CLINICAL STUDY PROTOCOL

TITLE PAGE

Protocol Title:	A Phase 2, Multicenter, Open-label, 2-Cohort Study to Investigate the Efficacy and Safety of PET Guided Neoadjuvant Treatment With Tislelizumab (BGB-A317) Plus Chemotherapy/Chemoradiotherapy in Patients With Resectable Esophageal Squamous Cell Carcinoma
Protocol Identifier: Phase:	BGB-A317-213
Investigational Product(s):	2
Indication:	Tislelizumab (BGB-A317)
Sponsor:	Neo-adjuvant treatment of resectable esophageal squamous cell carcinoma BeiGene (Shanghai) Co., Ltd. 4th Floor, Building D 780 Cailun Road China (Shanghai) Pilot-Free Trade Zone Shanghai, 201203 China
Sponsor Medical Monitor:	[redacted] Email: [redacted]
Original Protocol Version 0.0:	30 January 2021
Protocol Amendment 1.0:	22 July 2022

Confidentiality Statement
This Document Is Not for Distribution – Do Not Copy

FINAL PROTOCOL APPROVAL SHEET

[Protocol Title] A Phase 2, Multicenter, Open-label, 2-Cohort Study to Investigate the Efficacy and Safety of PET Guided Neoadjuvant Treatment With Tislelizumab (BGB-A317) Plus Chemotherapy/Chemoradiotherapy in Patients With Resectable Esophageal Squamous Cell Carcinoma

[redacted]

Approved Date 7/29/2022

[redacted]

INVESTIGATOR SIGNATURE PAGE

Protocol Title: A Phase 2, Multicenter, Open-label, 2- Cohort Study to Investigate the Efficacy and Safety of PET Guided Neoadjuvant Treatment with Tislelizumab (BGB-A317) Plus Chemotherapy/Chemoradiotherapy in Patients With Resectable Esophageal Squamous Cell Carcinoma

Protocol Identifier: BGB-A317-213

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 Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd., or one of its subsidiaries.

Instructions for Investigator: Please SIGN and DATE this signature page prior to implementation of this sponsor-approved protocol. PRINT your name, title, and the name 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: _____

_____

_____

_____

Approved Date 7/29/2022

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

SYNOPSIS

Name of Sponsor/Company: BeiGene (Shanghai) Co., Ltd.
Investigational Product: Tislelizumab (BGB-A317)
Title of Study: A Phase 2, Multicenter, Open-Label, 2-Cohort Study to Investigate the Efficacy and Safety of PET Guided Neoadjuvant Treatment with Tislelizumab (BGB-A317) Plus Chemotherapy/Chemoradiotherapy in Patients With Resectable Esophageal Squamous Cell Carcinoma
Protocol Identifier: BGB-A317-213
Phase of Development: 2
Number of Patients: Approximately 65
Study Centers: Approximately 5 centers (China)

Study Objectives:

Primary:

- To evaluate the pathological complete response (pCR) in patients receiving tislelizumab plus chemotherapy/chemoradiotherapy as neoadjuvant treatment.

Secondary:

- To evaluate the disease-free survival (DFS) of neoadjuvant treatment with tislelizumab plus chemotherapy/chemoradiotherapy after R0 resection.
- To evaluate the event-free survival (EFS) of neoadjuvant treatment with tislelizumab plus chemotherapy/chemoradiotherapy.
- To evaluate the R0 resection rate in patients receiving tislelizumab plus chemotherapy/chemoradiotherapy as neoadjuvant treatment.
- To evaluate the objective response rate (ORR) of neoadjuvant treatment with tislelizumab plus chemotherapy/chemoradiotherapy before surgery as assessed by the investigator.
- To evaluate the safety of tislelizumab combined with chemotherapy/chemoradiotherapy as neoadjuvant treatment.

Exploratory:

- To evaluate overall survival (OS) of neoadjuvant treatment with tislelizumab plus chemotherapy/chemoradiotherapy.
- To evaluate the potential association of biomarkers with clinical efficacy in patients receiving tislelizumab plus chemotherapy/chemoradiotherapy as neoadjuvant treatment.
- To evaluate the major pathological response (MPR) rate in patients receiving tislelizumab plus chemotherapy/chemoradiotherapy as neoadjuvant treatment.

Study Endpoints:

Primary:

- pCR rate - defined as the proportion of patients with absence of residual tumor in the resected primary tumor and all resected lymph nodes after completion of neoadjuvant treatment in the Efficacy Evaluable (EE) Analysis Set.

Secondary:

- 1-year/3-year DFS rate - defined as the proportion of patients free from disease events at the 1st year and 3rd year after the first date of no disease (R0 resection as surgery outcome) in an EE analysis set. DFS is defined as the time from the first date of no disease to local or distant recurrence or death due to any cause, whichever occurs first. DFS rate will be analyzed only for patients who undergo R0 resection.
- 1-year/3-year EFS rate - defined as the proportion of patients free from EFS events at 1st year and 3rd year after the first dose in the Safety Analysis Set. EFS is defined as time from first dose date to any of the following events whichever occurs first: progression of disease that precludes definitive surgery, local or distant recurrence, or death due to any cause.
- R0 resection rate - defined as the proportion of patients with R0 resection in an EE analysis set.
- ORR - defined as the proportion of patients with measurable disease at baseline who have a complete response or partial response before surgery as assessed by the investigator per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 in the Safety Analysis Set.
- The incidence and severity of treatment-emergent adverse events (TEAEs) are determined according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v5.0).

Exploratory:

- 1-year/3-year OS rate – defined as the proportion of patients alive at 1st year and 3rd year after first dose in the Safety Analysis Set.
- To evaluate the potential association of biomarkers (including PD-L1 expression and gene expression profile) with clinical efficacy (including but not limited to pCR, DFS, EFS, R0 resection, ORR, OS and MPR).
- MPR rate - defined as the proportion of patients with ≤ 10% residual viable tumor in the resected primary tumor and all resected lymph nodes after completion of neoadjuvant therapy in an EE analysis set.

Study Design:

This is a Phase 2, multicenter, open-label, 2-cohort study to investigate the efficacy and safety of Positron Emission Tomography (PET)-guided neoadjuvant treatment with tislelizumab plus chemotherapy/chemoradiotherapy in resectable esophageal squamous cell carcinoma (ESCC).

Evaluation with positron emission tomography-computed tomography (PET-CT) will be performed 2 times.

- The first time: After informed consent form is signed.
- The second time: 15 to 21 days after the last dose of induction therapy.

The study consists of a screening phase, treatment phase (includes induction phase, neoadjuvant phase, and surgery phase), safety follow-up phase, and disease/survival follow-up phase.

Induction Therapy (One 21-day Cycle):

- Chemotherapy doublet (cisplatin and paclitaxel) (1 cycle).

Neoadjuvant Phase (Three 21-day Cycles):

Patients will be grouped into 2 cohorts based on the change of PET Standardized Uptake Value (SUV)max.

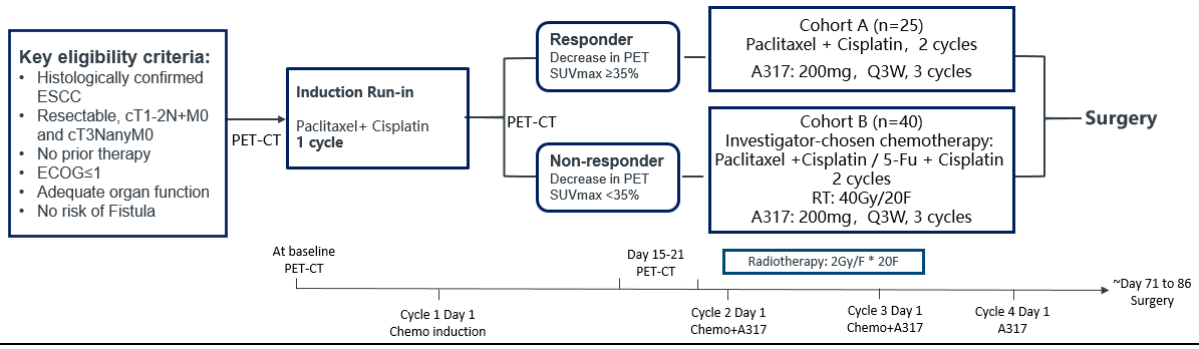
- Cohort A (responder: decrease in PET SUVmax ≥ 35%):
  - Tislelizumab 3 cycles + chemotherapy doublet (Cisplatin + Paclitaxel) 2 cycles
- Cohort B (non-responder: decrease in PET SUVmax < 35%):
  - Tislelizumab 3 cycles + investigator-chosen chemotherapy doublet (Paclitaxel + Cisplatin/5-Fu + Cisplatin) 2 cycles + concurrent radiotherapy (40 Gy/20 F).

Surgery:

Upon completion of neoadjuvant therapy, patients will undergo surgical resection of tumor after reassessment to reconfirm disease resectability. Surgical specimens will be assessed for pathological response (pCR and MPR).

The surgical procedure should be performed within 4-6 weeks from the last administered dose of chemotherapy treatment (the last dose of chemoradiotherapy in Cohort B).

The study schema is presented as below with estimates of patients in each cohort:



Abbreviations: A317: Tislelizumab; PET-CT, Positron Emission Tomography-Computed Tomography; Chemo, Chemotherapy; RT, Radiotherapy; 5-Fu, 5-fluorouracil; ESCC, esophageal squamous cell carcinoma; ECOG, Eastern Cooperative Oncology Group; N, number of patients; Q3W, once every 3 weeks.

Study Assessments:

Patients will undergo surgical resection of tumor and surgical specimens will be assessed for pathological response (pCR and MPR).

PET-CT will be performed at screening and 15-21 days after the last dose of induction, for evaluating SUVmax and to determine the subsequent treatment cohort. Before surgery, the investigator will reassess the patient to reconfirm disease resectability. The presurgical visit and associated assessments should occur within 7 days prior to surgery and in accordance with local institutional practice. After surgery, disease follow-up tumor assessment will be performed by neck, chest, and abdominal CT every 3 months for the first 2 years, every 6 months for Year 3 based on RECIST v1.1. Tumor assessments should continue per protocol until disease recurrence/progression, withdrawal of consent, death, loss to follow-up, or study termination by the sponsor, whichever occurs first.

All patients will be assessed for safety and tolerability on Day 1 of each cycle in the induction and neoadjuvant phases. Adverse events (AEs) will be evaluated according to NCI-CTCAE v5.0. After initiation of study drug(s), all AEs (serious or nonserious), regardless of relationship to study treatment will be reported until 30 days after the last study treatment (including chemotherapy, radiotherapy, tislelizumab and surgery). Immune- mediated AEs (imAE)(serious or nonserious) should be reported until 90 days after the last dose of tislelizumab, regardless of whether the patient starts a new anticancer therapy.

After the safety follow-up visit, survival follow-up will be periodically performed for survival status and any additional anticancer treatment every 3 months (± 14 days) via in-person or phone contact.

Duration of Patient Participation:

Duration of study participation will vary by patient, depending on the duration of treatment and treatment outcomes. The duration from first dose to surgery is approximately 71-86 days. The duration of the study from first enrolled patient to final analysis for pathological response is approximately 18 months.

Study Population: Approximately 65 patients who have histologically confirmed ESCC at Stage cT1-2N+M0 and cT3NanyM0 (AJCC 8th Edition, Rice et al 2017).

Key Eligibility Criteria:

Key Inclusion Criteria:

- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
- Histologically confirmed ESCC
- Stage cT1-2N+M0 and cT3NanyM0 (per AJCC 8th Edition)
- Evaluation by the investigator to confirm eligibility for an R0 resection with curative intent

- Adequate hematologic and organ function, defined by protocol-specified laboratory test results obtained within 14 days before first dose

Key Exclusion Criteria:

- Ineligible for treatment with any of the chemotherapy doublets of protocol-specified chemotherapy
- Any prior therapy for current ESCC, including investigational agents, chemotherapy, radiotherapy, targeted therapy, 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
- History of fistula due to primary tumor invasion
- Patients with high risk of fistula or sign of perforation evaluated by investigator
- Any condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone or equivalent) or other immunosuppressive medications within 14 days before first dose
    - Adrenal replacement steroid (dose ≤ 10 mg daily of prednisone or equivalent) and topical, ocular, intra-articular, intranasal, or inhaled corticosteroid with minimal systemic absorption, and short course (≤ 7 days) of corticosteroid prescribed prophylactically or for the treatment of a non-autoimmune condition are permitted.
- Active autoimmune diseases or history of autoimmune diseases that may relapse
    - Controlled Type I diabetes, hypothyroidism only requiring hormone replacement, controlled celiac disease, skin diseases (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
- History of interstitial lung disease, non-infectious pneumonitis or uncontrolled diseases including pulmonary fibrosis, acute lung diseases, etc.
- With infections requiring systemic antibacterial, antifungal, or antiviral therapy, including tuberculosis infection, etc.
    - Severe infections within 4 weeks before first dose, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia.
    - Receive therapeutic oral or intravenous (IV) antibiotics within 2 weeks before first dose.

Investigational Product, Dose, and Mode of Administration:

Tislelizumab will be administered at a dose of 200 mg intravenously on Day 1 of every 21-day cycle, cumulative 3 cycles. Tislelizumab will be given in combination with the chemotherapy doublet or concurrent chemoradiotherapy after induction therapy, and as a monotherapy for Cycle 4 (1 to 3 weeks before surgery).

Reference Therapy, Dose, and Mode of Administration:

- Cisplatin + paclitaxel:
  - Cisplatin 80 mg/m^2 IV on Day 1 Q3W
  - Paclitaxel 135 mg/m^2 IV on Day 1 Q3W
    - Depending on local guidelines, cisplatin may be given in 3 divided doses on Days 1, 2, and 3. The total dose given must be 80 mg/m2 per cycle.
- Cisplatin + 5-FU (PET-Non-responder Cohort, by the investigator's choice, chemotherapy regimen could be changed to Cisplatin + 5-FU):
  - Cisplatin 80 mg/m2 IV on Day 1, Q3W
  - 5-FU 1000 mg/m2 IV on Days 1-4, Q3W
- Radiotherapy: A total dose of 40 Gy in 20 fractions (2 Gy/fraction and 5 fractions/week)

Statistical Methods:

This study is designed to evaluate the safety and efficacy of neoadjuvant treatment with Tislelizumab (BGB-A317, an anti-PD-1 antibody) plus chemotherapy/chemoradiotherapy in resectable ESCC. Details of statistical analyses will be described in Statistical Analysis Plan.

Analysis Sets:

- The Efficacy Evaluable (EE) Analysis Set includes all patients who receive neoadjuvant treatment followed by surgery. This will be the primary analysis set for the efficacy analyses.
- The Safety Analysis Set includes all enrolled patients who receive ≥ 1 dose of any component of study drugs; it will be the primary analysis set for the safety analyses. Patients will be analyzed according to the actual treatment regimen received.

Efficacy Analysis:

The efficacy endpoints pCR, 1-year/3-year DFS rate, 1-year/3-year EFS rate, R0 resection rate, ORR, 1-year/3-year OS rate and MPR will be summarized to evaluate the efficacy of neoadjuvant treatment with tislelizumab plus chemotherapy/chemoradiotherapy in resectable Esophageal Squamous Cell Carcinoma.

Descriptive statistics will be used to summarize the efficacy analysis in Cohorts A and B. The 95% confidence interval (CI) will be calculated for pCR, 1-year/3-year DFS rate, 1-year/3-year EFS rate, R0 resection rate, ORR, 1-year/3-year OS rate and MPR.

Primary Efficacy Endpoint Analyses:

pCR rate is the primary endpoint of the study.

The pCR rate in cohort A (Responder: decrease in PET SUVmax ≥ 35%) and the pCR rate in Cohort B (Non-Responder: decrease in PET SUVmax < 35%) will be summarized. Clopper-Pearson 95% confidence interval (CI) of pCR rate in cohort A and B will be calculated.

These analyses will be performed in the EE analysis set as the primary analysis. The analysis

of pCR rate will occur after all the patients in the EE analysis set have been assessed for pathological response.

Secondary Efficacy Endpoint Analyses:

DFS rate will be estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula for patients who undergo R0 resection in cohorts A and B in the EE analysis set.

1-year/3-year Event-Free Survival (EFS) rate will be estimated in cohorts A and B by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula for patients in the Safety Analysis Set.

R0 resection rate defined as the proportion of patients with R0 resection will be summarized in cohorts A and B in the EE analysis set.

Objective response rate (ORR) is the proportion of patients who have a complete response or partial response before surgery as assessed by the investigator per RECIST v1.1 in all patients with measurable disease at baseline in the Safety Analysis Set. ORR will be summarized in cohorts A and B.

Safety Analyses:

All AEs graded by NCI-CTCAE v5.0, 2018 and verbatim AE terms will be mapped to the corresponding Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms. All TEAEs will be summarized. A TEAE is defined as an AE that has an onset date or a worsening in severity from baseline (pre-treatment) on or after the first dose of study treatment and up to 30 days following study treatment discontinuation or initiation of new anti-cancer therapy, whichever occurs first. Immune-mediated AEs will be identified from all adverse events that have an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of tislelizumab and up to 90 days after the last dose of tislelizumab, regardless of whether the patient starts a new anticancer therapy. If an imAE occurs outside of the above-mentioned treatment-emergent adverse event window, it will not be classified as a treatment-emergent adverse event. All imAEs will be reported separately. TEAEs of ≥ Grade 3; treatment-related TEAEs, serious TEAEs, deaths, TEAEs that lead to treatment discontinuation and TEAEs that lead to treatment modification will be summarized.

Sample Size Considerations:

Approximately 65 patients are expected to be enrolled in this study, considering approximately 10% of patients not receiving surgery. It is assumed that 25 patients will be categorized into cohort A and 40 patients will be categorized into cohort B according to their PET SUVmax decrease. The actual number of patients in each cohort will be based on the actual ratio of responders and non-responders observed in the study and may vary from this assumption.

The pCR rate of responders was reported about 21.9% - 31.8% in historical studies (Buschenfelde et al 2011; Ilson et al 2012; Greally et al 2018). The pCR rate in cohort A is assumed to be 37%. If there are 23 evaluable patients in cohort A, it will provide the probability of 66.2% to observe 8 pCRs out of 23 evaluable patients with an estimated pCR rate of 34.7% for cohort A, which is greater than the historical pCR rate.

The pCR rate of non-responders was reported about 4% - 13.6% in historical studies (Buschenfelde et al 2011; Ilson et al 2012; Greally et al 2018). The pCR rate in cohort B is assumed to be 22%. If there are 35 evaluable patients in cohort B, it will provide a probability of 91.0% to observe 5 pCR out of 35 evaluable patients with an estimated pCR rate of 14.3%, which is greater than the historical pCR rate in cohort B.

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody dependent cellular phagocytosis
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BGB-A317	Tislelizumab
cCRT	concurrent chemoradiotherapy
CL	clearance
CR	complete response
CT	computed tomography
DCR	disease control rate
DFS	disease-free survival
DOR	duration of response
EC	esophageal carcinoma
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EE	Efficacy Evaluable
ESCC	esophageal squamous cell carcinoma
eCRF	electronic case report form
EDC	electronic data capture (system)
EFS	event-free survival
FcγR	fragment crystallizable region (typically, of immunoglobulin G)
FDG	Fluorodeoxyglucose
GEJ	gastroesophageal junction
HBV	hepatitis B virus
HCC	hepatocellular cancer
HCV	hepatitis C virus
IB	investigator's brochure
ICC	investigator chosen chemotherapy
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	investigational medicinal product

IV	intravenous
Ig	immunoglobulin
imAE	immune-mediated adverse event
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	infusion related reaction
MedDRA	Medical Dictionary for Regulatory Activities
MPR	major pathological response
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NMPA	National Medical Products Administration
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
pCR	pathological complete response
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-CT	positron emission tomography-computed tomography
PK	pharmacokinetic(s)
PR	partial response
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TRAE	treatment-related adverse event
ULN	upper limit of normal
Vc	central volume

1. INTRODUCTION

1.1. Background Information on Esophageal Carcinoma

Esophageal cancer is the seventh most common cancer worldwide (572,000 new cases) and the sixth most common cause of death (509,000 deaths) from cancer (Bray et al 2018). The incidence, prevalence, and histologic type of esophageal cancer vary between geographic regions (Arnold et al 2015), approximately 75% of all cases occur in Asia with China bearing the largest burden, accounting for about 50% of total cases and cancer-specific deaths. In China, esophageal cancer is the third most common cancer and the fourth leading cause of death from cancer, based on an estimation of 477,900 new esophagus cancer cases and 375,000 deaths from this disease expected in 2015 (Chen et al 2016).

Two most common histologic subtypes (esophageal squamous cell carcinoma [ESCC] and adenocarcinoma have quite different etiologies. Heavy drinking and smoking and their synergistic effects are the major risk factors for SCC in Western settings (Blot et al 2017). However, in low-income countries, such as in parts of Asia and Sub-Saharan Africa, the major risk factors for ESCC (which usually comprises over 90% of all esophageal cancer cases) have yet to be elucidated.

