1	Maintain dose level
	≥ 2	1st occurrence: 1st reduced dose level

		2nd occurrence: 2nd reduced dose level 3rd occurrence: Stop treatment permanently

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

Table 3: BGB-A317-305 Dose Modifications for Non-hematologic Toxicities of Chemotherapy

AE	Grade	Dose Modifications
Capecitabine		
Diarrhea	2	Immediately interrupted, 1st reduced dose level
	3 or 4	Immediately interrupted, 2nd reduced dose level
Nausea/vomiting	2	Immediately interrupted, 1st reduced dose level
	3 or 4	Immediately interrupted, 2nd reduced dose level
Hand/foot syndrome	2 or 3	Immediately interrupted, 1st reduced dose level
Stomatitis	2 or 3	Immediately interrupted, 1st reduced dose level
	4	Immediately interrupted, 2nd reduced dose level
Cardiac toxicity	≥ 2	Stop capecitabine permanently
Oxaliplatin		
Respiratory symptoms indicative of pulmonary fibrosis	any	Interrupt treatment and investigate cause of symptoms
Nausea and/or vomiting	3 or 4	1st reduced dose level
Diarrhea	3 or 4	1st reduced dose level
Peripheral neuropathy (Paresthesia)	2	Last < 21 days: Maintain dose level Last ≥ 21 days: Delay then 1st reduced dose level
	3	Last < 7 days: Maintain dose level Last ≥ 7 days: 1st reduced dose level Last ≥ 21 days: Stop Oxaliplatin permanently
	4	Stop Oxaliplatin permanently
5-FU		
Nausea and/or Vomiting	3 or 4	1st reduced dose level
Diarrhea	3 or 4	1st reduced dose level
Stomatitis	3	1st reduced dose level
	4	2nd reduced dose level
Cardiac toxicity	≥ 2	Stop 5-FU permanently

Skin toxicities	3 or 4	2nd reduced dose level
Cisplatin		
eGFR: ≥ 60 mL/min	1	Maintain dose level
eGFR: 51-59 mL/min	2	1st reduced dose level
eGFR: 41-50 mL/min	2	2nd reduced dose level
eGFR: ≤ 40 mL/min[1]	2	Stop cisplatin permanently
Nausea or Vomiting	3 or 4	1st reduced dose level
Ototoxicity	2	1st reduced dose level
	3 or 4	Stop cisplatin permanently
Sensory neuropathy	2	1st reduced dose level
	3 or 4	Stop cisplatin permanently

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

Obtained from http://ascopubs.org/doi/abs/10.1200/jco.2010.28.18_suppl.lba4007. Accessed Jan 22nd, 2018.

APPENDIX 11. EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER QUALITY OF LIFE CANCER QUESTIONNAIRE QLQ-C30

EORTC QLQ-C30 (version 3)

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

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

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

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

Please go on to the next page

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

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

APPENDIX 12. EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER QUALITY OF LIFE GASTRIC CANCER MODULE QLQ-STO22

EORTC QLQ – STO22

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. Have you had problems eating solid foods?	1	2	3	4
32. Have you had problems eating liquidised or soft foods?	1	2	3	4
33. Have you had problems drinking liquids?	1	2	3	4
34. Have you had discomfort when eating?	1	2	3	4
35. Have you had pain in your stomach area?	1	2	3	4
36. Have you had discomfort in your stomach area?	1	2	3	4
37. Did you have a bloated feeling in your abdomen?	1	2	3	4
38. Have you had trouble with acid or bile coming into your mouth?	1	2	3	4
39. Have you had acid indigestion or heartburn?	1	2	3	4
40. Have you had trouble with belching?	1	2	3	4
41. Have you felt full up too quickly after beginning to eat?	1	2	3	4
42. Have you had trouble enjoying your meals?	1	2	3	4
43. Has it taken you a long time to complete your meals?	1	2	3	4
44. Have you had a dry mouth?	1	2	3	4
45. Did food and drink taste different from usual?	1	2	3	4
46. Have you had trouble with eating in front of other people?	1	2	3	4
47. Have you been thinking about your illness?	1	2	3	4
48. Have you worried about your weight being too low?	1	2	3	4
49. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
50. Have you worried about your health in the future?	1	2	3	4
51. Have you lost any hair?	1	2	3	4
52. Answer this question only if you lost any hair: If so, were you upset by the loss of your hair?	1	2	3	4

ENGLISH

APPENDIX 13. EUROPEAN QUALITY OF LIFE 5-DIMENSIONS 5-LEVELS HEALTH QUESTIONNAIRE

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

MOBILITY

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

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 ❑

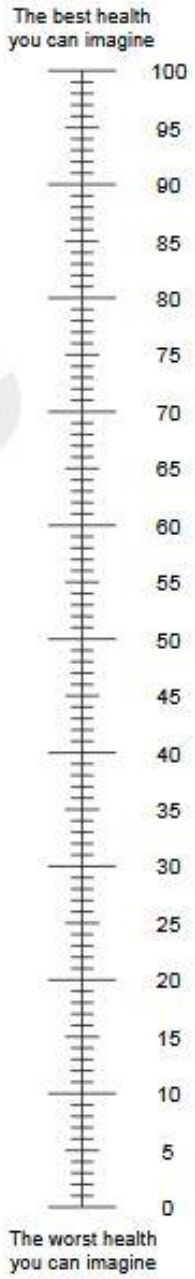
ANXIETY / DEPRESSION

- 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 ❑

2

- 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 14. PRINCIPLES OF PATHOLOGIC REVIEW AND HER2-NEU TESTING

Assessment of overexpression of HER2-neu in gastric cancer for patients with inoperable locally advanced, recurrent, or metastatic adenocarcinoma of the stomach or gastroesophageal junction (GEJ), assessment for tumor HER2-neu overexpression using immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) or other in situ hybridization method is recommended. The following criteria used in the ToGA trial are recommended:

Table 1: Immunohistochemical Criteria for Scoring HER2-neu Expression in Gastric and Esophagogastric Carcinoma*

	Surgical Specimen Expression Pattern, Immunohistochemistry	**Biopsy Specimen Expression Pattern, Immunohistochemistry**	**HER2-neu Overexpression Assessment**
0	No reactivity or membranous reactivity in < 10% of cancer cells	No reactivity or no membranous reactivity in any cancer cell	Negative
1+	Faint or barely perceptible membranous reactivity in ≥ 10% of cancer cells; cells are reactive only in part of their membrane	Cancer cell cluster with a faint or barely perceptible membranous reactivity irrespective of percentage of cancer cells positive	Negative
2+	Weak to moderate complete, basolateral, or lateral membranous reactivity in ≥ 10% of cancer cells	Cancer cell cluster with a weak to moderate complete, basolateral, or lateral membranous reactivity irrespective of percentage of cancer cells positive	Equivocal
3+	Strong complete, basolateral, or lateral membranous reactivity in ≥ 10% of cancer cells	Cluster of five or more cancer cells with a strong complete, basolateral, or lateral membranous reactivity irrespective of percentage of cancer cells positive	Positive

*The NCCN Guidelines panel recommends that cases showing 2+ expression of HER2-neu by immunohistochemistry should be additionally examined by FISH or other in situ hybridization methods. Cases with 3+ overexpression by IHC or FISH positive (HER2:CEP17 ratio ≥ 2) are considered positive.

Approval with eSignature	[redacted]