CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 2, Multicenter, Randomized, Placebo-Controlled Study to Compare the Efficacy of Anti-PD-1 Monoclonal Antibody Tislelizumab (BGB-A317) Plus Anti-TIGIT Monoclonal Antibody Ociperlimab (BGB-A1217) Versus Tislelizumab Plus Placebo as Second-Line Treatment in Patients With PD-L1 Tumor Area Positivity (TAP) ≥ 10% Unresectable, Locally Advanced, Recurrent or Metastatic Esophageal Squamous Cell Carcinoma
Protocol Number:	BGB-A317-A1217-203 (AdvanTIG-203)
Phase:	2
Investigational Products:	Ociperlimab (BGB-A1217) and Tislelizumab (BGB-A317)
Reference Number	EudraCT 2020-004658-32
Proposed Indication(s):	PD-L1 TAP ≥ 10% Unresectable, Locally Advanced, Recurrent or Metastatic Esophageal Squamous Cell Carcinoma (ESCC)
Sponsor:	BeiGene, Ltd. c/o BeiGene USA, Inc. 1840 Gateway Drive, Third Floor San Mateo, CA 94404, USA
Sponsor Medical Monitor:	[redacted]
Original Protocol Version 0.0:	16 September 2020
Protocol Amendment 1.0:	03 June 2022
Protocol Amendment 2.0:	27 February 2023

FINAL PROTOCOL APPROVAL SHEET

A Phase 2, Multicenter, Randomized, Placebo-Controlled Study to Compare the Efficacy of Anti-PD-1 Monoclonal Antibody Tislelizumab (BGB-A317) Plus Anti-TIGIT Monoclonal Antibody Ociperlimab (BGB-A1217) Versus Tislelizumab Plus Placebo as Second-Line Treatment in Patients With PD-L1 Tumor Area Positivity (TAP) ≥ 10% Unresectable, Locally Advanced, Recurrent or Metastatic Esophageal Squamous Cell Carcinoma

BeiGene, Ltd., Approval:

[redacted]

Sponsor Medical Monitor

INVESTIGATOR SIGNATURE PAGE

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Protocol Identifier: BGB-A317-A1217-203

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 Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd., or one of its subsidiaries.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. PRINT your name, title, and the name and address of the center in which the study will be conducted.

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

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

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SYNOPSIS

Name of Sponsor/Company:	BeiGene, Ltd
Investigational Product(s):	Ociperlimab (also known as BGB-A1217) and tislelizumab (BGB-A317)
Title of Study:	A Phase 2, Multicenter, Randomized, Placebo-Controlled Study to Compare the Efficacy of Anti-PD-1 Monoclonal Antibody Tislelizumab (BGB-A317) Plus Anti-TIGIT Monoclonal Antibody Ociperlimab (BGB-A1217) Versus Tislelizumab Plus Placebo as Second-Line Treatment in Patients With PD-L1 Tumor Area Positivity (TAP) ≥ 10% Unresectable, Locally Advanced, Recurrent or Metastatic Esophageal Squamous Cell Carcinoma
Protocol Identifier:	BGB-A317-A1217-203 (AdvanTIG-203)
Phase of development:	2
Planned Number of Patients:	Approximately 120 patients
Study Centers:	Approximately 100 centers globally

Study Objectives:

Primary:

- To compare the objective response rate (ORR) as assessed by the investigator according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), of tislelizumab plus ociperlimab with tislelizumab plus placebo as second-line treatment in patients with programmed cell death ligand-1 (PD-L1) TAP ≥ 10% unresectable, locally advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) in the Intent-to-Treat (ITT) Analysis Set.

Secondary:

- To compare the overall survival (OS) of tislelizumab plus ociperlimab with tislelizumab plus placebo as second-line treatment in patients with PD-L1 TAP ≥ 10% ESCC in the ITT Analysis Set.
- To compare the following endpoints between tislelizumab plus ociperlimab and tislelizumab plus placebo based on tumor assessments per RECIST v1.1:
- Progression-free survival (PFS) assessed by both the Independent Review Committee (IRC) and the investigator.
- Duration of response (DOR), disease control rate (DCR), and clinical benefit rate (CBR) assessed by both the IRC and the investigator.
- ORR assessed by the IRC.
- To compare the safety and tolerability between tislelizumab plus ociperlimab and tislelizumab plus placebo.

- To compare the health-related quality of life (HRQoL) via cancer-specific patient-reported outcomes (PROs) between tislelizumab plus ociperlimab and tislelizumab plus placebo.

Exploratory:

- To evaluate the potential association of biomarkers with patient prognosis, response or resistance to tislelizumab plus ociperlimab and tislelizumab plus placebo.
- To characterize the pharmacokinetics (PK) of ociperlimab and tislelizumab.
- To assess host immunogenicity to ociperlimab and tislelizumab.
- To compare the quality of life (QoL) via a generic PRO between tislelizumab plus ociperlimab and tislelizumab plus placebo.

Study Endpoints:

Primary:

- ORR, defined as the proportion of patients in the ITT Analysis Set who have confirmed complete response (CR) or partial response (PR) as assessed by the investigator per RECIST v1.1.

Secondary:

- OS, defined as the time from the date of randomization until the date of death due to any cause in patients in the ITT Analysis Set.
- ORR, defined as above and assessed by the IRC per RECIST v1.1 in the ITT Analysis Set.
- PFS, defined as the time from the date of randomization to the date of first documentation of progressive disease (PD) assessed by both the IRC and investigator per RECIST v1.1 or death, whichever occurs first in the ITT Analysis Set.
- DOR, defined as the time from the first determination of an objective response until the first documentation of PD as assessed by both the IRC and the investigator per RECIST v1.1, or death, whichever comes first in the ITT Analysis Set.
- DCR, defined as the proportion of patients in the ITT Analysis Set who have confirmed CR, confirmed PR, and stable disease assessed by both the IRC and the investigator per RECIST v1.1.
- CBR, defined as the proportion of patients who achieve confirmed CR, confirmed PR, and durable stable disease (stable disease ≥24 weeks).
- HRQoL, measured by the Global Health Status (GHS)/QoL and Physical Function scales of European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and scores of Dysphagia, Eating, Reflux and Pain of EORTC Quality of Life Oesophageal Cancer Questionnaires 18 (QLQ-OES18).
- Adverse events (AEs) and serious adverse events (SAEs) as characterized by type, frequency, severity (as graded by the National Cancer Institute-Common Terminology Criteria for Adverse Events [NCI-CTCAE] version 5.0 [v5.0]), timing, seriousness, and relationship to study drugs, physical examinations, electrocardiograms (ECGs), and laboratory assessments.

Exploratory:

- Evaluate status of exploratory biomarkers including but not limited to expression of TIGIT, CD226, CD155, CD112 and PD-L1, gene expression profiling (GEP), tumor mutation burden (TMB)/gene mutation/microsatellite instability (MSI), tumor infiltrating immune cells in archival and/or fresh tumor tissue and blood before and after study treatment or at PD/reoccurrence, and the association between these biomarkers and clinical efficacy, disease status, and resistance.
- Serum ociperlimab and tislelizumab concentrations at specified timepoints.
- Immunogenic responses to ociperlimab and tislelizumab, evaluated through the detection of antidrug antibodies (ADAs).
- QoL, measured by assessment of European Quality of Life 5-Dimensional 5-Level (EQ-5D-5L) and visual analog scale (VAS) in the ITT Analysis Set.

Study Design

This is a multicenter, randomized, investigator- and patient-blinded, sponsor-unblinded, placebo-controlled global Phase 2 study to compare the efficacy, as measured by ORR of anti-programmed cell death protein 1 (anti-PD-1) monoclonal antibody tislelizumab (BGB-A317) plus anti-TIGIT monoclonal antibody ociperlimab versus tislelizumab plus placebo as second-line treatment in patients with PD-L1 TAP ≥ 10% unresectable, locally advanced, recurrent or metastatic ESCC.

After providing written informed consent, completing all prescreening and screening assessments, and being confirmed as eligible for study participation, approximately 120 patients will be randomized at a 1:1 ratio to receive 1 of the following treatment regimens:

- Arm A: tislelizumab + ociperlimab
- Arm B: tislelizumab + placebo

Eligible patients will be stratified by the following factors:

- Eastern Cooperative Oncology Group Performance Status (ECOG PS) score (0 versus 1)
- Number of organs with metastases (≤1 versus ≥2)
- Region (Asia versus non-Asia)

Study drugs (including placebo) will be administered until PD per RECIST v1.1, unacceptable toxicity, or withdrawal of informed consent, whichever occurs first.

No crossover between Arm A and Arm B will be allowed.

The study design schema is provided in Figure 1, Section 3.1.

Study Assessments:

Tumor Assessment:

Tumor imaging will be performed at baseline (≤ 28 days before randomization). During the study, tumor imaging will be performed approximately every 6 weeks (± 7 days) for the first 54 weeks and every 12 weeks (± 7 days) thereafter.

Response will be assessed using RECIST v1.1. If a patient can continue to benefit from study drugs after PD per RECIST v1.1, the patient may continue the study treatment at the investigator's discretion. The following criteria must be met in order to treat patients who may continue to benefit from study treatment after PD:

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

The decision to continue study drugs after initial PD must be agreed to by the medical monitor and documented in the study records. Patients who receive the study treatment after PD will undergo tumor assessments according to the original schedule until study treatment discontinuation.

A patient who discontinues study drugs early for reasons other than PD (eg, treatment toxicity) will continue to undergo tumor assessments according to the original plan until the patient experiences PD, withdraws consent, is lost to follow-up, dies, or until the study terminates, whichever occurs first.

PROs will be collected using the EORTC QLQ-C30, EORTC QLQ-OES18, and EQ-5D-5L before dosing of every treatment cycle, and at the on-site Safety Follow-up Visit.

Safety Assessment:

Patients will be evaluated for any AEs and SAEs occurring up to 30 days after the last dose of study drugs (all severity grades, per NCI-CTCAE v5.0) or initiation of a new anticancer therapy, whichever occurs first, and immune-mediated AEs (imAEs) occurring up to 90 days after the last dose of study drugs regardless of initiation of a subsequent anticancer therapy. All drug-related SAEs will be recorded by the investigator after treatment discontinuation until patient death, withdrawal of consent, or loss to follow-up, whichever occurs first, and will be followed until they resolve to baseline or ≤ Grade 1, are assessed by the investigator as stable and unlikely to improve, or the patient is lost to follow-up, whichever occurs first.

Duration of Patient Participation:

Duration of patient participation will vary by patient. Each patient's visit course will include: prescreening (up to 56 days before randomization) and screening (up to 28 days before randomization), treatment (until PD, intolerable toxicity, or withdrawal of informed consent), safety follow-up (30 [± 7], 60 [± 14], and 90 [± 14] days after the last dose of study drugs), and survival follow-up (approximately every 3 months ± 14 days after the last Safety Follow-up Visit).

Study Population:

The study will enroll approximately 120 patients who meet the inclusion/exclusion criteria, with approximately 60 patients in Arm A (tislelizumab plus ociperlimab) and 60 patients in Arm B (tislelizumab plus placebo).

Key Eligibility Criteria:

The population under study consists of adult patients (>18 years of age or the legal age of consent in the jurisdiction in which the study is taking place) with histologically confirmed diagnosis of ESCC with tumor progression during or after first-line systemic treatment for unresectable, locally advanced, recurrent or metastatic disease. Patients must submit qualified archival tumor tissue with an associated pathology report or agree to a tumor biopsy for determination of PD-L1 expression and other biomarker analyses. Patients must have PD-L1 TAP ≥ 10% in tumor tissues tested by the central lab. Patients who have received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, TIGIT or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways are excluded.

All patients are also required to have measurable disease per RECIST v1.1 within 28 days before randomization, an ECOG PS score of 0 or 1, life expectancy ≥ 12 weeks, and adequate organ function.

Investigational Product, Dose and Mode of Administration:

Tislelizumab, 200 mg administered by intravenous infusion once every 3 weeks.

Ociperlimab, 900 mg administered by intravenous infusion once every 3 weeks.

Reference Therapy, Dose, and Mode of Administration:

Tislelizumab, 200 mg administered by intravenous infusion once every 3 weeks.

Ociperlimab Placebo, administered by intravenous infusion once every 3 weeks.

Statistical Methods:

Analysis Sets

- The ITT Analysis Set, which includes all randomized patients, will be the primary analysis population for all efficacy analyses.
- The Safety Analysis Set (SAS), which includes all patients who received ≥ 1 dose of study drugs, will be the primary analysis set for safety analyses.
- The PK Analysis Set, which includes all patients who receive ≥ 1 dose of any component of study drugs per the protocol, and for whom any postdose PK data are available.
- The Immunogenicity Analysis Set, which includes all patients who receive at least 1 dose of any component of study drugs and for whom both baseline antidrug antibody and ≥ 1 postbaseline ADA results are available.

Efficacy Analyses:

The primary endpoint ORR will be tested at a 1-sided alpha of 0.025. If the null hypothesis for ORR in the ITT Analysis Set is rejected, the secondary endpoint OS in the ITT Analysis Set will be tested.

Primary Efficacy Analysis

Overall Response Rate by the Investigator's Review

ORR, assessed by the investigator per RECIST v1.1, will be compared between Arm A and Arm B. Patients with no postbaseline response assessment for any reason will be considered nonresponders.

The null hypothesis to be tested is:

H_0: ORR in Arm A ≤ ORR in Arm B

against the alternative:

H_1: ORR in Arm A > ORR in Arm B

The statistical significance of the difference in ORR between the 2 treatment arms in the ITT Analysis Set will be evaluated using the Cochran-Mantel-Haenszel method, adjusted by the selected stratification factors at randomization (ie, ECOG PS score [0 versus 1] and the number of organs with metastases [≤1 versus ≥2]). The difference in ORR will be calculated, as will the Clopper-Pearson 95% CIs for the ORR within each arm.

The final analysis of ORR will be performed at approximately 4 months after the last patient is randomized.

Secondary Efficacy Analysis

OS will be analyzed in the ITT Analysis Set. In the absence of death, patients will be censored either at the date when the patient is last known to be alive or the date of data cutoff, whichever comes earlier. A log-rank test stratified by the actual value of selected stratification factors at randomization (ie, ECOG PS score [0 versus 1] and the number of organs with metastases [≤1 versus ≥2]) will be used to

test the differences in OS between the 2 treatment arms. The median OS and the cumulative probability of OS at every 3 months, if estimable, will be calculated for each treatment arm and presented with 2 sided 95% CIs. Kaplan-Meier survival probabilities over time for each arm will be plotted. The treatment effect of OS will be estimated by fitting a Cox regression model with treatment arm adjusted by the selected stratification factors at randomization (ie, ECOG PS score [0 versus 1] and number of organs with metastases [≤1 versus ≥2]). From this model, the HR of OS will be estimated and presented with a 2-sided 95% CI. The final analysis of OS will take place when approximately 72 deaths (ie, 60% of the total sample size) have been observed.

ORR assessed by the IRC per RECIST v1.1 in the ITT Analysis Set will be analyzed similarly to the corresponding analysis of ORR assessed by the investigator. The 2-sided 95% CIs for the odds ratio and the difference in ORR will be calculated, as will the Clopper-Pearson 95% CIs for the ORR within each arm.

PFS based on assessment by the IRC and the investigator per RECIST v1.1 will be analyzed in the ITT Analysis Set. The PFS censoring rule will follow the United States (US) Food and Drug Administration (FDA) Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (FDA 2018). The median PFS and the cumulative probability of PFS at every 3 months, if estimable, will be calculated for each treatment arm and presented with 2-sided 95% CIs. Kaplan-Meier survival probabilities over time for each arm will be plotted. The treatment effect will be estimated by fitting a Cox regression model with treatment arm adjusted by the selected stratification factors at randomization (ie, ECOG PS score [0 versus 1] and the number of organs with metastases [≤1 versus ≥2]). From this model, the HR of PFS will be estimated and presented with a 2-sided 95% CI.

DOR will be analyzed among the responders in the ITT Analysis Set using methods similar to that described for PFS, based on assessment by the IRC and the investigator.

DCR and CBR assessed by the IRC and investigator per RECIST v1.1 will be summarized similarly as ORR in the ITT Analysis Set.

HRQoL is an assessment of a patient's health state using the scores of Global Health Status (GHS)/QoL and Physical Function of QLQ-C30 and Dysphagia, Eating, Reflux and Pain of OES18.

Safety Analyses

Extent of exposure to each study drug will be summarized by duration, dosage, and dose intensity for each arm.

Verbatim description of AEs will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA) terms and graded per NCI-CTCAE v5.0. All treatment-emergent AEs (TEAEs) will be summarized. A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug up to 30 days after study drug discontinuation or initiation of a new anticancer therapy, whichever occurs first. Immune-mediated AEs will be identified from all AEs that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to 90 days from the last dose of ociperlimab (or placebo) and/or tislelizumab, regardless of whether the patient starts a new anticancer therapy. If an imAE occurs outside of the above-mentioned TEAE window, it will not be classified as a TEAE. All imAEs will be reported separately.

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

Pharmacokinetic Analyses

Tislelizumab and ociperlimab serum concentration data will be tabulated and summarized by visit and/or cycle at which these concentrations are collected. Descriptive statistics will include means,

medians, ranges, and standard deviations, as appropriate. Additional PK analyses may be conducted as appropriate.

Sample Size

The sample size calculation is based on the primary efficacy analysis of ORR between Arm A and Arm B in the ITT Analysis Set.

With 120 randomized patients, the study has at least 80% power to detect a 24% difference in ORR (45% versus 21% in Arm A and Arm B, respectively) at a 1-sided type I error of 0.025.

The sample size is calculated by EAST (version 6.4.1).

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
ADAs	antidrug antibodies
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BOR	best overall response
CD	cluster of differentiation
CR	complete response
CT	computed tomography
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
EDC	electronic data capture (system)
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of Treatment (Visit)
EQ-5D-5L	European Quality of Life 5-Dimensional 5-Level
ESCC	esophageal squamous cell carcinoma
FDG	fluorine-18 [F-18] fluorodeoxyglucose
GCP	Good Clinical Practice
GEP	gene expression profiling
HBV	hepatitis B virus
HCV	hepatitis C virus
HR	hazard ratio
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	immunoglobulin G
imAE	immune-mediated adverse event
IRB	Institutional Review Board
IRC	Independent Review Committee
ITT	Intent-to-Treat (Analysis Set)
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events

Abbreviation	Definition
NK	natural killer (cells)
NSCLC	non-small cell lung cancer
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-OES18	Quality of Life Oesophageal Cancer Questionnaires 18
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PD	progressive disease
PD-1	programmed cell death protein-1
PD-L1	programmed cell death protein-ligand 1
PET	positron-emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PVR	poliovirus receptor
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
TAP	tumor area positivity
TEAE	treatment-emergent adverse event
TIGIT	T-cell immunoreceptor with Ig and ITIM domains
Tregs	regulatory T (cells)
BGB-A317	Tislelizumab
TIL	tumor-infiltrating lymphocyte
ULN	upper limit of normal

1. INTRODUCTION AND RATIONALES

1.1. Background Information on Esophageal Carcinoma

Esophageal cancer is the seventh most common cancer worldwide and the sixth most common cause of death from cancer. Globally, there were an estimated 572,000 cases and over 508,000 deaths in 2018 (GloboCan 2018). The global incidence of esophageal cancer shows wide geographic variation, with a 60-fold difference between high- and low- incidence regions. The highest incidence area, often referred to as the "esophageal cancer belt," spans from northern Iran through the Central Asian republics and into northern China. Other high-prevalence areas include southern and Eastern Africa and Northern France. In contrast, esophageal cancer is one of the least commonly diagnosed cancers in North America. Esophageal cancers are histologically classified as esophageal squamous cell carcinoma (ESCC) or adenocarcinoma (EAC), which differ from one another in the pathology, tumor location, and prognosis. ESCC is the most common histology in eastern Europe and Asia, while adenocarcinoma is the most common in North America and western Europe.

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

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

1.2. Current Treatment of Squamous Esophageal Carcinoma

The primary treatment of ESCC is based on tumor histology and the extent of disease at presentation. Therapeutic treatment modalities include endoscopic resection for focal disease or esophagectomy with lymph node resection for larger tumors in patients who are considered medically fit (Stahl et al 2009; Lordick et al 2016). Chemoradiation therapy may be given to those with larger tumors in the neoadjuvant, periadjuvant or in the adjuvant setting. Postoperative chemotherapy or chemoradiation is commonly given to patients who have microscopic or macroscopic residual cancer (R1 and R2 resection, respectively) after surgery. Systemic regimens given in the preoperative or perioperative setting commonly include chemotherapy doublets which include taxanes, platinum agents, fluorouracil, or irinotecan. Triplet combinations may also be considered but are more toxic and restricted to those patients who are medically fit (NCCN Guideline Version 2 2022).

For first-line therapy for unresectable locally advanced, recurrent or metastatic ESCC where local therapy is not indicated, the main recommendations is for a 2-drug cytotoxic regimen because of lower toxicity compared with three-drug regimens. However, 3-drug regimens should be reserved for medically fit patients with good performance status and access to frequent toxicity evaluation. Preferred regimens include fluoropyrimidines (either fluorouracil or

capecitabine) in combination with either cisplatin or oxaliplatin; other recommended regimens include fluorouracil and irinotecan, paclitaxel with cisplatin or carboplatin, docetaxel with cisplatin, DCF (docetaxel, platinum, fluorouracil) and ECF (epirubicin, platinum, fluorouracil). The objective response rate (ORR) to the first-line chemotherapy for advanced or metastatic disease ranges from 20% to 48% and 5-year survival rates of < 30% and with significant toxicity rates (Grunberger et al 2007).

For patients who progressed after first-line therapy, regimen selection is dependent upon prior therapy and performance status. Current recommendations for second-line treatment include single agent chemotherapy (eg, docetaxel, paclitaxel, irinotecan) or immunotherapy (ie, anti-programmed cell death protein-1 [PD-1] antibodies). Table 1 summarizes the second-line treatment and efficacy outcomes for ESCC. Generally, the ORR and median survival appear comparable and limited with treatment of paclitaxel, docetaxel, or irinotecan.