In the early and locally advanced stages, esophagectomy is recognized as the curative treatment. However, for patients with locally advanced ESCC, neo-adjuvant therapy followed by surgery showed a better clinical benefit compared with surgery only (Joel et al 2015). But prognostic for locally advanced ESCC is still poor, from 2009 to 2015, the overall 5-year relative survival rate for esophageal cancer (EC) was 21.4%, and the corresponding 5-year relative survival rates were 46.7% for localized cancer, 25.1% for regional metastasis, 4.8% for distant metastasis (Noone et al 2017). Poor prognostic factors for survival in patients with ESCC include advanced stage of disease at the initial diagnosis, poor performance status, and malnutrition with unintentional weight loss, etc.

1.2. Current Treatment of Resectable Esophageal Carcinoma and Unmet Clinical Needs

For patients with early stage of ESCC (pTis, T1a, T1b, N0), resection is a recommended modality, which includes endoscopic therapies and esophagectomy; for patients with locally advanced ESCC, preoperative chemoradiation followed by esophagectomy is recommended by international treatment guidelines ((NCCN) Guidelines Version 4, 2020). Postoperative chemotherapy or chemoradiation is commonly given to patients who have positive lymph nodes after R0 resection, or to those with microscopic or macroscopic residual cancer (R1 and R2 resection, respectively) after surgery.

The status of preoperative concurrent chemoradiotherapy as standard of care for ESCC is based on the CROSS study (van et al 2008), which demonstrated overall survival benefit with neoadjuvant concurrent chemoradiotherapy followed by surgery compared with surgery alone. Long-term results of the CROSS study (Joel et al 2015) showed that, median overall survival has been prolonged from 24.0 months to 48.6 months; and for patients with ESCC, median overall survival has been prolonged from 21.1 months to 81.6 months. Another study, NEOCRTEC5010 (Hong et al 2018) showed a similar trend, median overall survival was 100.1 months in neo-

adjuvant concurrent chemoradiotherapy (cCRT) followed by surgery group versus 66.5 months in surgery alone group.

In the preoperative setting for locally advanced esophageal cancer, preoperative chemotherapy also shows survival benefits compared with surgery alone. In the Medical Research Council OEO2 Trial (Allum et al 2009), median survival was 16.8 months in the preoperative chemotherapy group compared with 13.3 months in the surgery alone group, and the 2-year survival rates were 43% and 34%, respectively; Long-term follow-up confirmed the survival benefit of preoperative chemotherapy, with a 23% 5-year survival rate in the preoperative chemotherapy group compared with 17.1% in the surgery alone group. Although the benefit for neoadjuvant chemotherapy was not as great as for neoadjuvant chemoradiotherapy, a clear advantage of neoadjuvant chemoradiotherapy over neoadjuvant chemotherapy has not been established and further trials are warranted. (Shown in Table 2). In previous studies, although no difference has been demonstrated between the treatment groups in the frequency of postoperative complications, complications were significantly more severe in the (neoadjuvant chemoradiotherapy)nCRT arm, for example, increased the numbers of postoperative deaths (Klevebro et al 2016; Stahl et al 2017).

However, in clinical practice, because of safety concerns on adding radiotherapy to neo-adjuvant therapy and difficulties in collaborations cross clinical departments, patients with locally advanced ESCC who received preoperative chemotherapy rather than preoperative chemoradiotherapy may not receive the full benefit of neoadjuvant treatment. Other checkpoint inhibitors have data to suggest that adding immune-therapy and radiation to neoadjuvant chemotherapy can improve clinical outcomes.

Positron Emission Tomography-Computed Tomography (PET-CT) showed positive predictive data in PET-guided Studies (Buschenfelde et al 2011; Greally et al 2018’ Ilson 2012) (shown in Table 3). After induction therapy, patients were divided into PET responders (SUVmax ≥ 35%) and non-responders (SUVmax < 35%), pCR rates of 21.9-31.8% and 4-13.6% were observed in responders and non-responders who underwent surgery, respectively. Regarding the OS and PFS, PET-CT responders showed a median PFS of 24.7-70 months and a median OS of 40.2-85 months, while non responders showed a poorer prognosis with a median PFS of 7-7.7 months and a median OS of 17-25.5 months. Therefore, improving the survival benefit for the population of PET-CT non-responders is also an unmet medical need.

Table 1: Outcomes of Neoadjuvant CRT Followed by Surgery for EC

Reference	Population	Phase	Sample Size	treatment	Pathological Complete Response Rate	DFS (median months)	OS (median months)
Van et al, 2008	II – III (EC)	3	366	41.4Gy/23F CBP (AUC=2) +PTX 50mg/m2 weekly * 5w	EC:29% ESCC: 49%	EC: 37.7 ESCC: 74.7	EC: 49.4 ESCC: 81.6

Reference	Population	Phase	Sample Size	treatment	Pathological Complete Response Rate	DFS (median months)	OS (median months)
Lv et al, 2010	I- III （ESCC）	NA	238	40Gy/20F DDP 20mg/m2 d1-3+PTX 135mg/m2 2 cycles	NA	46.5	53
Christophe et al, 2014	I- II (EC)	3	195	45Gy/25F DDP 75mg/m2+5FU 800mg/m2 2 cycles	NA	27.8	31.8
Yang et al, 2018	II – III (ESCC)	3	451	40Gy/20F Vinorelbine 25mg/m2 d1,8 + DDP 75mg/m2 2 cycles	43.2%	100.1	100.1

Table 2: Outcomes of Neoadjuvant Chemotherapy Followed by Surgery for EC

Reference	Population	Phase	Sample Size	treatment	Pathological Complete Response Rate	DFS (median months)	OS (median months)
David et al, 2007	I- III (EC)	NA	227	Cisplatin and fluorouracil	NA	27.8	31.8
Jurjen et al, 2011	I – III (ESCC)	NA	195	Cisplatin 80 mg/m2 (d1), + Etoposide（d1-2） 100 mg/m2 + etoposide 200 mg/m2 (d3,5) , 2-4 cycles	7%	NA	16
Klevebro et al, 2010	I- III (EC)	2	181	Cisplatin, 100 mg/m2 d1, and fluorouracil 750 mg/m2/24 h, d 1–5, Q3w, 3 cycles	9%	3 yr DFS Rate: 44%	3 yr OS Rate: 49%

Reference	Population	Phase	Sample Size	treatment	Pathological Complete Response Rate	DFS (median months)	OS (median months)
Girling et al, 2002	Resectable (EC)	3	802	Cisplatin, 80 mg/m2 d1, and fluorouracil 1000 mg/m2/24 h, d 1–4, Q3w, 2 cycles	NA	NA	16.8

Table 3: Outcomes of Neoadjuvant CRT Followed by Surgery for EC Guided by PET After Induction Therapy

Reference	Population	Phase	Sample Size	Pathological Complete Response Rate	PFS (median months)	OS (median months)
Greally et al, 2018	locally advanced (ESCC)	2	111	R：31.8% NR：11.1%	R：70 NR：7	R：85 NR：17
Ilson et al, 2012	I – III (EC)	2	55	R：32% NR：4%	R：24.1 NR：7.7	R：40.2 NR：25.5
Goodman et al, 2010	Resectable (EAC/EGJ AC)	2	181	R：21.9% NR：13.6%	NA	R：2y OS 71% NR：2y OS 42%

Abbreviations: R: PET Responder; NR: PET Non-responder; EC: esophageal carcinoma; EAC: esophageal adenocarcinoma; EGJAC: Esophagogastric junction carcinoma; PTX: paclitaxel; DDP: cisplatin; CBP: carboplatin; 5-FU: 5- fluorouracil.

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

Clinical outcome data are available from early phase to late phase studies, from disease setting of metastases to locally advanced stage studies, to evaluate tislelizumab, nivolumab, and pembrolizumab in patients with advanced esophageal carcinoma. All data described below are supportive of the safety and antitumor activity of antiprogrammed cell death protein-1 (PD-1) monoclonal antibodies in esophageal carcinoma.

1.3.1. Tislelizumab

BGB-A317-205 (NCT03469557) (Xu et al 2020) is an open label Phase 2 study. As of 31 March 2019, 30 Chinese patients (Gastric/ gastroesophageal junction [GEJ], n =15; ESCC, n=15) were enrolled in the study BGB-A317-205. In the ESCC cohort, the median age of enrolled patients was 61 years (range: 47 to 68 years). Patients did not receive prior systemic therapy for advanced or metastatic disease. All patients experienced at least 1 treatment-emergent adverse event

(TEAE). Anemia (n=11) decreased appetite (n=11), nausea (9), and leukopenia (n=8) were the most common treatment-related AEs. Five patients experienced Grade 3 to 4 TEAE, in which the most common was vomiting (n=4). Fatal AE (hepatic dysfunction) was reported in 1 patient, mainly attributed to progressive disease, which may possibly be related to study treatment or confounded by underlying HBV infection. Efficacy data shows that the confirmed ORR is 46.7% (95% CI: 21.27, 73.4), disease control rate (DCR) is 80% (95% CI: 51.91, 95.67), duration of response (DOR) is 12.8 months (95% CI: 3.5, 12.8), and median OS is 14.31 months (95% CI: 6.01-NA).

BGB-A317-302 (NCT03430843) (Lin Shen et al 2022) is a global Phase 3 study comparing the efficacy of tislelizumab versus chemotherapy as second-line treatment in patients with advanced unresectable/metastatic ESCC. Overall, 512 patients (median age: 62 years; range 35-86 years) were randomized to receive either tislelizumab (n=256) or investigator chosen chemotherapy (ICC) (n=256). As of Dec 2020 (data cutoff), the study met its primary endpoint at its final analysis: tislelizumab clinically and significantly improved OS vs ICC in the ITT population (median OS: 8.6 vs 6.3 m; HR 0.70, 95% CI 0.57-0.85, p=0.0001). Survival benefit was consistently observed across pre-defined subgroups, including baseline PD-L1 status and region. Treatment with tislelizumab was also associated with a higher ORR (20.3% vs 9.8%) and more durable response (median DOR: 7.1 vs 4.0 m; HR 0.42, 95% CI 0.23-0.75) than ICC in the ITT population. The safety profile of tislelizumab was more favorable than ICC. Fewer patients had ≥ Grade 3 (46% vs 68%) treatment-emergent adverse events with tislelizumab compared with ICC.

BGB-A317-306 (NCT03783442) is a global Phase 3, randomized, placebo-controlled, double-blind study of tislelizumab in combination with chemotherapy as first-line treatment versus chemotherapy alone in patients with unresectable, locally advanced recurrent or metastatic ESCC. Approximately 649 study participants were randomized 1:1 to receive either tislelizumab plus chemotherapy or chemotherapy alone. Tislelizumab plus chemotherapy demonstrated a median OS of 17.2 months (CI, 15.8-20.1 months) versus 10.6 months (CI, 9.3-12.1 months) in patients receiving chemotherapy plus placebo and reduced the risk of death by 34% (hazard ratio=0.66; CI, 0.54-0.80, p<0.0001). Survival benefit was consistent across all other subgroups, including race, geographical region and investigator choice of chemotherapy. Tislelizumab plus chemotherapy also significantly improved progression-free survival (7.3 months vs 5.6 months; HR=0.62; CI, 0.52-0.75, p<0.0001) and objective response rate (63.5% vs 42.4%; odds ratio=2.38, p<0.0001). The incidence of treatment-related adverse events (TRAEs) was similar in both arms. The most common TRAEs for tislelizumab plus chemotherapy versus chemotherapy were anemia (68% vs 61%), decreased neutrophils (78% vs 80%), decreased white blood cell count (55% vs 65%), decreased appetite (39% vs 38%), nausea (37% vs 42%) and peripheral sensory neuropathy (26% vs 21%). Tislelizumab plus chemotherapy had a manageable safety profile in patients with advanced ESCC, with no new safety signal identified.

1.3.2. Pembrolizumab

KEYNOTE-181 (NCT 02564263), a Phase 3, open-label randomized study (Kojima et al 2019), recruited 628 patients with metastatic esophageal cancer and ≥ 2 prior lines of therapy. In the Pembrolizumab group, 63.1% of patients had ESCC, who received pembrolizumab 200 mg once every 3 weeks for up to 35 cycles, in control group, patients received investigator choose chemotherapy from paclitaxel 80-100 mg/m2 on days 1, 8, 15 Q4W, Docetaxel 75 mg/m2 Q3W,

or irinotecan 180 mg/m2 Q2W. As of 15 October 2018, in Intent-to-Treat (ITT) population, median overall survival was 7.1 months in both groups, in ESCC population, median overall survival in Pembrolizumab group was 8.2 months versus 7.1 months in control group, but P-value didn't meet statistical significance, and in PD-L1 CPS ≥10 population, median overall survival increased statistical significantly, which was 9.3 months in Pembrolizumab group versus 6.7 months in control group. In Pembrolizumab group, 202 (64.3%) experienced at least 1 treatment-related AE, 57 (18.2%) patients experienced Grade 3-5 treatment-related AE, and 18 (6.1%) lead to discontinuation, and 5 (1.5%) lead to death. Treatment-related AE ≥ 20% includes fatigue (22.3%), decreased appetite (24.8). Immune-mediated AEs and infusion reactions is 73 (23.2%).

KEYNOTE-590 (NCT 03189719), a phase 3, double-blinded randomized study (Kato 2020), recruited 749 patients with metastatic esophageal cancer with treatment naive; randomized patients received pembrolizumab or placebo plus chemotherapy. In Pembrolizumab plus chemotherapy group, 73.5% of patients had ESCC, who received pembrolizumab 200 mg once every 3 weeks for up to 35 cycles, 5-FU 800 mg/m^2 for Days 1-5 every 3 weeks for ≤ 35 cycles, and Cisplatin 80 mg/m^2 every 3 weeks for ≤ 6 cycles. As of 2 July 2020, in each predefined population, statistically significant overall survival benefit was observed. In Intent to Treat (ITT) population, the median overall survival was 12.4 months in the Pembrolizumab plus chemotherapy group versus 9.8 months in the placebo plus chemotherapy group; in the PD-L1 CPS ≥ 10 population, the median overall survival was 13.5 months versus 9.4 months; in the ESCC population, the median overall survival was 12.6 months versus 9.8 months; and in ESCC PD-L1 CPS ≥ 10 population, the median overall survival was 13.9 months versus 8.8 months. In the Pembrolizumab plus chemotherapy group, all patients experienced at least 1 treatment-related AE, 71.9% patients experienced Grade 3-5 treatment-related AE, 19.5% AEs lead to discontinuation, and 2.4% patients lead to death. Immune-mediated AEs and infusion reactions were 25.7%, in which ≥ Grade 3 was 7.0%.

NCT 02844075, a phase 2 trial preoperative chemoradiotherapy and Pembrolizumab (Lee et al 2019), recruited 28 patients with resectable locally advanced ESCC. Enrolled patients received chemoradiotherapy in combination with pembrolizumab followed by surgery. The median age of enrolled patients was 60 years (range: 46 to 76 years). As of February 2019, 26 patients underwent esophagectomy. The pCR rate was 23.1% for ypT0N0 and 46.1% for ypT0, 6-month OS rate was 89.3%, 12-month OS rate was 82.1%, 6-month Event Free Survival (EFS) rate was 85.3%, and 12-month EFS rate was 60.3%. The most common treatment-related AEs were neutropenia (50%), nausea (25%), esophagitis (21%), and leukopenia (21%); neutropenia was the only more than 10% treatment related AEs with Grade 3 -4 (18%); and no treatment discontinuation occurred due to AEs.

1.3.3. Nivolumab

Attraction 3 (NCT02569242), a Phase 3, open-label randomized study (Cho et al 2019), recruited 419 ESCC patients with refractory or intolerant to previous chemotherapy; patients were randomized to either nivolumab (240 mg for 30 minutes once every 2 weeks) or investigator's choice of chemotherapy (paclitaxel 100 mg/m² for at least 60 minutes once a week for 6 weeks then 1 week off or docetaxel 75 mg/m² for at least 60 minutes once every 3 weeks). As of 12 November 2018, median follow-up for overall survival was 10.5 months (4.5–19.0) in the nivolumab group and 8.0 months (4.6–15.2) in the chemotherapy group. At a minimum

follow-up time of 17.6 months, overall survival was significantly improved in the nivolumab group compared with the chemotherapy group (median 10.9 months, 95% CI 9.2–13.3 versus 8.4 months, 95% CI 7.2–9.9; hazard ratio for death 0.77, 95% CI 0.62–0.96; p = 0.019). Thirty-eight (18%) of 209 patients in the nivolumab group had Grade 3 or 4 treatment-related adverse events compared with 131 (63%) of 208 patients in the chemotherapy group. The most frequent Grade 3 or 4 treatment-related adverse events were anemia (4 [2%]) in the nivolumab group and decreased neutrophil count (59 (28%)) in the chemotherapy group. Five deaths were deemed treatment-related: 2 in the nivolumab group (1 each of interstitial lung disease and pneumonitis) and 3 in the chemotherapy group.

Checkmate 577 (NCT02743494) is a Phase 3, randomized, multi-center, double-blind study evaluating nivolumab as an adjuvant therapy in patients with resected esophageal or GEJ cancer who have received neoadjuvant CRT and have not achieved a pathological complete response. Adjuvant treatment with nivolumab demonstrated a statistically significant improvement in disease-free survival versus placebo (22.4 months vs 11.0 months; HR = 0.69; 96.4% CI: 0.56-0.86; p=0.0003) in patients who received neoadjuvant CRT and had residual pathologic disease at a prespecified interim analysis.

1.4. Background Information on Tislelizumab

1.4.1. Pharmacology

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

Tislelizumab acts by binding to the extracellular domain of human PD-1 with high specificity as well as high affinity (dissociation constant [K_D] = 0.15 nM). It competitively blocks binding efforts by both programmed cell death protein ligand-1 (PD-L1) and programmed cell death protein ligand-2 (PD-L2), thus inhibiting PD-1-mediated negative signaling in T cells. In in vitro cell-based assays, tislelizumab was observed to consistently and dose-dependently enhance the functional activity of human T cells and pre-activated, primary peripheral blood mononuclear cells. 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.

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 effects in humans (Labrijn et al 2009; Zhang et al 2018). Tislelizumab was specifically engineered to abrogate these potential mechanisms of T-cell clearance and potential resistance to anti-PD-1 therapy.

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

1.4.2. Toxicology

The toxicity and safety profile of tislelizumab was characterized in single-dose toxicology studies in mice and cynomolgus monkeys and in a 13-week, repeat-dose toxicology study in cynomolgus monkeys. Tissue cross-reactivity was evaluated in normal frozen tissues from both humans and monkeys. The cytokine release assays were conducted using fresh human whole blood cells. The pivotal toxicology studies were conducted following Good Laboratory Practice regulations. The single-dosing regimens spanned from the intended human doses to 10-fold higher than the maximum of the intended human doses, and the repeat-dosing regimens spanned to 3-fold higher than the maximum of the intended human doses. 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 the human whole-blood assay. 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 safety profile of tislelizumab is considered adequate to support the current study, BGB-A317-213.

Please refer to the tislelizumab IB for more detailed information on the toxicology of tislelizumab.

1.4.3. Clinical Pharmacology

Population pharmacokinetic (PK) analysis was conducted using data from 798 patients with solid tumors or classical Hodgkin lymphoma who received doses of 0.5, 2.0, 5.0, and 10 mg/kg once every 2 weeks, 2.0 and 5.0 mg/kg once every 3 weeks, and 200 mg once every 3 weeks. The PK of tislelizumab was best characterized using a 3-compartmental linear population PK model with linear clearance mechanisms. No time-varying clearance was observed in tislelizumab PK. The typical estimates of clearance (CL), central volume (V_c), and peripheral volumes (V_2, V_3), were 0.164 L/day, 2.92 L, 0.928 L, and 1.39 L, respectively, with moderate inter-individual variability in CL (32.2%), V_c (16.7%), V_2 (56.6%), and V_3 (94.2%). The volume of distribution at steady state was 5.238 L, which is typical of monoclonal antibodies with limited distribution, which is consistent with a standard IgG monoclonal antibody ((Deng R et al 2012) ; Dirks NLet al 2010; Keizer RJ et al 2020; Ryman JT et al 2017); . Based on the population PK analysis, tislelizumab PK was characterized by a terminal half-life of approximately 25.5 days, which is consistent with other therapeutic IgG monoclonal antibodies.

Population PK analysis demonstrated that baseline age, race, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, lactate dehydrogenase, estimated glomerular filtration rate, ECOG Performance Status, immunogenicity, and sum of products of perpendicular diameters in classical Hodgkin lymphoma patients did not show statistically significant impact on the PK of tislelizumab. Although tumor size, albumin, and tumor type were significant covariates on CL, while body weight, sex, and tumor type were significant covariates on V_c, these covariates are not expected to have a clinically relevant impact on tislelizumab exposure. Exposure-response analysis indicated that there was a lack of clinically significant exposure-response relationships for ORR and safety endpoints across a variety of

advanced solid tumors and classical Hodgkin lymphoma for tislelizumab. Population PK analysis supports fixed dosing across different ethnic groups.