In 2019, pembrolizumab was approved by the United States (US) Food and Drug Administration (FDA) for the treatment of patients who have recurrent locally advanced or metastatic ESCC whose tumors express programmed cell death protein-ligand 1 (PD-L1) (Combined Positive Score [CPS] ≥10, with progressive disease (PD) after ≥ 1 prior lines of systemic therapy (pembrolizumab USPI 2020). The efficacy of pembrolizumab as the second-line treatment was investigated in KEYNOTE-181 (NCT02564263), a multicenter, randomized, open-label, active-controlled trial that enrolled 628 patients with recurrent locally advanced or metastatic esophageal cancer who progressed on or after one prior line of systemic treatment for advanced disease. Of these 628 enrolled patients, 167 (27%) had ESCC that expressed PD-L1 with a CPS ≥10. Of these 167 patients, 85 were randomized to pembrolizumab and 82 to the investigator's treatment of choice (paclitaxel [n=50], docetaxel [n=19], or irinotecan [n=13]). Most patients were Asian (68%) and had distant metastasis of disease (90%). The result showed a significant improvement in the primary endpoint overall survival (OS) in patients randomized to pembrolizumab as compared with chemotherapy (10.3 months versus 6.7 months, hazard ratio [HR] 0.62; 95% confidence interval [CI]: 0.46 to 0.90). Improved ORR was also observed in the pembrolizumab arm (22% versus 7%) (Kim et al 2019). In 2020, nivolumab was approved by FDA for the treatment of patients with unresectable advanced, recurrent or metastatic ESCC after prior fluoropyrimidine- and platinum-based chemotherapy, regardless of PD-L1 expression status (nivolumab USPI 2020). In ATTRACTION-3 (NCT02569242), a multicenter, randomized (1:1), active-controlled, open-label trial, 419 patients with unresectable advanced, recurrent, or metastatic ESCC, who couldn't tolerate ≥ 1 fluoropyrimidine- and platinum-based regimen were randomized to receive either nivolumab or the investigator's choice of treatment (docetaxel: 65 patients, 31%; paclitaxel: 144 patients, 69%). Most patients (96%) were Asian. The results demonstrated a statistically significant improvement in the primary endpoint OS for patients treated with nivolumab as compared with the investigator's choice of taxane chemotherapy (10.9 months versus 8.4 months, HR, 0.77; 95% CI: 0.62 to 0.96). OS benefit was observed regardless of PD-L1 expression level (Kato et al 2019). In 2020, camrelizumab was approved by China National Medical Products Administration as second-line therapy for advanced or metastatic ESCC. In ESCORT, a multicenter, randomized, open-label, Phase 3 study, 457 patients were randomly assigned (1:1) to receive camrelizumab (200 mg intravenously administered every 2 weeks) or chemotherapy with docetaxel (75 mg/m² intravenously administered every 3 weeks) or irinotecan (180 mg/m² intravenously administered every

2 weeks). As of data cutoff on May 6, 2019, the median OS was 8.3 months (95% CI: 6.8 to 9.7) in the camrelizumab group and 6.2 months (95% CI: 5.7 to 6.9) in the chemotherapy group (HR, 0.71; 95% CI: 0.57 to 0.87; 2-sided p=0.0010) (Huang et al 2020).

Table 1: Second-Line Treatment and Outcomes for Esophageal Squamous Cell Carcinoma

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

Abbreviations: EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; NR, not reported; ORR, objective response rate; OS, overall survival; Q3W, every 3 weeks.
*Combined ESCC and EAC histology
** line of therapy not specified; all patients received prior treatment for esophageal cancer

1.3. Ociperlimab as a TIGIT Inhibitor

Ociperlimab is a humanized immunoglobulin G (IgG) 1 monoclonal antibody binding to T-cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif (ITIM) domain (TIGIT) under clinical development for the treatment of human malignancies.

TIGIT, also known as VSIG9, VSTM3, or WUCAM, is a 26 kDa type I transmembrane glycoprotein and an immune checkpoint receptor, a member of the poliovirus receptor (PVR)/nectin family that plays an important role in promoting T-cell exhaustion in both chronic viral infections and tumor escape from immune surveillance (Yu et al 2009; Boles et al 2009; Stanietsky et al 2009; Levin et al 2011; Johnston et al 2014). TIGIT was initially discovered in a genomic search for genes specifically expressed in T cells that had a protein domain that consisted of inhibitory signaling motifs. The genes and circulating DNAs (cDNAs) coding for TIGIT were cloned and characterized in mouse and human cells (Yu et al 2009). Mature human TIGIT contains 223 amino acid residues (National Center for Biotechnology Information 2022). Its extracellular domain consists of amino acid residues 1 to 120, and the transmembrane domain and cytoplasmic C-terminal tail comprises residues 121 to 223.

TIGIT-deficient mice ($TIGIT^{-/-}$) showed increased susceptibility to an experimental autoimmune model (Joller et al 2014). Natural killer (NK) cells which overexpressed TIGIT produced less interferon-gamma (IFN-γ) upon TIGIT/PVR ligation. In contrast, NK cells form TIGIT-deficient mice produced more IFN-γ in the presence of PVR-expressing target cells (Li et al 2014). Agonistic anti-TIGIT antibody could reduce the production of proinflammatory cytokines including IFN-γ and IL-17 by antigen-restimulated splenocytes and antigen-specific proliferation. Consistent with these observations, a blockade of the TIGIT pathway in vivo by TIGIT blocking antibody alone or in combination with an anti- programmed cell death protein 1 (PD-1) antibody reduced tumor growth in syngeneic mouse models (College of American Pathologist [CAP] guidelines 2018; Argast et al 2018; Dixon et al 2018). These findings strongly suggest that TIGIT is a critical immune checkpoint receptor in the maintenance of immune tolerance.

TIGIT is primarily expressed on immune cells, such as T cells, and NK cells (Manieri et al 2017). When expressed on effector T cells (cluster of differentiation [CD] 4^+ [CD4+] and $CD8^+$), activation of TIGIT has been shown to reduce cytokine production and T-cell proliferation; the reduction of cytokine production and T-cell proliferation could be rescued by TIGIT blocking antibodies or TIGIT expression knockdown (Lozano et al 2012; Joller et al 2014; Chauvin et al 2015). A similar phenomenon was also observed for NK cells (Stanietsky et al 2009; Zheng et al 2017).

TIGIT is also expressed on $FoxP3^+$ regulatory T (Treg) cells, especially in tumor tissues (Joller et al 2014; Kurtulus et al 2015). TIGIT-positive Treg cells demonstrated greater suppressive functions when compared to TIGIT-negative Treg cells, with higher expression of effector molecules, such as IL-10, granzymes, and Fgl2 (Joller et al 2014). A high TIGIT/CD226 ratio in Treg cells is associated with increased Treg frequencies in tumors and poor clinical

outcome upon immune checkpoint blockade (Fourcade et al 2018). Some studies have also shown that TIGIT suppresses immune responses mediated by dendritic cells by binding with PVR, especially in enhancement of IL-10 production and the inhibition of IL-12 production (Yu et al 2009).

As an immune "checkpoint" molecule, TIGIT initiates inhibitory signaling in immune cells when engaged by its ligands, PVR (CD155) and PVR–related 2 (PVR-L2) (CD112, or nectin-2). These ligands are primarily expressed on antigen-presenting cells and tumor cells (Casado et al 2009; Stanietsky et al 2009; Yu et al 2009; Levin et al 2011). The binding affinity of TIGIT to PVR (equilibrium dissociation constant [K_D]: approximately 1 nM) is much higher than to PVR-L2 and whether the TIGIT: PVR-L2 interaction is functionally relevant in mediating inhibitory signals remains to be determined. The co-stimulatory receptor, CD226, binds to the same ligands with lower affinity (K_D: approximately 100 nM) but delivers a positive signal and enhances cytotoxicity of T cells and NK cells (Bottino et al 2003; Stanietsky et al 2009). High affinity binding of TIGIT to PVR could compete off CD226-PVR interaction, therefore reducing T cells or NK cells activation (Stanietsky et al 2009).

The cytoplasmic tail of TIGIT has an inhibitory ITIM and an immunoreceptor tail tyrosine-like motif. In NK cells, TIGIT engagement induces the phosphorylation of tyrosine residues in its ITIM and immunoreceptor tail tyrosine-like motifs through the Src kinases Fyn and Lck. Then the phosphorylations of TIGIT would lead to binding of Grb2 and β-arrestin 2 and subsequently recruitment of SHIP-1 and SHP-2 to terminate PI3K and NK-κB signaling in the NK cells (Stanietsky et al 2009; Liu et al 2013). Engagement of agonistic TIGIT antibody induced T-cell receptor complex disruption (Stanietsky et al 2009). In addition, interaction between TIGIT and PVR on dendritic cells could lead to phosphorylation of PVR and modulation of ERK activation in dendritic cells (Yu et al 2009).

Up-regulation of TIGIT expression in tumor-infiltrating lymphocytes (TILs) has been reported in many types of cancers, such as lung (Tassi et al 2017), stomach (He et al 2017), breast (Gil Del Alcazar et al 2017; Gandara et al 2018), esophageal (Xie et al 2016), brain (Hung et al 2018), acute myeloid leukemia (Kong et al 2016), and melanoma (Mahnke and Enk 2016). Interestingly, TIGIT expression appears to be minimally expressed by peripheral effector cells while significantly up-regulated by tumor localized effector cells, which strongly suggests that the tumor microenvironment utilizes TIGIT signaling to further suppress/evade immune-mediated tumor cytotoxicity (Johnston et al 2014). Further, up-regulation of TIGIT signaling plays an important role in immune tolerance to cancer, similar to its function in the presence of chronic viral infections (Chauvin et al 2015; Yin et al 2018). The blockade of the TIGIT receptor alone or in combination with PD-1/PD-L1 blockade has been shown both in vitro and in vivo to rescue functionally "exhausted" T cells (Johnston et al 2014; Chauvin et al 2015). In mouse models, TIGIT blockade in combination with anti–PD-1/PD-L1 antibodies demonstrated significantly better antitumor efficacy than either monotherapy (Johnston et al 2014; Dixon et al 2018).

In mouse models, Fc with effector functions is critical for TIGIT antibody-mediated antitumor activity (College of American Pathologist [CAP] guidelines 2018; Argast et al 2018; Leroy et al 2018). In the CT26.WT mouse colon cancer model, anti-mouse TIGIT antibody of mIgG2a isotype (antibody-dependent cellular cytotoxicity [ADCC] enabling) demonstrated potent antitumor activity in monotherapy and in combination with anti-PD-1 antibody. In contrast,

anti-TIGIT antibody with Fc devoid of effector functions did not show any of the antitumor efficacies in the same model, indicating that Fc-mediated effector functions are required for TIGIT antibody-mediated antitumor effects. In addition, the observed efficacy was associated with an increased activity of effector T cells ($CD8^+$ and $CD4^+$) and also with Treg depletion within the tumor microenvironment. Argast and colleagues activity (CAP guidelines 2018; Argast et al 2018), also observed that effector functions were critical for TIGIT antibody-induced in vivo efficacy. Waight and colleagues (Waight et al 2018) reported that the interaction of anti-TIGIT with gamma fragment crystallizable region (Fc) receptor (FcγR) on antigen-presenting cells enhanced antigen-specific T cell responses and antitumor activity.

Taken as a whole, targeting TIGIT provides a potential mechanism to rescue immune cells (eg, T cells, NK cells, and dendritic cells) from the immunosuppressive tumor microenvironment, thereby inducing an efficient antitumor immune response. Blocking antibodies which target at the PD-1/PD-L1 pathway have achieved remarkable results in the treatment of many different tumor types. However, based upon the rate of primary and secondary resistance to PD-1 blockade, it is apparent that additional immuno-regulatory mechanism(s) underlie tumor immune escape. Indeed, research shows that the TIGIT pathway cooperates with PD-1 to maximize the suppression of effector TILs and promote resistance to anti-PD-1 therapy. Therefore, TIGIT represents an ideal target with the potential to significantly improve and/or extend the therapeutic benefit of anti-PD-1 therapy to a greater number of patients.

1.3.1. Nonclinical Experience

1.3.1.1. Pharmacology

Ociperlimab binds to the extracellular domain of human TIGIT with high specificity and affinity (equilibrium dissociation constant [K_D] = 0.135 nM), as demonstrated by target-binding assays and surface plasmon resonance (SPR) characterization. In in vitro cell-based assays, ociperlimab consistently and dose-dependently enhances the functional activities of activated human peripheral blood mononuclear cells (PBMCs). In the MC-38 mouse colon cancer model in humanized TIGIT knock-in mice, ociperlimab in combination with antimouse PD-1 enhanced the inhibition of tumor growth compared with either monotherapy.

Refer to the Ociperlimab Investigator's Brochure for detailed information regarding pharmacology studies.

1.3.1.2. Toxicology

Overall, no apparent toxicity was observed in the 13-week cynomolgus monkey or in the 4-week humanized TIGIT knock-in mouse studies. No specific tissue cross-reactivity was detected in normal human tissues. The safety profile of ociperlimab was considered adequate to support human studies.

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

1.3.2. Clinical Experience

1.3.2.1. Clinical Experience With Other TIGIT Inhibitors

To date, first-in-human Phase 1 and Phase 2 clinical studies have been initiated for 6 anti-TIGIT antibodies: MTIG7192A from Genentech/Roche (NCT02794571 and NCT03563716), BMS-986207 from Bristol-Myers Squibb (NCT02913313), MK-7684 from Merck Sharp & Dohme (NCT02964013), OMP-313M32 from OncoMed (NCT03119428), ASP8374 from Astellas/Potenza (NCT03260322), and AB-154 from Arcus (NCT03628677). The goals for these clinical studies are to evaluate the safety and efficacy of anti-TIGIT antibodies alone and/or in combination with anti-PD-1 or anti-PD-L1 antibodies.

To date, clinical data have been released for OncoMed's OMP-313M32 (Sharma et al 2018), Merck's MK-7684 (Golan et al 2018), and Genentech/Roche's tiragolumab (Bendell et al 2020; Rodriguez-Abreu et al 2020). A total of 68 patients have been treated with MK-7684 alone or MK-7684 in combination with pembrolizumab (an anti–PD-1 antibody) in a Phase 1 study sponsored by Merck Sharp & Dohme, with doses of MK-7684 ranging from 2.1 mg to 700 mg. The preliminary results showed that MK-7684 was well tolerated in the dose escalation phase of the study, with no dose-limiting toxicity (DLT). Adverse events (AEs) that occurred in > 15% of patients were fatigue (n = 5, 15%) for MK-7684 monotherapy and pruritus (n = 10, 21%) for MK-7684 and pembrolizumab combination therapy. Furthermore, only 2 treatment-related AEs ≥ Grade 3 were reported (Grade 3 anemia and Grade 3 diarrhea) for monotherapy and 5 treatment-related AEs ≥ Grade 3 were reported for combination with pembrolizumab (5 Grade 3: alanine aminotransferase [ALT] increased, colitis, Gamma-glutamyl transferase [γGT] increased, hypersensitivity, and rash maculopapular). Of the 34 evaluable patients treated with MK-7684 alone, one partial response (PR) (1/34 [3.0%]) and a 35% disease control rate (DCR) were observed. For combination of MK-7684 and pembrolizumab, 6 PRs (6/34 [18%]) and a 48% DCR were observed. In addition, pharmacokinetic (PK) findings were linear above 200 mg.

Eighteen patients have been treated with OMP-313M32 alone in a Phase 1 study sponsored by OncoMed, with doses ranging from 0.3 mg/kg to 20 mg/kg. The preliminary results showed that OMP-313M32 was well tolerated in the dose escalation phase of the study, with no DLT. Treatment-related AEs that occurred in > 15% of patients were rash (n = 5; 27.8%), fatigue (n = 3, 16.7%), nausea (n = 3, 16.7%), and pruritus (n = 3, 16.7%) for OMP-313M32 monotherapy. Grade ≥ 3 treatment-related AEs included rash (n = 3, 16.7%), fatigue (n = 1, 5.6%), hypophosphatemia (n = 1, 5.6%), and autoimmune hepatitis (n = 1, 5.6%). Based upon the safety profile of OMP-313M32 monotherapy, OncoMed has initiated the dose expansion with the combination of OMP-313M32 and nivolumab (an anti–PD-1 antibody) in patients with non-small cell lung, head and neck, esophageal, gastric, cervical, triple negative breast, anal, and hepatocellular cancers or with microsatellite instability-high tumors (NCT03119428).

The Phase 1 data for tiragolumab was released at the 2020 American Association of Cancer Research meeting (Bendell et al 2020). No objective responses occurred in 24 patients treated with tiragolumab monotherapy in Phase 1a. However, in Phase 1b, 5 of 44 patients (11.4%) treated with tiragolumab combined with atezolizumab had achieved PR (Bendell et al 2020). In the Phase 1a (tiragolumab monotherapy) cohort, there were no Grade 3-5 immune-mediated AEs (imAEs). Grade 1-2 imAEs included infusion-related reaction (n = 2, 8%), rash (n = 2, 8%),

hepatitis (n = 1, 4%), and pancreatitis (n = 1, 4%). In the Phase 1b (tiragolumab combined with atezolizumab) cohort, 4% of patients experienced Grade 3-5 imAEs; no Grade 5 imAEs were associated with tiragolumab and/or atezolizumab. These imAEs included infusion-related reaction (n = 4, 8%), rash (n = 14, 29%), hepatitis (n = 10, 20%), pancreatitis (n = 1, 2%), hyperthyroidism (n = 4, 8%), hypothyroidism (n = 3, 6%), and anemia (n = 1, 2%).

A total of 135 patients with previously untreated PD-L1–selected non-small cell lung cancer (NSCLC) were treated with tiragolumab 600 mg by intravenous infusion once every 3 weeks plus atezolizumab 1200 mg by intravenous infusion once every 3 weeks (n = 67) or atezolizumab 1200 mg by intravenous infusion once every 3 weeks plus placebo by intravenous infusion once every 3 weeks (n = 68) in a Phase 2 study (CITYSCAPE) sponsored by Genentech/Roche. Patients were randomly assigned to 1 of these treatment groups and were stratified by tumor proportion score (TPS) (1% to 49% or ≥ 50%), histology (squamous versus nonsquamous), and tobacco use (yes or no). Preliminary efficacy results showed a clinically meaningful improvement in ORR and PFS in patients treated with tiragolumab plus atezolizumab (ORR, 31%; PFS, 5.42 months) compared with those treated with atezolizumab plus placebo (ORR, 16%; PFS, 3.58 months). This improvement was still observed 6 months later: tiragolumab plus atezolizumab (ORR, 37%; PFS, 5.55 months) compared with atezolizumab plus placebo (ORR, 21%; PFS, 3.88 months). In addition, analysis at this 6-month follow-up timepoint showed a greater improvement in ORR in patients in the PD-L1 TPS ≥ 50% subgroup who received tiragolumab plus atezolizumab (ORR, 66%) compared with atezolizumab plus placebo (ORR, 24%). Preliminary safety results showed that study treatment with tiragolumab plus atezolizumab was well tolerated; results were generally similar between the 2 treatment groups. More patients in the tiragolumab plus atezolizumab group experienced imAEs compared with those in the atezolizumab plus placebo group (46 [69%] versus 32 [47%]); most imAEs were Grade 1 or Grade 2 events of infusion-related reaction and rash and were manageable. Based on these observed efficacy and safety results, Genentech/Roche is conducting an ongoing Phase 3 study (SKYSCRAPER-01) in first-line PD-L1 TPS ≥ 50% NSCLC (NCT04294810).

All of these findings support further development of anti-TIGIT antibody in combination with existing therapeutic modalities.

1.3.2.2. Preliminary Safety Profile

As of 28 July 2021, 6 studies with ociperlimab are ongoing and 3 studies have been planned (Ociperlimab Investigator's Brochure). Of the 6 ongoing studies, 2 (AdvanTIG-105 and AdvanTIG-202) have preliminary data available. For more detailed information on ociperlimab safety and efficacy data refer to the most recent edition of the Ociperlimab Investigator's Brochure.

A pooled analysis of monotherapy and combination therapies was conducted to provide a comprehensive safety assessment. As of the data cutoff date of 28 July 2021, a total of 133 patients received ociperlimab treatment in Study AdvanTIG-105 and Study AdvanTIG-202.

An overview of TEAEs, including serious TEAEs, TEAEs leading to discontinuation of ociperlimab, and TEAEs leading to death, is shown in Table 2.

Overall, of the 133 patients in the Safety Analysis Set, 117 (88%) experienced ≥ 1 TEAE and 77 patients (57.9%) experienced ≥ 1 TEAE related to ociperlimab. TEAEs ≥ Grade 3 in severity

were experienced by 53 of 133 patients (39.8%), and 8 patients (6.0%) experienced ≥ Grade 3 TEAE related to ociperlimab. Forty-seven patients (35.3%) had serious TEAEs, 7 (5.3%) of these were considered related to ociperlimab. Nine patients (6.8%) experienced TEAEs that led to discontinuation of ociperlimab. Six patients (4.5%) experienced TEAEs that led to death, but none of them were assessed as related to ociperlimab. No TEAEs were considered to be DLTs.