1.4.4. Prior Clinical Experience of Tislelizumab

As of 20 May 2021, there are 33 ongoing studies and 9 completed studies with over 3498 patients (2150 patients treated with monotherapy and 1348 patients treated with combination therapy) treated with tislelizumab. Of the 33 ongoing studies, 15 studies have preliminary data available in the IB Edition 9, 20 October 2021: 6 monotherapy studies, 2 chemotherapy combination therapy studies, and 7 targeted therapy combination studies.

Refer to the tislelizumab IB for more detailed information on tislelizumab safety and efficacy data when given as monotherapy or in combination with chemotherapy.

1.4.4.1. Pooled Safety Assessment of Monotherapy Studies

A pooled analysis of 10 monotherapy studies was conducted to provide a comprehensive safety assessment separately from combination therapy.

Overall, a total of 2150 patients were treated in the monotherapy studies included in the pooled safety analysis. Within the 7 solid tumor monotherapy studies, 1992 patients were treated. Within the 3 hematologic malignancy monotherapy studies, 158 patients were treated.

The 7 solid tumor studies included the following: BGB-A317- 001 (Phase 1a /1b Advanced Solid Tumors), BGB-A317-102 (Phase 1 /2 Advanced Solid Tumors), BGB-A317-204 (Phase 2 Locally Advanced or Metastatic Urothelial Bladder Cancer), BGB-A317-208 (Phase 2 Locally Advanced or Metastatic Urothelial Bladder Cancer), BGB-A317-209 (Phase 2 Previously Treated Locally Advanced Unresectable or Metastatic Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors), BGB-A317-302 (Phase 3 Advanced Unresectable/Metastatic ESCC), and BGB-A317-303 (Phase 3 Non−Small Cell Lung Cancer Who Have Progressed on a Prior Platinum-Containing Regimen). The 3 studies in hematologic malignancies are BGB-A317-203 (Phase 2 Relapsed or Refractory Classical Hodgkin Lymphoma), BGB-A317-207 (Phase 2 Relapsed or Refractory Mature T- and NK-cell Neoplasms) and BGB-A317-210 (Phase 2 Relapsed or Refractory Classical Hodgkin Lymphoma).

Refer to the tislelizumab IB for more detailed information on tislelizumab safety data when given as monotherapy.

1.4.4.1.1. Pooled Demographics and Baseline Characteristics

Table 4 shows the demographics and baseline characteristics for the patients treated in the pooled monotherapy studies of solid tumors.

Table 4: Demographics, Baseline Characteristics, Treatment Exposure Duration, and Study Follow-up Duration in Pooled Monotherapy Studies of Solid Tumors

Measure	Overall[a] N = 1992
Age (years)	
Median	60.0
Min, Max	18, 90
Sex, n (%)	
Male	1437 (72.1)
Female	555 (27.9)
Race, n (%)	
Asian	1383 (69.4)
White	532 (26.7)
Missing	22 (1.1)
Other	55 (2.8)
Prior systemic anti-cancer therapy regimens[b]	
Median	1.0
Min, Max	0, 12
Prior systemic anti-cancer therapy regimens (grouped)[b], n (%)	
0	318 (16.0)
1	1055 (53.0)
2	393 (19.7)
≥3	226 (11.3)
Study treatment exposure duration (months)	
Median	4.070
Min, Max	0.10, 41.46

Measure	Overall[a] N = 1992
Study follow-up duration (months)	
Median	11.530
Min, Max	0.07, 58.91

Source: Tislelizumab Investigator's Brochure.
Abbreviations: N, total number of patients treated; n, number of patients within each category.
Data cut-off 20 May 2021.
[a] Solid Tumor Studies include: A317-BGB-A317-001, BGB-A317-102, BGB-A317-204, BGB-A317-208, BGB-A317-209, BGB-A317-302, and BGB-A317-303 and Hematology Studies include: BGB-A317-203, BGB-A317-207, and BGB-A317-210
[b] Only systemic therapies were selected.

The patients in the solid tumor group of pooled monotherapy studies had a median treatment exposure duration of 4.07 months (range: 0.10 to 41.46) and median study follow-up duration of 11.53 months (range: 0.07 to 58.91). The median age of the patients was 60 years and 72.1% were male. These patients had a median of 1.0 prior systemic anticancer therapy regimens (range: 0 to 12) and their most common tumor types were non-small cell lung cancer (NSCLC) (639 of 1992 patients, 32.1%), ESCC (15.9%), hepatocellular carcinoma (HCC; 15.9%), urothelial bladder cancer (5.7%), and colorectal cancer (5.2%).

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

Of the 1992 patients in the solid tumor group of pooled monotherapy studies, 1391 (69.8%) experienced ≥ 1 treatment related TEAE. The most commonly occurring treatment related TEAEs were AST increased (250 of 1992 patients, 12.6%), ALT increased (12.1%), hypothyroidism (9.9%), anaemia (9.3%), and rash (8.0%).

Of the 1992 patients in the solid tumor group of pooled monotherapy studies, 269 (13.5%) experienced ≥ 1 tislelizumab-related TEAE of ≥ Grade 3 severity. The most commonly occurring ≥ Grade 3 TEAEs were AST increased (25 of 1992 patients, 1.3%), ALT increased (1.0%), and anemia (1.0%). All other events occurred in < 1% of patients.

1.4.4.1.3. Treatment-Emergent Serious Treatment Emergent Adverse Events

Of the 1992 patients in the solid tumor group of pooled monotherapy studies, 706 (35.4%) experienced ≥ 1 treatment emergent serious TEAE. The most commonly occurring serious TEAEs were pneumonia (95 of 1992 patients, 4.8%), pneumonitis (1.7%), dysphagia (1.2%), pleural effusion (1.0%), and pyrexia (1.0%).

1.4.4.1.4. Immune-Mediated Adverse Events

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

Immune-mediated AEs are consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. Immune-mediated AEs can include events with an alternate etiology which

were exacerbated by the induction of autoimmunity. There is a potential temporal relationship between the initiation of treatment with tislelizumab and onset of an imAE that spans a window of days to several months.

All imAEs presented here are assessed as related to study drug by the investigator and categorized by the BeiGene Safety/Pharmacovigilance team. Certain imAEs have multiple Medical Dictionary for Regulatory Activities (MedDRA) terms associated with the same category. Special categories have been created to group patients experiencing these events.

All imAEs that occur in ≥ 1% in the total pooled monotherapy studies of solid tumors are shown in Table 5.

Table 5: Immune-Mediated Adverse Events of Any Grade Occurring in ≥ 1% in Pooled Monotherapy Studies of Solid Tumors

Categories Preferred Term	Total (N = 1912)	
	Any Grade n (%)[a]	**Grade ≥ 3 n (%)[a]**
Patients with at least one potential immune-mediated AE[a]	286 (15.0)	73 (3.8)
Immune-Mediated Hypothyroidism	118 (6.2)	1 (0.1)
Hypothyroidism	115 (6.0)	1 (0.1)
Immune-Mediated Pneumonitis	70 (3.7)	28 (1.5)
Pneumonitis	41 (2.1)	15 (0.8)
Immune-Mediated Hepatitis	34 (1.8)	19 (1.0)
Immune-Mediated Skin Adverse Reaction	24 (1.3)	9 (0.5)

Source: Tislelizumab Investigator's Brochure.
Abbreviations: AE, adverse event; N, total number of patients treated; n, number of patients within each category; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PT, preferred term;.
Note: Maximum NCI-CTCAE grade was selected per patient under each PT. Potential immune-mediated AE is identified based on a predefined list of AEs and assessed as treatment-related by investigators. Sorted in descending order of the number of patients in SOC and PT in Any Grade under the Total column. Data cut-off 20 May 2021.
[a] Percentages are based on the total population.

Of the 1912 patients in the adjudicated solid tumor group of pooled monotherapy studies, 73 (3.8%) experienced ≥ 1 imAE that was ≥ Grade 3 in severity. The most commonly occurring ≥ Grade 3 imAEs were pneumonitis (15 of 1912 patients, 0.8%), interstitial lung disease (0.4%), ALT increased (0.3%), AST increased (0.3%), and hepatitis (0.3%).

1.4.4.1.5. Infusion-Related Reactions

Of the 1992 patients in the solid tumor group of pooled monotherapy studies, 58 (2.9%) experienced ≥ 1 infusion related reaction (IRR) of any grade. The most commonly occurring IRRs were "infusion-related reaction" (28 of 1992 patients, 1.4%), pyrexia (0.9%), rash (0.3%), hypotension (0.2%), nausea (0.2%), and pruritus (0.2%).

1.4.4.1.6. Fatal Adverse Events

A summary of the treatment-emergent fatal AEs that occurred in the pooled monotherapy studies of solid tumors are shown in Table 6.

Table 6: Treatment-Emergent Fatal Adverse Events Regardless of Causality in Pooled Monotherapy Studies of Solid Tumors (in ≥ 2 patients)

	Overall (N = 1992) n (%)
Patients with at Least One TEAE Leading to Death	141 (7.1)
General disorders and administration site conditions	38 (1.9)
Death	16 (0.8)
Multiple organ dysfunction syndrome	11 (0.6)
General physical health deterioration	10 (0.5)
Respiratory, thoracic and mediastinal disorders	32 (1.6)
Respiratory failure	10 (0.5)
Acute respiratory failure	3 (0.2)
Haemoptysis	2 (0.1)
Pleural effusion	2 (0.1)
Pneumonitis	2 (0.1)
Pulmonary embolism	2 (0.1)
Pulmonary haemorrhage	2 (0.1)
Infections and infestations	20 (1.0)
Pneumonia	14 (0.7)
Sepsis	2 (0.1)
Hepatobiliary disorders	15 (0.8)
Hepatic failure	10 (0.5)
Acute hepatic failure	2 (0.1)
Gastrointestinal disorders	14 (0.7)
Upper gastrointestinal haemorrhage	7 (0.4)
Ascites	2 (0.1)
Nervous system disorders	10 (0.5)
Cerebral infarction	2 (0.1)
Hepatic encephalopathy	2 (0.1)
Cardiac disorders	8 (0.4)
Acute myocardial infarction	2 (0.1)

Source: Tislelizumab Investigator's Brochure.
Abbreviations: TEAE: treatment-emergent adverse event. N, total number of patients treated; n, number of patients within each category.
Data cut-off 20 May 2021.

Of the 1992 patients in the solid tumor group of pooled monotherapy studies, 141 (7.1%) experienced ≥ 1 TEAE leading to death. The most commonly occurring TEAEs leading to death were "death" (16 of 1992 patients, 0.8%), pneumonia (0.7%), multiple organ dysfunction syndrome (0.6%), general physical health deterioration (0.5%), hepatic failure (0.5%), and respiratory failure (0.5%).

1.5. Study Rationales

1.5.1. Rationale for Tislelizumab in the Treatment of Esophageal Carcinoma

High levels of FcγR-expressing myeloid derived suppressor cells 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 ADCP depletion of effector T cells (Gül et al, 2015; Prieto et al 2015; Makarova-Rusher et al, 2015). As a no- to low-FcγR-binding agent (thus causing minimal ADCC/ADCP effect), tislelizumab may show improved efficacy and reduced toxicity in esophageal carcinoma Available data from a clinical study with other anti-PD-1 monoclonal antibodies, nivolumab and pembrolizumab, has shown the drug to have both a manageable safety profile and promising antitumor activity in patients with EC (Section 1.1).

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

1.5.2. Rationale for Selection of Tislelizumab Dose

The clinical fixed dose of 200 mg intravenously once every 3 weeks was selected based on comparable safety and efficacy profiles between 2 and 5 mg/kg in BGB-A317_Study_001:

- Rates of treatment-related AEs and serious adverse events (SAEs) observed in patients receiving 2 mg/kg and 5 mg/kg once every 2 weeks and once every 3 weeks were comparable, suggesting no clear dose-dependence across these regimens. Additionally, PK data also showed no relationship between exposure and treatment-emergent imAEs (Wu et al 2019a).
- Confirmed response rates in patients treated with tislelizumab on a once every 3 weeks schedule were more favorable compared to those treated on a once every 2 weeks schedule. While there are differences in response rates between dose levels, this is more likely a reflection of small sample size and patient heterogeneity than dose response.
- Clearance of tislelizumab was not dependent on body weight, and the observed serum exposure of a 200 mg dose fell between serum exposure observed after 2 mg/kg and 5 mg/kg doses. Therefore, clinical activity with a manageable and tolerable safety profile is expected to be maintained in patients receiving tislelizumab 200 mg once every 3 weeks.
- Exposure-response analysis indicated that there was a lack of clinically significant exposure-response relationships for ORR and safety endpoints across a variety of advanced solid tumors and classical Hodgkin lymphoma for tislelizumab. These findings support 200 mg once every 3 weeks dose regimen for pivotal studies.

In conclusion, the observed clinical activity in patients with advanced tumors, coupled with a manageable safety profile and supportive data, support the proposed tislelizumab dose of 200 mg intravenously once every 3 weeks as the recommended dose for pivotal studies, please refer to the Tislelizumab Investigator's Brochure.

1.5.3. Rationale for Study Population

This study will enroll patients with resectable cT1-2N+M0 and cT3NanyM0 ESCC as determined at screening regardless of PD-L1 expression.

Esophageal cancer consists of two major histologic subtypes: esophageal squamous cell carcinoma (ESCC) and adenocarcinoma (EAC). Both histologic subtypes have distinct risk factors and epidemiology, and different response from immunotherapy. ESCC continues to be the major subtype of EC in China and showed better response from immunotherapy, which was demonstrated in Keynote-181 study, for ITT (Intent to Treated) population, patients with ESCC showed a lower HR (hazard ratio) than patients with EAC. Additionally, Attraction 3 Study demonstrated that there was not a significant difference for Hazard Ratio between patients with PD-L1 ≥ 1 and PD-L1 < 1, who were treated with nivolumab as the second-line therapy for ESCC, which means even with lower PD-L1 expression, patients may also get potential benefit from PD-1 inhibitor therapy. Therefore, this study will focus on resectable locally advanced ESCC regardless of PD-L1 expression.

As in NCCN guidelines Version 4 2020 for esophageal and esophagogastric junction cancers, neoadjuvant chemoradiotherapy is recommended for ESCC with Stage cT1-2N+M0 or cT3-T4aNanyM0. However, in this study, patients in Cohort A will receive neoadjuvant chemotherapy rather than chemoradiotherapy, and patients in Cohort B will receive neoadjuvant chemoradiotherapy. To ensure patients' resectability after neoadjuvant therapy, patients with Stage T4a will not be included. Therefore, clinical stage of disease for eligibility is defined as cT1-2N+M0 and cT3NanyM0.

Supporting clinical outcomes with neoadjuvant chemotherapy/chemoradiotherapy and encouraging data on the use of immunotherapy in the neoadjuvant setting have been provided in Section 1.2 and Section 1.3.2. Patients treated with neo-adjuvant chemotherapy followed by surgery demonstrated unsatisfied prognosis. It is worth to explore if treatment regimen selection could be guided with effective modality (PET), and if neoadjuvant systemic therapy could bring similar or better benefit than neoadjuvant chemoradiotherapy to patients with PET response after induction therapy, there may be an opportunity to avoid radiotherapy for these patients.

1.5.4. Rationale for Tislelizumab in the Perioperative Treatment of Resectable ESCC

As discussed in Section 1.3, PD-1 inhibitors have demonstrated significant benefit from 2nd Line therapy to 1st Line ESCC and in combination with chemotherapy in a number of early-stage solid tumors (Kato 2020; Kojima et al 2019; Lee et al 2019). Nonclinical studies showed that the immune-suppressive PD-1 axis is activated early in solid tumor (Chiari et al, 2018) and induction of an immune response before surgery may lead to durable protection. Immunotherapy effects could be even better prior to surgery considering that after surgical resection, tumor antigens decrease dramatically and intact blood vessels and lymph nodes for drug delivery are removed which may influence immunotherapy effects. Several Phase1/2 and phase 2 studies showed manageable safety profiles and preliminary efficacy when adding PD-1/PD-L1 inhibitor to

perioperative treatment for patients with resectable EC (Lee et al 2019; Ende et al 2019; Uboha et al 2019).

Study BGB-A317-205, as discussed in Section 1.3.1, has also demonstrated preliminary antitumor activity in patients with ESCC, with a confirmed ORR of 46.7%, DCR of 80%, DOR of 12.8 months, and median OS of 14.31 months. Additionally, 3 Phase 3 pivotal studies in ESCC area are ongoing (Study BGB-A317-302, BGB-A317-306, and BGB-A317-311).

As discussed in Section 1.3, PD-1 inhibitor has already demonstrated significant benefit from second-line therapy to first-line therapy. Given the evidence of clinical activity of immunotherapy in ESCC patients with advanced disease as well as the need to improve upon survival and decrease recurrence rates for patients with resectable early-stage disease, studies exploring anticancer activities of immunotherapies for the treatment of resectable disease emerged in large numbers. Preliminary data indicated promising signal of immunotherapy as neo-adjuvant therapy. (Lee et al 2019)

Therefore, adding Tislelizumab to the neoadjuvant phase may be a potential regimen to improve benefit for patients with resectable locally advanced ESCC.

1.5.5. Rationale for Tislelizumab in Combination with Chemotherapy for Cohort A

Patient in Cohort A is the PET responders (decrease of SUVmax ≥ 35%) after induction chemotherapy. Induction chemotherapy is the first treatment phase in this study. Previous studies showed that the use of induction chemotherapy before neoadjuvant cCRT was associated with much fewer distant relapses, and favorable outcomes in patients with ESCC achieving pCR, and there was no significant difference in the rate of postoperative complications of Grade 2 or higher between the induction chemotherapy group and noninduction chemotherapy group. (Lu et al 2019; Satake et al 2013)

As discussed in Section 1.3.2, interim analysis from Keynote-590 Study (Kato et al 2020) showed promising efficacy data for the ESCC population treated with pembrolizumab in combination with chemotherapy. As discussed in Section 1.3.1, Study BGB-A317-205 (Xu et al 2020) showed Tislelizumab in combination with chemotherapy demonstrated preliminary efficacy and safety data. Based on the improvement of clinical benefit, Tislelizumab in combination with chemotherapy could be respected to synergistic antitumor activity for patients with locally advanced ESCC.

In a subsequent review of therapeutic PET response in patients with ESCC who received preoperative chemotherapy, patients with a complete metabolic response following chemotherapy had improved clinical benefit (Yanagawa et al, 2012). Clinical evidence suggested PET responders had similar efficacy compared with patients who received cCRT. And safety profile favored that neoadjuvant chemotherapy may be a potential acceptable modality. Therefore, it is expected that patients with PET responses are supposed to achieve a similar benefit from the neoadjuvant chemotherapy (radiotherapy free) as the traditional neoadjuvant cCRT, and additional toxicities related to radiation could be avoided. In addition, shifting the immunotherapy in combination with chemotherapy to earlier treatment setting may further improve pathological response and outcome.

1.5.6. Rationale for Tislelizumab in Combination with CRT for Cohort B

Patient in Cohort B is the PET non-responders (decrease of SUVmax < 35%) after induction chemotherapy. Induction chemotherapy followed by neoadjuvant chemoradiotherapy can be well tolerated, as discussed in Section 1.5.5, but the outcome for the PET nonresponse population is still very poor (Buschenfelde et al 2011; Greally et al 2018; Ilson et al 2012).

It is now known that both chemotherapy and radiotherapy can upregulate the expression of PD-L1 ((Zhang et al 2008; Deng et al 2014)) due to the release of cytokines and other inflammatory molecules, which could make such tumors sensitive to a PD-1/PD-L1 directed therapy. Elimination of cancer cells by chemoradiotherapy triggers release of antigens, which can turn poorly immunogenic or immunosuppressive tumors into an immunogenic environment (Vanneman et al 2012). In addition, radiotherapy has an impact on the immune system by engaging both the innate and the adaptive arms, eliciting tumor-specific T-cells and establishing an immune memory against the tumor. This prolongs the effect of radiation, improving locoregional control, decreasing metastatic spread, and increasing OS (Formenti et al 2013).

Several early-stage studies have demonstrated preliminary antitumor activity and clinical benefit from PD-1 inhibitor in combination with neoadjuvant CRT. As discussed in Section 1.3.2, NCT 02844075 (Lee et al 2019), a phase 2 trial of preoperative chemoradiotherapy and Pembrolizumab, in which the result showed that pCR rate was 23.1% for ypT0N0 and 46.1 for ypT0, 12-month OS rate was 82.1%, and 12-month EFS rate was 60.3%, and with no new toxicity signals observed. Based on the above interactional mechanism between PD-1 inhibitor and CRT, and clinical data, adding Tislelizumab to neo-adjuvant CRT may be a potential regimen to improve prognosis for PET non-responder patients.

1.6. Benefit-Risk Assessment

1.6.1. Benefit-Risk Assessment of Cohort A

The use of PET to guide neoadjuvant chemotherapy for patients with resectable locally advanced ESCC, who may benefit from concurrent immunotherapy and chemotherapy similar to standard of care (SOC) but avoiding receiving radiotherapy in neoadjuvant phase, would meet great medical need. The overall safety experience with tislelizumab, as a monotherapy or in combination with other therapeutics, is based on experience in 1917 patients treated as of the cutoff date 20 May 2020. The safety profile is consistent with the known class effects of anti-PD-1 antibodies and includes mostly mild/moderate AEs. Grade 3 or 4 imAEs have been observed and have been generally reversible and manageable with study drug interruption and/or steroid treatment. Fatal imAEs are rare. The safety profiles of combination therapy with tislelizumab have been consistent across different platinum-based doublet chemotherapy regimens. AEs with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like symptoms, endocrinopathies, hepatitis or transaminitis, pneumonitis, and colitis have been observed. AEs that were most frequently reported with combination therapy were generalized symptoms such as fatigue, nausea, and vomiting, as well as those specific to cytotoxic chemotherapy such as hematologic toxicities and peripheral neuropathy. As discussed in Section 1.3.1, BGB-A317-205 study, which enrolled 15 patients treated with tislelizumab in combination with chemotherapy in the ESCC cohort, demonstrated that tislelizumab in combination with chemotherapy has a manageable safety profile. Among the 15 patients, 1 patient experienced a Grade 5 hepatic dysfunction (possibly from progressive

disease and underlying hepatitis) which was possibly related to study treatment according to the investigator. Four patients discontinued study treatment due to AEs (Grade 3 tracheal fistula, Grade 3 lung infection, Grade 2 pneumonitis, and Grade 3 increase in aspartate aminotransferase) (Xu et al 2020) To date, the adverse events could be manageable with treatment or interruption of tislelizumab treatment. Based on the benefit-risk assessment, it is expected that the PET responders can have at least similar efficacy outcomes and better tolerability by adding tislelizumab to neo-adjuvant chemotherapy comparing with neo-adjuvant cCRT. The result from this study will provide patients one more option of radiotherapy-free treatment in the neoadjuvant treatment setting. The benefit-risk ratio for tislelizumab plus cisplatin-based doublet chemotherapy in the neoadjuvant setting is expected to be favorable.

1.6.2. Benefit-Risk Assessment of Cohort B

Data from a Phase 2 clinical study of Pembrolizumab (Lee et al 2019), another anti-PD-1 antibody, in combination with cCRT followed by surgery indicated an increased pCR rate of 23.1% for ypT0N0 and 46.1% for ypT0 compared with historical data, and showed a potential of durable response, which suggests the potential efficacy of anti-PD-1 antibodies in combination with neo-adjuvant concurrent chemoradiotherapy for patients with locally advanced ESCC (for additional discussion, see Section 1.3). No treatment discontinuation occurred due to AEs, and adding Pembrolizumab to CRT followed by surgery did not show new significant safety signal.

Considering the extremely poor outcome of patients who did not respond to PET after induction chemotherapy, even if received standard neoadjuvant chemoradiotherapy, meanwhile, based on the mechanism of synergistic effect between PD-1/PD-L1 inhibitor and chemoradiotherapy, and the preliminary efficacy data of PD-1/PD-L1 inhibitors in combination with neoadjuvant chemoradiotherapy, it's expected that PET non-responder can get better efficacy outcome with tolerable toxicities by adding Tislelizumab to neo-adjuvant cCRT comparing with neo-adjuvant cCRT only. The benefit-risk ratio for Tislelizumab in combination with neoadjuvant chemoradiotherapy followed by surgery would be considered favorable.

To assess the potential efficacy and safety of tislelizumab in combination with neo-adjuvant chemotherapy or chemoradiotherapy guided by PET, a phase 2 Study BGB-A317-213 will be conducted.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

- To evaluate the pathological complete response (pCR) in patients receiving tislelizumab plus chemotherapy/chemoradiotherapy as neoadjuvant treatment.

2.1.2. Secondary Objectives

- To evaluate the disease-free survival (DFS) of neoadjuvant treatment with tislelizumab plus chemotherapy/ chemoradiotherapy after R0 resection.
- To evaluate the Event-free survival (EFS) of neoadjuvant treatment with tislelizumab plus chemotherapy/chemoradiotherapy.
- To evaluate the R0 resection rate in patients receiving tislelizumab plus chemotherapy/ chemoradiotherapy as neoadjuvant treatment.
- To evaluate objective response rate (ORR) of neoadjuvant treatment with tislelizumab plus chemotherapy/chemoradiotherapy before surgery as assessed by the investigator.
- To evaluate the safety of tislelizumab combined with chemotherapy/chemoradiotherapy as neoadjuvant treatment.

2.1.3. Exploratory Objectives

- To evaluate overall survival (OS) of neoadjuvant treatment with tislelizumab plus chemotherapy/chemoradiotherapy.
- To evaluate the potential association of biomarkers with clinical efficacy in patients receiving tislelizumab plus chemotherapy/chemoradiotherapy as neoadjuvant treatment.
- To evaluate the major pathological response (MPR) rate in patients receiving tislelizumab plus chemotherapy/chemoradiotherapy as neoadjuvant treatment.

2.2. Study Endpoints

2.2.1. Primary Endpoint

- pCR rate - defined as the proportion of patients with absence of residual tumor in the resected primary tumor and all resected lymph nodes (ypT0N0) after completion of neoadjuvant therapy in an EE analysis set.

2.2.2. Secondary Endpoints

- 1-year/3-year Disease-Free Survival (DFS) rate - defined as the proportion of patients free from disease events at 1st year and 3rd year after the first date of no disease in an EE analysis set. DFS is defined as the time from the first date of no disease (R0 resection as surgery outcome) to local or distant recurrence or death due to any cause,

whichever occurs first. DFS rate will be analyzed only for patients who undergo R0 resection.

- 1-year/3-year Event-Free Survival (EFS) rate - defined as the proportion of patients free from EFS events at 1st year and 3rd year after the first dose in an Safety Analysis Set. EFS is defined as time from first dose date to any of the following events which occurs first: progression of disease that precludes definitive surgery, local or distant recurrence, or death due to any cause.
- R0 resection rate - defined as the proportion of patients with R0 resection in an EE analysis set.
- Objective response rate (ORR) is the proportion of patients who had complete response or partial response before surgery as assessed by the investigator per RECIST v1.1 in all patients with measurable disease at baseline in the Safety Analysis Set.
- The incidence and severity of treatment-emergent adverse events (TEAEs) is determined according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v5.0).

2.2.3. Exploratory Endpoints

- 1-year/3-year OS rate – defined as the proportion of patients alive at 1st year and 3rd year after first dose in the Safety Analysis Set.
- To evaluate the potential association of biomarkers (including PD-L1 and gene expression profile) with clinical efficacy (including but not limited to pCR, DFS, EFS, R0 resection, ORR, OS and MPR).
- MPR rate - defined as the proportion of patients with ≤ 10% residual viable tumor in the resected primary tumor and all resected lymph nodes after completion of neoadjuvant therapy in an EE analysis set.

3. STUDY DESIGN

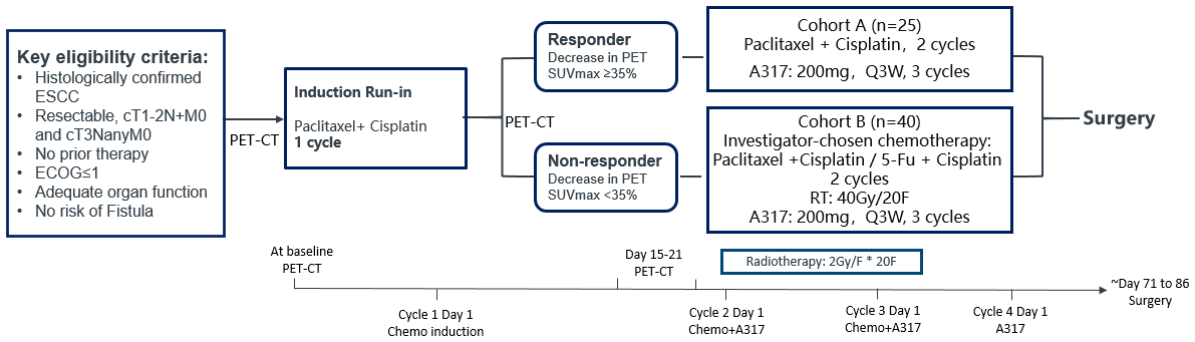
3.1. Summary of Study Design

This is a Phase 2, multicenter, open-label, 2-cohort study to investigate the efficacy and safety of PET guided neoadjuvant treatment with tislelizumab plus chemotherapy/chemoradiotherapy in resectable Esophageal Squamous cell Carcinoma.

The study consists of a screening phase, treatment phase (includes induction phase, neoadjuvant phase, and surgery phase), safety follow-up phase, and survival/disease follow-up phase.

The study design schematic is presented in Figure 1.

Figure 1: Study Schema



Abbreviations: A317: Tislelizumab; PET-CT, Positron Emission Tomography-Computed Tomography; Chemo, Chemotherapy; RT, Radiotherapy; 5-Fu, 5-fluorouracil; ESCC, esophageal squamous cell carcinoma; ECOG PS, Eastern Cooperative Oncology Group Performance Status; N, number of patients; Q3W, once every 3 weeks.

For all study procedures, see Section 7 and Appendix 1.

3.2. Screening Period

Screening evaluations will be performed within 28 days prior to first dose of study drug. Patients who agree to participate in this study will sign the informed consent form (ICF) prior to undergoing any screening procedure. 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. After signing the ICF, patient will receive PET-CT evaluation at baseline.

Archival tumor tissue (formalin-fixed paraffin-embedded [FFPE] block [preferred] or approximately 15 [at least 6] freshly cut unstained slides) is highly recommended to be collected for purpose of biomarker analysis. Information on previous histopathology reports and previous molecular analysis (if applicable) is required to accompany the tissue samples. Fresh tumor biopsies are strongly recommended at baseline in patients with readily accessible tumor lesions and who consent to the biopsies. If archival tumor tissues are not available, a fresh tumor biopsy is optional at baseline. Baseline tumor tissue samples can be collected at any stage of this study after local regulation approval. Refer to Section 7.6 for details.

3.3. Treatment Period

Induction Phase:

After completing all screening activities, eligible patients will receive one cycle induction therapy of chemotherapy doublet (cisplatin and paclitaxel). (As described in Section 5.2)

Neoadjuvant Phase:

All patients will be grouped into two cohorts based on the change of PET SUVmax (15-21 days after the last dose of induction therapy):

- Cohort A (Responder: decrease in PET SUVmax ≥ 35%):
  - Tislelizumab 3 cycles + chemotherapy doublet (cisplatin and paclitaxel) 2 cycles (as described in Section 5.2)
- Cohort B (Non-Responder: decrease in PET SUVmax < 35%):
  - Tislelizumab 3 cycles + chemotherapy doublet 2 cycles + radiotherapy (40Gy/20F)

    Note: Chemotherapy doublets (Paclitaxel + Cisplatin/5-Fu + Cisplatin (Investigator-chosen)) (as described in Section 5.2)

In Cycle 4 (neoadjuvant phase), Tislelizumab (without chemotherapy) will be administered 1-3 weeks prior to surgery, which could ensure the exposure dose of Tislelizumab and enough duration for patients to recover from toxicities of chemotherapy/chemoradiotherapy.

During the neoadjuvant phase, patients who are found to have disease progression assessed by the investigator at any time during neoadjuvant treatment and are still deemed resectable and nonmetastatic will proceed to receive surgery and will remain eligible for all on-study evaluations based on investigator's judgement. Patients who discontinue neoadjuvant treatment early because of disease progression or intolerable AEs and do not proceed to surgery will be discontinued from further in-clinic study procedures and will proceed to receive other treatment as determined by the investigator. These patients will remain in the study for survival follow-up.

Surgery

Upon completion of neoadjuvant therapy, the investigator will reassess the patient to reconfirm disease resectability. The Presurgical Visit and associated assessments should occur within 7 days of surgery and in accordance with local institutional guidelines. Patients will undergo surgical resection of tumor. Surgical specimens will be assessed for pathological response (MPR and pCR) by local pathological department.

The surgical procedure should be performed within 4-6 weeks from the last administered dose of chemotherapy treatment (the last dose of chemoradiotherapy in Cohort B) regardless the last dose of Tislelizumab.

After surgery, disease follow-up tumor assessment will be performed by neck, chest, abdominal CT every 3 months after surgery for the first 2 years, every 6 months Since Year 3 based on RECIST v1.1.

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, 2018)) and laboratory results. Vital signs, physical examinations, ECOG Performance

Status change, electrocardiogram (ECG) results, and other examinations will also be used for safety assessment. Safety assessments are further detailed in Section 8 and the Schedule of Assessments.

If patients undergo surgery, surgical tumor tissue (FFPE block [preferred] or approximately 15 [≥ 6] freshly cut unstained slides) are required to be collected and will be sent to central laboratory for biomarker analysis (including PD-L1 expression and gene expression profile). Surgical tumor samples can be collected at any stage of this study after local regulation approval.

3.4. End of Treatment/Safety Follow-up

The End-of-Treatment (EOT) Visit/Safety Follow-up will be conducted as follows:

EOT/ Safety Follow-up 1: Patients who receive surgery, will be asked to return to the clinic for the End of Treatment (EOT)/Safety Follow-up Visit (to occur within 30 days [± 7 days] after the surgery, or before the initiation of a new anticancer treatment, whichever occurs first.)

EOT/ Safety Follow-up 2: Patients who discontinue preoperative treatment for any reason and surgery will not be conducted, will be asked to return to the clinic for the Safety Follow-up Visit (to occur within 30 days [± 7 days] after the last dose of study treatment [including chemotherapy, radiotherapy and tislelizumab], or before the initiation of a new anticancer treatment, whichever occurs first.)

If routine laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the EOT/Safety Follow-up Visit, these tests need not be repeated. Tumor assessment is not required at the EOT/Safety Follow-up, and should follow the regular schedule of assessment in Section 7.5.

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

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

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

3.5. Survival Follow-up

Patients who discontinue study drug(s) 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 (precluding definitive surgery), local or distant recurrence, or death; until the patient withdraws consent, is lost to follow-up; or until study termination by the sponsor, whichever occurs first.

Patients will be followed for survival and further anticancer therapy information after discontinuation of study treatment via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (± 14 days) after the safety follow up visit or as directed by

the sponsor until death, loss to follow-up, withdrawal of consent, or study completion by the sponsor.

3.6. Discontinuation From the Study Treatment or From the Study

3.6.1. Patient Discontinuation from Study Treatment

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

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

- Treatment completed
- Disease Progression (radiographic progression or clinical progression as per investigator assessment)
- Adverse event
- Patient Decision
- 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 anticancer therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents
- 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.

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
- Patients have completed all study assessments

3.7. End of Study

The end of study is defined as the timepoint when the final data point is collected from the last patient in the study. This is when the last patient has completed the last visit: completes the 3-year survival/disease follow-up, dies, withdraws consent, or is lost to follow-up, whichever occurs first. Alternatively, the end of study is when the sponsor decides to terminate the study.

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

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

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

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

4. STUDY POPULATION

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

4.1. Inclusion Criteria

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

1. Able to provide written informed consent and can understand and agree to comply with the requirements of the study and the schedule of assessments
2. Age ≥ 18 years on the day of signing the informed consent form (or the legal age of consent in the jurisdiction in which the study is taking place)
3. Pathologically (histologically) confirmed diagnosis of potential resectable ESCC with Stage cT1-2N+M0 and cT3NanyM0 (AJCC Edition 8th [(Rice et al 2017)])
4. confirmed eligibility for an R0 resection with curative intent
5. Evaluable disease as assessed by the investigator per RECIST v1.1
6. ECOG Performance Status 0 or 1
7. Adequate hematologic and organ function as indicated by the following laboratory values ≤ 14 days prior to first dose of study drug:
   a. Patients must not have required blood transfusion or growth factor support ≤ 14 days before sample collection at screening for the following:
      i. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
      ii. Platelets ≥ 100 x 10^9/L
      iii. Hemoglobin ≥ 90 g/L
   b. Serum creatinine ≤ 1.5 x ULN (upper limit of normal)
   c. Serum total bilirubin ≤ 1.5 x ULN (total bilirubin must be < 3 x ULN for patients with Gilberts syndrome).
   d. AST and ALT ≤ 2.5 x ULN
8. Females of childbearing potential must be willing to use a highly effective method of birth control for the duration of the study, for ≥ 120 days after the last dose of tislelizumab, and for ≥ 180 days after the last dose of chemotherapy and radiotherapy and have a negative urine or serum pregnancy test ≤ 7 days before first dose of study drug. See Appendix 9.
9. Non-sterile males must be willing to use a highly effective method of birth control for the duration of the study, for ≥ 120 days after the last dose of tislelizumab and for ≥ 180 days after the last dose of chemotherapy and radiotherapy.
   - A sterile male is defined as one for whom azoospermia has been previously demonstrated in a semen sample examination as definitive evidence of infertility.
   - Males with known “low sperm counts” (consistent with “sub-fertility”) are not to be considered sterile for purposes of this study.

4.2. Exclusion Criteria

Patients who meet any of the following criteria are not eligible to enroll:

1. Any prior therapy for current ESCC, including chemotherapy, radiotherapy, targeted therapy agents or 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
2. Ineligible to receive a platinum-based doublet chemotherapy regimen, chemoradiotherapy, or surgery
3. Cervical esophageal squamous cell carcinoma
4. History of fistula due to primary tumor invasion
5. Patients with high risk of fistula or sign of perforation evaluated by investigator
6. Severe malnutrition
7. Prior participation in a tislelizumab study regardless of the treatment arm, until the primary and key secondary endpoints of the study have read out.
8. Active autoimmune diseases or history of autoimmune diseases that may relapse.

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

   a. Controlled Type I diabetes
   b. Hypothyroidism (provided it is managed with hormone replacement therapy only)
   c. Controlled celiac disease
   d. Skin diseases not requiring systemic treatment (eg, vitiligo, psoriasis, or alopecia)
   e. Any other disease that is not expected to recur in the absence of external triggering factors
9. Any active malignancy ≤ 2 years before first dose of study drug except for the specific cancer under investigation in this study and any locally recurring cancer that has been treated curatively (eg, resected basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix or breast)
10. Any condition that required systemic treatment with either corticosteroids (> 10 mg daily of prednisone or equivalent) or other immunosuppressive medication ≤ 14 days before first dose of study drug

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

    a. Adrenal replacement steroid (dose ≤ 10 mg daily of prednisone or equivalent)
    b. Topical, ocular, intra-articular, intranasal, or inhaled corticosteroid with minimal systemic absorption
    c. Short course (≤ 7 days) of corticosteroid prescribed prophylactically (eg, for contrast dye allergy) or for the treatment of a non-autoimmune condition (eg, delayed-type hypersensitivity reaction caused by contact allergen

11. With uncontrolled diabetes or > Grade 1 laboratory test abnormalities in potassium, sodium, or corrected calcium despite standard medical management or ≥ Grade 3 hypoalbuminemia ≤ 14 days before first dose of study drug
12. Uncontrollable pleural effusion, pericardial effusion, or ascites requiring frequent drainage (recurrence within 2 weeks of intervention)
13. With history of interstitial lung disease, non-infectious pneumonitis or uncontrolled lung diseases including pulmonary fibrosis, acute lung diseases, etc.
14. Infection (including tuberculosis infection, etc) requiring systemic antibacterial, antifungal, or antiviral therapy
    a. Severe infections within 4 weeks before first dose, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
    b. Receive therapeutic oral or IV antibiotics within 2 weeks before first dose

    Note: Antiviral therapy is permitted for patients with chronic hepatitis B virus (HBV) infection.
15. Untreated chronic hepatitis B or chronic HBV carriers with HBV DNA > 500 IU/mL (or > 2500 copies/mL) or patients with active hepatitis C virus (HCV)

    Note: Patients with non-active hepatitis C and inactive hepatitis B surface antigen (HBsAg) carriers, treated and stable hepatitis B (HBV DNA < 500 IU/mL or < 2500 copies/mL) can be enrolled. Patients with detectable hepatitis B surface antigen (HBsAg) or detectable HBV DNA should be managed per treatment guidelines.
16. Known history of HIV infection
17. Any major surgical procedure ≤ 28 days before first dose of study drug. Patients must have recovered adequately from the toxicity and/or complications from the intervention prior to first dose of study drug.
18. Prior allogeneic stem cell transplantation or organ transplantation
19. 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 first dose of study drug
    b. Pulmonary embolism ≤ 28 days before first dose of study drug
    c. Any history of acute myocardial infarction ≤ 6 months before first dose of study drug
    d. Any history of heart failure meeting New York Heart Association (NYHA) Classification III or IV (Appendix 6) ≤ 6 months before first dose of study drug
    e. Any event of ventricular arrhythmia ≥ Grade 2 in severity ≤ 6 months before first dose of study drug
    f. Any history of cerebrovascular accident ≤ 6 months before first dose of study drug
    g. Uncontrolled hypertension that cannot be managed by standard anti-hypertension medications ≤ 28 days before first dose of drug
    h. Any episode of syncope or seizure ≤ 28 days before first dose of study drug
20. A history of severe hypersensitivity reactions to other monoclonal antibodies

21. Has received any immunotherapy (eg, interleukin, interferon, or thymosin) or any investigational therapies within 14 days or 5 half-lives (whichever is shorter) before the first dose of study drug.
22. Patients with toxicities (as a result of prior anticancer therapy) which have not recovered to baseline or stabilized, except for AEs not considered a likely safety risk (eg, alopecia, neuropathy and specific laboratory abnormalities)
23. Was administered a live vaccine ≤ 28 days before first dose of study drug
    Note: Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed.
24. Underlying medical conditions (including laboratory abnormalities) or alcohol or drug abuse or dependence that will be unfavorable for the administration of study drug, or affect the explanation of drug toxicity or AEs, or result in insufficient or impaired compliance with study conduct
25. Women who are pregnant or are breastfeeding
26. Concurrent participation in another therapeutic clinical study

5. STUDY TREATMENT

5.1. Formulation, Packaging, and Handling

5.1.1. Tislelizumab

Tislelizumab is a monoclonal antibody formulated for intravenous injection in a single-use vial (20R glass, United States Pharmacopeia [USP] type I), containing a total of 100 mg of antibody in 10 mL of isotonic solution. Tislelizumab has been aseptically filled in a single-use glass vial 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 condition as specified on the label.