Table 2: Overview of Treatment-Emergent Adverse Events (Safety Analysis Set)

	Ociperlimab Monotherapy (N = 9) n (%)	Ociperlimab + Tislelizumab (N = 99) n (%)	Ociperlimab + Tislelizumab + Chemotherapy (N = 25) n (%)	Total (N = 133) n (%)
Patients with any TEAE	8 (88.9)	88 (88.9)	21 (84.0)	117 (88.0)
Related to Ociperlimab	7 (77.8)	57 (57.6)	13 (52.0)	77 (57.9)
≥ Grade 3 TEAE	4 (44.4)	38 (38.4)	11 (44.0)	53 (39.8)
Related to Ociperlimab	1 (11.1)	5 (5.1)	2 (8.0)	8 (6.0)
Serious TEAE	4 (44.4)	33 (33.3)	10 (40.0)	47 (35.3)
Related to Ociperlimab	0 (0.0)	6 (6.1)	1 (4.0)	7 (5.3)
TEAE Leading to Discontinuation of Ociperlimab	1 (11.1)	7 (7.1)	1 (4.0)	9 (6.8)
Related to Ociperlimab	0 (0.0)	1 (1.0)	1 (4.0)	2 (1.5)
TEAE Leading to Death	2 (22.2)	2 (2.0)	2 (8.0)	6 (4.5)
Related to Ociperlimab	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dose-Limiting Toxicity Event	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Ociperlimab Investigator's Brochure.
Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event.
Note: A patient with multiple occurrences of an AE is counted only once in the AE category.

1.3.2.3. Clinical Pharmacology

Preliminary pharmacokinetic (PK) data are available from a total of 51 patients treated with ociperlimab at 50-, 150-, 450-, 900-, and 1800-mg dose levels in combination with tislelizumab at 200 mg in the dose-escalation and dose-verification portions of Study AdvanTIG-105. In Cycle 1, ociperlimab exposures (AUC and C_{max}) increased approximately dose proportionally from the 50 mg to the 1800 mg dose. Across dose groups, serum concentrations of ociperlimab decreased in a biexponential manner after administration. The mean elimination half-life ranged from 7.1 to 10.5 days. Postdose PK sampling duration may not be sufficient for robust characterization of elimination half-life using noncompartmental analysis (NCA); hence, the reported half-life values should be interpreted with caution.

Peripheral TIGIT receptor occupancy data were available for 32 enrolled patients treated with ociperlimab at 50-, 150-, 450-, 900-, and 1800-mg dose levels in Study AdvanTIG-105. Complete TIGIT receptor occupancy (100%) at all tested dose levels was observed on $CD8^+$, $CD4^+$, and regulatory T cells in peripheral blood.

Refer to the Ociperlimab Investigator's Brochure for detailed information on ociperlimab clinical PK and pharmacodynamics.

1.3.2.4. Efficacy

Preliminary efficacy data for ociperlimab are available from Study AdvanTIG-105, which is a Phase 1/1b study of ociperlimab in combination with tislelizumab with or without chemotherapy in patients with unresectable locally advanced or metastatic solid tumors. The ociperlimab dose of 900 mg once every 3 weeks combined with tislelizumab 200 mg once every 3 weeks was selected as the recommended Phase 2 dose (RP2D) for further investigation based on data from the ongoing Phase 1/1b Study AdvanTIG-105.

Refer to Ociperlimab Investigator's Brochure further details on the efficacy of ociperlimab.

1.4. Tislelizumab as a PD-1 Inhibitor

1.4.1. Pharmacology

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

Tislelizumab acts by binding to the extracellular domain of human PD-1 with high specificity as well as high affinity (dissociation constant [K_D] = 0.15 nM). It competitively blocks binding efforts by both 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 PBMC. Tislelizumab has demonstrated in-vivo antitumor activity in several allogeneic xenograft models, in which PBMC 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 with low affinity to FcγRs such as FcγRI and FcγRIIIA, and complement 1q (C1q), a subunit of complement 1. In vitro assays with tislelizumab suggest either low or no ADCC, antibody-dependent cellular phagocytosis, or complement-dependent cytotoxicity effects in humans (Labrijn et al 2009). 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 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 single-dosing regimens spanned from the intended human doses to 10-fold higher than the maximum of the intended human doses, and the repeated-dosing regimens spanned to 3-fold higher than the maximum of the intended human dose. The cynomolgus monkey was the only relevant species based on the target sequence homology and binding activity.

Overall, no apparent toxicity was noted in mouse 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 NOAEL 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-A1217-203.

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

1.4.3. Clinical Pharmacology

Based on pooled data from 2596 patients across 12 clinical studies, 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 C_{max} and AUC increased in a nearly dose-proportional manner from 0.5 mg/kg to 10 mg/kg. The terminal half-life ($t_{1/2}$) was estimated to be approximately 23.8 days, and the steady state is expected to be reached in 12 weeks.

Refer to the Tislelizumab Investigator's Brochure for more detailed information on the clinical pharmacology of tislelizumab

1.4.4. Prior Clinical Experience of Tislelizumab

As of 20 May 2021, 33 studies with tislelizumab are ongoing and 9 studies have been completed. Of these, 15 studies have preliminary data available in the Investigator's Brochure Edition 9.0, 20 October 2021: 6 monotherapy studies, 2 chemotherapy combination therapy studies, and 7 investigational agent combination therapy studies.

Refer to the Tislelizumab Investigator's Brochure 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 monotherapy studies was conducted to provide a comprehensive safety assessment separate from combination therapy. Data from patients with solid tumors were analyzed separately from patients with hematologic malignancies.

As of May 2021, data are available from patients treated in 7 pooled solid tumor monotherapy studies (Tislelizumab Investigator's Brochure).

For monotherapy, the safety profile of tislelizumab was considered adequate, and tislelizumab was well tolerated. In pooled solid tumor studies, the majority of AEs were Grade 1 or 2, and most ≥ Grade 3 TEAEs were assessed as unrelated to tislelizumab. Adverse events were generally reversible and manageable. The percentage of patients with ≥ Grade 3 immune-mediated adverse events (imAEs), ≥ Grade 3 infusion-related AEs, and TEAEs leading to tislelizumab discontinuation was small.

The data collected shows that tislelizumab monotherapy has an adequate safety profile. The safety profile for single-agent tislelizumab is similar to that observed with other PD-1 inhibitors in solid tumors.

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

1.4.4.2. Efficacy Assessment of Tislelizumab

Efficacy data are available from 6 monotherapy studies and 8 combination therapy studies. Among these 14 studies, 12 studies were in patients with solid tumors, and 2 studies were in patients with hematologic malignancies.

The data collected show that tislelizumab monotherapy can result in antitumor activity across a variety of tumor types, and the antitumor activity has been observed across the dose ranges evaluated in patients.

Please refer to the Tislelizumab Investigator's Brochure for detailed efficacy information.

1.5. Study Rationale

As described earlier, despite the wealth of evidence supporting the role of TIGIT in promoting tumor immune tolerance, TIGIT blockade alone (ie, ociperlimab monotherapy) is unlikely to result in an effective antitumor response according to existing anti-TIGIT clinical data (see Section 1.3). Therefore, the clinical development of ociperlimab focuses on rational combinations, such as with tislelizumab. Taking this into account, the combinations of ociperlimab plus tislelizumab and tislelizumab plus placebo are designed to evaluate the effect of combining ociperlimab with tislelizumab to maximize the patient's potential therapeutic benefit while simultaneously achieving the clinical objective of characterizing the safety and efficacy of ociperlimab combined with tislelizumab.

1.5.1. Rationale for Dose Selection

1.5.1.1. Rationale for the Selection of Ociperlimab Dose in Combination with Tislelizumab

The ociperlimab dose of 900 mg once every 3 weeks combined with tislelizumab 200 mg once every 3 weeks was selected as the RP2D for further investigation based on clinical safety, tolerability, PK, and pharmacodynamic data from the ongoing Phase 1/1b Study AdvanTIG-105.

Complete TIGIT receptor occupancy was observed in circulating T cells in peripheral blood at all the tested doses of ociperlimab in Study AdvanTIG-105. However, the correlation between TIGIT receptor occupancy in the periphery and in tumor tissues is unknown. In a previous Phase 1 study of tiragolumab, another anti-TIGIT antibody, complete peripheral receptor occupancy was reached at the 30 mg dose level, but the clinical dose of 600 mg was determined as the RP2D, which was 20 times the 30 mg dose (Bendell et al 2020). Similarly, although complete peripheral receptor occupancy was observed at the 50 mg dose level of ociperlimab, the RP2D of 900 mg is approximately 20 times the dose of 50 mg, to ensure sufficient TIGIT occupancy in the tumor tissue.

As of February 2021, a total of 3 patients were assessed to have a confirmed PR, 1 patient each in the 450 mg, 900 mg, and 1800 mg cohorts. Ociperlimab exposure in all 3 patients with a PR is consistent with that expected at the 900 mg dose level. The confirmed disease control rates observed in the 450 mg, 900 mg, and 1800 mg cohorts were 60% (3 of 5 patients), 64.3% (9 of 14 patients), and 60% (3 of 5 patients), respectively.

Although the best overall response rate and disease control rate were numerically comparable at the 450 mg and 900 mg dose levels, the 900 mg dose was chosen as the RP2D for the following reasons:

- 900 mg was well tolerated in patients enrolled in Study AdvanTIG-105
- Exposure in all 3 patients with a PR was consistent with that expected at the 900 mg dose
- Lack of sufficient information on the impact of immunogenicity on ociperlimab PK
- An overall intent to minimize exposure overlap with doses < 450 mg.

1.5.1.2. Rationale for the Selection of Tislelizumab Dose

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

- All dosages tested, including 200 mg once every 3 weeks, were tolerated. The maximum tolerated dose was not reached with dosages up to 10 mg/kg once every 2 weeks. The observed serum concentration after 200 mg dosing was within the range seen after 2 mg/kg and 5 mg/kg dosing.
- Preliminary clinical activity was observed at this dosage.
- Exposure-response relationships were flat for ORR and safety endpoints across a variety of tumor types (data from Studies BGB-A317_Study_001, BGB-A317-102, BGB-A317-203, and BGB-A317-204). In addition, population PK analysis based on 2596 cancer patients demonstrated that no covariates had clinically relevant effect on tislelizumab PK, suggesting no dose modification is needed based on patient demographics and characteristics.
- Compared with doses based on patient weight, a fixed dose simplifies dose administration and reduces the chance of medical errors.
- Compared with a once every 2 weeks schedule, a once every 3 weeks schedule allows for more convenient integration with common chemotherapeutic regimens and increases patient convenience.

1.5.2. Rationale for Combination of Ociperlimab and Tislelizumab as Second-Line Treatment in Unresectable, Locally Advanced, Recurrent or Metastatic ESCC

Esophageal cancer is the seventh most common cancer worldwide and the sixth most common cause of death from cancer. The highest incidence area spans from northern Iran through the Central Asian republics and into northern China. The most common histologic type of esophageal cancer is ESCC, which is even more common in Eastern Europe and Asia. More than two-thirds of patients diagnosed with esophageal cancer will have advanced or metastatic disease, with a median survival of 8 to 10 months and an expected 5-year survival rate < 5%. These data, combined with the relative lack of highly effective treatment, are indicative of the large unmet medical need in patients diagnosed with esophageal cancer.

Anti-PD-1 therapies have shown superior efficacy compared with chemotherapy as the second-line treatment of ESCC. In KEYNOTE-181 trial that enrolled 628 patients with recurrent locally advanced or metastatic esophageal cancer who progressed on or after one prior line of systemic treatment for advanced disease, a significant improvement was observed in the primary endpoint OS in patients treated with pembrolizumab as compared with chemotherapy (10.3 months versus 6.7 months, HR, 0.62; 95% CI: 0.46 to 0.90). In ATTRACTION-3 trial that enrolled 419 patients with unresectable advanced, recurrent, or metastatic ESCC, who were refractory or intolerant to ≥ 1 fluoropyrimidine-and platinum-based regimen, a significant improvement was reported in the primary endpoint OS for patients treated with nivolumab as compared with the investigator's choice of taxane chemotherapy (10.9 months versus 8.4 months; HR, 0.77; 95% CI: 0.62 to 0.96). OS benefit was observed regardless of PD-L1 expression level. Potential efficacy was also observed in ESCC treated with tislelizumab. BGB-A317_Study_001 and BGB-A317-102 showed potential efficacy of tislelizumab in esophageal cancer as mentioned above. The efficacy of tislelizumab in ESCC is under further investigation in Study BGB-A317-302, a randomized, controlled, open-label, global Phase 3 study comparing the efficacy of tislelizumab versus chemotherapy as second-line treatment in patients with advanced unresectable/metastatic ESCC.

As described earlier, targeting TIGIT provides a potential mechanism to rescue immune cells from the immunosuppressive tumor microenvironment, thereby inducing an efficient antitumor immune response. Research shows that the TIGIT pathway cooperates with PD-1 to maximize the suppression of effector TILs as well as promote resistance to anti-PD-1 therapy. Blocking antibodies targeting the PD-1/PD-L1 pathway have achieved remarkable results in the treatment of ESCC as mentioned above. Therefore, TIGIT represents an ideal target with the potential to significantly improve and/or extend the therapeutic benefit of anti-PD-1 therapy in ESCC.

Given the promising anti-tumor activity of anti-PD-1 antibodies reported in ESCC and given the scientific rationale that TIGIT may improve the therapeutic benefit of anti-PD-1 therapy, the combination of ociperlimab and tislelizumab may bring significant clinical benefit in this indication and support further clinical development.

1.5.3. Biomarker Strategy Rationale

Biomarker analyses including but not limited to PD-L1 expression, TIGIT pathway molecules, gene expression profiling (GEP), tumor mutations, and tumor infiltration immune cells will be

performed to explore the association with patient prognosis, response, and potential resistance to tislelizumab plus ociperlimab and tislelizumab plus placebo.

PD-L1 was expressed in tumor and tumor-infiltrating immune cells in ESCC, and its expression level was shown to be correlated with clinical efficacy of anti-PD-1 treatment in multiple studies (KEYNOTE-181, ATTRACTION-3). The potential predictive role of PD-L1 in checkpoint blockade was first reported in KEYNOTE-181 study, in which the HR for OS in patients with ESCC whose tumors expressed PD-L1 CPS ≥10 was 0.64 (95% CI: 0.46 to 0.90), and the median OS was 10.3 months (95% CI: 7.0 to 13.5) and 6.7 months (95% CI: 4.8 to 8.6) in the pembrolizumab and control arms, respectively. Clinical efficacy in PD-L1 positive (PD-L1+) patients was superior to PD-L1 negative (PD-L1-) patients. Although the predictive role of PD-L1 in combination treatment of anti-PD-1 and anti-TIGIT with esophageal squamous cell carcinoma is still not clear, there is a hint based on CITYSCAPE study which compares atezolizumab (anti-PD-L1) plus tiragolumab (anti-TIGIT) with atezolizumab alone in NSCLC patients. It was reported that only patients with high PD-L1 levels showed better ORR in combination therapy than monotherapy, suggesting PD-L1 is probably a predictive biomarker for PD-1 and TIGIT pathway co-targeting treatment. Here in this study, another PD-L1 score algorithm, named Tumor Area Positivity (TAP) score (previously known as visually estimated CPS [vCPS] in the original protocol) will be assessed centrally and its predictive role will be assessed in patients treated with tislelizumab plus ociperlimab and tislelizumab plus placebo.

In addition to PD-L1, high TIGIT/CD226 ratio on Treg cells correlated with poor clinical outcome upon anti-PD1 or anti-PD-L1 antibody treatment in melanoma patients, which suggest signaling through TIGIT pathway in tumor tissues might contribute to resistance to current immune checkpoint inhibitors targeting PD-1 or PD-L1 (Fourcade et al 2018). Furthermore, clinical data from various studies suggested tumor mutational burden, abundance and location of TILs and immune related gene expression profile are a few factors associated with response to immunotherapies including anti-PD-1 antibodies in different cancers (Vilain et al 2017; Goodman et al 2017; Gandara et al 2018; Jiang et al 2018). Therefore, expression of TIGIT pathway molecules (eg, TIGIT, CD226, CD155, CD112), as well as tumor mutation, TILs and GEP will be studied to explore the relationship with clinical response to tislelizumab plus ociperlimab and tislelizumab plus placebo, and to explore potential predictive biomarkers.

Beside biomarkers, mechanisms of resistance to immunotherapy are also not well understood and need more exploration. Identification tumor and immune-mediated features that are associated with PD or acquired resistance to ociperlimab and tislelizumab might increase our understanding of disease pathobiology and collecting biological evidence for combination strategies.

1.6. Benefit-Risk Assessment

Patients with unresectable, locally advanced, recurrent or metastatic ESCC whose disease progressed on first-line chemotherapy represent a population with a great unmet medical need. Anti-PD-1 therapies such as pembrolizumab and nivolumab have shown superior efficacy compared with chemotherapy as the second-line treatment of ESCC. Tislelizumab has been approved in China by the National Medical Products Administration (NMPA) for second-line treatment of patients with ESCC whose disease progressed after chemotherapy.

The safety profile of tislelizumab monotherapy is considered as acceptable based on previous nonclinical and clinical data. Ociperlimab combined with tislelizumab 200 mg once every 3 weeks is safe and well-tolerated, with no DLTs, no treatment related SAEs, or high-grade AEs occurred during the treatment period for each dose level in the ongoing Study AdvanTIG-105 Phase 1/1b study as of 28 July 2021.

Given the unmet medical need and limited treatment options in this indication, the benefit/risk assessment, based on the available safety data of anti-TIGIT monoclonal antibodies in combination of anti-PD-1/PD-L1 antibodies and the available efficacy data from the PD-1 antibodies in this indication, the combination of tislelizumab and ociperlimab is considered favorable. This Phase 2 study will be conducted in order to compare the potential benefit and safety of tislelizumab plus ociperlimab and tislelizumab plus placebo.

1.7. Study Conduct

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

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objectives

- To compare the objective response rate (ORR), as assessed by the investigator according to RECIST v1.1, of tislelizumab plus ociperlimab with tislelizumab plus placebo as second-line treatment in patients with PD-L1 TAP ≥ 10% unresectable, locally advanced, recurrent or metastatic ESCC in the Intent-to-Treat (ITT) Analysis Set.

2.1.2. Secondary Objectives

- To compare the overall survival (OS) of tislelizumab plus ociperlimab with tislelizumab plus placebo as second-line treatment in patients with PD-L1 TAP ≥ 10% ESCC in the ITT Analysis Set.
- To compare the following endpoints between tislelizumab plus ociperlimab and tislelizumab plus placebo based on tumor assessments per RECIST v1.1:
  - Progression-free survival (PFS) assessed by both Independent Review Committee (IRC) and the investigator.
  - Duration of response (DOR), DCR, and clinical benefit rate (CBR) assessed by both the IRC and the investigator.
  - ORR assessed by the IRC.
- To compare the safety and tolerability between tislelizumab plus ociperlimab and tislelizumab plus placebo.
- To compare the health-related quality of life (HRQoL) via cancer-specific patient-reported outcomes (PROs) between tislelizumab plus ociperlimab and tislelizumab plus placebo.

2.1.3. Exploratory Objectives

- To evaluate the potential association of biomarkers with patient prognosis, response or resistance to tislelizumab plus ociperlimab and tislelizumab plus placebo.
- To characterize the PK of ociperlimab and tislelizumab.
- To assess host immunogenicity to ociperlimab and tislelizumab.
- To compare the quality of life (QoL) via a generic PRO between tislelizumab plus ociperlimab and tislelizumab plus placebo.

2.2. Study Endpoints

2.2.1. Primary Endpoints

- ORR, defined as the proportion of patients who have confirmed CR or PR by the investigator's review per RECIST v1.1 in the ITT Analysis Set.

2.2.2. Secondary Endpoints

- OS, defined as the time from the date of randomization until the date of death due to any cause in all randomized patients in the ITT Analysis Set.
- ORR, defined as above and assessed by the IRC per RECIST v1.1 in the ITT Analysis Set.
- PFS, defined as the time from the date of randomization to the date of first documentation of PD assessed by both the IRC and the investigator per RECIST v1.1 or death, whichever occurs first in the ITT Analysis Set.
- DOR, defined as the time from the first determination of an objective response until the first documentation of PD as assessed by both the IRC and the investigator per RECIST v1.1, or death, whichever comes first in the ITT Analysis Set.
- DCR, defined as the proportion of patients who have confirmed CR, confirmed PR, and stable disease assessed by both the IRC and the investigator per RECIST v1.1 in the ITT Analysis Set.
- CBR, defined as the proportion of patients who achieve confirmed CR, confirmed PR, and durable stable disease (stable disease ≥ 24 weeks).
- HRQoL, assessed by the scores of Global Health Status (GHS)/QoL and Physical Function of European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and scores of Dysphagia, Eating, Reflux and Pain scales of EORTC Quality of Life Oesophageal Cancer Questionnaires 18 (QLQ-OES18).
- AEs and SAEs as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Event [NCI-CTCAE] version 5.0 [v5.0]), timing, seriousness, and relationship to study drugs, physical examinations, electrocardiograms (ECGs), and laboratory assessments.

2.2.3. Exploratory Endpoints

- Evaluate status of exploratory biomarkers including but not limited to expression of TIGIT, CD226, CD155, CD112 and PD-L1, GEP, tumor mutation burden (TMB)/gene mutation/microsatellite instability (MSI), tumor infiltrating immune cells in archival and/or fresh tumor tissue and blood before and after study treatment or at PD/reoccurrence, and the association between these biomarkers and clinical efficacy, disease status, and resistance.
- Serum ociperlimab and tislelizumab concentrations at specified timepoints.
- Immunogenic responses to ociperlimab and tislelizumab, evaluated through the detection of ADAs.
- QoL, defined as assessment of the European Quality of Life 5-Dimensional 5-Level (EQ-5D-5L) and visual analog scale (VAS) in the ITT Analysis Set.

3. STUDY DESIGN

3.1. Summary of Study Design

This is a multicenter, randomized, investigator- and patient-blinded, sponsor-unblinded, placebo-controlled global Phase 2 study in which ORR are measured to compare the efficacy of anti-PD-1 monoclonal antibody tislelizumab (BGB-A317) plus anti-TIGIT monoclonal antibody ociperlimab versus tislelizumab plus placebo as second-line treatment in patients with PD-L1 TAP ≥ 10% unresectable, locally advanced, recurrent or metastatic ESCC.

After providing written informed consent, completing all prescreening and screening assessments, and being confirmed as eligible for study participation, approximately 120 patients will be randomized at a 1:1 ratio to receive 1 of the following treatment regimens:

- Arm A: tislelizumab + ociperlimab
- Arm B: tislelizumab + placebo

Eligible patients will be stratified by the following factors:

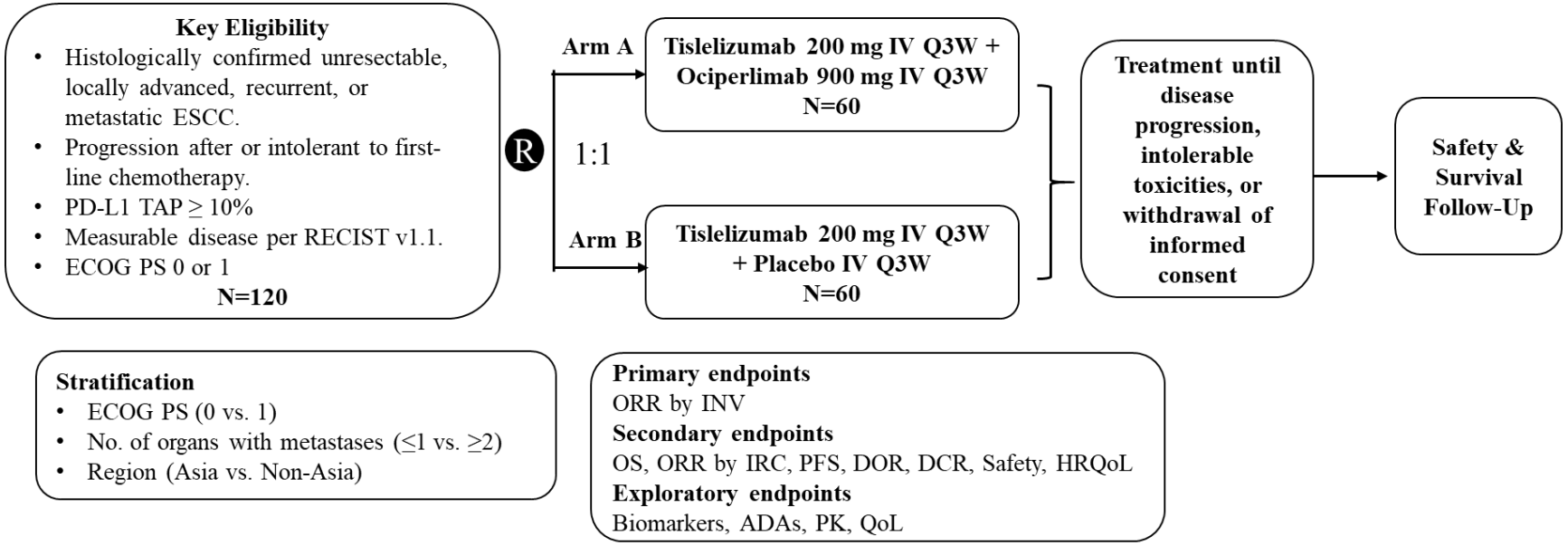
- ECOG PS score (0 versus 1)
- Number of organs with metastases (≤1 versus ≥2)
- Region (Asia versus non-Asia)

Study drugs (including placebo) will be administered until PD per RECIST v1.1, unacceptable toxicity, or withdrawal of informed consent, whichever occurs first.

No crossover between Arm A and Arm B will be allowed.

The study design schema is in Figure 1.

Figure 1: Study Schema



Abbreviations: ADA, antidrug antibody; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ESCC, esophageal squamous cell carcinoma; HRQoL, Health Related Quality of Life; INV, investigator; IRC, Independent Review Committee; IV, intravenously; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death protein-ligand 1 (PD-L1); PFS, progression-free survival; PK, pharmacokinetics; Q3W, once every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TAP; Tumor Area Positivity.
Note: The initial infusion (Cycle 1 and Cycle 2, Day 1) will be administered over a period of 60 minutes. If this infusion is well tolerated, subsequent infusions may be administered over 30 minutes. After infusion, patients will be further monitored for at least 1 hour during Cycles 1 and 2. From Cycle 3 onward, a postinfusion monitoring period of at least 30 minutes will be required.
At the discretion of the investigator, patients may continue tislelizumab and ociperlimab or tislelizumab alone after PD under protocol defined conditions.

3.2. Prescreening Period

All patients regardless of PD-L1 expression status are required to provide tumor tissues for central confirmation of PD-L1 expression during the prescreening period (defined as ≤ 56 days before randomization). A separate prescreening informed consent must be obtained.

Patients must submit qualified archival tumor tissue (formalin-fixed paraffin-embedded [FFPE] block containing tumor [preferred] or approximately 15 [≥ 6] unstained slides) with an associated pathology report, or agree to a tumor biopsy for determination of PD-L1 expression and other exploratory biomarker analyses (fresh tumor biopsies are strongly recommended at baseline in patients who have readily accessible tumor lesions and who consent to the biopsies) (Section 7.8). If no archival samples are available, a fresh tumor biopsy at baseline is mandatory.

3.3. Screening Period

Screening evaluations will be performed within 28 days before randomization. Patients whose tumors express PD-L1 TAP ≥ 10% in prescreening period and agree to participate in this study will sign the informed consent form (ICF) before 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.

3.4. Treatment Period

After providing written informed consent, completing all prescreening and screening assessments, and being confirmed as eligible for study participation, approximately 120 patients will be randomized at a 1:1 ratio to receive 1 of the following treatment regimens:

- Arm A: tislelizumab 200 mg + ociperlimab 900 mg intravenously once every 3 weeks until PD assessed by the investigator per RECIST v1.1, unacceptable toxicity, or withdrawal of informed consent, whichever should occur first.
- Arm B: tislelizumab 200 mg + placebo intravenously once every 3 weeks until PD assessed by the investigator per RECIST v1.1, unacceptable toxicity, or withdrawal of informed consent, whichever should occur first.

No crossover between Arm A and Arm B will be allowed.

Eligible patients will be stratified by the following factors:

- ECOG PS (0 versus 1)
- Number of organs with metastases (≤1 versus ≥2)
- Region (Asia versus non-Asia)

Tumor imaging will be performed at baseline (≤ 28 days before randomization). During the study, tumor imaging will be performed approximately every 6 weeks (± 7 days) for the first 54 weeks and every 12 weeks (± 7 days) thereafter.

Patients who discontinue the study treatment for reasons other than radiographic PD (eg, toxicity) will continue with the scheduled tumor assessments until radiographic PD per

RECIST v1.1, withdrawal of consent, loss to follow-up, study termination by sponsor, start of a new anticancer therapy, or death, whichever occurs first.

Response will be assessed using RECIST v1.1. If a patient can continue to benefit from study drugs after PD per RECIST v1.1, the patient may continue the study treatment at the investigator's discretion. The following criteria must be met in order to treat patients who may continue to benefit from study treatment after PD:

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

The decision to continue study drugs after initial PD must be agreed to by the medical monitor and documented in the study records. Patients who receive study treatment after PD will undergo tumor assessments according to the original schedule until study treatment discontinuation.

PROs will be collected using EORTC QLQ-C30, EORTC QLQ-OES18, and EQ-5D-5L questionnaires (provided in Appendix 8, Appendix 9, and Appendix 10, respectively) before dosing on Day 1 of every other treatment cycle during the first 54 weeks, Day 1 of every 4 cycles thereafter, and at the on-site Safety Follow-up Visit (defined in Section 3.5).

To determine the PK properties of tislelizumab and ociperlimab, and host immunogenic response to tislelizumab and ociperlimab, blood samples will be collected at various timepoints as outlined in Appendix 1.

An optional blood sample will be taken at baseline (predose on Day 1 of Cycle 1), at the time of first tumor response (predose on Day 1 of the following cycle) and at the End of Treatment (EOT) Visit after PD (10 mL each timepoint) for all randomized patients to explore the association of blood-based biomarkers with response, prognosis, and resistance to tislelizumab in combination with ociperlimab/placebo.

Safety will be assessed throughout the study by monitoring AEs, SAEs (toxicity grades assigned per NCI-CTCAE v5.0), and laboratory results. Vital signs, physical examinations, ECOG PS change, ECG results, and other examinations will also be used for safety assessments. Safety assessments are further detailed in Section 7.5 and the Schedule of Assessments (Appendix 1).

3.5. End of Treatment/Safety Follow-up

The EOT Visit is conducted when the investigator determines that study drugs will no longer be used. If routine laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the EOT Visit, these tests need not be repeated. Tumor assessment is not required at the EOT Visit, and should follow the regular schedule of assessment in Appendix 1.

Patients who discontinue from study treatment for any reason will be asked to return to the clinic for the EOT Visit, which must be conducted within 7 days of the EOT decision is made unless

otherwise specified or before the initiation of a new anticancer treatment, whichever occurs first. An on-site Safety Follow-up Visit at 30 days (± 7 days) after last dose of study drugs is required. If the time windows of this Safety Follow-up Visit and EOT Visit are overlapped, this safety follow-up visit can be exempted and the tests required at the on-site Safety Follow-up Visit will be conducted at the EOT Visit.

Additional Safety Follow-up Visits at 60, 90, and 120 days (this visit is only required for women of childbearing potential) can be required (in clinic or over the phone, as needed based on assessments required). Patients will be contacted by telephone to assess imAEs and relevant concomitant medications (ie, those associated with an imAE or any new anticancer therapy). These contacts should be made at 60 days (± 14 days) and 90 days (± 14 days) after the last dose of study treatment, regardless of whether the patient starts a new anticancer therapy. For women of childbearing potential (see Appendix 6), an additional visit to perform a pregnancy test will occur at approximately 120 days after the last dose of study treatment. If a patient reports a suspected imAE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated.

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

Patients who discontinue from study treatment before PD will need to undergo tumor assessments as outlined in Section 7.6.

If clinically feasible, it is highly recommended to obtain a tumor biopsy from accessible tumor sites at the EOT Visit for patients with confirmed PD during the study (see Section 7.8).

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

3.6. Survival Follow-up

Patients will be followed for survival and further anticancer therapy information after discontinuation of study treatment (for reasons other than PD [eg, toxicity] or death) via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (± 14 days) after the last 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.

3.7. Discontinuation From the Study Treatment or From the Study

3.7.1. 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 study treatment at any time. Patients who discontinue from study treatment for reasons other than PD should be followed for an assessment of antitumor activity (Section 7.6), safety (Section 7.5) and survival (Section 3.6), if possible.

If the decision to discontinue from study treatment is made, both study drugs should be discontinued.

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

- Radiographic PD per RECIST v1.1
- 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 (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents [including Chinese (or other country) herbal medicine and Chinese (or other country) patent medicines] for the treatment of cancer) (Section 6.3)
- 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 if they are consistently noncompliant.

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

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

- Patient withdrawal of consent
- Death
- Loss to follow up
- Patients have completed all study assessments

3.8. 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 dies, withdraws consent, completes all study assessments, or is lost to follow up. 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 (within 7 days).

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.

At the end of study, any patients who, in the opinion of the investigator, continue to benefit from study drugs at study termination, will be offered the option to continue the study drug(s) in a company-sponsored clinical trial (if available in that patient's country) or patient supply treatment program until it is commercially available in the country of the patient's residence.

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

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- GCP noncompliance
- Study activity is completed (ie, all patients have completed all scheduled study procedures and all obligations have been fulfilled.)

4. STUDY POPULATION

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

4.1. Inclusion Criteria

Each patient eligible to participate in this study must meet all 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. Histologically confirmed diagnosis of ESCC.
4. Have PD during or after first-line of systemic treatment for unresectable, locally advanced, recurrent or metastatic ESCC (Appendix 2).
    a. Patients with PD that occurs during treatment or within ≤ 6 months (180 days) after cessation of neoadjuvant/adjuvant treatment (chemotherapy or chemoradiotherapy) using standard of care agents are eligible if all other criteria are met.
    b. A line of treatment begins with the administration of the first agent in a regimen and ends with PD. Regimen might be changed due to toxicities/intolerability but the changed regimen will not constitute a new line of therapy.
    c. Patients who can't tolerate the most recent regimen due to Grade 4 hematologic toxicity or Grade 3 or 4 non-hematologic toxicity may also be eligible.
5. Have measurable disease as assessed by RECIST v1.1.

    Note: A lesion in an area subjected to prior locoregional therapy, including previous radiotherapy, is not considered measurable unless there has been demonstrated progression in the lesion as defined by RECIST v1.1 since the therapy.

6. Have confirmed PD-L1 TAP ≥ 10% in tumor tissues tested by the central lab.

    Note: Patients must submit qualified archival tumor tissue (FFPE block containing tumor [preferred] or approximately 15 [≥ 6] unstained slides) with an associated pathology report, or agree to a tumor biopsy for determination of PD-L1 expression and other biomarker analyses (fresh tumor biopsies are strongly recommended at baseline in patients with readily accessible tumor lesions and who consent to the biopsies). If no archival samples are available, a fresh tumor biopsy at baseline is mandatory.

    PD-L1 expression will be assessed centrally. PD-L1 TAP ≥ 10% is determined using the VENTANA PD-L1 (SP263) Assay.

    Note: The TAP score is defined as the total percentage of the tumor area (tumor and any desmoplastic stroma) covered by tumor cells with PD-L1 membrane staining at any intensity and tumor-associated immune cells with PD-L1 staining at any intensity, as visually estimated.

7. ECOG PS score of 0 or 1.

8. Life expectancy of ≥ 12 weeks.
9. Patient must have adequate organ function as indicated by the following screening laboratory values obtained ≤ 7 days before randomization:
    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 ≥ 1.5×10^9/L
        ii. Platelets ≥ 75×10^9/L
        iii. Hemoglobin ≥ 9 g/dL or ≥ 5.6 mmol/L
    b. Serum creatinine ≤ 1.5 × upper limit of normal (ULN) or estimated glomerular filtration rate ≥ 60 mL/min/1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration equation (Appendix 11).
    c. Serum total bilirubin ≤ 1.5 × ULN (total bilirubin must be < 3 × ULN for patients with Gilbert syndrome).
    d. AST and ALT ≤ 2.5 × ULN or ≤ 5 × ULN if hepatic metastases are present.
10. Females of childbearing potential must be willing to use a highly effective method of birth control for the duration of the study, and for ≥ 120 days after the last dose of study drug, and they must have a negative urine or serum pregnancy test ≤ 7 days before randomization (see Appendix 6).
11. Nonsterile males must be willing to use a highly effective method of birth control for the duration of the study and for ≥ 120 days after the last dose of study drugs.
    a. A sterile male is defined as one for whom azoospermia has been previously demonstrated in a semen sample examination as definitive evidence of infertility.
    b. Males with known "low sperm counts" (consistent with "subfertility") 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. Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, TIGIT or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways.
2. Prior randomization in a tislelizumab or ociperlimab study, regardless of the treatment arm, until the primary and key secondary endpoints of the study have read out.
3. Patients with evidence of fistula (either esophageal/bronchial or esophageal/aorta).
4. Evidence of complete esophageal obstruction not amenable to treatment.
5. Active leptomeningeal disease or uncontrolled, untreated brain metastasis.
   Note: Patients with a history of treated and, at the time of screening, stable central nervous system (CNS) metastases are eligible, provided that they meet all the following:
    a. Brain imaging at screening shows no evidence of PD, is clinically stable for at least 2 weeks and have no evidence of new brain metastases.

b. Have measurable and/or evaluable disease outside the CNS.

c. No ongoing requirement for corticosteroids as therapy for CNS disease; is off steroids for ≥ 3 days before randomization; anticonvulsants at a stable dose are allowed.

d. No stereotactic radiation or whole-brain radiation within 14 days before randomization.

6. Active autoimmune diseases or history of autoimmune diseases that may relapse (see Appendix 5).

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

   a. Controlled type I diabetes.

   b. Hypothyroidism (provided it is managed with hormone replacement therapy only).

   c. Controlled celiac disease.

   d. Skin diseases not requiring systemic treatment (eg, vitiligo, psoriasis, alopecia).

   e. Any other disease that has resolved and is not expected to recur in the absence of external triggering factors.

7. Any active malignancy ≤ 2 years before randomization except for the specific cancer under investigation in this study and any locally recurring cancer that has been treated curatively (eg, resected basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix or breast).
8. Any condition that requires systemic treatment with either corticosteroids (> 10 mg daily of prednisone or equivalent) or other immunosuppressive medication ≤ 14 days before randomization.
   Note: Patients who are currently or have previously been on any of the following steroid regimens are not excluded:

   a. Adrenal replacement steroid (dose ≤ 10 mg daily of prednisone or equivalent).

   b. Topical, ocular, intra-articular, intranasal, or 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).

9. Uncontrolled diabetes or > Grade 1 laboratory test abnormalities in potassium, sodium, or corrected calcium despite standard medical management or ≥ Grade 3 hypoalbuminemia ≤ 14 days before randomization.

Note: If corrected calcium is not reported in a laboratory report, it is required to calculate corrected calcium irrespective of the presence of hypoalbuminemia at screening. Please select the appropriate formula to calculate the corrected calcium value depending on the

laboratory unit used (mmol/L or mg/dL). A web-based formula is available via https://www.mdapp.co/hypoalbuminemia-corrected-calcium-calculator-103/

- Corrected Calcium (in mmol/L) = Serum Calcium (in mmol/L) + 0.02 x (40 – Albumin [in g/L]) or
- Corrected Calcium (in mg/dL) = Serum Calcium (in mg/dL) + 0.8 x (4 – Albumin [in g/dL])

10. Uncontrollable pleural effusion, pericardial effusion, or ascites requiring frequent drainage (recurrence within 2 weeks after intervention).
11. History of interstitial lung disease, noninfectious pneumonitis or uncontrolled lung diseases including pulmonary fibrosis, acute lung diseases, etc.
    Note: Patients with significantly impaired pulmonary function, or who require supplemental oxygen at baseline must undergo an assessment of pulmonary function at screening.
12. Infection (including tuberculosis infection, etc) that requires systemic antibacterial, antifungal or antiviral therapy within 14 days before randomization or patients who tested positive for COVID-19 antigen by a licensed test during screening.
    Note: Antiviral therapy is permitted for patients who have chronic hepatitis B virus (HBV) infection.
13. Untreated chronic hepatitis B or chronic HBV carriers with HBV DNA > 500 IU/mL (or > 2500 copies/mL) at screening.
    Note: Patients who are inactive hepatitis B surface antigen (HBsAg) carriers, or who have treated and stable hepatitis B (HBV DNA < 500 IU/mL or < 2500 copies/mL) can be enrolled. Patients with detectable HBsAg or detectable HBV DNA should be managed per treatment guidelines. Patients receiving antivirals at Screening should have been treated for > 2 weeks before randomization.
14. Patients with active hepatitis C.
    Note: Patients with a negative HCV antibody test at screening or positive HCV antibody test followed by a negative HCV RNA test at screening are eligible. The HCV RNA test will be performed only for patients who test positive for HCV antibody. Patients receiving antivirals at screening should have been treated for > 2 weeks before randomization.
15. Known history of human immunodeficiency virus (HIV) infection.
16. Any major surgical procedure ≤ 28 days before randomization.
    Note: Patients must have recovered adequately from the toxicity and/or complications from the intervention before randomization if any major surgical procedure was performed > 28 days before randomization.
17. Prior allogeneic stem cell transplantation or organ transplantation.
18. Any of the following cardiovascular risk factors:
    a. Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living, ≤ 28 days before randomization.
    b. Pulmonary embolism ≤ 28 days before randomization.
    c. Any history of acute myocardial infarction ≤ 6 months before randomization.

d. Any history of heart failure meeting New York Heart Association (NYHA) Classification III or IV (Appendix 7) ≤ 6 months before randomization.

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

f. Any history of cerebrovascular accident ≤ 6 months before randomization.

g. Uncontrolled hypertension that cannot be managed by standard antihypertension medications ≤ 28 days before randomization.
Note: For France only, specify: Uncontrolled hypertension is defined as systolic pressure ≥ 140 mmHg or diastolic pressure ≥ 90 mmHg on repeated measurements.

h. Any episode of syncope or seizure ≤ 28 days before randomization.

19. A history of severe hypersensitivity reactions to other monoclonal antibodies.
20. Has received any chemotherapy, immunotherapy (eg, interleukin, interferon, thymosin, etc) or any investigational therapies within 14 days or 5 half-lives (whichever is longer) before the first dose of study drug. Or has received palliative radiation treatment or other local regional therapies within 14 days before the first dose of study drug.
21. Patients with toxicities (as a result of prior anticancer therapy) that have not recovered to ≤Grade 2 or stabilized, except for AEs not considered a likely safety risk (eg, alopecia, neuropathy, and specific laboratory abnormalities).
22. Has received a live vaccine ≤ 28 days before randomization.
Note: Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed.
23. Underlying medical conditions (including laboratory abnormalities) or alcohol or drug abuse or dependence that will be unfavorable for the administration of study drugs, or affect the explanation of drug toxicity or AEs, or result in insufficient or impaired compliance with study conduct.
24. Women who are pregnant or breastfeeding.
25. Concurrent participation in another therapeutic clinical study.
Note: Concurrent participation in observational or noninterventional studies is allowed. In addition, patients who have completed active treatment in a clinical study and are in the follow-up period can be enrolled in this study.

5. STUDY TREATMENT

5.1. Formulation, Packaging, and Handling

5.1.1. Ociperlimab

Ociperlimab is a monoclonal antibody formulated for intravenous infusion in a single-use vial (20 mL glass vial, USP type I) containing a total of 200 mg antibody in 10 mL (or 300 mg antibody in 15 mL) of buffered isotonic solution. Ociperlimab has been aseptically filled in single-use vials with a Flurotec-coated butyl rubber stopper and an aluminum cap. Each vial is packaged into a single-carton box.

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

The study drug must be kept at the temperature and conditions specified on the label. Shaking should be avoided.