Refer to the Pharmacy Manual for details regarding intravenous administration, accountability, and disposal. Please also refer to the IB for other details regarding tislelizumab.

5.1.2. Chemotherapy

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

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

5.2. Dosage, Administration, and Compliance

Dosing schedules are provided in Table 7. The first dose of study drug is to be administered within 2 business days of enrollment. All patients will be monitored continuously for AEs. Treatment modifications (eg, dose delay, reduction, interruption, or discontinuation) will be based on specific laboratory and AE criteria, as described in Section 5.5.

Table 7: Selection and Timing of Dose for Each Patient

Treatment phase	Study Drug	Dose	Day(s) of treatment	Route of Administration	Duration of Treatment
Induction phase	Paclitaxel	135 mg/m^2	1	Intravenous	1 cycle
	Cisplatin	80 mg/m^2	1	Intravenous	1 cycle
Neo-adjuvant phase (Cohort A and Cohort B with regimen not changed)	Tislelizumab	200 mg	1	Intravenous	3 cycles (Cycles 2-4)
	Cisplatin*	80 mg/m^2	1	Intravenous	2 cycles (Cycles 2-3)
	Paclitaxel	135 mg/m^2	1	Intravenous	2 cycles (Cycles 2-3)
Neo-adjuvant phase (Cohort B with regimen changed)	Tislelizumab	200 mg	1	Intravenous	3 cycles (Cycles 2-4)
	Cisplatin*	80 mg/m^2	1	Intravenous	2 cycles (Cycles 2-3)
	5-Fluorouracil**	1000 mg/m^2	4	Intravenous	2 cycles (Cycles 2-3)
Concurrent radiotherapy***	40Gy/20F (2 Gy/fraction and 5 fractions/week)				

Note: For patients who are PET non-responders, in neo-adjuvant phase, chemotherapy regimen can be switched from Paclitaxel plus Cisplatin to 5-Fluorouracil plus Cisplatin by investigator's choice.

*In regimen of Paclitaxel plus Cisplatin, cisplatin may be administered on Day 1 or 2, or in 3 divided doses on Days 1, 2, and 3 depending on local guidelines. The total dose given must be 80 mg/m^2 per cycle.

**In Cohort B, chemotherapy may be switched from Paclitaxel+ Cisplatin to Fluorouracil + Cisplatin, by investigator's choice.

*** Concurrent radiotherapy will be conducted for patients in Cohort B

5.2.1. Tislelizumab

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

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

As a routine precaution, after infusion of tislelizumab on Day 1 of Cycle 2 and Cycle 3, patients must be monitored for at least 60 minutes afterward in an area with resuscitation equipment and emergency agents. From Cycle 4 onward, a ≥ 30-minute monitoring period is required in an area with resuscitation equipment and emergency agents.

The initial infusion (Cycle 2, Day 1) will be delivered ≥ 60 minutes; if this is well tolerated, then the subsequent infusions may be administered ≥ 30 minutes, which is the shortest time period

permissible for infusion. Tislelizumab must not be concurrently administered with any other drug (refer to Section 6).

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

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

5.2.2. Cisplatin in Combination with Paclitaxel

After all procedures/assessments have been completed as detailed in Appendix 1 and Section 3.3, cisplatin will be administered on Day 1 or 2, given every 21 days at a dose of 80 mg/m2 by IV infusion over 6 to 8 hours (or in doses consistent with local or country-specific treatment guidelines, or according to manufacturer standards or institutional standards). Alternatively, depending on local guidelines, cisplatin may be given in 3 divided doses on Days 1, 2, and 3. The total dose given should be 80 mg/m2 per cycle. Also, paclitaxel will be administered on Day 1, given Q3W at a dose of 135 mg/m2 by IV infusion for at least 3 hours. The initial treatment of cisplatin in combination with paclitaxel will be administered within 2 business days of eligibility confirmed by investigator. Alternate dose and dosing schedules are allowed according to local and institutional guidelines.

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

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

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

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

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

5.2.3. Cisplatin in Combination with 5-Fluorouracil

Through evaluation with PET-CT after induction therapy, if patients divided into Cohort B (PET non-responders), chemotherapy regimen may be switched from paclitaxel plus cisplatin to 5-fluorouracil plus cisplatin based on investigator's choice. Cisplatin will be administered on Day 1 given every 21 days at a dose of 80 mg/m2 by IV infusion over 6 to 8 hours (or in doses consistent with local or country-specific treatment guidelines, or according to manufacturer standards or institutional standards). Alternatively, depending on local guidelines, cisplatin may be given in divided doses. The total dose given should be 80 mg/m2 per cycle. Also, 5-FU will be administered on Days 1 to 4, given Q3W at a dose of 1000 mg/m2 per cycle by continuous IV infusion over 24 hours. The actual infusion time of 5-FU should be recorded, and a total infusion time of 96 ± 3 hours is acceptable. Alternate dose and dosing schedules are allowed according to local and institutional guidelines.

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

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

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

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

5.2.4. Radiotherapy

All patients in Cohort B will receive preoperative chemoradiotherapy. The total dose of radiotherapy will be 40Gy, administered in 20 once-daily fractions of 2Gy and 5 fractions per week. Alternate dose and dosing schedules for radiotherapy are allowed according to local and institutional guidelines.

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

5.2.5. Surgery

A thoracic surgeon with experience in locally advanced resectable ESCC should evaluate patients at screening to determine eligibility for surgical resection. Patients should be eligible for an R0 resection with curative intent at time of screening. Before surgery, the investigator will reassess the patient to reconfirm disease. The presurgical visit and associated assessments should occur within 7 days of surgery and in accordance with local institutional practice. Preoperative

evaluation should be performed per local standard of care (including, but not limited to, blood tests, organ function tests (as indicated), and other evaluation procedures).

The surgical procedure should be performed within 4-6 weeks after the last dose of neoadjuvant study treatment (in Cohort A, the last dose of chemotherapy; in Cohort B, the last dose of chemoradiotherapy) as best as possible. If surgery cannot be performed within this time window (eg, because of a prolonged AE), the investigator and the medical monitor will determine the acceptable length of this time window. If surgery is planned beyond 8 weeks after the last dose of study treatment, a repeated-CT scan should be obtained before the planned surgery. Resection may be accomplished via an open or minimally invasive procedure (eg, video-assisted thoracic surgery).

The performed surgical procedure should be documented and reported in the eCRF. If, after neoadjuvant treatment or during the operation, the surgeon determines that the patient should not proceed with the planned surgery, the reason should be documented and reported in the eCRF as well.

5.3. Overdose

Any overdose (defined as ≥ 600 mg of tislelizumab in a 24-hour period) or incorrect administration of study drug should be noted in the patient's chart and on the appropriate eCRF. AEs associated with an overdose or incorrect administration of study drug will be recorded on the AE eCRF. Any SAEs associated with an overdose or incorrect administration must be reported within 24 hours of awareness via the SAE reporting process described in Section 8.4. 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, cisplatin, 5-FU, and paclitaxel) will be provided by the sponsor, as required by local or country-specific guidance. The investigational site will acknowledge receipt of IMPs. Any damaged shipments will be replaced.

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

5.5. Dose Delay or Modification

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

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

5.5.1. General Guidance Regarding Dose Modifications

Reasons for dose modifications or delays, the supportive measures taken, and the outcome will be documented in the patient's chart and recorded in the eCRF. The severity of AEs will be graded according to the NCI-CTCAE v5.0 grading system. The drug-related toxicities should be managed according to the prescribing information for the approved product or institutional standard practices. The general guidance in this section is for reference of this study:

- The first doses of chemotherapy are dependent upon the patient's baseline body weight. Subsequent doses must be recalculated if the change of body weight from baseline is ≥ 10%. Subsequent doses should not be recalculated if the change (increase or decrease) of body weight from baseline is < 10% unless there is persistent toxicity that requires dose adjustment. If the dose is recalculated because of a ≥ 10% change in body weight from baseline, this body weight will then be used as the new baseline to calculate the dose of chemotherapy in subsequent cycles.
- In case of chemotherapy-related toxicity, chemotherapy will be delayed until it resolves to baseline or ≤ Grade 1 (whichever is more severe) prior to administering the next dose of chemotherapy, with the exception of alopecia, Grade 2 fatigue, or other AEs which, in the opinion of the investigator, would not affect the safety evaluation of the study drugs. If the AE resolves to baseline or ≤ Grade 1 within 21 days from C1D1, chemotherapy will be administered on C2D1 as scheduled. If the AE dose not resolve within 21 days from C1D1, chemotherapy will be delayed until the AE is resolved. If AE dose not resolve within 21 days from planned C2D1, chemotherapy should be discontinued. For Cohort A, Tislelizumab should continue as scheduled if there is not safety impact. For Cohort B, Tislelizumab and radiotherapy should continue as scheduled if there is not safety impact. The administration of chemotherapy and tislelizumab will be resynchronized at the subsequent cycle, which will be scheduled according to the chemotherapy dose administration date.
- In case of tislelizumab-related toxicity, tislelizumab will be delayed until it resolves to baseline or ≤ Grade 1 (whichever is more severe) prior to administering the next dose of tislelizumab or, with the exception of alopecia, Grade 2 fatigue, or other AEs which, in the opinion of the investigator, would not affect the safety evaluation of the study drugs. Chemotherapy and radiotherapy (for Cohort B) should continue as scheduled if there is not safety impact. If the AE resolves within 10 days, tislelizumab will be administered. The administration of chemotherapy and tislelizumab will be scheduled according to the chemotherapy dose administration date. If the AE does not resolve within 10 days from the scheduled date of dose administration, tislelizumab will be omitted from the current cycle and administration should continue at the start of the next cycle. If AE resolves to baseline or ≤ Grade 1 in Cycle 4, tislelizumab will be administered on Cycle 4 Day 1. If AE dose not resolve to baseline or ≤ Grade 1 in Cycle 4, tislelizumab will be discontinued.
- In case of both tislelizumab and chemotherapy toxicity, treatment in any patient may be temporarily withheld if the toxicity is considered to be related to tislelizumab and chemotherapy. If the administration delay is ≤ 10 days for any delayed drug, the

delayed drug will be administered; if the delay is >10 days, the delayed drug will be omitted in this cycle and the next cycle will be administered as planned as long as the AE resolves within 21 days. If the AE resolves to baseline or ≤ Grade 1 within 21 days from C2D1, chemotherapy and tislelizumab will be administrated on C3D1 as scheduled. If the AE dose not resolve in planned C3D1, chemotherapy will be delayed until the AE is resolved. For Cohort B, radiotherapy should continue as scheduled if there is no safety impact. The administration of chemotherapy and tislelizumab will be resynchronized at the subsequent cycle, which will be scheduled according to the chemotherapy dose administration date.

5.5.2. Dose Delay or Modification for Tislelizumab

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

Tislelizumab treatment may be temporarily suspended if the patient experiences a toxicity that is considered related to tislelizumab and requires a dose to be withheld. Tislelizumab treatment should resume as soon as possible after the AEs recover to baseline or Grade 1 (whichever is more severe).

If a patient is benefiting from the study treatment while meeting the discontinuation criteria, the patient may continue to receive tislelizumab after discussion and agreement with the medical monitor.

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

5.5.3. Dose Delay, Interruption, or Modifications for Chemotherapy

Dose modifications for chemotherapy should be performed per applicable local prescribing information and per local practice according to the investigator's clinical judgment. Dose modification guidelines for chemotherapy, described in this section, depend on the severity of toxicity and an assessment of the risk versus benefit for the patient.

Recommended dose modifications in this section serve as guidelines and do not replace the investigator's judgment and applicable local label recommendations.

If the patient develops a confirmed allergic reaction to the chemotherapy, the investigator may change the chemotherapeutic agent to one of the other agents allowed per protocol. Only one change in chemotherapeutic agent is allowed.

Table 8: Dose Reduction Level of Chemotherapy

Drug Dose	**Level 1 (Standard level) (Every 3 weeks as a cycle)**	**Level -1**	**Level -2**
Cisplatin	80 mg/m^2	60 mg/m^2	40 mg/m^2
Paclitaxel	135 mg/m^2	100 mg/m^2	50 mg/m^2
5-FU	1000 mg/m^2	800 mg/m^2	600 mg/m^2

Dose Modification based on Hematologic Nadir Values Prior to the Next Dose

ANC x 10^9/L		PLT x 10^9/L	Dose level for chemotherapy
≥ 1	and	≥ 75	1
0.5-1	or	50-75	-1
< 0.5	or	< 50	-2

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

Dose Modifications for Cisplatin

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

Adverse Event	Recommended Cisplatin Dose
Serum creatinine ≥ 1.5 mg/100 mL	Hold treatment until serum creatinine < 1.5 mg/100 mL
BUN ≥ 25 mg/100 mL	Hold treatment until BUN < 25 mg/100 mL
Auditory acuity by audiometric analysis out of range	Hold treatment until auditory acuity is within normal limits

Abbreviations: BUN, blood urea nitrogen.

Dose Modifications for Paclitaxel

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

Paclitaxel Dose Modification for Hepatic Impairment

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

Abbreviation: ULN, upper limit of normal.

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

Allergic Reaction/Hypersensitivity

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

Paclitaxel Dose Modification for Other Toxicities

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

Dose Modifications for 5-Fluorouracil

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

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

5.5.4. Dose Delay, Interruption, or Modifications for Radiotherapy (for Cohort B)

Radiotherapy may continue if a patient develops Grade 1-2 radiation related toxicities such as dermatitis, mucositis, pneumonia, or esophagitis. If a patient develops ≥ Grade 3 esophagitis and suspected esophageal fistula, all the anti-tumor treatment, including Tislelizumab, chemotherapy, and radiotherapy should be delayed until recovery through standard of treatment. If there is ≥ Grade 3 radiation pneumonia, severe esophagitis with weight loss more than 15%, esophageal fistula, or ≥ Grade 4 thrombocytopenia with infective fever (≥ 38°C), which are considered as unrecoverable, all the anti-tumor treatment, including Tislelizumab, chemotherapy and radiotherapy should be discontinued.

6. PRIOR AND CONCOMITANT THERAPY

6.1. Prior Therapy

The exclusion criteria (Section 4.2) specify that patients must not have received prior therapy for current esophageal cancer, including chemotherapy and radiotherapy, and prior treatment with anti-PD-1, anti-PD-L1, anti-PD-L2 or anti-CTLA-4 (Section 4.2), or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways. All prior and concomitant medications (eg, prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, and nutritional supplements) given to patients within 30 days before the first dose and 30 days after the last dose of study treatment (as of safety follow-up visit) should be recorded on the CRF.

6.2. Concomitant Therapy

6.2.1. Permitted Concomitant Medications/Procedures

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

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

6.2.1.1. Systemic Corticosteroids

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

6.2.1.2. Hepatitis B Treatment

Patients with active hepatitis B, defined as HBV DNA ≥ 500 IU/mL at screening, must initiate treatment 2 weeks before first dose, and continue until 6 months after the last dose of study drug(s). 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 may use other antiviral agents, if appropriate, following local guidelines. However, interferon-based therapy for hepatitis B is not permitted on study.

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

enrollment and continue treatment during the study and for 6 months after study drug treatment discontinuation.

6.2.2. Prohibited Concomitant Medications/Procedures

Live vaccines ≤ 28 days before first dose of study drug and ≤ 60 days after the last dose of study treatment are prohibited.

The following medications are prohibited during Screening and through the End-of-Treatment visit:

- Any concurrent anti-cancer therapy, including chemotherapy, hormonal therapy, targeted therapy, immunotherapy, and investigational anticancer agents. However, patient who underwent surgery with R1/R2 resection as the surgery outcome could receive adjuvant therapy according to the guideline/local practice. Medications approved for the adjuvant setting by the China National Medical Products Administration (NMPA) are allowed to be used according to their approved label.
- Herbal remedies for the treatment of cancer or Chinese patent medicines with approval from the China NMPA for use as anticancer treatment (regardless of cancer type)
- Herbal remedies with immune-stimulating properties (eg, mistletoe extract) or that are known to potentially interfere with liver or other major organ functions (eg, hypericin)

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

6.2.3. Restricted Concomitant Medications/Procedures

The following medications are restricted during the study:

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

6.3. Potential Interactions Between the Study Drugs and Concomitant Medications

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

- **Cisplatin**

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

- **Paclitaxel**

The metabolism of paclitaxel is catalyzed by cytochrome P-450 (CYP)2C8 and CYP3A4. Caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit or induce either CYP2C8 or CYP3A4 (eg, ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) because the toxicity of paclitaxel may be increased due to higher paclitaxel exposure. Administering paclitaxel concomitantly with medicines known to induce either CYP2C8 or CYP3A4 (eg, rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) is not recommended because efficacy may be compromised because of lower paclitaxel exposures.

- **5-Fluorouracil**

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

7. STUDY ASSESSMENTS AND PROCEDURES

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

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

7.1. Screening

Screening evaluations will be performed within 28 days prior to first dose of study drug. Patients who agree to participate will sign the ICF prior to undergoing any screening procedure. The Screening period begins on the first day a screening procedure is conducted. 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 the first dose 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)

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

7.1.1. Informed Consent and Screening Log

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

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before the first dose of study drug. 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.

7.1.2. Pulmonary Function Tests

All patients 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.

7.2.2. Patient Numbering

Each patient enrolled in this study will receive a unique identification number after signing the ICF. Patient numbers will be assigned in chronological order starting with the lowest number. Once an identification number has been assigned to a patient, it cannot be reassigned to any other patient. Re-screened patients will sign a new ICF and receive a new identification number.

7.3. Tislelizumab and Chemotherapy Dispensation

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

7.4.2. Physical Examinations

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

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

7.4.3. Eastern Cooperative Oncology Group Performance Status

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

7.4.4. Laboratory Safety Tests

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

If laboratory tests at screening are not performed within 7 days before the administration of study drug(s) on Cycle 1 of Day 1, these tests should be repeated and reviewed before administration

of study drug(s). 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 Cycle 4. After Cycle 1, results are to be reviewed within 48 hours before study drug administration.

Thyroid assessments will be performed as specified in Appendix 1.

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 used consistently throughout the study.

7.4.5. Electrocardiograms

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper or electronic copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Patients should rest for at least 10 minutes prior to ECG collection.

7.4.6. Adverse Events

AEs will be graded and recorded throughout the study according to NCI-CTCAE v5.0. Characterization of toxicities will include severity, duration, and time to onset.

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

7.4.7. Hepatitis B and C Testing

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

7.5. Tumor and Response Evaluations

Tumor imaging will be performed within 28 days before first dose of study drug. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and ≤ 28 days prior to the first dose of study drug may be used for the purposes of screening rather than repeating the standard-of-care tests.

Patient will undergo 2 times of PET-CT (including neck, chest, and abdomen), the first is at screening and the second is from 15 to 21 days after induction therapy. Patient will undergo computed tomography (CT) scans or magnetic resonance imaging (MRI) of the neck, chest, and abdomen before surgery to re-confirm the resectability. Other known or suspected sites of disease must be included in the imaging assessments (bone, brain, etc).

Disease follow-up tumor assessment will be performed by CT or MRI (including neck, chest, and abdomen) every 3 months after study treatment discontinuation (including chemotherapy, radiotherapy, tislelizumab and surgery) for the first 2 years, every 6 months in Years 3 based on RECIST v1.1. The allowed time window for disease follow-up assessments is ± 2 weeks in Years 1 to 2, and ± 4 weeks in Year 3.

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 and parameters are required to be used throughout the study.