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

5.1.2. Tislelizumab

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

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

The study drug must be kept at the temperature and conditions specified on the label. Shaking should be avoided.

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

5.1.3. Matched Placebo

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

Ociperlimab placebo is a sterile, preservative-free solution for infusion formulated in the same buffer as ociperlimab active drug. All excipients used for the manufacture of the placebo are of pharmacopeial grade. No animal-derived components are used in the manufacture of placebo. The placebo will be provided in a single-use vial (20R glass, USP type I), containing 10 mL (or 15 mL) of isotonic solution. These single-use vials contain a Flurotec-coated butyl rubber stopper and an aluminum cap. Each vial is packaged into a single carton box.

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

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

5.2. Dosage, Administration, and Compliance

Planned dosage and dosing frequency for tislelizumab plus ociperlimab (Arm A) and tislelizumab plus placebo (Arm B) are presented in Table 3.

The first dose of study drugs is to be administered within 2 business days after randomization. The initial infusion (Day 1, Cycle 1 and Cycle 2) will be delivered over 60 minutes for each dose of tislelizumab, ociperlimab, and placebo; if this is well tolerated, then the subsequent infusions of each drug may be administered over 30 minutes, which is the shortest period permissible for infusion (see Table 4).

Accurate records of all study drugs received, dispensed, returned, and disposed of should be maintained in the site's Drug Inventory Log. Refer to the Pharmacy Manual for details of study drug management, drug preparation, storage, and administration.

Table 3: Planned Dose, Frequency of Administration, and Route of Administration for Study Drugs

Study drugs	Dose	Timing of Administration	Route of Administration	Duration of Treatment
Ociperlimab	900 mg	Day 1 of each 21-day cycle	Intravenous	Refer to Section 3.4.
Tislelizumab	200 mg	Day 1 of each 21-day cycle	Intravenous	Refer to Section 3.4.
Placebo	N/A	Day 1 of each 21-day cycle	Intravenous	Refer to Section 3.4.

Table 4: Administration of Study Drugs and Monitoring Time

Cycle	Tislelizumab Plus Ociperlimab/Tislelizumab Plus Placebo
Day 1, Cycle 1 and Cycle 2	Tislelizumab infusion over 60 (± 5) minutes followed by ociperlimab (Arm A) or placebo (Arm B) infusion over 60 (± 5) minutes Patient monitoring for ≥ 120 minutes
Day 1, Cycle 3 onwards	Tislelizumab infusion over 30 (± 5) minutes followed by ociperlimab (Arm A) or placebo (Arm B) infusion over 30 (± 5) minutes Patient monitoring for ≥ 30 minutes

Patients will receive tislelizumab 200 mg on Day 1 of each 21-day cycle (ie, once every 3 weeks) followed by the administration of ociperlimab 900 mg (Arm A) or placebo (Arm B). The study drugs must be administered by intravenous infusion through an intravenous line containing a sterile, nonpyrogenic, low-protein-binding 0.2- or 0.22-micron in-line or add-on filter. Specific instructions for product preparation and administration are provided in the Pharmacy Manual.

Use of a volumetric pump is recommended to control the infusion speed and to avoid potential infusion reactions associated with too rapid administration. The pump may not be needed if the infusion speed is controlled through alternative means and is consistent with approved institutional procedures.

At the end of the infusion period, flush the line with enough normal saline to make sure that all of the study drugs are administered to the patient.

As a routine precaution, after infusion of the study drugs on Day 1 of Cycle 1 and Cycle 2, patients must be monitored for ≥ 120 minutes afterward in an area with resuscitation equipment and emergency agents. From Cycle 3 onward, a ≥ 30-minute monitoring period is required in an area with resuscitation equipment and emergency agents.

The study drugs must not be concurrently administered with any other drug.

All patients will be monitored continuously for AEs. Treatment modifications (eg, dose delay, interruption or discontinuation) will be based on specific laboratory and AE criteria, as described in Section 5.5. Guidelines for dose modification, treatment interruption, or discontinuation and for managing imAEs and infusion-related reactions are provided in Section 8.7 and Appendix 12.

5.3. Incorrect Administration or Overdose

Any incorrect administration of ociperlimab or overdose of tislelizumab (defined as ≥ 600 mg in a 24-hour period) should be noted in the patient's chart and on the appropriate eCRF.

AEs associated with an incorrect administration or overdose of study drugs will be recorded on the AE eCRF. Any SAEs associated with an incorrect administration or overdose must be reported within 24 hours of awareness via the SAE reporting process as described in Section 8.6.2. 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 (ociperlimab, tislelizumab, and ociperlimab placebo) will be provided by the sponsor. The investigational site will acknowledge receipt of the IMPs. Any damaged shipments will be replaced.

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

5.5. Dose Delay or Modification

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

Guidelines for treatment modification or discontinuation as well as the management of infusion-related reactions are provided in Section 8.7 and Appendix 12.

For AEs that are assessed as related to tislelizumab and/or ociperlimab, the following general guidance should be followed unless otherwise specified:

- AEs ≤ Grade 2: Maintain dose level.
- AEs of Grade 3: Hold dose until resolved to ≤ Grade 1 or baseline except for alopecia or AEs that, in the opinion of the investigator, are not considered a safety risk for the patient.

- AEs of Grade 4: Permanent discontinuation of the patient from the study. Exceptions may be considered following consultation with the medical monitor.

5.5.1. Dose Modifications for Study Drugs

No dose reduction is allowed for any of the 3 study drugs in this study.

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

If a dose delay is required, both study drugs are to be delayed (ie, tislelizumab and ociperlimab or tislelizumab and placebo must both be delayed and restarted at the same time if applicable). Exceptions may be considered after consultation between the investigator and the medical monitor.

If treatment is delayed due to TEAEs, treatment may resume only after the AEs have returned to baseline or ≤ Grade 1 severity, excluding alopecia or any AE that, in the opinion of the investigator, are not considered a safety risk to the patient. If a treatment delay is due to worsening of hematologic or biochemical parameters, the frequency of relevant blood tests should be increased as clinically indicated.

In general, dose delays for reasons other than management of AEs are prohibited. A dose delay of ≤ 12 weeks is allowed under the following guidance and at the discretion of the investigator after consultation with the medical monitor or designee.

If a dose is delayed for the study drugs for ≤ 10 days during a planned dosing cycle (eg, Cycle 3 Day 1), the drugs should be administered at the end of the delay. If the delay is > 10 days, the patient should skip the study drugs. The study drugs will be administered on Day 1 of the next planned cycle (eg, Cycle 4 Day 1).

If treatment-related AEs are persistent without any improvement for more than 12 weeks, permanent discontinuation of the study drugs should be considered. In this situation, both assigned study drugs should be discontinued because the causality may not be distinguished from one study drug to the other.

If the patient recovers from the treatment-related AE after 12 weeks, reinitiation of study drugs is permitted only in patients who are deemed to be deriving clinical benefit per the opinion of the investigator after agreement between the investigator and the medical monitor.

Management guidelines for imAEs and infusion-related reactions in patients are presented in Section 8.7 and Appendix 12, respectively.

The tumor assessment schedule will not be altered even if the administration of study drugs is delayed.

5.6. Blinding

This is a randomized, investigator- and patient-blinded, sponsor-unblinded, placebo-controlled Phase 2 study. Patients will be randomized to receive tislelizumab plus ociperlimab versus tislelizumab plus placebo. Patients, investigators, and site staff will remain blinded to study treatments but the sponsor will remain unblinded.

The following actions should be taken in case of unblinding:

- Emergency unblinding

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

In an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the medical monitor before unblinding a patient's treatment assignment unless doing so could delay emergency treatment of the patient. If a patient's treatment assignment is unblinded, the sponsor must be notified immediately.

- Inadvertent unblinding

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

Additionally, there may be ethical reasons to have the patient remain on the study treatment. For patients to continue on study treatment in the event of unblinding, the investigator must obtain specific approval from the medical monitor for the patient to continue in the study.

6. PRIOR AND CONCOMITANT THERAPY

6.1. Prior Therapy

The exclusion criteria (Section 4.2) specify that patients should not have received prior therapies targeting PD-1, PD-L1, PD-L2, TIGIT, T-cell costimulation or checkpoint pathways, or chemotherapy, immunotherapy (eg, interleukin, interferon, or thymosin), or investigational therapy within 14 days or 5 half-lives (whichever is longer) before the first dose of study drugs.

6.2. Permitted Concomitant Medications/Procedures

Unless noted otherwise, most concomitant medications and therapies are allowed at the discretion of the investigator if they are deemed necessary and are in keeping with local standards of medical care for supportive care (eg, antiemetics, antidiarrheals, hematopoietic growth factors, red blood cell/platelet transfusions) and in a patient's interest. 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.

All concomitant medications will be recorded on the eCRF, including all prescription and over-the-counter medicines, herbal supplements, and intravenous medications and fluids.

Bisphosphonates and receptor activator of NF-kB ligand (RANKL) inhibitors are allowed for bone metastases if initiated before enrollment and at a stable dose. Bisphosphonates are permitted during the study for a nonmalignant indication. Use of potentially hepatotoxic drugs in patients who have impaired hepatic function is allowed but should be carefully monitored.

6.2.1. Systemic Corticosteroids

Systemic corticosteroids administered for the control of imAEs must be tapered gradually (see Appendix 12) and must be administered at nonimmunosuppressive doses (≤ 10 mg/day of prednisone or equivalent) before the next administration of the study drugs. The short-term use of steroids as prophylactic treatments (eg, patients with contrast allergies to diagnostic imaging contrast dyes) is permitted.

6.2.2. Hepatitis B Treatment

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 discontinuation.

6.2.3. Radiation Therapy

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

- Repeat imaging demonstrates no new sites of bone metastases;
- The lesion being considered for palliative radiation is not a target lesion per RECIST v1.1;

- The case is discussed with the medical monitor and he/she agrees that the conditions required to receive palliative radiation are met.

Additionally, palliative radiation or other focally ablative therapy for other nontarget sites of the disease is permitted if clinically indicated per the investigator's discretion and after consultation with the medical monitor. Whenever possible, these patients should have a tumor assessment of the lesion(s) before receiving the radiation therapy to rule out PD. It is not required to withhold study drugs during palliative radiotherapy.

6.2.4. COVID-19 Vaccines

Vaccines for COVID-19 are allowed except for any live vaccine that may be developed. It is recommended to avoid COVID-19 vaccination within 72 hours before or after study drug administration during the first 2 treatment cycles, and within 24 hours before or after study drug administration thereafter (ie, from Cycle 3 onwards).

Vaccinations are considered a concomitant medication and hence should be entered on the eCRF. Instead of generic language (eg, "COVID-19 vaccination"), the specific COVID-19 vaccine should be recorded, mRNA-1273 vaccine (Moderna), BioNTech vaccine (Pfizer), etc.

6.3. Prohibited Concomitant Medications/Procedures

The following medications are prohibited:

- Any concurrent anticancer therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents including Chinese [or other country] herbal medicine and Chinese [or other country] patent medicines for the treatment of cancer [regardless of cancer type]) ≤14 days (or ≤5 half-lives, whichever is longer) before the first dose of study drugs and during the study.
- Live vaccines within 28 days before the first dose of study drugs and 60 days after the last dose of study drugs.
- 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) within 14 days (or within 5 half-lives, whichever is longer) before the first dose of study drugs and during the study. Patients must notify the investigator of all herbal remedies used during the study.

6.4. 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.
- Radiation therapy is not allowed, except for palliative radiation therapy described in Section 6.2.3.

6.5. Potential Interactions Between the Study Drugs and Concomitant Medications

Information regarding clinical drug interactions with ociperlimab is not available and no dedicated drug-drug interaction studies are planned. However, the potential for drug-drug interaction between the study drugs (ociperlimab and tislelizumab) and other drug products is very low because ociperlimab and tislelizumab are therapeutic monoclonal antibodies. Because ociperlimab and tislelizumab are expected to be degraded into amino acids and recycled into other proteins, they unlikely influence drug-metabolizing enzymes or transporters.

7. STUDY ASSESSMENT 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. Prescreening

Patients must undergo examination of PD-L1 expression in tumor tissues by a central laboratory within 56 days before randomization. The details for collection, storage, shipment, and analysis of tissue block are detailed in the laboratory manual.

At prescreening period, the following criteria are a prerequisite for the confirmation of randomization by the central laboratory:

- Adult patients (>18 years of age or the legal age of consent in the jurisdiction in which the study is taking place) with histologically confirmed diagnosis of ESCC with tumor progression during or after first-line systemic treatment for unresectable, locally advanced, recurrent or metastatic disease.
- Mandatory availability for shipment of FFPE, tumor-containing tissue blocks (preferred) or approximately 15 (≥ 6) unstained tumor specimen slides from primary tumor and/or metastatic site. 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 mandatory at baseline.

Written informed consent for collection, storage and analysis of tissue block must be obtained from the patient according to International Council for Harmonisation (ICH) GCP, and national/local regulations.

7.2. Screening Period

Screening evaluations will be performed ≤ 28 days before randomization. A patient whose tumor tissues have PD-L1 TAP ≥ 10% in prescreening and agrees to participate in this study will sign the ICF before undergoing any screening assessment. The screening period begins on the first day that a screening assessment 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 before informed consent has been obtained and ≤ 28 days before randomization may be used for the purposes of screening rather than repeating the standard-of-care tests unless otherwise indicated.

Procedures conducted only during the Screening Visit 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 7.5), Tumor and Response Evaluations (Section 7.6), PK and ADA Assessments (Section 7.7), and Tumor Tissue and Biomarker Assessment Procedures (Section 7.8).

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

7.2.1. Informed Consent and Screening Log

Voluntary, written informed consent for participation in the study must be obtained before any study-specific procedures are performed. The ICFs 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 drugs. 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.

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

7.2.2. Demographic Data and Medical History

Demographic data will include age or date of birth, sex, and self-reported race or ethnicity.

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

Cancer history will include an assessment of prior surgery, prior radiotherapy, and prior drug therapy including start and stop dates, best response, and reason for discontinuation. Radiographic studies performed before study entry may be collected for review by the investigator.

7.2.3. Females of Childbearing Potential and Contraception

Childbearing potential is defined as having the physiological ability to become pregnant. Refer to Appendix 6 for contraception guidelines and definitions of "women of childbearing potential" and "women of no childbearing potential."

7.2.4. Pulmonary Function Tests

Patients who are suspected of having or known to have serious and/or severe respiratory conditions, or who exhibit significant respiratory symptoms unrelated to the underlying cancer, or who have a history of thoracic radiotherapy will undergo pulmonary function testing that may include but is not limited to spirometry and assessment of diffusion capacity done during the screening period to assist the determination of suitability for the study.

The test may be repeated as clinically indicated while on study (refer to Appendix 1 for details).

7.3. Enrollment

7.3.1. Confirmation of Eligibility

The investigator is responsible for ensuring that each patient meets the eligibility criteria for this study. All results from the screening procedures and relevant medical history must be available before eligibility can be determined. No eligibility waivers will be granted.

The sponsor's medical monitor will support the investigator and/or site staff by answering any queries or questions relating to protocol eligibility criteria.

7.3.2. Patient Numbering

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

7.3.3. Randomization

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

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

7.4. Study Drug Dispensation

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

7.5. Safety Assessment

7.5.1. Vital Signs

Vital signs will include measurements of body temperature (˚C), pulse rate, respiratory rate, and blood pressure (systolic and diastolic). Pulse rate and blood pressure will be measured while the patient is in a seated position after resting for 10 minutes. If coinciding with administration of study drugs, the patient's vital signs are required to be recorded within 60 minutes before, during, and 30 minutes after the first cycle of study drug administration. For subsequent cycles, vital signs will be collected within 60 minutes before study drug infusion and if clinically indicated, during and 30 minutes after study drug infusion. Height should only be measured and

recorded during screening. Weight will be measured before study drug administration in every cycle.

7.5.2. Physical Examinations

During the Screening Visit, a complete physical examination will be conducted, including evaluations of 1) head, eyes, ears, nose, and 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.

7.5.3. Eastern Cooperative Oncology Group Performance Status

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

7.5.4. Laboratory Safety Tests

Local and/or central laboratory assessments of clinical chemistry, hematology, coagulation, and urinalysis will be conducted, of which certain elements will be collected as specified in Appendix 3.

If laboratory tests at screening are not performed ≤ 7 days before study drug administration on Day 1 of Cycle 1, these tests should be repeated and reviewed before study drug administration. 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 should use results from the same local laboratories for assessing eligibility, safety monitoring, and dosing decision for each patient.

7.5.4.1. Cardiac Enzyme Monitoring

Although immune-mediated myocarditis is a rare complication of immune checkpoint inhibitors, serum creatine kinase (CK) and CK-MB are monitored in all tislelizumab studies to protect study patients and to quantify the risk of muscle inflammation (see Appendix 1 for the blood collection schedule and Appendix 12 for guidelines for management of suspected immune-mediated myocarditis, respectively).

CK and CK-MB testing will be implemented for all patients at screening, predose on Day 1 of every cycle, the EOT Visit, and the on-site Safety Follow-up Visit (30 days after the last dose). If CK-MB fractionation is not available, serum troponins (troponin I and/or T) measurements will be performed instead per local guidelines if used consistently throughout the study.

7.5.5. Electrocardiograms

The ECG recordings will be obtained during screening, the EOT Visit, the on-site Safety Follow-up Visit, and as clinically indicated.

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.

The patient should rest in semirecumbent supine position for ≥ 10 minutes in the absence of environmental distractions that may induce changes in heart rate (eg, television, radio, conversation, etc) before each ECG collection.

7.5.6. 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 8.3.4.

7.5.7. Hepatitis B and C Testing

Testing will be performed by a central laboratory and/or the local laboratory at screening (and as clinically indicated) and will include HBV/HCV serology (HBsAg, hepatitis B surface antibody [HBsAb], hepatitis B core antibody [HBcAb], and HCV antibody) and viral load assessment (HBV DNA and HCV RNA), which will be assessed only when HBsAg or HCV antibody is positive, respectively. For patients who have detectable HBV DNA at screening, a respective viral load test will be performed every 4 cycles (ie, Day 1 of Cycle 5, 9, 13, etc) starting from Cycle 5.)

7.6. Tumor and Response Evaluations

Tumor imaging will be performed ≤ 28 days before randomization. Results of standard-of-care tests or examinations performed before obtaining informed consent and ≤ 28 days before randomization may be used for the purposes of screening rather than repeating the standard-of-care tests. During the study, tumor imaging will be performed approximately every 6 weeks (± 7 days), from Day 1 of Cycle 1, for the first 54 weeks and every 12 weeks (± 7 days) thereafter, based on RECIST v1.1. If a tumor assessment is missed or conducted outside of the specified assessment window, all subsequent scans should be conducted according to the planned schedule.

Screening assessments and each subsequent assessment must include computed tomography (CT) scans (with oral/intravenous contrast) of the neck, chest, abdomen, and pelvis. If a contraindication exists, other modalities can be allowed after consultation with the medical monitor (eg, magnetic resonance imaging [MRI], CT without contrast); bone scan or positron-emission tomography (PET) is required if clinically indicated. Other known or suspected sites of disease must be included in the imaging assessments (brain, etc). For patients who are suspected to have CNS metastases, CT/MRI of the head is required at baseline.

All measurable and evaluable lesions should be assessed and documented at the Screening Visit and reassessed at each subsequent tumor evaluation. The same radiographic procedure used to

assess disease sites at screening must be used throughout the study (eg, the same contrast protocol for CT scans).

- If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the study, a noncontrast CT of the chest plus a contrast-enhanced MRI (if possible) of abdomen and pelvis should be performed.
- If a CT scan for tumor assessment is performed on a PET/CT scanner, the CT acquisition must be consistent with the standards of a diagnostic CT scan.
- Bone scans (Technetium-99m [TC-99m]) or PET should be performed at screening if clinically indicated. If bone metastases are present at screening and cannot be seen on CT or MRI scans, TC-99m or PET bone scans should be repeated when a CR is suspected in target lesion or when progression in bone is suspected.
- CT scans of the head or extremities should be performed at screening only if clinically indicated and should be repeated throughout the study if there is evidence of metastatic disease in these regions at screening.
- At the investigator's discretion, other methods of assessment of target lesion and non-target lesions per RECIST v1.1 may be used.

Response will be assessed by the investigator and IRC using RECIST v1.1 (see Appendix 13). The same evaluator should perform assessments, if possible, to ensure internal consistency across visits.

After first documentation of response (CR or PR), confirmation of tumor response should occur at 4 weeks or later after the first response or at the next scheduled assessment timepoint.

If, at the investigator's discretion, a patient could continue to benefit from study drugs after PD per RECIST v1.1 criteria, the patient may continue the study treatment. The following criteria must be met in order to treat patients who may continue to benefit from study treatment after PD:

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

The decision to continue study drugs after initial PD must be agreed to by the medical monitor and documented in the study records.

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

A patient who discontinues study drugs early for reasons other than PD (eg, toxicity) will continue to undergo tumor assessments in accordance with the original plan until the patient

experiences PD, withdraws consent, is lost to follow-up, dies, or until the study terminates, whichever occurs first.

Tumor assessments must be performed on schedule regardless of whether study treatment has been administered or withheld. That is, they should not be adjusted for delays in cycles.

7.7. Pharmacokinetic and Antidrug Antibody Assessments

Ociperlimab and tislelizumab may elicit an immune response. Patients with signs of any potential immune response will be closely monitored. Validated screening and confirmatory assays will be employed to detect ADAs at multiple timepoints throughout the study. In addition, blood samples will be collected for characterization of ociperlimab and tislelizumab PK at the timepoints specified in the Schedule of Assessments (Appendix 1).

PK and ADA assays of ociperlimab and tislelizumab will be managed through a central laboratory. Serum samples will be assayed for ociperlimab and tislelizumab concentrations using validated immunoassays. Placebo samples will be collected but not analyzed.