If a CT scan for tumor assessment is performed on a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards of a diagnostic CT scan.

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

7.6. Biomarkers

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

Archival tumor tissue (formalin-fixed paraffin-embedded [FFPE] block (preferred) or approximately 15 [at least 6] freshly cut unstained slides) is highly recommended to be collected for the purpose of biomarker analysis (including PD-L1 expression and gene expression profile). Information on previous histopathology reports and previous molecular analysis (if applicable) is required to accompany the tissue samples. Fresh tumor biopsies are strongly recommended at baseline in patients with readily accessible tumor lesions and who consent to the biopsies. If archival tumor tissues are not available, a fresh tumor biopsy is optional at baseline. For fresh biopsy specimens, acceptable samples include core needle biopsies for deep tumor tissue or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.

If patients undergo surgery, surgical tumor tissue (FFPE block [preferred] or approximately 15 [≥ 6] freshly cut unstained slides) are required to be collected and will be sent to central laboratory for biomarker analysis (including PD-L1 expression and gene expression profile).

Tumor tissue should be of good quality based on total and viable tumor content. Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. Written informed consent is required for any of the fresh tumor biopsies. Tumor tissue samples can be collected at any stage of this study after local regulation approval.

7.7. Visit Windows

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

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

Appendix 1), with subsequent visits conducted according to the planned schedule every 3 weeks from Day 1 of Cycle 1 during preoperative treatment phase.

7.8. Unscheduled Visits

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

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

8. SAFETY MONITORING AND REPORTING

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

8.1. Risks Associated with Study Drug

8.1.1. Risks Associated with Tislelizumab

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

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

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

8.1.2. Risks Associated with Chemotherapy

Cisplatin

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

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

Loss of motor function has also been reported.

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

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

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

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

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

Paclitaxel

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

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

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

5-Fluorouracil

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

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

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

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

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

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

8.1.3. Risks Associated with Radiotherapy

The most notable AEs for radiotherapy included dermatitis, mucositis, hypothyroidism, pneumonia, esophageal obstruction, fistula, or esophagitis. The majority of AEs were mild to moderate in severity and manageable. Although not life-threatening, these AEs can severely impact the physical, psychological, and social well-being of patients receiving radiotherapy and can lead to dose reductions and discontinuations.

Some toxicities are rare but can be fatal, including esophageal fistula, bleeding, or myocarditis.

8.2. General Plan to Manage Safety Concerns

8.2.1. Eligibility Criteria

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

8.2.2. Safety Monitoring Plan

Safety will be evaluated in this study through the monitoring of all AEs, defined and graded according to NCI-CTCAE v5.0. All enrolled patients will be evaluated clinically and with standard laboratory tests at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of AEs (see Table 9), physical examinations, laboratory measurements (hematology, chemistry, etc) 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 infections or autoimmune conditions.

At the start of each cycle, study drug(s) will only be administered after clinical laboratory results have been reviewed. Administration of study drug(s) will be performed in a setting where emergency medical equipment and staff who are trained to respond to medical emergencies are available (see Section 8.3).

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

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

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

The potential safety issues anticipated in this study, as well as measures intended to avoid or minimize such toxicities, are outlined in Section 8.7.

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 preexisting condition, including an increase in severity, frequency, duration, and/or has an association with a significantly worse outcome
- Detection or diagnosis of a new condition after study drug administration, even though the condition may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concurrent medication (overdose per se should not be reported as an AE or SAE)

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

8.3.2. Assessment of Severity

The investigator will assess the severity of each AE and SAE reported during the study. AEs and SAEs should be assessed and graded based upon the NCI-CTCAE 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 (eg, 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 **Error! Reference source not found.**.

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 only limited information to include in the initial report to the sponsor. However, it is very important that the investigator always assesses causality for every SAE prior to transmission of the SAE report to the sponsor, because the causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator may subsequently change his/her opinion of causality considering follow-up information and may amend the SAE report accordingly.

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

- Temporal relationship of the AE to the administration of study treatment/study procedure
- Whether an alternative etiology has been identified

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

8.3.4. Follow-up of Adverse Events

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

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

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

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

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

8.3.5. Laboratory Test Abnormalities

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

- are associated with clinical signs or symptoms, or

- require active medical intervention, or
- lead to dose interruption or discontinuation, or
- require close observation, more frequent follow-up assessments, or further diagnostic investigation.

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

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

8.4. Definition of a Serious Adverse Event

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

- Results in death
- Is life-threatening
  Note: The term "life-threatening" in the definition of "serious" refers to an AE in which the patient was at risk of death at the time of the AE. It does not refer to an AE that 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 with 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 to be SAEs:

- Hospitalization for elective treatment of a preexisting 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 (i.e., not present in the product's Reference Safety Information [RSI]) and meets the definition of a serious adverse drug reaction, 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 Recording 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 study treatment (including chemotherapy, radiotherapy, tislelizumab and surgery) or initiation of new anticancer therapy, whichever occurs first. Immune-mediated AEs (serious or non-serious) should be reported until 90 days after the last dose of tislelizumab, regardless of whether or not the patient starts a new anticancer therapy. 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 9. For the follow-up period for AEs, see Section 8.3.4. For the definition of TEAEs, see Section 9.3.2.

Table 9: Guidance for Duration of Recording New or Worsening Adverse Events

Event type	Record new or worsening events that occur during this period	
	Begin	End
SAEs [a]	Signing of informed consent	Up to 30 days after last study treatment, initiation of new anticancer therapy, death, withdrawal of consent, or loss to follow-up, whichever occurs first
Nonserious AEs due to PD	Do not record (see Section 8.6.4)	
All nonserious AEs, except those due to PD	First dose of study drug	Up to 30 days after last study treatment, 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 of tislelizumab (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.
[a] All SAEs considered related to the study drug(s) that are brought to the attention of the Investigator should be reported regardless of time since the last dose of treatment.

8.6.2. Reporting Serious Adverse Events

8.6.2.1. Prompt Reporting of Serious Adverse Events

As soon as the investigator determines that an AE meets the protocol definition of an SAE, the event must be reported promptly (within 24 hours) to the sponsor or designee as described in **Error! Reference source not found.**.

Table 10: Timeframes and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

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

Abbreviations: AE, adverse event; SAE, serious adverse event.

8.6.2.2. Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a patient, he/she is to report the information to the sponsor within 24 hours as outlined above in Section **Error! Reference source not found.**. The SAE Report will always be completed as thoroughly as possible with all available details of the event and forwarded to the sponsor or designee within the designated time frames.

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

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

The sponsor will provide contact information for SAE receipt.

8.6.2.3. Regulatory Reporting Requirements for Serious Adverse Events

The investigator will report all SAEs to the sponsor in accordance with the procedures detailed in Section **Error! Reference source not found.**. 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 **Error! Reference source not found.**).

8.6.5. Deaths

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

8.6.6. Pregnancies

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

than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

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

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

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

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

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

- Tislelizumab Investigator's Brochure
- Cisplatin prescribing information
- Paclitaxel prescribing information
- 5-FU prescribing information

8.6.8. Assessing and Recording Immune-mediated Adverse Events

Since treatment with anti-PD-1 therapy can cause autoimmune disorders, AEs considered by the investigator to be immune-mediated (see Section 8.7.3) should be classified as imAEs and identified as such in the eCRF AE page. Not all tislelizumab studies include a section on the eCRF AE page where imAEs are clearly identified. Therefore, all studies will rely on the company list of Potential imAEs to identify all cases in each study to be further assessed as immune-mediated AEs by the sponsor, in addition to those imAEs reported by the investigator via the AE CRF page.

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

An extensive list of potential imAEs appears in Table 12. All conditions similar to those listed should be evaluated to determine whether they are imAEs, based on a similar diagnostic process to those reactions that are presented in more detail in Appendix 7.

8.6.9. Recording Infusion-Related Reactions

The symptoms of infusion-related reactions may include, but are not limited to, fever, chills/rigor, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness, or hypertension. Severe reactions may include acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, or cardiogenic shock. These infusion-related AEs should be recorded as "infusion-related reaction" instead of the individual signs and symptoms.

8.7. Management of AE of Special Interest

As a routine precaution, after infusion of tislelizumab on Day 1 of Cycle 2 and Cycle 3, patients must be monitored for at least 60 minutes afterward in an area with resuscitation equipment and emergency agents. From Cycle 4 onward, a minimum of a 30-minute monitoring period is required in an area with resuscitation equipment and emergency agents.

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

8.7.1. Managing Infusion-Related Reactions

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

Treatment modifications for symptoms of infusion-related reactions due to study drug(s) is provided in Table 11.

Table 11: Treatment Modifications for Symptoms of Infusion-Related Reactions Due to Study Drug(s)

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

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

Once the tislelizumab infusion rate has been decreased by 50% or suspended due to an infusion-related reaction, it must remain decreased for all subsequent infusions 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.

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

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.

8.7.2. Severe Hypersensitivity Reactions and Flu-Like Symptoms

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

In the event of a systemic anaphylactic/anaphylactoid reaction the infusion must be immediately stopped, and the patient discontinued from the study. 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/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 hypersensitivity reaction is observed. The patient should then be placed on monitor immediately, and ICU should be alerted for possible transfer if needed.

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

8.7.3. Immune-Mediated Adverse Events

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

A list of potential imAEs is shown below in Table 12. All conditions similar to those listed should be evaluated in patients receiving tislelizumab to determine whether they are immune-mediated.

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

Table 12: 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 syndrome
Skin (severe-rare)	full-thickness necrolysis/Stevens-Johnson syndrome
Gastrointestinal	colitis (includes diarrhea with abdominal pain or endoscopic/radiographic evidence of inflammation); pancreatitis; hepatitis; aminotransferase (ALT/AST) elevation; bowel perforation
Endocrine	thyroiditis, hypothyroidism, hyperthyroidism; hypophysitis with features of hypopituitarism, eg, fatigue, weakness, weight gain; insulin-dependent diabetes mellitus; diabetic ketoacidosis; adrenal insufficiency
Respiratory	pneumonitis/diffuse alveolitis
Eye	episcleritis; conjunctivitis; iritis/uveitis
Neuromuscular	arthritis; arthralgia; myalgia; neuropathy; Guillain-Barre syndrome; aseptic meningitis; myasthenic syndrome/myasthenia gravis, meningoencephalitis; myositis
Blood	anemia; leukopenia; thrombocytopenia
Renal	interstitial nephritis; glomerulonephritis; acute renal failure
Cardiac	pericarditis; myocarditis; heart failure

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

Recommendations for managing imAEs are detailed in Appendix 7.

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

9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

The statistical analyses will be performed by the sponsor or designee after the 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. Analysis Sets

The Efficacy Evaluable (EE) Analysis Set includes all patients who receive neoadjuvant treatment followed by surgery. This will be the primary analysis set for the efficacy analyses.

The Safety Analysis Set includes all enrolled patients who receive at least 1 dose of any component of study drugs; it will be the primary analysis set for the safety analyses. Patients will be analyzed according to the actual treatment regimen received.

9.1.2. Patient Disposition

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

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

9.1.3. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics of the Safety Analysis Set will be summarized using descriptive statistics. Continuous variables include age, weight, vital signs, time since initial cancer diagnosis, and time since current cancer diagnosis. Categorical variables include histology, stage of disease, gender, age, race.

9.1.4. Prior and Concomitant Medications

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

9.2. Efficacy Analyses

9.2.1. Primary Efficacy Analysis

pCR rate

pCR rate is the primary endpoint of the study. pCR rate is defined as the proportion of patients with absence of residual tumor in the resected primary tumor and all resected lymph nodes after completion of neoadjuvant therapy followed by surgery as assessed by the investigator in the EE set.

The pCR rate in Cohort A (Responder: decrease in PET SUVmax ≥ 35%) and Cohort B (Non-Responder: decrease in PET SUVmax<35%) will be summarized. Clopper-Pearson 95% confidence interval (CI) of pCR in Cohorts A and B will be calculated.

These analyses will be performed in the EE analysis set as the primary analysis. A sensitivity analysis of the pCR rate will also be performed in the Safety Analysis Set, and those patients who are not receiving surgery will be treated as non-pCR. The analysis of pCR rate will occur after all the patients in the EE analysis set have been assessed for pathological response.

9.2.2. Secondary Efficacy Analysis

1-year/3-year disease-free survival (DFS) rate

The 1-year/3-year Disease-Free Survival (DFS) rate is defined as the proportion of patients free from disease event at 1st year and 3rd year after the first date of no disease (R0 resection as surgery outcome). DFS is defined as the time from the first date of no disease to local or distant recurrence or death due to any cause, whichever occurs first. If patients were alive without recurrence, DFS would be determined from the first date of no disease to the date of last adequate tumor assessment and will be censored on the date of the last adequate tumor assessment. DFS rate will be estimated in cohort A and B by Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula for patients who undergo R0 resection in the EE analysis set.

1-year/3-year event-free survival (EFS) rate

The 1-year/3-year Event-Free Survival (EFS) rate is defined as the proportion of patients free from EFS events including progression of disease that precludes definitive surgery, local or distant recurrence, or death due to any cause at the 1st year and 3rd year after the first dose date.

Progression of disease that precludes definitive surgery is defined as radiographic progression per RECIST 1.1 as assessed by the investigator that precludes surgery for both curative intent and R0 outcome (i.e. definitive surgery). Local recurrence is defined as recurrence in the area of the anastomosis or regional lymph node diagnosed by radiological examination and/or histopathological confirmation after definitive surgery. Distant recurrence is defined as extra-regional lymph node metastasis, distant organ metastasis, or pleural or peritoneal dissemination diagnosed by radiological examination and/or histopathological confirmation after definitive surgery.

Patients who died without a disease progression precluding definitive surgery or disease recurrence will be considered to have experienced an event on the date of their death. Patients who did not report progression precluding definitive surgery or recurrence of disease or death

will be censored on the date of their last evaluable tumor assessment. Patients who started any subsequent anticancer therapy without a prior reported progression precluding definitive surgery or recurrence of disease will be censored at the last evaluable tumor assessment before initiation of subsequent anticancer therapy or missed ≥ 2 tumor assessments. The EFS rate will be estimated in cohorts A and B by the Kaplan-Meier method with 95% CIs estimated using the Greenwood's formula for patients in the Safety Analysis Set.

The following scenarios are planned for sensitivity analysis of EFS: regardless of whether the patient starts a new anticancer therapy, regardless of patients missing 2 consecutive tumor assessments, and only considering curative surgery intent rather than outcome of the surgery for definitive surgery.

R0 resection rate

R0 resection rate defined as the proportion of patients with R0 resection will be summarized in cohort A and B in the EE analysis set.

Objective response rate (ORR)

Objective response rate (ORR) is the proportion of patients with measurable disease at baseline who have a complete response or partial response before surgery as assessed by the investigator per RECIST v1.1 in the Safety Analysis Set. ORR will be summarized in cohort A and B.

9.2.3. Exploratory Efficacy Analysis

1-year/3-year OS rate is defined as the proportion of patients alive at 1st year and 3rd year after first dose. Data for patients who are not reported as having died at the time of analysis will be censored at the date last known to be alive. OS rate will be estimated in cohort A and B by Kaplan-Meier method for patients in the Safety analysis set.

Biomarker analysis including Programmed death ligand 1 [PD-L1] expression and gene expression profile will be examined in the EE analyses set. Any potential association between biomarkers and treatment effects (including but not limited to pCR, DFS, EFS, R0 resection, ORR, OS and MPR) may be explored.

MPR rate is defined as the proportion of patients with ≤ 10% residual viable tumor in the resected primary tumor and all resected lymph nodes after completion of neoadjuvant therapy followed by surgery. MPR rate will be summarized in cohorts A and B in the EE analysis set.

9.3. Safety Analyses

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

9.3.1. Extent of Exposure

Extent of exposure to each study drug will be summarized descriptively as the number of cycles received (number and percentage of patients), duration of exposure (days), cumulative total dose received per patient (mg, mg/m2, and Gy), dose intensity, and relative dose intensity.

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

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

9.3.2. Adverse Events

The AE verbatim descriptions (the investigator's description from the eCRF) will be coded using MedDRA. AEs will be coded to MedDRA by lower level term, Preferred Term, and Primary System Organ Class.

A TEAE is defined as an AE that has an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drugs and up to 30 days after study treatment discontinuation or initiation of new anticancer therapy, whichever occurs first. Only those AEs that were treatment emergent will be included in summary tables. Immune-mediated AEs will be identified from all adverse events that have an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of tislelizumab and up to 90 days after the last dose of tislelizumab, regardless of whether the patient starts a new anticancer therapy. If an imAE occurs outside of the above-mentioned treatment-emergent adverse event window, it will not be classified as a treatment-emergent adverse event. All imAEs will be reported separately. All AEs, treatment emergent or otherwise, will be presented in patient data listings.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by system organ class and preferred term. A patient will be counted only once by the highest severity grade per NCI-CTCAE v5.0 within a system organ class and preferred term, even if the patient experienced more than 1 TEAE within a specific system organ class and preferred term. The number (percentage) of patients with TEAEs will also be summarized by relationship to the study drug(s). Treatment-related AEs include those events considered by the investigator to be related to study treatment or with missing assessment of the causal relationship. SAEs, deaths, TEAE with ≥ Grade 3 severity, imAEs, treatment related TEAEs, and TEAEs that led to treatment discontinuation, dose interruption, dose reduction, or dose delay will be summarized.

9.3.3. Laboratory Analyses

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

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

9.3.4. Vital Signs

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

9.3.5. Pulmonary Function Test

Pulmonary function test results will be listed by patient.

9.4. Sample Size Consideration

Approximately 65 patients are expected to be enrolled in this study, considering about 10% patients not receiving surgery. It is assumed that 25 patients will be categorized into cohort A and 40 patients will be categorized into cohort B according to their PET SUVmax decrease. The actual number of patients in each cohort will be based on the actual ratio of responder versus non-responder and may vary from this assumption.

The pCR rate of responders was reported about 21.9% - 31.8% in historical studies (Buschenfelde et al 2011; Ilson et al 2012; Greally et al 2018). The pCR rate in cohort A is assumed to be 37%. Assuming there are 23 evaluable patients in cohort A, it will provide the probability of 66.2% to observe 8 pCRs out of 23 evaluable patients with point of estimate of pCR rate = 34.7% greater than the historical pCR rate in cohort A.

The pCR rate of non-responders was reported about 4% - 13.6% in historical studies (Buschenfelde et al 2011; Greally et al; 2018, Ilson et al 2012). The pCR rate in cohort B is assumed to be 22%. Assuming there are 35 evaluable patients in cohort B, it will provide a probability of 91.0% to observe 5 pCRs out of 35 evaluable patients with point of estimate of pCR rate = 14.3% greater than the historical pCR rate in cohort B.

Table 13 presents the estimates of the 95% CI around the observed pCR in cohort A for several potential outcomes using the sample sizes of 23 evaluable patients using the Clopper-Pearson method.

Table 13. Estimates of 95% CI Using Clopper-Pearson After Enrollment of 23 Evaluable Patients in Cohort A

Number of pCR Among 23 Evaluable Patients	Observed pCR	95% CI of Observed pCR
7	30.4%	13.2% – 52.9%
8	34.7%	16.4% – 57.3%
9	39.1%	19.7% – 61.5%

Table 14 presents the estimates of the 95% CI around the observed pCR in cohort B for several potential outcomes using the sample sizes of 35 evaluable patients using the Clopper-Pearson method.

Table 14. Estimates of 95% CI Using Clopper-Pearson After Enrollment of 35 Evaluable Patients in Cohort B

Number of pCR Among 35 Evaluable Patients	Observed pCR	95% CI of Observed pCR
4	11.4%	3.2% – 26.7%
5	14.3%	4.8% – 30.3%
6	17.1%	6.6% – 33.6%
7	20.0%	8.4% – 36.9%

10. 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.

10.1. Access to Information for Monitoring

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

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

10.2. Access to Information for Auditing or Inspections

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

11. QUALITY ASSURANCE AND QUALITY CONTROL

11.1. Regulatory Authority Approval

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

11.2. 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.

11.3. 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.

11.4. Drug Accountability

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

At study initiation, the monitor will evaluate the site's standard operating procedure for study drug disposal/destruction to ensure that it complies with BeiGene requirements specified in the Pharmacy Manual. At appropriate times during the conduct of the study or at the end of the study following 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 BeiGene's requirements specified in the Pharmacy Manual for disposal, arrangements will be made between the site and BeiGene or its representative for destruction or return of unused study drug supplies.

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

12. ETHICS/PROTECTION OF HUMAN PATIENTS

12.1. Ethical Standard

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

12.2. 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 IEC/IRB correspondence and approval of the amended ICF/other information and the approved amended ICF/other information must be forwarded to the sponsor promptly.

The principal investigator is responsible for providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC. Investigators are also responsible for promptly informing the IRB/IEC of any protocol amendments. In addition to the requirements for reporting all AEs to the sponsor, investigators must comply with requirements for reporting SAEs to the local health authority and IRB/IEC. Investigators may receive written investigational new drug (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.

12.2.1. 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.