- ADA assays: serum samples will be tested for the presence of ADAs to ociperlimab and tislelizumab using a validated immunoassay
- PK assays: serum samples will be assayed for ociperlimab and tislelizumab concentrations with a validated immunoassay

Refer to the laboratory manual for instructions regarding sample collection, handling, labeling, storage, and shipping of laboratory samples.

7.8. Tumor Tissue and Biomarker Assessment Procedures

Shipping, storage, and handling of blood as well as archival tumor and/or fresh tumor tissues for the assessment of biomarkers will be handled by a central laboratory. Refer to the laboratory manual for details of sample handling and the Schedule of Assessments (Appendix 1) for timepoints.

Patients are required to provide tumor tissues (archival tumor tissues [FFPE blocks or approximately 15 [≥ 6] freshly cut unstained slides] or fresh biopsy) for biomarker analysis (eg, TIGIT, CD226, CD155, CD112 and PD-L1), GEP, TMB/gene mutation/MSI, tumor infiltrating immune cells, and GEP signatures before and after study treatment or at PD/reoccurrence, and the association between these biomarkers and clinical efficacy, disease status, and resistance. If no archival samples are available, a fresh tumor biopsy at baseline is mandatory. Acceptable fresh biopsy samples include core needle biopsies for deep tumor tissue or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.

If clinically feasible, it is highly recommended to obtain a tumor biopsy from accessible tumor sites at the EOT Visit for the patients who have confirmed PD, which could be used to explore the immune- or tumor-related biomarkers and biological changes that might drive PD or acquired resistance to study drugs. If feasible, any follow-up biopsy should, ideally, be taken from the same tumor lesion as the baseline biopsy. Written informed consent is required for fresh tumor biopsies.

An optional blood sample will be taken at baseline (predose on Day 1 of Cycle 1), at the time of first tumor response (predose on Day 1 of the following cycle) and at the EOT Visit after PD (10 mL each timepoint) (Appendix 1) to explore association of blood-based biomarkers with response, resistance and prognosis.

Written informed consent is required for any of the fresh tumor biopsies. Tumor tissue should be of good quality in terms of total and viable tumor content. Fine needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable.

7.9. Health-Related Quality of Life/Quality of Life

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

7.10. Visit Windows

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

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other events, the visit should be scheduled for 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.

7.11. Unscheduled Visits

Unscheduled visits may be performed at any time at the patient's or the investigator's request and may include vital signs/physical examination; ECOG PS; AE review; concomitant medications and procedure reviews; radiographic assessments; physical examination of liver, spleen, and lymph nodes; disease-related constitutional symptoms; and hematology and clinical 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 PD, then diagnostic tests may be performed based on the investigator assessment as appropriate, and the results of these tests should be entered on the unscheduled visit eCRF.

8. SAFETY MONITORING AND REPORTING

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

8.1. Risks Associated With Study Drugs

8.1.1. Risks Associated With Ociperlimab and Tislelizumab

Ociperlimab and tislelizumab are investigational agents that are currently in clinical development. Limited safety data are available in patients, and the full safety profile has not been characterized. The following recommendation is based on results from nonclinical and clinical studies with tislelizumab and ociperlimab 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. Ociperlimab-mediated TIGIT inhibition may increase the risk of immune mediated AEs. However, no apparent immunotoxicity, or toxicity in general, has been observed in animal models treated with ociperlimab. Furthermore, in the absence of activation, peripheral effector T-cells do not typically express TIGIT, thereby minimizing any potential negative additive effect as it relates to peripheral immune tolerance.

Although most imAEs observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Suggested workup procedures for suspected imAEs are provided in Appendix 12.

8.1.2. Risks Associated With Placebo

There are no specific risks associated with the placebo.

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 ociperlimab and tislelizumab, as well as the nonclinical/clinical data from other PD-L1/PD-1 inhibitors, were considered. Specifically, patients who are at risk for study-emergent active autoimmune diseases or who have 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 viral vaccine ≤ 28 days before randomization are excluded from the study. Refer to Section 4.2 for the full list of exclusion criteria.

8.2.2. Safety Monitoring Plan

Safety will be evaluated in this study through the monitoring of all AEs, defined and graded according to NCI-CTCAE v5.0. Patients will be assessed for safety (including laboratory values) according to the schedule in Appendix 1.

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 5), physical examinations, laboratory measurements (hematology, clinical 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 autoimmune conditions or infection.

At the start of each cycle, study drug(s) will be administered only after clinical laboratory results have been reviewed. Administration of study drugs will be performed in a setting where emergency medical equipment and staff who are trained to respond to medical emergencies are available (for additional information, see Section 5.2).

Serum samples will be drawn for determination of ADAs to ociperlimab and tislelizumab in all randomized patients.

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 study drugs, whether considered related to study drugs or not.

Examples of AEs include:

- Worsening of a chronic or intermittent pre-existing condition, including an increase in severity, frequency, duration, and/or has an association with a significantly worse outcome
- New conditions detected or diagnosed after study drug administration even though the condition might have been present before the start of the study
- Signs, symptoms, or clinical sequelae of a suspected interaction
- Signs, symptoms, or clinical sequelae of a suspected overdose of either study drugs 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 obscured on the copies of the medical records before 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 NCI-CTCAE v5.0.

Toxicities that are not specified in 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
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care, activities of daily living
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

Note: The terms "severe" and "serious" are not synonymous. Severity is a measure of intensity (for example, grade of a specific AE, mild [Grade 1], moderate [Grade 2], severe [Grade 3], or life-threatening [Grade 4]); whereas seriousness is classified by the criteria based on the regulatory definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the sponsor to applicable regulatory authorities as described in Section 8.6.2.

8.3.3. Assessment of Causality

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

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

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

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

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

- There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
- There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
- There is some evidence to suggest a causal relationship (eg, the AE occurred within a reasonable time after administration of the study drug[s]). 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, 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 that worsen significantly during the study. The definition of clinically significant is based on the judgement 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 × ULN associated with cholestasis), only the diagnosis (ie, cholestasis) should be recorded on the Adverse Event eCRF.

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

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

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 the outcomes listed above)

The following are NOT considered SAEs:

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

8.5. Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is a serious adverse reaction that is both unexpected (ie, not present in the study drug's reference safety information [RSI]) and meets the definition of an serious adverse drug reaction (SADR), the specificity or severity of which is not consistent with those noted in the Tislelizumab Investigator's Brochure and the Ociperlimab Investigator's Brochure.

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

8.6.1. Adverse Event Reporting Period

After the ICF has been signed, but before the administration of the study drugs, only SAEs should be reported to the sponsor.

After initiation of study drugs, all AEs and SAEs, regardless of relationship to study drugs, will be reported until either 30 days after last dose of study drugs or initiation of subsequent anticancer therapy, whichever occurs first. Serious or nonserious imAEs should be reported until 90 days after the last dose of study drugs, regardless of whether the patient starts a subsequent 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 5. For the follow-up period for AEs, see Section 8.3.4. For the definition of TEAEs, see Section 9.3.2.

Table 5: Guidance for Duration of Recording New or Worsening Adverse Events in Both Arms

Event Type	Record New or Worsening Events That Occur During This Period	
	Begin	**End**
SAEs[a]	Signing of informed consent	Up to 30 days after last dose, initiation of a new anticancer therapy, death, withdrawal of consent, or loss to follow-up, whichever occurs first
Nonserious AEs due to PD	Do not record (see Section 8.6.4)	
All nonserious AEs, except those due to PD	First dose of study drug	Up to 30 days after last dose, initiation of a new anticancer therapy, death, withdrawal of consent, or loss to follow-up, whichever occurs first
Immune-mediated AEs (serious or nonserious)	First dose of study drug	Up to 90 days after last dose (regardless of initiation of new anticancer therapy), death, withdrawal of consent, or loss to follow-up, whichever occurs first

Abbreviations: AE, adverse event; PD, progressive disease; SAE, serious adverse event.
[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 Table 6.

Table 6: Time Frames and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

	Time Frame for Making Initial Report	Documentation Method	Time Frame for Making Follow-up Report	Documentation Method	Reporting Method
All SAEs	Within 24 hours after first knowledge of the AE	SAE report	As expeditiously as possible	SAE report	Email or fax SAE form or pregnancy form

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

8.6.2.2. Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a patient, he/she is to report the information to the sponsor within 24 hours, as outlined above in Section 8.6.2.1. The SAE report

should always be completed as thoroughly as possible, including 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 promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 8.6.2.1. The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a drug under clinical investigation.

The investigator, or other 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 ociperlimab and 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

PD, 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 PD should not be recorded. However, if there is any uncertainty as to whether a nonserious AE is due to PD, it should be recorded as an AE. All SAEs and deaths regardless of relatedness to PD should be recorded and reported (see Section 8.6.2).

8.6.5. Deaths

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

8.6.6. Pregnancies

If a female patient or the partner of a male patient becomes pregnant while receiving study drugs or within 120 days after the last dose of study drugs, a pregnancy report form must 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 after 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 always be reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a patient exposed to the study drugs 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 documents:

- Tislelizumab Investigator's Brochure
- Ociperlimab Investigator's Brochure

8.6.8. Assessing and Recording Immune-Mediated Adverse Events

Because treatment with anti-PD-1 or immune checkpoint inhibitors 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 on the eCRF AE page until Day 90 after treatment discontinuation.

Investigators should consult the guidance on diagnostic evaluation and management of imAEs, which are commonly seen with immune checkpoint inhibitors, in Appendix 12.

An extensive list of potential imAEs appears in Section 8.7.3, Table 8. All conditions like those listed should be evaluated to determine whether they are imAEs based on a similar diagnostic process to those reactions that are presented in more detail in Appendix 12.

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. Each individual sign and symptom of an infusion reaction should be recorded each as a separate AE in the eCRF and identified as an infusion-related reaction. Refer to the eCRF completion guidelines for details.

8.7. Management of Adverse Events of Special Interest

As a routine precaution, after infusion of the study drugs on Day 1 of Cycle 1 and Cycle 2, patients must be monitored for ≥ 120 minutes afterwards in an area with resuscitation equipment and emergency agents. From Cycle 3 onward, at least a 30-minute monitoring period is required in an area with resuscitation equipment and emergency agents.

The management for infusion-related reactions, severe hypersensitivity reactions, and imAEs according to the NCI-CTCAE criteria are outlined in the following subsections.

8.7.1. Infusion-Related Reactions

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

Treatment modification for symptoms of infusion-related reactions due to study drugs is provided in Table 7.

Table 7: Treatment Modification for Symptoms of Infusion-Related Reactions Due to Study Drugs

NCI-CTCAE Grade	Treatment Modification for Study Drugs
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.
Grade 2 - moderate Therapy or infusion interruption indicated but the patient responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, intravenous fluids); prophylactic medications indicated for ≤ 24 hours.	Stop infusion. Infusion may be resumed at 50% of previous rate after infusion-related reactions have resolved or decreased to Grade 1 in severity. Any worsening is closely monitored. Proper medical management should be instituted as described in the text that follows this table.
Grade 3 – severe Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms after initial	Immediately stop the infusion. Proper medical management should be instituted as described in the text that follows this table. The patient should be withdrawn from study drug treatment.

NCI-CTCAE Grade	Treatment Modification for Study Drugs
improvement; hospitalization indicated for clinical sequelae.	
Grade 4 – life-threatening Life-threatening consequences; urgent intervention indicated.	Immediately stop the infusion. Proper medical management should be instituted as described in the text that follows this table. The patient should be withdrawn from study drug treatment. Hospitalization is recommended.

Abbreviations: NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

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

NCI-CTCAE Grade 1 or 2 infusion reactions: 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, the patient should receive oral premedication with an antihistamine (eg, diphenhydramine or equivalent) and an antipyretic (eg, paracetamol or equivalent), and the patient should be closely monitored for clinical signs and symptoms of an infusion reaction.

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

8.7.2. Severe Hypersensitivity Reactions and Flu-Like Symptoms

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

If a systemic anaphylactic/anaphylactoid reaction occurs, the infusion must be stopped immediately and the patient discontinued from the study. Systemic anaphylactic/anaphylactoid reactions typically manifest within minutes after the administration of the drug/antigen and are characterized by respiratory distress, laryngeal edema, and/or intense bronchospasm, and are 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.

Epinephrine injection and dexamethasone infusion will be administered to patients if hypersensitivity reaction is observed, and then the patient should be placed on monitor immediately and an Intensive Care Unit should be alerted for possible transfer if needed.

For prophylaxis of flu-like symptoms, a dose of 25 mg indomethacin or a comparable dose of nonsteroidal anti-inflammatory drugs (ie, 600 mg ibuprofen, 500 mg naproxen sodium) may be administered 2 hours before and 8 hours after the start of each dose of study drug infusion. Alternative treatments for fever (ie, paracetamol) may be administered to the patient 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, PD, 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 on the eCRF AE page should be checked.

A list of potential imAEs is shown below in Table 8. All conditions similar to those listed should be evaluated in patients 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 et al 2018) and common immune-mediated toxicities are detailed in Appendix 12. For any AEs not included in Appendix 12, refer to the ASCO Clinical Practice Guideline (Brahmer et al 2018) for further guidance on diagnostic evaluation and management of immune-mediated toxicities.

Table 8: 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

Body System Affected	Events
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 12.

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

9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

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

The following descriptive statistics will be used to summarize the study data on the basis of their nature unless otherwise specified:

- Continuous variables: number of nonmissing observations, mean, standard deviation, median, minimum, and maximum
- Categorical variables: frequencies and percentages
- Time-to-event variables: the number of nonmissing observations (N), median, minimum and maximum. Kaplan-Meier event rates may also be provided if applicable for specific time to event variables

9.1.1. Analysis Sets

The following analysis sets will be used for analysis in this study:

- The ITT Analysis Set, which includes all randomized patients, will be the primary analysis population for all efficacy analyses, including HRQoL analysis.
- The Safety Analysis Set (SAS), which includes all patients who received ≥ 1 dose of study drugs, will be the primary analysis set for safety analyses.
- The PK Analysis Set, which includes all patients who receive ≥ 1 dose of any component of study drugs per the protocol, and for whom any postdose PK data are available.
- The Immunogenicity Analysis Set, which includes all patients who receive ≥ 1 dose of any component of study drugs and for whom both baseline antidrug antibody and at least 1 postbaseline antidrug antibody result are available.

9.1.2. Patient Disposition

The number of patients randomized, treated, and discontinued from study drugs and/or study and those with critical protocol deviations will be counted. The primary reason for study drug and/or the 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.

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

9.1.3. Demographic and Other Baseline Characteristics

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

include age (≤ 65 years old and >65 years old), sex, ECOG PS, region/country, race, TNM Classification of Malignant Tumors staging, smoking status (never, previous, and current), alcohol consumption (never, previous, and current), primary tumor location (cervical, upper, middle, and lower), and previous treatment (chemotherapy, radiation therapy, and surgery), anatomic locations of metastases, and number of metastatic lesions (≤ 1 site versus ≥ 2 sites), etc.

9.1.4. Prior and Concomitant Medications

Prior medications will be defined as medications that stopped before the day of the first dose of study drugs. Concomitant medications will be defined as medications that 1) started before the first dose of study drugs and were continuing at the time of the first dose of study drugs, or 2) started on or after the date of the first dose of study drugs up to 30 days after the patient's last dose (as of the on-site Safety Follow-up Visit).

Concomitant medications will be coded using the World Health Organization Drug Dictionary drug codes and further coded to the appropriate Anatomical Therapeutic Chemical code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class in the clinical study report (CSR) for this protocol.

9.2. Efficacy Analyses

The primary endpoint ORR will be tested at a 1-sided alpha of 0.025. If the null hypothesis for ORR in the ITT Analysis Set is rejected, the secondary endpoint OS in the ITT Analysis Set will be tested.

9.2.1. Primary Efficacy Analysis

Overall Response Rate by the Investigator's Review

ORR will be compared between Arm A and Arm B. Patients with no postbaseline response assessment (for any reason) will be considered nonresponders.

The null hypothesis to be tested is:

H_0: ORR in Arm A ≤ ORR in Arm B

against the alternative:

H_1: ORR in Arm A > ORR in Arm B

The statistical significance of the difference in ORR between the 2 treatment arms in the ITT Analysis Set will be evaluated using the Cochran-Mantel-Haenszel method, adjusted by the selected stratification factors at randomization (ie, ECOG PS score [0 versus 1] and the number of organs with metastases [⩽1 versus ⩾2]). The difference in ORR will be calculated, as will the Clopper-Pearson 95% CIs for the ORR within each arm.

The final analysis of ORR will be performed at approximately 4 months after the last patient is randomized.

9.2.2. Secondary Efficacy Analysis

Overall Survival

OS will be analyzed in the ITT analysis set. In the absence of death, patients will be censored either at the date when the patient is last known to be alive or the date of data cutoff, whichever comes earlier. A log-rank test adjusted by the selected stratification factors at randomization (ie, ECOG PS score [0 versus 1] and the number of organs with metastases [⩽1 versus ⩾2]) will be used to test the differences in OS between the 2 treatment arms. The median OS and the cumulative probability of OS at every 3 months, if estimable, will be calculated for each treatment arm and presented with 2-sided 95% CIs. Kaplan-Meier survival probabilities over time for each arm will be plotted.

The treatment effect of OS will be estimated by fitting a Cox regression model with the treatment arm adjusted by selected stratification factors at randomization (ie, ECOG PS score [0 versus 1] and the number of organs with metastases [⩽1 versus ⩾2]). From this model, the HR of OS will be estimated and presented with a 2-sided 95% CI.

The final analysis of OS will take place when approximately 72 deaths (ie, 60% of the total sample size) have been observed.

Overall Response Rate

ORR assessed by the IRC per RECIST v1.1 in the ITT Analysis Set will be analyzed similarly to the corresponding analysis of ORR assessed by the investigator. The 2-sided 95% CIs for the odds ratio and the difference in ORR will be calculated, as will the Clopper-Pearson 95% CIs for the ORR within each arm.

Progression-Free Survival

PFS based on assessment by the IRC and the investigator per RECIST v1.1 will be analyzed in the ITT Analysis Set. The PFS censoring rule will follow the US FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (FDA 2018). The median PFS and the cumulative probability of PFS at every 3 months, if estimable, will be calculated for each treatment arm and presented with 2-sided 95% CIs. Kaplan-Meier survival probabilities over time for each arm will be plotted. The treatment effect will be estimated by fitting a Cox regression model with treatment arm adjusted by the actual value of selected stratification factors at randomization (ie, ECOG PS score [0 versus 1] and the number of organs with metastases [≤1 versus ≥2]). From this model, the HR of PFS will be estimated and presented with a 2-sided 95% CI.

Duration of Response

DOR will be analyzed among the responders in the ITT Analysis Set using methods similar to that described for PFS, based on assessment by the IRC and the investigators.

Disease Control Rate and Clinical Benefit Rate

DCR and CBR assessed by the IRC and investigator per RECIST v1.1 will be summarized similarly as ORR in the ITT Analysis Set.

Health-Related Quality of Life

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

The proportion of patients showing clinically meaningful change at each assessment timepoint will be calculated. Completion and compliance rates will be summarized at each timepoint.

Time to deterioration (TTD) is defined as at least 10-point change on GHS of QLQ-C30 and will be calculated using Kaplan-Meier estimates.

9.3. Safety Analyses

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

9.3.1. Extent of Exposure

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

The number (percentage) of patients requiring dose interruption, dose delay, and drug discontinuation because of AEs will be summarized for each study drug. Reasons for above dose modifications and discontinuation will be summarized as well.

Patient data listings will be provided for all dosing.

9.3.2. Adverse Events

The AE verbatim descriptions (investigator's description from the eCRF) will be classified into standardized medical terminology using MedDRA. AEs will be coded to MedDRA (version 24.0 or higher) lowest level term closest to the verbatim term, preferred term (PT), and primary system organ class (SOC).

A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drugs up to 30 days of study drugs after last dose or initiation of subsequent anticancer therapy, whichever comes first. Only those AEs that were treatment emergent will be included in summary tables of TEAE. Immune-mediated AEs will be identified from all AEs that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to 90 days from the last dose of ociperlimab (or placebo) and/or tislelizumab, regardless of whether the patient starts a new anticancer therapy. If an imAE occurs outside of the above-mentioned TEAE window, it will not be classified as a TEAE. 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 SOC and PT. A patient will be counted only once by the highest severity grade per

NCI-CTCAE v5.0 within an SOC and PT, even if the patient experienced > 1 TEAE within a specific SOC and PT.

SAEs, deaths, ≥ Grade 3 TEAEs, imAE, treatment-related TEAEs, and TEAEs that led to treatment discontinuation, dose interruption or dose delay will be summarized.

9.3.3. Laboratory Analyses

Clinical laboratory (eg, hematology, clinical chemistry, coagulation, and 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, and 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 change.

Laboratory parameters that are graded in NCI-CTCAE v5.0 or higher 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, calcium, glucose, magnesium, potassium, and sodium) will be summarized separately.

9.3.4. Vital Signs

Descriptive statistics for vital sign parameters (body temperature, pulse rate, respiratory rate, and blood pressure [systolic and diastolic]) and weight and their changes from baseline will be presented by visit.

9.4. Pharmacokinetic Analyses

Pharmacokinetic samples will be collected in this study as outlined in Appendix 1.

Tislelizumab and ociperlimab serum concentration data will be tabulated and summarized by visit/cycle at which these concentrations are collected. Descriptive statistics will include means, medians, ranges, and standard deviations, as appropriate.

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

9.5. Immunogenicity Analyses

Samples to assess anti-ociperlimab and anti-tislelizumab antibodies will be collected only in patients who receive study drugs and at sites that are able to adequately perform sampling, handling, and processing as outlined in the laboratory manual.

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

9.6. Other Exploratory Analyses

Summary statistics will be provided for exploratory biomarkers including but not limited to expression of PD-L1, TIGIT, CD226, CD155, and CD112 in tumor tissues, and TMB/gene mutation/MSI and GEP in tumor tissues and/or peripheral blood.

An exploratory analysis on a potential correlation of these tumor tissue or blood-based biomarkers with response, resistance and prognosis will be performed to understand disease pathobiology and explore potential predictive biomarker.

For QoL, EQ-5D-5L descriptive and VAS scores will be compared between the 2 arms. Descriptive statistics (mean, median standard deviation, and change of scores from baseline) will be used to show the changes from baseline in each arm.

9.7. Sample Size Consideration

The sample size calculation is based on the primary efficacy analysis of ORR between Arm A and Arm B in the ITT Analysis Set.

With 120 randomized patients, the study has at least 80% power to detect a 24% difference in ORR (45% vs 21% in Arm A and Arm B, respectively) at a 1-sided type I error of 0.025.

The sample size is calculated by EAST (version 6.4.1).

9.8. Interim Analyses

No formal interim analyses will be conducted. Summaries of efficacy and safety data may be generated to inform subsequent clinical development planning.

10. STUDY COMMITTEES AND COMMUNICATION

10.1. Blinded Independent Review Committee

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

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

11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

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

11.1. Access to Information for Monitoring

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

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

11.2. Access to Information for Auditing or Inspections

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

12. QUALITY ASSURANCE AND QUALITY CONTROL

12.1. Regulatory Authority Approval

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

12.2. Quality Assurance

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

12.3. Study Site Inspections

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

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

12.4. Drug Accountability

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

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

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

13. ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1. Ethical Standard

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

13.2. Institutional Review Board/Independent Ethics Committee

This protocol, the ICFs, any information to be given to the patient, and relevant supporting information must be submitted, reviewed, and approved by the IRB/IEC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/IEC. Copies of the IRB/IEC correspondence and approval of the amended ICF/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 Safety Reports or other safety-related communications from the sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/IEC and archived in the site's study file.

13.2.1. Protocol Amendments

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

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

13.3. Informed Consent

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

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

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

Patients must 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.

13.4. 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 data set transmitted to any sponsor location.

Patient medical information obtained during this study is confidential and may be disclosed to third parties only 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 National Medical Products Administration and all other national and local health authorities; by sponsor monitors, representatives, and collaborators; and by the IRBs/IECs for each study site, as appropriate.

The investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. The investigator agrees that all information received from the sponsor, including but not limited to the Tislelizumab Investigator's Brochure, Ociperlimab Investigator's Brochure, this protocol, eCRFs, the information on the

investigational new drugs, 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 that includes confidentiality provisions inconsistent with this section is executed, that contract's provisions shall apply to the extent they are inconsistent with this section.

13.5. Financial Disclosure

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

14. DATA HANDLING AND RECORD KEEPING

14.1. Data Collection and Management Responsibilities

14.1.1. Data Entry in the Electronic Case Report Form

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

14.1.2. Data Collection

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

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

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

14.1.3. Data Management/Coding

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

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

During the course of the study, a study monitor 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, giving due consideration 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. Concomitant medications will be coded using the World Health Organization Drug Dictionary. Concomitant diseases/medical history will be coded using MedDRA.

14.2. 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. In addition, the central imaging vendor will perform the central imaging review without knowledge of treatment arm assignment. Analyses or summaries generated by randomized treatment assignment and actual treatment received will be limited and documented.

14.3. Study Records Retention

The investigator must maintain adequate and accurate records so that the conduct of the study can 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: the investigator's study file or the patient clinical source documents.

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

Patient clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the eCRFs) would include, but not be limited to, documents such as 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, and screening and enrollment log, etc.

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

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

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

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and the sponsor to

store these in sealed containers at a separate location so that they can be sealed and returned 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.

At the conclusion of this study, biological samples may be retained as outlined in the agreement with the contract research organization managing the biological samples, for a period of up to 10 years or as allowed by the IRB/IEC, whichever is shorter.

14.4. Protocol Deviations

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

The investigator is to document and explain any deviations from the approved protocol. In accordance with established IRB/IEC policies and procedures, 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.

14.5. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency(ies). The sponsor will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). 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. For 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 or stricter local criteria (International Committee of Medical Journal Editors 2022).

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 sponsors to protect proprietary information, provide comments based on information from other studies that may not yet be available to the investigator, and ensure scientific and clinical accuracy. Each investigator agrees that, in accordance with the terms of the clinical study agreement, a further delay of the publication/presentation may be requested by the sponsor to allow for patent filings and/or protection in advance of the publication/presentation.

14.6. Study and Study Center Closure

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

- Return/provide all study data to the sponsor
- Resolution and closure of all data queries
- Accountability, reconciliation, and arrangements for unused study drugs
- Review of study records for completeness
- Collection of all study documents for the trial master file filing according to GCP and local regulation
- Shipment of samples (including but not limited to those for PK, ADA, and biomarkers) to the assay laboratory for central laboratory analysis according to protocol and laboratory manual requirements

In addition, the sponsor reserves the right to suspend the enrollment or prematurely discontinue this study either at a single study center or at all study centers at any time for any reasons. 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 and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IRB/IEC promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must still be provided to the sponsor. In addition, arrangements will be made for all unused study drugs in accordance with the applicable sponsor procedures for the study.

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

14.7. Information Disclosure and Inventions

All rights, title, and interests in any inventions, expertise, 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 IRB/IEC solely for the evaluation of the study
- Information that is necessary to disclose to provide appropriate medical care to a patient
- Study results that may be published as described in Section 14.5.

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

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16. Appendices

APPENDIX 1. SCHEDULE OF ASSESSMENTS

Assessment	Prescreening[a]	Screening[a]	Treatment Cycles	EOT Visit[b]	Safety Follow-up Visits[b]				Survival Follow-up[c]
Days (Window)	**-56 to ~ -1**	**-28 to ~ -1**	**1 (±3)**	**Within 7 Days After EOT Decision**	**30 (±7) After Last Dose (on-site)**	**60 (±14) After Last Dose (Phone call)**	**90 (±14) After Last Dose (Phone call)**	**120 ± 14 Days After last Dose (for pregnancy testing)**	**Every 3 Months (±14 days)**
Informed consent [a]	x	x							
Inclusion/exclusion criteria		x							
Randomization [d]		x							
Demographics/medical history/prior medications [e]		x							
Vital signs/height and weight [f]		x	x	x	x				
Physical examination [g]		x	x	x	x				
ECOG PS		x	x	x	x				
12-lead ECG [h]		x	As clinically indicated	x	x				
Adverse events [i]		x	x	x	x	x	x		
Concomitant medications		x	x	x	x	x	x		
Hematology [j]		x[a]	x	x	x				
Serum chemistry [j]		x[a]	x	x	x				
Total CK and CK-MB [j]		x[a]	x	x	x				

Assessment	Prescreening[a]	Screening[a]	Treatment Cycles	EOT Visit[b]	Safety Follow-up Visits[b]				Survival Follow-up[c]
Days (Window)	**-56 to ~ -1**	**-28 to ~ -1**	**1 (±3)**	**Within 7 Days After EOT Decision**	**30 (±7) After Last Dose (on-site)**	**60 (±14) After Last Dose (Phone call)**	**90 (±14) After Last Dose (Phone call)**	**120 ± 14 Days After last Dose (for pregnancy testing)**	**Every 3 Months (±14 days)**
Coagulation parameters [j]		x	As clinically indicated	x	x				
Urinalysis [j]		x	As clinically indicated						
Pregnancy test [k]		x	x	x	x	x	x	x	
Thyroid function [l]		x[1]	x (every 3 cycles)	x	x				
HBV/HCV tests [m]		x	Every 4 cycles and as clinically indicated						
Pulmonary function tests [n]			As clinically indicated						
Pharmacokinetics [o]			x (Cycles 1, 2, 5, 9, and 17)		x				
Anti-drug antibodies [p]			x (Cycles 1, 2, 5, 9, and 17)		x				
Tumor assessment [q]		x	Every 6 weeks (± 7 days) for the first 54 weeks. Every 12 weeks (± 7 days) thereafter.						x
Archival/fresh tumor tissue [r]	x			x (optional)					
Blood biomarker (optional) [s]			Baseline, first response, and confirmed PD as clinically indicated						

Assessment	Prescreening[a]	Screening[a]	Treatment Cycles	EOT Visit[b]	Safety Follow-up Visits[b]				Survival Follow-up[c]
Days (Window)	**-56 to ~ -1**	**-28 to ~ -1**	**1 (±3)**	**Within 7 Days After EOT Decision**	**30 (±7) After Last Dose (on-site)**	**60 (±14) After Last Dose (Phone call)**	**90 (±14) After Last Dose (Phone call)**	**120 ± 14 Days After last Dose (for pregnancy testing)**	**Every 3 Months (±14 days)**
Study drug administration [t]			x						
EORTC QLQ-C30 [u]			Every 2 cycles for the first 54 weeks. Every 4 cycles thereafter (Cycle 1 as baseline).		x				
EORTC QLQ-OES18 [u]			Every 2 cycles for the first 54 weeks. Every 4 cycles thereafter (Cycle 1 as baseline).		x				
EQ-5D-5L [u]			Every 2 cycles for the first 54 weeks. Every 4 cycles thereafter (Cycle 1 as baseline).		x				
Survival status									x

Abbreviations: AE, adverse event; CNS, central nervous system; CK, creatine kinase; CK-MB, creatine kinase-muscle/brain; CT, computed tomography; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-OES18, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Oesophageal Carcinoma-18 Questions; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EOT, end of treatment; EQ-5D-5L, European Quality of Life 5-Dimensional 5-Level; FFPE, formalin-fixed paraffin-embedded; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; imAE, immune-mediated adverse event; IRB, Institutional Review Board; IEC, Independent Ethics Committee; IRT, interactive response technology; MRI, magnetic resonance imaging; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PD, progressive disease; PET, positron emission tomography; PK, pharmacokinetic; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone; v, version.

a. Written informed consent is required before performing any study-specific tests or procedures. Results of standard of care tests or examinations performed before obtaining informed consent and within 28 days before the first dose of study drugs may be used for screening assessments rather than repeating such tests (only applicable if the same radiographic procedure will be used throughout the study).
b. The Safety Follow-up Visit is required to be conducted 30 days (± 7 days) after the last dose of study treatment or before the initiation of a new anticancer treatment, whichever occurs first. In addition, telephone contacts with patients will be conducted to assess all imAEs and relevant concomitant medications (ie, associated with an imAE or is a new anticancer therapy) at 60 days and 90 days (±14 days) after the last dose of study treatment, regardless of whether the patient starts a new anticancer therapy. For women of childbearing potential (see Appendix 6), an additional visit to perform a pregnancy test will occur at approximately 120 days (± 14 days) after the last dose of study drugs. Visits are performed in clinic or over the phone, as needed based on assessments required.
c. Survival Follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months after the last Safety Follow-up Visit until death, loss to follow-up, withdrawal of consent, or study termination by the sponsor. All patients will be followed for survival and subsequent anticancer therapy information unless a patient requests to be withdrawn from follow-up.
d. Patients will be randomized into either Arm A or Arm B via IRT in an investigator- and patient-blinded and sponsor-unblinded fashion. All patients are required to receive study treatment within 2 business days of randomization.
e. Includes age or year of birth, sex, 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 before study entry may be collected for review by the investigator. Pre-existing AEs at baseline should be recorded as medical history.
f. Vital signs collected on study include body temperature, pulse rate, respiratory 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 30 minutes after the first infusion of study drugs. For subsequent infusions, vital signs will be collected within 60 minutes before infusion and if clinically indicated, during and 30 minutes after the infusion. Height should only be measured and recorded during screening. Weight will be measured before study drug administration in every cycle.
g. During the Screening Visit, a complete physical examination will be conducted. At subsequent visits (and as clinically indicated), limited, symptom-directed physical examinations will be performed.
h. The ECG recordings will be obtained during screening, at EOT Visit/on-site Safety Follow-up Visit, and as clinically indicated at other timepoints. Patients should be resting in semirecumbent supine position for ≥ 10 minutes before each ECG measurement.
i. 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 before the administration of study drug, only SAEs should be reported. After the first dose of study drug, all AEs and SAEs, regardless of their assessed relationship to study drug, are to be reported until either 30 days after the last dose of study treatment or the initiation of new anticancer therapy, whichever occurs first. In addition, telephone contacts with patients should be conducted to assess immune-mediated AEs and concomitant medications (if appropriate, ie, 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 study treatment, regardless of whether the patient starts a new anticancer therapy. Immune-mediated AEs (serious or nonserious) will be reported until 90 days after the last dose of ociperlimab (or placebo) and/or tislelizumab, regardless of whether the patient starts a new anticancer therapy. The investigator should report any SAEs that are assessed as related to study drug(s), at any time after treatment discontinuation.
j. Local and/or central laboratory assessments on serum chemistry, hematology, coagulation, and urinalysis will be conducted, of which certain elements will be collected as specified in Appendix 3. If laboratory tests at screening are not performed within 7 days before the first dose of study drugs, these tests should be repeated and reviewed before study drug administration. After Cycle 1, these laboratory tests are to be performed and reviewed within 48 hours before study drug administration. Urinalysis is to be conducted during the treatment period only if clinically warranted. Refer to Section 7.5.4 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.

Serum CK and CK-MB testing is included in total CK and CK-MB assessment, which will be implemented for all patients at screening, predose on Day 1 of every cycle, at the EOT Visit, and at the on-site Safety Follow-up Visit. If CK-MB fractionation is not available, serum troponins (troponin I and/or T) measurements will be performed instead.

k. 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 randomization. Urine pregnancy test will be performed at each visit prior to study treatment, the EOT Visit, and each safety follow-up visit, including 120 days after the last dose of study drugs; a serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.

l. Analysis of free T3, free T4, and TSH will be performed by a central laboratory or the local study site laboratory. Thyroid function tests will be performed at screening and every 3 cycles (ie, Day 1 of Cycles 4, 7, 10, etc), the EOT Visit, and the on-site Follow-up Visit. For sites where tests for free T3 or free T4 are not available, alternative tests can be considered after communication with medical monitor.

m. Testing will be performed by a central laboratory and/or the local laboratory at screening and will include HBV/HCV serology (HBsAg, HBsAb, HBcAb, and HCV antibody) and viral load assessment (HBV DNA and HCV RNA), which will be assessed only when HBsAg or HCV antibody is positive, respectively. Patients who have detectable HBV DNA at screening will perform the respective viral load test every 4 cycles (ie, Day 1 of Cycle 5, 9, 13, etc) from Cycle 5 onwards.

n. Pulmonary function testing includes spirometry and assessment of oxygenation, at a minimum pulse oximetry at rest and with exercise, or alternatively, assessment of diffusion capacity. Patient who are suspected of having serious/severe respiratory conditions, or who exhibit significant respiratory symptoms unrelated to the underlying cancer, or with a history of thoracic radiotherapy should be evaluated for the suitability on the study at screening. Tests may be repeated as clinically indicated while on study. Respective test results need to be submitted to the sponsor.

o. Procedures for collection of PK samples are described in the Laboratory Manual. Predose (within 60 minutes before starting infusion) samples are required to be collected on Day 1 of Cycles 1, 2, 5, 9, and 17. A postdose (within 30 minutes after completing infusion) sample is required to be collected on Day 1 of Cycles 1 and 5. An additional PK sample is required to be collected at the on-site Safety Follow-up Visit. Should a patient present with any ≥ Grade 3 imAE, an additional blood PK sample may be taken to determine the serum concentration of tislelizumab and/or ociperlimab. These tests are required when it is allowed by local regulations/IRBs/IECs.

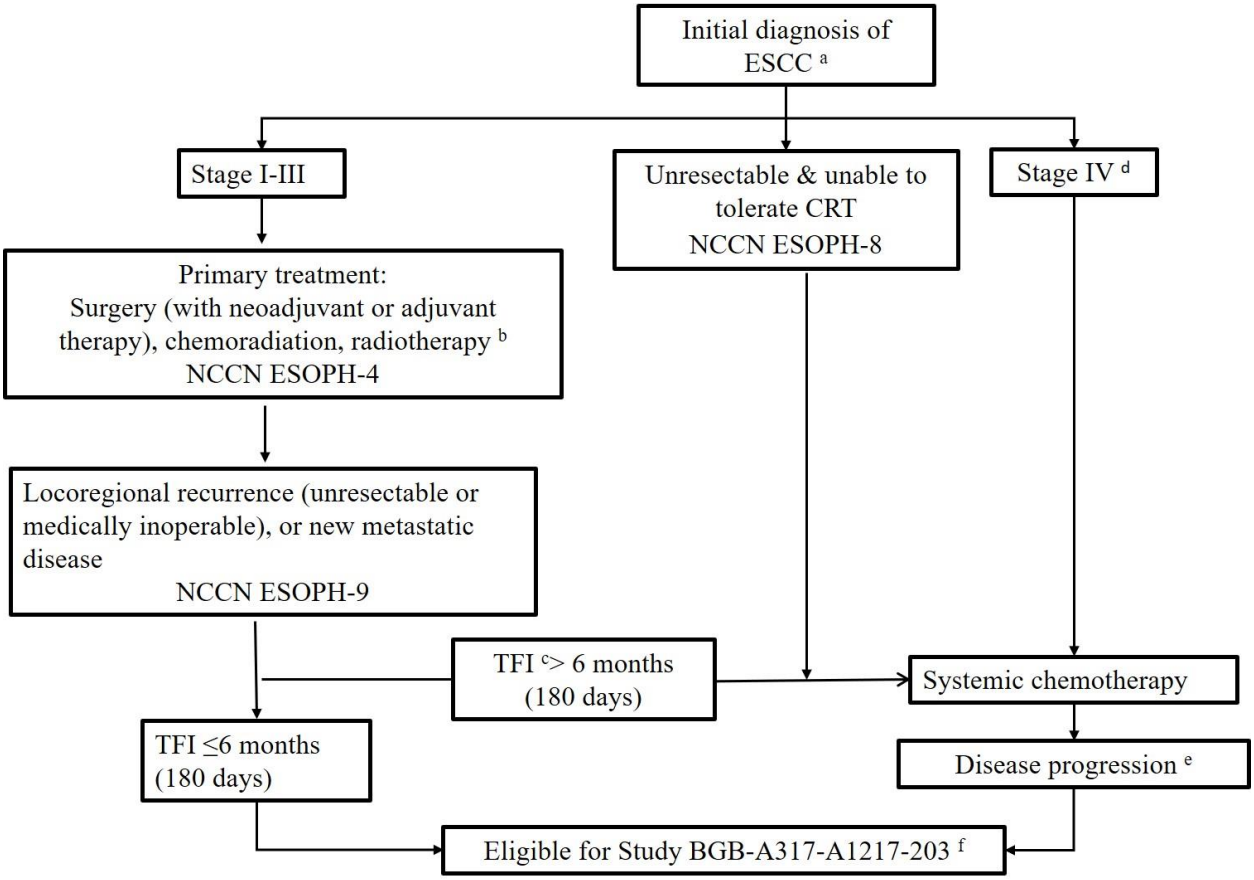
p. For both arms, blood used to test for anti-tislelizumab/anti-ociperlimab antibodies should be collected within 60 minutes before beginning the Day 1 infusion of Cycles 1, 2, 5, 9, and 17 and at the on-site Safety Follow-up Visit. All samples should be drawn at the same time as blood collection for predose PK analysis. These tests are required when it is allowed by local regulations/IRBs/IECs.

q. Radiological images captured as standard of care before obtaining written informed consent and within 28 days before randomization may be used rather than repeating tests, provided they meet the protocol specifications. All measurable and evaluable lesions are required to be assessed and documented at the Screening Visit and reassessed at each subsequent tumor evaluation. CT/MRI of the head at baseline is required for patients who are suspected to have CNS metastases; bone scan or PET is required if clinically indicated. The same radiographic procedure must be used throughout the study for each patient. The investigator must review radiograph results before dosing at the next cycle. Patients will undergo tumor assessments approximately every 6 weeks (± 7 days) for the first 54 weeks, and every 12 weeks (± 7 days) thereafter (based on RECIST v1.1 assessment). The investigator may perform additional scans or more frequent assessments if clinically indicated. Patients who discontinue from study treatment early for reasons other than PD (eg, toxicity) will continue to undergo tumor assessments following the original plan until the patient experiences PD, withdraws consent, dies, or until the study terminates, whichever occurs first. Patients who continue study treatment after radiographic PD will be monitored with a follow-up scan no more than 6 to 8 weeks after the initial diagnosis of radiographic PD before discontinuation of treatment.

r. Patients are required to provide archival tumor tissues (FFPE blocks or approximately 15 [≥ 6] unstained slides) for biomarker analysis. Fresh biopsy: In the absence of archival tumor tissues, a fresh biopsy of a tumor lesion at baseline is mandatory. Prescreening samples will be subjected to PD-L1 testing centrally. An optional biopsy will be taken at the EOT Visit for patients with confirmed PD during the study.

s. An optional blood sample will be taken at baseline (predose on Cycle 1 Day 1), at the time of first tumor response (predose on Day 1 of the following cycle) and at EOT Visit after PD (10 mL each timepoint) to explore the association with response, resistance and prognosis.
t. The first dose of study drug is to be administered within 2 business days after randomization. The initial infusions (Cycle 1 and Cycle 2, Day 1) will be delivered over 60 minutes for each dose of tislelizumab, ociperlimab, and placebo; if this is well tolerated, then the subsequent infusions may be administered over 30 minutes for each drug, which is the shortest period permissible for infusion. Treatment could continue after progression if clinical benefit is seen and treatment is tolerated per the investigator's discretion. Patients should sign an additional informed consent form for continued treatment after PD per RECIST v1.1 (see Section 5.2).
u. To be completed before any clinical activities during on-site visits. EORTC QLQ-C30, EORTC QLQ-OES18, and EQ-5D-5L will be completed before dosing on Day 1 of every other treatment cycle during the first 54 weeks, Day 1 of every 4 cycles thereafter, and at the on-site Safety Follow-up Visit.