12.3. Informed Consent

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

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

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

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

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

12.4. Patient and Data Confidentiality

The principal investigator and sponsor will maintain confidentiality and privacy standards by following applicable data privacy laws covering the collection, storage, transmission, and processing of patients' personal and medical information.

The principal investigator shall code the medical information obtained during the study with a unique patient identification number assigned to each patient enrolled in the study. This approach ensures that patients' names are not included in any dataset transmitted to any sponsor location.

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

In the event of a breach of the confidentiality of a patient's personal and medical information, the principal investigator and sponsor, as appropriate, shall fulfill all mediation steps and reporting obligations under applicable data privacy laws.

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

Data generated during this study must be available for inspection upon request by representatives of the China NMPA; by sponsor monitors, representatives, and collaborators; and by the IRBs/IECs for each study site, as appropriate.

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

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

12.5. Financial Disclosure

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

13. DATA HANDLING AND RECORD KEEPING

13.1. Data Collection and Management Responsibilities

13.1.1. 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.

13.1.2. 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 BeiGene and should not be made available in any form to third parties without written permission from BeiGene, except for authorized representatives of BeiGene or appropriate regulatory authorities.

13.1.3. Data Management/Coding

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

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

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

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

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

13.2. Data Integrity and In-house Blinding

Functions/persons with access to the EDC system shall be prohibited from using the EDC system to generate unnecessary listings/summaries that may introduce unwanted bias or to share such outputs from the EDC system with other functions/persons who do not have access to the EDC.

13.3. 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 2 categories: 1) investigator's study file, and/or 2) patient clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRF and query forms, IRB/IEC and governmental approval with correspondence, informed consent forms, 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.

Following closure of the study, the investigator must maintain all study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval when needed (eg, audit or inspection) and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and personnel. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (eg, microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must 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 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 off-site facility, or transfer of ownership of or responsibility for the records in the event the investigator leaves the study center.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and BeiGene to store these in sealed containers outside of the site so that they can be returned sealed to the

investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the site.

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

13.4. Protocol Deviations

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

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

13.5. Study Report and Publications

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

The results of this study will be published or presented at scientific meetings in a timely, objective, and clinically meaningful manner that is consistent with good science, industry and 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 trial will be presented in the investigator's clinical study agreement. Each investigator agrees that, in accordance with the terms of the clinical study agreement, a further delay of the publication/presentation may be requested by the sponsor to allow for patent filings and/or protection in advance of the publication/presentation.

13.6. 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 biomarkers) to the assay lab for central lab analysis according to protocol and lab 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 IEC/IRB 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.

13.7. 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:

- Information that becomes publicly available through no fault of the investigator or study center personnel
- Information that is necessary to disclose in confidence to an IEC/IRB solely for the evaluation of the study
- Information that is necessary to disclose to provide appropriate medical care to a patient
- Study results that may be published as described in Section 13.5

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

14. REFERENCES

AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology. 2015;62(3):932-54

About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

Allum W H , Stenning S P , Bancewicz J , et al. Long-Term Results of a Randomized Trial of Surgery With or Without Preoperative Chemotherapy in Esophageal Cancer[J]. Journal of Clinical Oncology, 2009, 27(30):5062-5067.

Arnold M, Soerjomataram I, Ferlay J, et al. Global incidence of esophageal cancer by histological subtype in 2012. Gut. 2015;64(3):381-7.

Beers SA, Glennie MJ, White AL. Influence of immunoglobulin isotype on therapeutic antibody function. Blood. 2016;127(9):1097-101

BeiGene Investigator's Brochure, Tislelizumab (BGB-A317). Edition 9.0, October 2021

Blot WJ, Tarone RE. Esophageal cancer. In:Thun MJ, Linet MS, Cerhan JR, Haiman CA, Schottenfeld D, eds. Cancer Epidemiology and Prevention. 4th ed. New York: Oxford University Press; 2017 2018:579-592.

Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2018;36(17):1714-68

Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries[J]. CA Cancer J Clin, 2018, 68(6): 394-424. DOI: org / 10.3322 / caac.21492

Buschenfelde CMZ, Herrmann K, Schuster T, et al. 18F-FDG PET-Guided Salvage Neoadjuvant Radiochemotherapy of Adenocarcinoma of the Esophagogastric Junction: The MUNICON II Trial[J]. Journal of Nuclear Medicine, 2011.

Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. CA Cancer J Clin. 2016;66(2): 115-32.

Chiari R, Sidoni A, Metro G. Early stage resectable non-small cell lung cancer: is neoadjuvant immunotherapy the right way forward? J Thorac Dis. 2018;10(Suppl 33):S3890-4.

Cho BC, Kato K, Takahashi M, et al. LBA11Nivolumab versus chemotherapy in advanced esophageal squamous cell carcinoma (ESCC): The phase III ATTRACTION-3 study[J]. Annals of Oncology, 2019, 30(Supplement_5): v873-v874.

Clinical Trials Facilitation Group (CTFG). Recommendations related to contraception and pregnancy testing in clinical trials. September 15, 2014

Dahan R, Sega E, Engelhardt J, et al. FcgRs Modulate the Antitumor Activity of Antibodies Targeting the PD-1/PD-L1 Axis. Cancer Cell. 2015;28(3):285-95.

Deng L, Liang H, Burnette B, et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. J Clin Invest. 2014;124(2):687-95.

Deng L, Liang H, Burnette B, et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. J Clin Invest. 2014;124(2):687-95.

Deng R, Jin F, Prabhu S, et al. Monoclonal antibodies: what are the pharmacokinetic and pharmacodynamic considerations for drug development? Expert Opin Drug Metab Toxicol. 2012;8(2):141-60.

Dirks NL, Meibohm B. Population pharmacokinetics of therapeutic monoclonal antibodies. Clin Pharmacokinet. 2010;49(10):633-59

Dolgin M, Association NYH, Fox AC, Gorlin R, et al. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, MA: Lippincott Williams and Wilkins; March 1, 1994

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

Ende TVD, Clercq NCD, Henegouwen M, et al. A phase II feasibility trial of neoadjuvant chemoradiotherapy combined with atezolizumab for resectable esophageal adenocarcinoma: The PERFECT trial[J]. Journal of Clinical Oncology, 2019, 37(15):4045-4045.

Formenti SC, Demaria S. Combining radiotherapy and cancer immunotherapy: a paradigm shift. J Natl Cancer Inst. 2013;105(4):256-65.

Greally M, Chou JF , Molena D, et al. Positron-Emission Tomography Scan–Directed Chemoradiation for Esophageal Squamous Cell Carcinoma: No Benefit for a Change in Chemotherapy in Positron-Emission Tomography Nonresponders[J]. Journal of Thoracic Oncology, 2018.

Gül N, van Egmond M. Antibody-Dependent Phagocytosis of Tumor Cells by Macrophages: A Potent Effector Mechanism of Monoclonal Antibody Therapy of Cancer. Cancer Res. 2015;75(23):5008-13.

Haanen JBAG, Carbonnel F, Robert C, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. Ann Oncol. 2017:28 (suppl 4):iv119-iv142

Hong Yang, Hui Liu, Yuping Chen, et, al. Neoadjuvant Chemoradiotherapy Followed by Surgery Versus Surgery Alone for Locally Advanced Squamous Cell Carcinoma of the Esophagus (NEOCRTEC5010): A Phase III Multicenter, Randomized, Open-Label Clinical Trial. jco.org. 2018;36(27)

http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Accessed 25 November 2018.NCI-CTCAE v5.0

Ilson DH, Minsky BD, Ku GY, et al. Phase 2 trial of induction and concurrent chemoradiotherapy with weekly irinotecan and cisplatin followed by surgery for esophageal cancer.[J]. Cancer, 2012, 118(11):2820-2827.

International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. 2018.

http://www.icmje.org/icmje-recommendations.pdf. Published December 2018. Accessed 10 September 2019

International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. 2018. http://www.icmje.org/icmje-recommendations.pdf. Published December 2018. Accessed 10 September 2019

Joel Shapiro, J Jan B van Lanschot, et, al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol 2015; 16: 1090–98

Kato K. KEYNOTE-590: Phase III study of first-line chemotherapy with or without pembrolizumab for advanced esophageal cance. Presented in ESMO 2020

Keizer RJ, Huitema AD, Schellens JH, et al. Clinical pharmacokinetics of therapeutic monoclonal antibodies. Clin Pharmacokinet. 2010;49(8):493-507.

Klevebro F, Alexandersson v D G, Wang N , et al. A randomized clinical trial of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the oesophagus or gastro-oesophageal junction.[J]. Annals of Oncology Official Journal of the European Society for Medical Oncology, 2016:660.

Kojima T, Muro K, Francois E, et al. Pembrolizumab versus chemotherapy as second-line therapy for advanced esophageal cancer: Phase III KEYNOTE-181 study. [J]. Journal of Clinical Oncology, 2019, 37(4_suppl):2-2.

Koren E, Smith HW, Shores E, et al. Recommendations on risk-based strategies for detection and characterization of antibodies against biotechnology products. J Immunol Methods. 2008;333(1 2):1-9.

Labrijn AF, Buijsse AO, van den Bremer ET, et al. Therapeutic IgG4 antibodies engage in Fab-arm exchange with endogenous human IgG4 in vivo. Nat Biotechnol. 2009;27(8):767-71

Lee S, Ahn BC, Park S Y, et al. A phase II trial of preoperative chemoradiotherapy and pembrolizumab for locally advanced esophageal squamous cell carcinoma (ESCC) [J]. Annals of Oncology, 2019, 30(Supplement_5):v754.

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

Lu, SL, Hsu FM, Tcai CL, et al. Improved prognosis with induction chemotherapy in pathological complete responders after trimodally treatment for esophageal squamous cell carcinoma: Hypothesis generating for adjuvant treatment. European Journal of Surgical Oncology (2019).

Makarova-Rusher OV, Medina-Echervez J, Duffy AG, et al. The yin and yang of evasion and immune activation in HCC. J Hepatol. 2015;62(6):1420-9

National Comprehensive Cancer Network (NCCN) Guidelines Version 4. (2020). Esophageal and Esophagogastric Junction Cancers

Noone AM, Howlader N, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2015. National Cancer Institute, 2017 [resource on the Internet]. Available from: https://seer.cancer.gov/csr/1975_2015/.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group, 1982

Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;25(5):948-68.

Prieto J, Melero I, Sangro B. Immunological landscape and immunotherapy of hepatocellular carcinoma. Nat Rev Gastroenterol Hepatol. 2015;12(12):681-700

Rice TW, Ishwaran H , Ferguson MK, et al. Cancer of the Esophagus and Esophagogastric Junction: An Eighth Edition Staging Primer[J]. Journal of Thoracic Oncology, 2017, 9(1):E282.

Ryman JT, Meibohm B. Pharmacokinetics of monoclonal antibodies. CPT Pharmacometrics Syst Pharmacol. 2017;6(9):576–88.

Satake H, et al. Phase I/II trial of induction chemotherapy with docetaxel, cisplatin, and fluorouracil (DCF) followed by concurrent chemoradiotherapy in locally advanced esophageal squamous cell carcinoma. " Journal of Clinical Oncology 31.15(2013)

Soar J, Pumphrey R, Cant A, et al. Emergency treatment of anaphylactic reactions--guidelines for healthcare providers. Resuscitation. 2008;77(2):157-69

Stahl M, Walz M K , Riera-Knorrenschild J , et al. Preoperative chemotherapy versus chemoradiotherapy inlocally advanced adenocarcinomas of the oesophagogastric junction (POET): Long-term results ofa controlled randomised trial[J]. European Journal of Cancer, 2017, 81:183.

Terrault NA, Bzowej NH, Chang KM, et al. AASLD guidelines for treatment of chronic hepatitis B. Hepatology. 2016;63(1):261-83.

TTRACTION-3 study[J]. Annals of Oncology, 2019, 30(Supplement_5): v873-v874.

Uboha N V , Maloney J D , Mccarthy D , et al. Safety of neoadjuvant chemoradiation (CRT) in combination with avelumab (A) in the treatment of resectable esophageal and gastroesophageal junction (E/GEJ) cancer.[J]. Journal of Clinical Oncology, 2019, 37(15):4041-4041.

US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf. Published 27 November 2018. Accessed 26 August 2019

van Heijl M, van Lanschot JJB, Koppert LB, et al. Neoadjuvant chemoradiation followed by surgery versus surgery alone for patients with adenocarcinoma or squamous cell carcinoma of the esophagus (CROSS). BMC Surg 2008; 8: 21.

Vanneman M, Dranoff G. Combining immunotherapy and targeted therapies in cancer treatment. Nat Rev Cancer. 2012;12(4):237-51

Worobec AS and Rosenberg AS. A Risk-Based Approach to Immunogenicity Concerns of Therapeutic Protein Products, Part 1: Considering Consequences of the Immune Response to a Protein. BioPharm Intl. 2004a;17(11).

Wu CY, Budha N, Gao Y, et al. Tislelizumab Exposure-Response Analyses of Efficacy and Safety in Patients with Advanced Tumors [ESMO Abstract 482P]. Ann Oncol. 2019a; 30(suppl 5): mdz244.04

Xu J, Bai Y, Xu N, et al. Tislelizumab Plus Chemotherapy as First-line Treatment for Advanced Esophageal Squamous Cell Carcinoma and Gastric/Gastroesophageal Junction Adenocarcinoma[J]. Clinical Cancer Research, 2020, 26(17)

Shen L, Kato K, Kim SB, et al. RATIONALE-302 Investigators. Tislelizumab Versus Chemotherapy as Second-Line Treatment for Advanced or Metastatic Esophageal Squamous Cell Carcinoma (RATIONALE-302): A Randomized Phase III Study. J Clin Oncol. 2022 Apr 20.

Yanagawa M, Tatsumi M, Miyata H, et al. Evaluation of Response to Neoadjuvant Chemotherapy for Esophageal Cancer: PET Response Criteria in Solid Tumors Versus Response Evaluation Criteria in Solid Tumors[J]. Journal of Nuclear Medicine, 2012, 53(6):872-880.

Zhang P, Su DM, Liang M, Fu J. Chemopreventive agents induce programmed death-1-ligand 1 (PD-L1) surface expression in breast cancer cells and promote PD-L1-mediated T cell apoptosis. Mol Immunol. 2008;45(5):1470-6.

Zhang T, Song X, Xu L, et al. The binding of an anti-PD-1 antibody to FcγRI has a profound impact on its biological functions. Cancer Immunol Immunother. 2018;67(7):1079-90

Buschenfelde CMZ , Herrmann K, Schuster T, et al. 18F-FDG PET-Guided Salvage Neoadjuvant Radiochemotherapy of Adenocarcinoma of the Esophagogastric Junction: The MUNICON II Trial[J]. Journal of Nuclear Medicine, 2011.

APPENDIX 1. SCHEDULE OF ASSESSMENTS

Assessment	Screening[a]	Treatment				EOT/ Safety Follow-up Visit[b]	Survival follow-up[t]
		preoperative treatment Cycles 1 to 4 (every 21 days)			Surgery		
Days (window)	**-28 to ~ -1**	**1 (± 3)**	**8 (± 2)**	**15 (± 2)**		**30 ± 7 Days after treatment**	**Every 3 Months (± 14) Days**
Informed consent[a]	x						
Inclusion/exclusion criteria	x						
Demographics/medical history/prior medications[c]	x						
Vital signs/ height and weight[d]	x	x			x	x	
Physical examination[e]	x	x			x	x	
ECOG Performance Status	x	x			x	x	
12-lead ECG[f]	x				x	x	
Adverse events[g]	x	x	x	x	x	x	
Concomitant medications	x	x	x	x	x	x	
Hematology[h]	x[a]	x	x	x	x	x	
Serum chemistry[h]	x[a]	x	x	x	x	x	
CK and CK-MB[i]	x[a]	x	x	x	x	x	
Coagulation parameters[h]	x	x			x	x	
Urinalysis[j]	x	As clinically indicated					
Pregnancy test[j]	x	x			x	x	
Thyroid function[k]	x				x	x	
HBV/HCV tests[l]	x	As clinically indicated					

Assessment	Screening[a]	Treatment				EOT/ Safety Follow-up Visit[b]	Survival follow-up[t]
		preoperative treatment Cycles 1 to 4 (every 21 days)			Surgery		
Days (window)	**-28 to ~ -1**	**1 (± 3)**	**8 (± 2)**	**15 (± 2)**		**30 ± 7 Days after treatment**	**Every 3 Months (± 14) Days**
Pulmonary function tests[m]	x				x		
Baseline tumor tissue sample[n]	x						
Surgical tumor tissue and lymph node sample[o]					x (after surgery)		
Pathological response assessment					x (after surgery)		
PET-CT[p]	x	15-21 days after the last dose of induction therapy					
Tumor assessment[q]	x[q]				x[q] (prior to surgery)		x[q]
Tislelizumab administration[r]		x (Cycles 2-4)					
Chemotherapy administration[s]		x (Cycles 1-3)					

Abbreviations: AE, adverse event; CK, creatine kinase; CK-MB, creatine kinase cardiac muscle isoenzyme; CT, computed tomography; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, end-of-treatment; FFPE, formalin-fixed paraffin-embedded; FT3, free triiodothyronine; FT4, free thyroxine; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; IRB, institutional review board; MRI, magnetic resonance imaging; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PET, positron emission tomography; SAE, serious adverse event; TSH, thyroid stimulating hormone; v, version.

[a] Written informed consent is required prior to performing any study-specific tests or procedures. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to the first dose may be used for screening assessments rather than repeating such tests.

[b] The EOT Visit /Safety Follow-up is conducted when the investigator determines that study treatment will no longer be used, or all the study treatment is complete. If routine laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the EOT Visit, tests need not be repeated. Patients who discontinue study treatment prior to disease progression will need to undergo tumor assessments as outlined in Section 7.5.

The EOT/Safety Follow-up Visit is required to be conducted 30 days (± 7 days) after the last study treatment (including chemotherapy, radiotherapy, tislelizumab and surgery), or before the initiation of a new anticancer treatment, whichever occurs first.

[c] Includes age or year of birth, gender, and self-reported race/ethnicity; history of treatment for the primary diagnosis, including prior medication, loco-regional treatment(s), and surgical treatment(s). Information on radiographic studies performed prior to study entry may be collected for review by the investigator. Pre-existing AEs at baseline should be recorded as medical history.

[d] Vital signs collected on study include temperature, pulse rate, and blood pressure (systolic and diastolic) while the patient is in a seated position after resting for 10 minutes. The patient's vital signs are required to be recorded within 60 minutes before, during, and within 30 minutes after the first infusion of tislelizumab. For subsequent infusions, vital signs will be collected within 60 minutes before infusion and, if clinically indicated, during and 30 minutes after the infusion.

[e] Investigators should solicit patients regarding changes in vision, visual disturbance, or ocular inflammation at each scheduled study visit during tislelizumab treatment. For any change in vision, referral to an appropriate specialist will be made for further management guidance.

[f] The ECG recordings will be obtained during screening, Safety Follow-up Visit, before surgery and as clinically indicated at other time points.

[g] 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 first administration of study drug, only SAEs should be recorded. After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until either 30 days after last study treatment or initiation of new anticancer therapy, whichever occurs first. Immune-mediated AEs (serious or non-serious) should be reported until 90 days after the last dose of tislelizumab, regardless of whether or not the patient starts a new anticancer therapy. 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.

[h] Local laboratory assessments on serum chemistry, hematology, coagulation, and urinalysis will be conducted, of which certain elements will be collected as specified in Appendix 2. If laboratory tests at screening are not performed within 7 days of first dose, these tests should be repeated and reviewed before dosing. Hematology and serum chemistry (including liver function tests) will be performed weekly for the first 3 cycles and then at the beginning of Cycle 4(data collected as specified in Appendix 2). After Cycle 1, results are to be reviewed within 48 hours before study drug administration. Urinalysis is to be conducted during the treatment period only if clinically warranted. Refer to Section 8.3.5 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.

[i] All patients will have CK and CK-MB testing at screening, repeated at all scheduled visits. If CK-MB fractionation is not available, troponin I and/or troponin T may be tested instead. Refer to Section 8.3.5 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.

[j] Urine or serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 7 days prior to the first dose. Urine pregnancy tests will be performed at each visit prior to dosing, and at the EOT/Safety Follow-up Visit. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.

[k] Analysis of FT3, FT4, and TSH will be performed by the local study site laboratory. Thyroid function tests will be performed at screening, Presurgical Visit , and at Safety Follow-up Visit.

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

[m] All patients will have pulmonary function testing which may include, but is not limited to, spirometry and assessment of diffusion capacity done during the Screening Period to assist the determination of suitability on the study.

[n] A pretreatment tumor tissue (archival or freshly obtained, FFPE block [preferred] or approximately 15 [≥ 6] unstained freshly cut slides), is highly recommended to be collected. If archival tissue is unavailable or is deemed to be unsuitable for testing, a pretreatment tumor biopsy is optional. PD-L1

expression and gene expression profile at baseline will be assessed at the central laboratory. Baseline tumor tissue samples can be collected at any stage of this study after local regulation approval. Refer to Section 7.6 for more details.

[o] Tumor tissue and lymph node tissue obtained from surgical resection is required for pathological response analysis. Assessments on surgical specimen will be done for MPR, pCR, and exploratory biomarker analysis (including PD-L1 expression and gene expression profile) Surgical tumor tissue samples can be collected at any stage of this study after local regulation approval. (Section 7.6)

[p] The first PET-CT will be performed as the baseline data after the informed consent form is signed, and the second PET-CT will be performed 15-21 days after the last dose of induction therapy. Patients will be allocated to 2 cohorts based on the change of SUVmax of PET-CT, in which, patients with a decrease of SUVmax ≥ 35% will be defined as PET responders and allocated to Cohort A, while patients with a decrease of SUVmax < 35% will be defined as PET non-responders and allocated to Cohort B.

[q] For screening period, if the CT scan performed on a PET-CT scanner is consistent with the standards of a diagnostic CT scan, there is no need to perform a separate CT; otherwise, a sperate CT scan is needed. After study treatment discontinuation, patients will undergo scheduled disease follow-up assessments by CT or MRI of the neck, chest, and abdomen every 3 months for the first 2 years based on RECIST v1.1. Patients who have not experienced recurrence of disease will continue disease follow-up assessments every 6 months during Year 3. Disease follow-up assessments should occur within the allowed time window. The allowed time window for disease follow-up assessments is ± 2 weeks in Years 1 to 2, and ± 4 weeks in Year 3. See also Section 7.5 .

[r] 21 days after induction therapy, Tislelizumab will be given intravenously once every 3 weeks (totally 3 cycles). The initial infusion will be delivered for ≥ 60 minutes. If well tolerated, subsequent infusions can be administered for at least 30 minutes. Patients must be monitored for 60 minutes after infusion of tislelizumab on Cycle 2 and Cycle 3 of tislelizumab administration, on Cycle 4 of tislelizumab administration, at least a 30-minute monitoring period is required.

[s] Chemotherapy (paclitaxel and cisplatin) will be administrated in Cycle 1 as induction therapy. After induction therapy, in Cohort A, chemotherapy (paclitaxel and cisplatin, 2 cycles) in combination with Tislelizumab will be administrated once every 3 weeks. In Cohort B, concurrent chemoradiotherapy (paclitaxel/5-FU and cisplatin, 2 cycles, once every 3 weeks, plus radiotherapy: 40Gy/20F) in combination with Tislelizumab will be administrated.

[t] After the safety follow-up visit, information on survival follow-up and new anticancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (± 14 days) (unless the patient withdraws consent or the sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (eg, county records) in accordance with local regulations to obtain information about survival status only.

APPENDIX 2. CLINICAL LABORATORY ASSESSMENTS

Serum Chemistry	Hematology	Coagulation	Urinalysis [c]	Thyroid function
Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Albumin Bicarbonate or total carbon dioxide Total bilirubin Direct bilirubin Blood urea nitrogen or urea Magnesium Chloride Phosphorus Potassium Sodium Corrected calcium [a] Creatinine Glucose Lactate dehydrogenase Total protein Creatinine Kinase [b] CK-MB [b] Lipase and/or Amylase	RBC count Hemoglobin Hematocrit WBC count Platelet count Neutrophil count Eosinophil count Basophil count Monocyte count Lymphocyte count	Prothrombin time Partial thromboplastin time or activated partial thromboplastin time International normalized ratio	pH Specific gravity Glucose Protein Ketones Blood	Free triiodothyronine Free thyroxine Thyroid stimulating hormone

Abbreviations: CK-MB, creatine kinase cardiac isoenzyme; WBC, white blood cell.

[a] Total calcium values will be corrected for patients with hypoproteinemia.

[b] All patients will have creatine kinase and CK-MB testing at screening, and to be repeated at all scheduled visits if CK-MB fractionation is not available, assess troponin I and/or troponin T instead. Refer to Section 8.3.5 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.

[c] On routine urinalysis, if urine protein is ≥ 2+ by dipstick, then obtain a 24-hour urine sample for total protein.

APPENDIX 3. EASTERN COOPERATIVE ONCOLOGY GROUP (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

Source: (Oken et al 1982) . Eastern Cooperative Oncology Group, Robert Comis MD, 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 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)
- 20 mm by chest X-ray (if clearly defined and surrounded by aerated lung)

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

Nonmeasurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter < 10 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 as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are nonmeasurable.

Cystic lesions:

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

Lesions with prior local treatment:

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

Target Lesions

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

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan, this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm 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").

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

normalize for a patient to be considered in CR. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and prostate-specific antigen response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

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

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

- CR: Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (< 10 mm short axis).
- Non-CR/Non-PD: Persistence of one or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits
- PD: Unequivocal progression (as detailed below) of existing nontarget lesions. (Note: The appearance of one or more new lesions is also considered progression.)
- When the patient also has measurable disease: In this setting, to achieve "unequivocal progression" on the basis of the nontarget disease, there must be an overall level of substantial worsening in nontarget disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more nontarget lesions is usually not sufficient to qualify for unequivocal progression status. The

designation of overall progression solely on the basis of change in nontarget disease in the face of SD or PR of target disease will therefore be extremely rare.

- When the patient has only nonmeasurable disease: This circumstance arises in some phase 3 trials when it is not a criterion of trial entry to have measurable disease. The same general concept applies here as noted above; however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in nonmeasurable disease burden. Because worsening in 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: i.e., an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase diameter in a measurable lesion).
- Examples include an increase in a pleural effusion from "trace" to "large," an increase in lymphangitic disease from localized to widespread, or may be described in protocols as "sufficient to require a change in therapy." If "unequivocal progression" is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to nonmeasurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of 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 trial in an anatomical location that was *not* scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain scan ordered that reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

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

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

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up, is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a 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 time point, a response assessment occurs. The following table provides a summary of the overall response status calculation at each time point 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)
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 taking into account any requirement for confirmation. On occasion a

response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and nontarget disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the trial and the protocol requirements, it may also require confirmatory measurement. Specifically, in nonrandomized trials 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 trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a 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 time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later).

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

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

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

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

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual

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

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes, or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If 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 the case of SD, measurements must have met the SD criteria at least once after trial entry at a minimum interval (in general not less than 6 weeks).

Duration of Overall Response

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

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

Duration of Stable Disease

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

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

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

APPENDIX 5. PREEXISTING IMMUNE DEFICIENCIES OR AUTOIMMUNE DISEASES

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

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

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

APPENDIX 6. NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

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

Adapted from (Dolgin M 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. IMMUNE-MEDIATED ADVERSE EVENT EVALUATION AND MANAGEMENT

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

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

- What was the temporal relationship between initiation of tislelizumab and the 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.

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

Immune-mediated Toxicity	Diagnostic Evaluation Guideline
Neurological Toxicity	Perform a comprehensive neurological examination and brain MRI for all CNS symptoms; review alcohol history and other medications. Conduct a diabetic screen and assess blood B12/folate, HIV status, TFTs, and consider autoimmune serology. Consider the need for brain/spine MRI/MRA and nerve conduction study for peripheral neuropathy. Consult with a neurologist if there are abnormal findings.
Colitis	Review dietary intake and exclude steatorrhea. Consider comprehensive testing, including the following: FBC, UEC, LFTs, CRP, TFTs, stool microscopy and culture, viral PCR, *Clostridium difficile* toxin, and cryptosporidia (drug-resistant organism). In case of abdominal discomfort, consider imaging, eg, X-ray, CT scan. If a patient experiences bleeding, pain, or distension, consider colonoscopy with biopsy and surgical intervention as appropriate.
Eye Disorders	If a patient experiences acute, new onset, or worsening of eye inflammation; blurred vision; or other visual disturbances, refer the patient urgently to an ophthalmologist for evaluation and management.
Hepatitis	Check ALT/AST/total bilirubin, INR/albumin; the frequency will depend on severity of the AE (eg, daily if Grade 3 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.

Treatment of Immune-mediated Adverse Events

- Immune-mediated AEs can escalate quickly. Study treatment interruption, close monitoring, timely diagnostic work-up, and treatment intervention as appropriate 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.
- Tislelizumab must be permanently discontinued for any onset of Grade 4 or recurrent Grade 3 immune-mediated AEs.

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.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	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.
	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. Discontinuation is usually not necessary.
Pneumonitis	**1** Radiographic changes only	Monitor symptoms every 2-3 days. If appearance worsens, treat as Grade 2.	Consider holding study treatment until appearance improves and cause is determined.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	2 Symptomatic: exertional breathlessness	Commence antibiotics if infection suspected. Add oral prednisolone 1 mg/kg/day if symptoms/appearance persist for 48 hours or worsen. Consider *Pneumocystis* infection prophylaxis. Taper corticosteroids over at least 6 weeks. Consider prophylaxis for adverse steroid effects: eg, blood glucose monitoring, vitamin D/calcium supplement.	Hold study treatment. Retreatment is acceptable if symptoms resolve completely or are controlled on prednisolone ≤ 10 mg/day. Discontinue study treatment if symptoms persist with corticosteroid treatment.
	3-4 Severe or life-threatening symptoms: breathless at rest	Admit to a hospital and initiate treatment with intravenous methylprednisolone 2-4 mg/kg/day. If there is no improvement, or worsening after 48 hours, add infliximab 5 mg/kg (if no hepatic involvement). Convert to oral prednisolone and taper over at least 2 months. Cover with empiric antibiotics and consider prophylaxis for *Pneumocystis* infection and other adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement.	Discontinue study treatment.
Neurological Toxicity	**1** Mild symptoms	–	Continue study treatment.
	2 Moderate symptoms	Treat with oral prednisolone 0.5-1 mg/kg/day. Taper over at least 4 weeks. Obtain neurology consultation.	Hold study treatment; resume when resolved/improved to Grade 0-1.
	3-4 Severe/life-threatening 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.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Colitis/Diarrhea	**1** Mild symptoms: ≤ 3 liquid stools per day over baseline and feeling well	Symptomatic management: fluids, loperamide, avoid high fiber/lactose diet. If Grade 1 persists for > 14 days, manage as a Grade 2 event.	Continue study treatment.
	2 Moderate symptoms: 4-6 liquid stools per day over baseline, or abdominal pain, or blood in stool, or nausea, or nocturnal episodes	Oral prednisolone 0.5 mg/kg/day (nonenteric coated). Do not wait for any diagnostic tests to start treatment. Taper steroids over 2-4 weeks. Consider endoscopy if symptoms are recurring.	Hold study treatment; resume when resolved/improved to baseline grade.
	3 Severe symptoms: > 6 liquid stools per day over baseline, or if episodic within 1 hour of eating	Initiate intravenous methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Consider prophylaxis for adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement. 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.
	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.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	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): including Stevens-Johnson syndrome (all grades), and toxic epidermal necrolysis>>	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.
	2 ALT or AST 3-5 x ULN	Recheck LFTs every 48-72 hours. For persistent ALT/AST elevation: consider oral prednisolone 0.5-1 mg/kg/day for 3 days, then taper over 2-4 weeks. For rising ALT/AST: start oral prednisolone 1 mg/kg/day and taper over 2-4 weeks; re-escalate dose if LFTs worsen, depending on clinical judgement.	Hold study treatment; treatment may be resumed when resolved/improved to baseline Grade and prednisolone tapered to ≤ 10 mg.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3 ALT or AST 5-20 x ULN	ALT/AST < 400 IU/L and normal bilirubin/INR/albumin: Initiate oral prednisolone 1 mg/kg and taper over at least 4 weeks. ALT/AST > 400 IU/L or raised bilirubin/INR/low albumin: Initiate intravenous (methyl)prednisolone 2 mg/kg/day. When LFTs improve to Grade 2 or lower, convert to oral prednisolone and taper over at least 4 weeks.	Hold study treatment until improved to baseline grade; reintroduce only after discussion with the study medical monitor.
	4 ALT or AST > 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 methylprednisolone, 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 0.5-1 mg/kg and taper over at least 2 weeks. Repeat creatinine/U&E every 48-72 hours.	Hold study treatment. If not attributed to drug toxicity, restart treatment. If attributed to study drug and resolved/improved to baseline grade: Restart study drug if tapered to < 10 mg prednisolone.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3 Creatinine > 3 x baseline or > 3-6 x ULN	Hospitalize patient for monitoring and fluid balance; repeat creatinine every 24 hours; refer to a nephrologist and discuss need for biopsy. If worsening, initiate 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.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	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.	Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1.
Ocular Toxicity	**1** Asymptomatic eye examination/test abnormality	Consider alternative causes and prescribe topical treatment as required.	Continue study treatment.
	2 Anterior uveitis or mild symptoms	Refer patient to an ophthalmologist for assessment and topical corticosteroid treatment. Consider a course of oral steroids.	Continue study treatment or hold treatment if symptoms worsen or if there are symptoms of visual disturbance.
	3 Posterior uveitis/panuveitis or significant symptoms	Refer patient urgently to an ophthalmologist. Initiate oral prednisolone 1-2 mg/kg and taper over at least 4 weeks.	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.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	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 limited	Refer patient urgently to a rheumatologist for assessment and management. Initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks.	Hold study treatment unless improved to Grade 0-1; reintroduce only after discussion with the study medical monitor.
Mucositis/ stomatitis	**1** Test findings only or minimal symptoms	Consider topical treatment or analgesia as per local guideline.	Continue study treatment.
	2 Moderate pain, reduced oral intake, limited instrumental activities	As per local guidelines, treat with analgesics, topical treatments, and oral hygiene care. Ensure adequate hydration. If symptoms worsen or there is sepsis or bleeding, manage as a Grade 3 event.	Continue study treatment.
	3 Severe pain, limited food and fluid intake, daily living activity limited	Admit to hospital for appropriate management. Initiate intravenous (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when symptoms 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.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Myositis/ Rhabdomyolysis	**1** Mild weakness with/without pain	Prescribe analgesics. If CK is significantly elevated 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 troponin OR clinically significant intraventricular conduction delay	Initiate cardiac evaluation under close monitoring with repeat serum testing and including ECG, cardiac echo/MUGA, 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) equation ((Levey et al 2009), and the Modification of Diet in Renal Disease (MDRD) Study equation. The National Kidney Disease Education Program (NKDEP) calculators rely on creatinine determinations which are isotope dilution mass spectrometry (IDMS) traceable. All laboratories should be using creatinine methods calibrated to be IDMS traceable.

This CKD-EPI equation calculator should be used when serum creatinine (S_{cr}) is reported in mg/dL. This equation is recommended when eGFR values above 60 mL/min/1.73 m^2 are desired.

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

where:

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

κ is 0.7 for females and 0.9 for males,

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

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

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

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

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

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 trials include the use of highly effective forms of birth control (Clinical Trials Facilitation Group 2014). 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, 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.
- An intrauterine device
- Intrauterine hormone-releasing system
- 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, sympto-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," "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 (i.e., 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 mIU/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, 2014) .

[redacted]

BGB-A317-213
PROTOCOL AMENDMENT 1.0
SUMMARY OF CHANGES

BGB-A317-213 Protocol Amendment 1.0 Summary of Key Changes (Edition 1.0 to Edition 0.0)

The main purpose is to update the sample size of responder cohort A (40→ approx. 25) and non-responder cohort B (25→ approx. 40) based on the actual ratio of responders vs non-responders observed, and Study LBL-007-CN-003, and to clarify the definition of EFS.

Contents from IB 9.0 was included to update relevant sections in original protocol.

Minor changes have been made to correct typos and to enhance clarity and readability.

The key changes from Edition 1.0 to Edition 0.0 (Original) are summarized by section in the following table:

Section	Key Change	Rationale for change	Substantial change (Y/N)	Potential Impact on the Safety of Patients, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
1.3. Anti-PD-1 Therapy for Esophageal Squamous Cell Carcinoma	• Update information about the latest readout of tislelizumab trial in ESCC	• Add most up-to-date readout of several Phase III clinical trials of tislelizumab in ESCC	N	N/A
1.4.4. Prior Clinical Experience of Tislelizumab	• Include information from IB 9.0	• To provide the latest safety information of tislelizumab based on IB 9.0.	N	N/A
2. Study Objectives and Endpoints	• Clarification of the definition of EFS • Move MPR to exploratory objectives	• To clarify the definition of EFS and keep consistency throughout the protocol. • MPR is common endpoint in lung cancer, but not well established in esophageal cancer	N	N/A
3.4 End of Treatment/Safety Follow-up	• Update definition of last study treatment	• Include surgery as study treatment	N	N/A
4.1 Inclusion Criteria	• Deleted Inclusion Criteria 7 ii: Platelets ⩾ 75 x 109/L • Add: "and ⩾ 180 days after the last dose of chemotherapy and radiotherapy" in Inclusion Criteria 9	• Platelets ⩾ 75 x 109/L is for Monotherapy • Add contraception period for chemotherapy and radiotherapy	N	N/A
4.2 Exclusion Criteria	• For Exclusion Criteria 1, Add "or other targeted therapy agents".	• Patient with prior targeted therapy agents for ESCC is not eligible	N	N/A

5.2.2 Cisplatin in Combination with Paclitaxel	• ondansetron 8 mg/kg IV updated to 8 mg IV or equivalent • paclitaxel will be administered on Day 1, given Q3W at a dose of 135 mg/mg2 by IV infusion for at least 3 hours, Update to 135mg/m2	• Error of dose • Typo	N	N/A
6.2.2 Prohibited Concomitant Medications/Procedures	• Update prohibited medication for adjuvant treatment for patients with R1/R2 resection	• Medications approved for the adjuvant setting by the NMPA are allowed to be used according to their approved label.	N	N/A
7.4.7 Hepatitis B and C Testing AND Appendix 1 point l	• If HBsAg or HBcAb is positive, then an HBV DNA test will be triggered. Delete "or HBcAb"	• Error wording	N	N/A
7.6 Biomarkers	• Delete blood in "Shipping, storage, and handling of blood, archival tumor, fresh tumor, and leftover tumor tissue for the assessment of biomarkers will be managed through a central laboratory".	• Blood biomarkers were not collected for this study.	N	N/A
8.6.1 Adverse Event Recording Period	• All AEs and SAEs, regardless of relationship to study drug, will be reported until either 30 days after last dose of study drug(s) Update to "30 days after last study treatment (including chemotherapy, radiotherapy, tislelizumab and surgery)"	• Take surgery into consideration of AE reporting period	N	N/A

9.2 Efficacy Analyses	• EFS rate will be analyzed similarly as the DFS rate for patients in the EE analysis set. Update to "SAF analysis set". • Delete ITT set • Add definition for no disease in DFS (R0 resection as surgery outcome) • Add scenarios of sensitivity analysis	• The Efficacy Evaluable (EE) Analysis Set includes all patients who receive neoadjuvant treatment followed by surgery per protocol, but for EFS, there may be patient who didn't have surgery. • Since 213 is not a randomized study, ITT set is not applicable • To clarify the definition of no disease of DFS	N	N/A
9.3.2 Adverse Events	• Update definition of imAE and TEAE to be consistent with tislelizumab compound level TEAE definition	• Separate imAE from TEAE to be consistent with tislelizumab compound level TEAE definition	N	N/A
9.4 Sample Size Consideration	• Update the sample size of patients for Cohort A and B • Update Estimates of 95% CI Using Clopper-Pearson in Cohort A and B	• Based on the actual ratio of responders vs non-responders observed.	N	N/A
Appendix 2	• Add footnote for "Random urine protein to creatinine ratio": if urine protein is ≥ 2+ by dipstick, then obtain a 24-hour urine sample for total protein or random urine protein to creatinine ratio • Add test of Thyroid function	• To keep consistent with compound level protocol template	N	N/A
Appendix 9	• FSH concentration > 30 IU/mL updated to ">30 mIU/mL "	• Error unit	N	N/A
List of Abbreviations and Definitions of Terms	• Update to List of Abbreviations and Definitions of Terms	• Update table of abbreviations	N	N/A

List of Tables	• Up numbering, referring and naming of tables • Delete duplicate tables 2, 9 and 10 in the main text	• Numbering and references of tables were disordered.	N	N/A
Table 5: Immune-Mediated Adverse Events of Any Grade Occurring in ≥ 1% in Pooled Monotherapy Studies	• Update footnote NCI CTCAE v4.03 to v5.0	• To keep consistent with other parts in the protocol	N	N/A
Table 7 Selection and Timing of Dose for Each Patient	• Update footnote "The total dose given must be between 60 to 80 mg/m2 per cycle." Delete "between 60 to".	• To keep consistent with other part of the protocol, dose of cisplatin should be 80 mg/m2	N	N/A
Table 8: Dose Modification based on Hematologic Nadir Values Prior to the Next Dose	• Delete "Level 1 (Standard level) (Every 3 weeks as a cycle)" in the second column	• Not relevant title	N	N/A
Table 9: Guidance for Duration of Recording New or Worsening Adverse Events	• Update reporting period of imAE to "Up to 90 days after last dose of tislelizumab"	• Keep consistent with compound level imAE definition	N	N/A