APPENDIX 2. FLOWCHART FOR DETERMINING THE LINE OF TREATMENT IN ESOPHAGEAL SQUAMOUS CELL CARCINOMA



Abbreviations: CRT, conformal radiation therapy; ESCC, esophageal squamous cell carcinoma; NCCN ESOPH, National Comprehensive Cancer Network Esophageal Neoplasms Practice Guidelines; TFI, treatment-free interval.

a. This is a general guide to determine the line of therapy and cannot cover all possibilities; if you have questions, please consult the medical monitor.
b. For the primary treatment, single drug regimen or regimens used for radiotherapy sensitization (the dose is lower than the NCCN treatment guidance recommended standard systematic treatment dose) should not be considered as one line of therapy.
c. TFI is defined as the duration from the last day (administration day/infusion day) of prior treatment cycle to the date of PD.
d. Patients with stage IV disease at first diagnosis are eligible for this study if their cancer has progressed after the first-line of systemic chemotherapy, regardless of the length of the TFI.
e. Patients intolerant to most recent regimen due to Grade 4 hematologic toxicity or Grade 3 or 4 non-hematologic toxicity may also be eligible
f. Patients must meet all inclusion and exclusion criteria to be enrolled into this study.

APPENDIX 3. CLINICAL LABORATORY ASSESSMENTS

Clinical Chemistry	Hematology	Coagulation	Urinalysis
Alkaline phosphatase	Hematocrit	Prothrombin time	pH
ALT	Hemoglobin	Partial thromboplastin time or activated partial thromboplastin time	Specific gravity
AST	Platelet counts	International normalized ratio	Glucose
Albumin	White blood cell count		Protein
Total bilirubin	Neutrophil count		Ketones
Direct bilirubin	Lymphocyte count		
Blood urea nitrogen or urea			Blood
Potassium			24-hour protein[a]
Sodium			
Calcium			
Phosphorus			
Magnesium			
Chloride			
Creatinine			
Glucose			
Lactate dehydrogenase			
Total protein			
Creatine kinase/CK-MB [b]			

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK-MB, creatine kinase-muscle/brain.

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

[b] Cardiac enzyme testing has been added to monitor for potential event of immune-mediated myocarditis. If CK-MB fractionation is not available, assess troponin I and/or troponin T instead. Investigators should make every effort to perform either CK-MB, troponin I and/or troponin T consistently at screening and at follow-up visits.

APPENDIX 4. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, 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 5. PRE-EXISTING IMMUNE DEFICIENCIES OR AUTOIMMUNE DISEASES

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

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 myasthenia 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-Koyanagi-Harada disease

APPENDIX 6. CONTRACEPTION GUIDELINES AND DEFINITIONS OF "WOMEN OF CHILDBEARING POTENTIAL," "NO CHILDBEARING POTENTIAL"

Contraception Guidelines

The Clinical Trials Facilitation Group's recommendations related to contraception and pregnancy testing in clinical trials include the use of highly effective forms of birth control (Clinical Trials Facilitation Group 2020). 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
- Intrauterine device.
- Intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Vasectomized male partner, provided that the vasectomized partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of surgical success.
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of exposure associated with the study treatment).

  NOTE: Total sexual abstinence should only be used as a contraceptive method if it is in line with the patient's usual and preferred lifestyle.

  Periodic abstinence (eg, calendar, ovulation, symptothermal, or postovulation methods), declaration of abstinence for the duration of exposure to study drugs, and withdrawal are not acceptable methods of contraception.

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

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

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

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

- Surgically sterile (ie, through bilateral salpingectomy, bilateral oophorectomy, or hysterectomy)

- Postmenopausal, defined as:
  - FE

Adapted from: Recommendations related to contraception and pregnancy testing in clinical trials

APPENDIX 7. NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

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

Adapted from Dolgin 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 8. EORTC-QLQ-C30 QUESTIONNAIRE

EORTC QLQ-C30 (version 3)

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

Please fill in your initials: _ _ _ _

Your birthdate (Day, Month, Year): _ _ _ _ _ _ _ _

Today's date (Day, Month, Year): 31 _ _ _ _ _ _ _ _

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

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

Please go on to the next page

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

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

APPENDIX 9. EORTC QLQ-OES18 QUESTIONNAIRE

EORTC QLQ – OES18

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

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

APPENDIX 10. EQ-5D-5L QUESTIONNAIRE

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

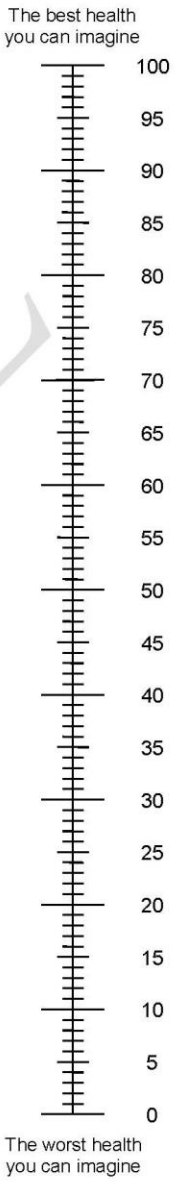
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

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

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

YOUR HEALTH TODAY = ☐



APPENDIX 11. CHRONIC KIDNEY DISEASE EPIDEMIOLOGY COLLABORATION (CKD-EPI) EQUATION

In adults, the most widely-used equations for estimating glomerular filtration rate (GFR) from serum creatinine are the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (Levey et al 2009) equation and the Modification of Diet in Renal Disease Study equation. National Kidney Disease Education Program calculators rely on creatinine determinations which are isotope dilution mass spectrometry traceable. All laboratories should be using creatinine methods calibrated to be isotope dilution mass spectrometry traceable.

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

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

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 12. IMMUNE-MEDIATED ADVERSE EVENT EVALUATION AND MANAGEMENT

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

Criteria used to diagnose imAEs include blood tests, diagnostic imaging, histopathology, and microbiology assessments to exclude alternative causes such as infection, PD, 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 study drugs and the AE?
- How did the patient respond to withdrawal of study drugs?
- Did the event recur when study drugs was/were reintroduced?
- Was there a clinical response to corticosteroids?
- Is the event an autoimmune endocrinopathy?
- Is PD 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 electronic case report form should be checked.

Recommended Diagnostic Tests in the Management of Possible Immune-Mediated Adverse Events	
Immune-Mediated Toxicity	**Diagnostic Evaluation Guideline**
Thyroid disorders	Scheduled and repeat thyroid function tests (TSH and T4).
Hypophysitis	Check visual fields and consider pituitary endocrine axis blood profile. Perform pituitary and whole brain MRI in patients with headache, visual disturbance, unexplained fatigue, asthenia, weight loss, and unexplained constitutional symptoms. Consider consultation with an endocrinologist if an abnormality is detected.
Pneumonitis	All patients presenting with new or worsened pulmonary symptoms or signs, such as an upper respiratory infection, new cough, shortness of breath or hypoxia should be assessed by high-resolution CT. Consider pulmonary function test including *D*LCO. Radiographic appearance is often nonspecific. Depending on the location of the abnormality, bronchoscopy and bronchoalveolar lavage or lung biopsy may be considered. Consult with a respiratory medicine physician for cases of uncertain cause.
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

Recommended Diagnostic Tests in the Management of Possible Immune-Mediated Adverse Events	
Immune-Mediated Toxicity	**Diagnostic Evaluation Guideline**
	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 ≥ 3-4; every 2-3 days if Grade 2, until recovering). Review medications (eg, statins, antibiotics) and alcohol history. Perform liver screen including hepatitis A/B/C serology, hepatitis E PCR and assess anti-ANA/SMA/LKM/SLA/LP/LCI, iron studies. Consider imaging (eg, ultrasound scan for metastases or thromboembolism). Consult with a hepatologist and consider liver biopsy.
Renal toxicity	Review hydration status and medication history. Test and culture urine. Consider renal ultrasound scan, protein assessment (dipstick/24-hour urine collection), or phase-contrast microscopy. Refer to nephrology for further management assistance.
Dermatology	Consider other causes by conducting a physical examination; consider dermatology referral for skin biopsy.
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 I and consider a muscle biopsy.
Myocarditis	Perform ECG, echocardiogram, troponin I, and refer to a cardiologist.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; CK, creatine kinase; 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; INR, international normalized ratio; LCI, liver cytosolic antigen; LFT, liver function test; LKM, liver kidney microsomal antibody; LP, liver pancreas antigen; MRA, magnetic resonance angiogram; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; SLA, soluble liver antigen; SMA, smooth muscle antibody; T4, thyroxine; TFT, thyroid function tests; TSH, thyroid-stimulating hormone; UEC, urea electrolytes and creatinine.

Treatment of Immune-mediated Adverse Events

- Immune-mediated AEs can escalate quickly; study treatment interruption, close monitoring, timely diagnostic work-up, and treatment intervention, as appropriate, with patients is required
- Immune-mediated AEs should improve promptly after introduction of immunosuppressive therapy. If this does not occur, review the diagnosis, seek further specialist advice, and contact the medical monitor

- For some Grade 3 toxicities that resolve quickly, rechallenge with study drugs may be considered if there is evidence of a clinical response to study treatment after consultation with the medical monitor
- Steroid dosages in the table below are for oral or intravenous (methyl)prednisolone. Equivalent dosages of other corticosteroids can be substituted. For steroid-refractory imAEs, consider use of steroid-sparing agents (eg, mycophenolate mofetil [MMF])
- Consider prophylactic antibiotics for opportunistic infections if the patient is receiving long-term immunosuppressive therapy

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Thyroid disorders	**1-2** Asymptomatic TFT abnormality or mild symptoms	Replace thyroxine if hypothyroid, until TSH/T4 levels return to normal range. Thyrotoxic patients should be referred to an endocrinologist. In cases with systemic symptoms: withhold study treatment, treat with a beta blocker and consider oral prednisolone 0.5 mg/kg/day for thyroid pain. Taper corticosteroids over 2-4 weeks. Monitor thyroid function regarding the need for hormone replacement.	Continue study treatment or withhold treatment in cases with systemic symptoms.
	3-4 Severe symptoms, hospitalization required	Refer patient to an endocrinologist. If hypothyroid, replace with thyroxine 0.5-1.6 µg/kg/day (for the elderly or those with co-morbidities, the suggested starting dose is 0.5 µg/kg/day). Add oral prednisolone 0.5 mg/kg/day for thyroid pain. Thyrotoxic patients require treatment with a beta blocker and may require carbimazole until thyroiditis resolves.	Hold study treatment; resume when resolved/improved to Grade 0-1.
Hypophysitis	**1-2** Mild symptoms	Refer patient to an endocrinologist for hormone replacement. Add oral prednisolone 0.5-1 mg/kg/day for patients with pituitary inflammation. Taper corticosteroids over at least 1 month. If there is no improvement in 48 hours, treat as Grade 3-4. Taper corticosteroids over at least 1 month.	Continue study treatment.

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

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3-4 Severe/life-threatening, Grade 3 or 4 encephalitis, or Guillain-Barré syndrome	Initiate treatment with oral prednisolone or IV methylprednisolone 1-2 mg/kg/day, depending on symptoms. Taper corticosteroids over at least 4 weeks. Consider azathioprine, MMF, cyclosporine if no response within 72-96 hours. Guillain-Barré syndrome: Start intravenous immunoglobulin 0.4 g/kg/day for 5 days or plasmapheresis. Consider corticosteroids (methylprednisolone 2 to 4 mg/kg/day) followed by a slow taper. Monitor for concurrent autonomic dysfunction.	Discontinue study treatment.
Colitis/diarrhea	**1** Mild symptoms: < 3 liquid stools per day over baseline and feeling well	Symptomatic management: fluids, loperamide, avoid high fiber/lactose diet. If Grade 1 persists for > 14 days manage as a Grade 2 event.	Continue study treatment.
	2 Moderate symptoms: 4-6 liquid stools per day over baseline, or abdominal pain, or blood in stool, or nausea, or nocturnal episodes	Oral prednisolone 0.5 mg/kg/day (non-enteric coated). Do not wait for any diagnostic tests to start treatment. Taper steroids over 2-4 weeks, consider endoscopy if symptoms are recurring.	Hold study treatment; resume when resolved/improved to baseline grade.
	3 Severe symptoms: > 6 liquid stools per day over baseline, or if episodic within 1 hour of eating	Initiate IV methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Consider prophylaxis for adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement. If no improvement in 72 hours or symptoms worsen, consider infliximab 5 mg/kg; if no perforation, sepsis, TB, hepatitis, NYHA Grade III/IV CHF or other immunosuppressive treatment: MMF or tacrolimus. Consult gastroenterologist to conduct colonoscopy/sigmoidoscopy.	Hold study treatment; retreatment may be considered when resolved/improved to baseline grade and after discussion with the study medical monitor.
	4 Life-threatening symptoms		Discontinue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
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.	Consider holding study treatment and monitor weekly for improvement. If not resolved, interrupt treatment until improved to Grade 1.
	3 Rash covers > 30% BSA or Grade 2 with substantial symptoms	Avoid skin irritants and sun exposure; topical emollients recommended. Initiate steroids as follows based on clinical judgement: For moderate symptoms: oral prednisolone 0.5-1 mg/kg/day for 3 days then taper over 2-4 weeks. For severe symptoms: IV methylprednisolone 0.5-1 mg/kg/day; convert to oral prednisolone and taper over at least 4 weeks.	Hold study treatment. Re-treat when AE is resolved or improved to mild rash (Grade 1-2) after discussion with the study medical monitor.
	4 Skin sloughing > 30% BSA with associated symptoms (eg, erythema, purpura, epidermal detachment)	Initiate IV methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Admit to a hospital and seek urgent dermatology consultation.	Discontinue study treatment.
Hepatitis	**1** ALT or AST > ULN to 3X ULN	Check LFTs within 1 week and before the next dose check LFTs to verify that there has been no worsening. If LFTs are worsening, recheck every 48-72 hours until improvement is seen.	Continue study treatment if LFTs are unchanged or improving. Hold study treatment if LFTs are worsening until improvement is seen.
	2 ALT or AST 3-5X ULN	Recheck LFTs every 48-72 hours: For persistent ALT/AST elevation: consider oral prednisolone 0.5-1 mg/kg/day for 3 days then taper over 2-4 weeks. For rising ALT/AST: start oral prednisolone 1 mg/kg/day and taper over 2-4 weeks; re-escalate dose if LFTs worsen, depending on clinical judgement.	Hold study treatment; treatment may be resumed when resolved/improved to baseline grade and prednisolone tapered to ≤ 10 mg.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3 ALT or AST 5-20X ULN	Immediately start methylprednisolone 1 to 2 mg/kg (or equivalent). Monitor closely. If no improvement after 3 days, consider additional treatment options (MMF or azathioprine).	If ALT and AST ≤ 10 x ULN: Hold study treatment until improved to baseline grade; reintroduce only after discussion with the medical monitor. If ALT or AST > 10 x ULN: Discontinue study treatment.
	4 ALT or AST > 20X ULN	Initiate IV methylprednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over ≥ 6 weeks.	Discontinue study treatment.
	Worsening LFTs despite steroids: If on oral prednisolone, change to pulsed IV methylprednisolone If on IV, add MMF 500-1000 mg twice a day If worsens on MMF, consider addition of tacrolimus Duration and dose of steroid required will depend on severity of event		
Nephritis	**1** Creatinine 1.5X baseline or > ULN to 1.5X ULN	Repeat creatinine weekly. If symptoms worsen, manage as per criteria below.	Continue study treatment.
	2 Creatinine > 1.5X-3X baseline or > 1.5X-3X ULN	Ensure hydration and review creatinine in 48-72 hours; if not improving, consider creatinine clearance measurement by 24-hour urine collection. Discuss with nephrologist the need for kidney biopsy. If attributed to study drug, initiate oral prednisolone 0.5-1 mg/kg and taper over at least 2 weeks. Repeat creatinine/U&E every 48-72 hours.	Hold study treatment. If not attributed to drug toxicity, restart treatment. If attributed to study drug and resolved/improved to baseline grade: Restart study drug if tapered to < 10 mg prednisolone.
	3 Creatinine > 3X baseline or > 3X-6X ULN	Hospitalize patient for monitoring and fluid balance; repeat creatinine every 24 hours; refer to a nephrologist and discuss need for biopsy. If worsening, initiate IV (methyl)prednisolone 1-2 mg/kg. Taper corticosteroids over at least 4 weeks.	Hold study treatment until the cause is investigated. If study drug suspected: Discontinue study treatment.
	4 Creatinine > 6X ULN	As per Grade 3, patient should be managed in a hospital where renal replacement therapy is available.	Discontinue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
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
	3 Fasting glucose value 250-500 mg/dL; 13.9-27.8 mmol/L	Admit patient to hospital and refer to a diabetologist for hyperglycemia management. Corticosteroids may exacerbate hyperglycemia and should be avoided.	Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1.
	4 Fasting glucose value > 500 mg/dL; > 27.8 mmol/L	Admit patient to hospital and institute local emergency diabetes management. Refer the patient to a diabetologist for insulin maintenance and monitoring.	
Ocular toxicity	**1** Asymptomatic eye exam/test abnormality	Consider alternative causes and prescribe topical treatment as required.	Continue study treatment.
	2 Anterior uveitis or mild symptoms	Refer patient to an ophthalmologist for assessment and topical corticosteroid treatment. Consider a course of oral steroids.	Continue study treatment or hold treatment if symptoms worsen or if there are symptoms of visual disturbance.
	3 Posterior uveitis/panuveitis or significant symptoms	Refer patient urgently to an ophthalmologist. Initiate oral prednisolone 1-2 mg/kg and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1; reintroduce only after discussion with the study medical monitor.
	4 Blindness (at least 20/200) in the affected eyes	Initiate IV (methyl)prednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks.	Discontinue study treatment.
Pancreatitis	**2** Asymptomatic, blood test abnormalities	Monitor pancreatic enzymes.	Continue study treatment.
	3 Abdominal pain, nausea and vomiting	Admit to hospital for urgent management. Initiate IV (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when amylase/lipase improved to Grade 2, and taper over at least 4 weeks.	Hold study treatment; reintroduce only after discussion with the study medical monitor.

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

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
		symptoms do not improve add immunosuppressant therapy. Taper oral steroids over at least 4 weeks.	evidence of myocardial involvement.
Myocarditis	**< 2** Asymptomatic but significantly increased CK-MB or increased troponin OR clinically significant intraventricular conduction delay	Admit to hospital and refer to a cardiologist. Transfer all patients with moderate/severe cardiac symptoms or any increase in cardiac serum markers to the coronary care unit. Initiate oral prednisolone or IV (methyl)prednisolone at 1-2 mg/kg/day. Manage symptoms of cardiac failure according to local guidelines. If no immediate response change to pulsed doses of (methyl)prednisolone 1 g/day and add MMF, infliximab or anti-thymocyte globulin.	Hold study treatment until completely resolved or myocarditis has been ruled out.
	2 Symptoms on mild-moderate exertion		Discontinue study treatment unless cardiac involvement has been excluded and symptoms have completely resolved.
	3 Severe symptoms with mild exertion		
	4 Life-threatening		

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

APPENDIX 13. THE RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) GUIDELINES, VERSION 1.1

The text below was obtained from the following reference: Eisenhauer et al 2009.

DEFINITIONS

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

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

Measurable Disease

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

- 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm).
- 10 mm caliper measurement by clinical examination (when superficial).
- 20 mm by chest x-ray (if clearly defined and surrounded by aerated lung).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT or MRI scan (CT/MRI scan slice thickness recommended to be ≥ 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable Disease

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

Bone lesions:

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

Cystic lesions:

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

Lesions with prior local treatment:

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

Target Lesions

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

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

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

Non-target Lesions

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

GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE

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

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

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

- Chest x-ray: Chest CT is preferred over chest x-ray, particularly when progression is an important endpoint, because 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 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 to differentiate between response (or stable disease) and PD.

RESPONSE CRITERIA

Evaluation of Target Lesions

- CR: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- PD: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of 1 or more new lesions is also considered progression).
- Stable disease: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
- Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the “sum” of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report recorded in a separate section where, to qualify for CR, each node must achieve a short axis < 10 mm. For PR, stable disease,

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 non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.
- Lesions that split or coalesce on treatment: When non-nodal lesions "fragment," the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion."

Evaluation of Non-target Lesions

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

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

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

- When the patient has only non-measurable disease: This circumstance arises in some Phase 3 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 non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase diameter in a measurable lesion).
- Examples include an increase in a pleural effusion from "trace" to "large," an increase in lymphangitic disease from localized to widespread, or may be described in protocols as "sufficient to require a change in therapy." If "unequivocal progression" is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

New Lesions

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

A lesion identified on a follow-up trial in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate PD. An example of this is the patient who has visceral disease at baseline and while on trial 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 fluorine-18 [F-18] fluorodeoxyglucose (FDG)-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible "new" disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

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

Evaluation of Best Overall Response

The BOR is the best response recorded from the start of the study drug treatment until the end of treatment considering any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of BOR. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's BOR assignment will depend on the findings of both target and non-target 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 "BOR."

The BOR is determined once all the data for the patient is known. Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all timepoints (for example, a patient who has stable disease at first assessment, PR at second assessment, and PD on last assessment has a BOR of PR). When stable disease 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 stable disease is otherwise the best timepoint response, the patient's best response depends on the subsequent assessments. For example, a patient who has stable disease at first assessment, PD at second and does not meet minimum duration for stable disease, will have a best response of PD. The same patient lost to follow-up after the first stable disease assessment would be considered inevaluable.

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
Stable disease	Non-PD or not all evaluated	No	Stable disease
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.

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

In trials where confirmation of response is required, repeated 'NE' timepoint 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 timepoint responses of PR-not evaluable-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of PD 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 at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

Confirmation

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

In the case of stable disease, measurements must have met the stable disease 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 disease or PD is objectively documented (taking as reference for PD 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 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 DOR and stable disease as well as the PFS are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should consider many parameters including disease types and stages, treatment periodicity, and standard practice. However, these limitations of the precision of the measured endpoint should be considered if comparisons between trials are to be made.

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