CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 2, Multicenter, Randomized, 3-Arm, Open-Label Study to Investigate the Preliminary Efficacy and Safety of the Anti-TIGIT Monoclonal Antibody Ociperlimab (BGB-A1217) Plus Tislelizumab Plus Concurrent Chemoradiotherapy in Patients With Untreated Limited-Stage Small Cell Lung Cancer
Protocol Identifier:	AdvanTIG-204
Phase:	2
Investigational Products:	Ociperlimab (BGB-A1217) and tislelizumab (BGB-A317)
Indication:	Untreated limited-stage small cell lung cancer (LS-SCLC)
Sponsor:	BeiGene, Ltd. c/o BeiGene USA, Inc. 2955 Campus Drive, Suite 200 San Mateo, California 94403 USA
Sponsor Medical Monitor:	[redacted] Telephone: [redacted] Email: [redacted]
Original Protocol Version 0.0:	25 February 2021
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Protocol Amendment Version 3.0:	08 October 2021

Confidentiality Statement

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FINAL PROTOCOL APPROVAL SHEET

A Phase 2, Multicenter, Randomized, 3-Arm, Open-Label Study to Investigate the Preliminary Efficacy and Safety of the Anti-TIGIT Monoclonal Antibody Ociperlimab (BGB-A1217) Plus Tislelizumab Plus Concurrent Chemoradiotherapy in Patients With Untreated Limited-Stage Small Cell Lung Cancer

INVESTIGATOR SIGNATURE PAGE

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Protocol Identifier: AdvanTIG-204

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 Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd., or one of its subsidiaries.

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

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

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

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SYNOPSIS

Name of Sponsor/Company: BeiGene, Ltd.
Investigational Products: Ociperlimab (BGB-A1217) and tislelizumab (BGB-A317)
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Protocol Identifier: AdvanTIG-204
Phase of Development: 2
Number of Patients: Approximately 120
Study Centers: Approximately 30 to 40 centers internationally
Study Objectives: **Primary:** • To compare progression-free survival (PFS) between Arm A (ociperlimab [BGB-A1217] plus tislelizumab plus concurrent chemoradiotherapy [cCRT]) and Arm C (cCRT only) and between Arm B (tislelizumab plus cCRT) and Arm C as assessed by the investigator according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) in the Intent-to-Treat (ITT) Analysis Set **Secondary:** • To compare the following between Arm A and Arm C and between Arm B and Arm C as assessed by the investigator according to RECIST v1.1 in the ITT Analysis Set: - Complete response (CR) rate - Overall response rate (ORR) - Duration of response (DOR) - Overall survival (OS) - Distant metastasis-free survival (DMFS) • To evaluate the correlation of programmed cell death ligand-1 (PD-L1) and T-cell immunoglobulin and ITIM domain (TIGIT) expression with ORR, PFS, and OS • To evaluate the safety and tolerability of ociperlimab combined with tislelizumab plus cCRT and tislelizumab plus cCRT **Exploratory:** • To explore prognostic and predictive effects of tissue- and blood-based biomarkers on efficacy and their association with mechanisms of resistance • To evaluate health-related quality of life (HRQoL) • To assess the utility of circulating tumor DNA (ctDNA) level change as a surrogate marker for efficacy

- To assess the pharmacokinetics (PK) of ociperlimab and tislelizumab
- To assess the immunogenicity of ociperlimab and tislelizumab

Study Endpoints:

Primary:

- PFS, defined as the time from the date of randomization to the date of the first documented disease progression as determined by the investigator per RECIST v1.1 or death from any cause (whichever occurs first), in the ITT Analysis Set of Arms A, B, and C

Secondary Endpoints:

- CR rate, defined as the proportion of patients who had CR as assessed by the investigator per RECIST v1.1, in the ITT Analysis Set of Arms A, B, and C
- ORR, defined as the proportion of patients who had CR or partial response (PR) as assessed by the investigator per RECIST v1.1, in the ITT Analysis Set of Arms A, B, and C
- DOR, defined as the time from the date of the first occurrence of a documented objective response to the date of documented disease progression as assessed by the investigator per RECIST v1.1 or death from any cause (whichever occurs first), in the ITT Analysis Set of Arms A, B, and C
- OS, defined as the time from the date of randomization to the date of death due to any cause, in the ITT Analysis Set of Arms A, B, and C
- DMFS, defined as the time from the date of randomization to the date of the first documented distant metastasis as assessed by the investigator per RECIST v1.1 or death from any cause (whichever occurs first), in the ITT Analysis Set of Arms A, B, and C
- ORR, PFS, and OS in subgroups based on PD-L1 and TIGIT expression levels
- The incidence and severity of treatment-emergent adverse events (TEAEs) graded according to National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v5.0).

Exploratory Endpoints:

- Biomarkers from patient-derived tumor tissue(s) and/or blood samples obtained before, during, and/or after treatment including but not limited to gene expression profile, tissue- or blood-based gene mutations and tumor mutational burden (TMB)/microsatellite instability (MSI), CD155/CD226 expression, and small cell lung cancer (SCLC) subtyping (ASCL1/NEUROD1/POU2F3/YAP1)
- HRQoL assessment using 2 patient-reported outcomes (PROs) including the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and its lung cancer module Quality of Life Questionnaire Lung Cancer 13 (QLQ-LC13)
- The ctDNA level change before, during, and after treatment as a surrogate marker for efficacy
- Serum concentrations of ociperlimab and tislelizumab at specified timepoints
- Assessment of immunogenicity of ociperlimab and tislelizumab by determining the incidence of antidrug antibodies (ADAs)

Study Design

This is a Phase 2, multicenter, randomized, 3-arm, open-label study to investigate the preliminary efficacy and safety of the anti-TIGIT monoclonal antibody ociperlimab plus tislelizumab plus cCRT followed by ociperlimab plus tislelizumab (Arm A) and tislelizumab plus cCRT followed by tislelizumab only (Arm B) compared with cCRT only (Arm C) in patients with previously untreated limited-stage small cell lung cancer (LS-SCLC).

The primary endpoint is investigator-assessed PFS in the ITT Analysis Set for the comparisons of Arm A versus Arm C and Arm B versus Arm C.

Approximately 120 patients will be randomized in a 1:1:1 ratio to receive the study treatment in the following 3 arms:

- Arm A: Ociperlimab 900 mg intravenously once every 3 weeks plus tislelizumab 200 mg intravenously once every 3 weeks combined with cCRT for 4 cycles, followed by ociperlimab 900 mg intravenously once every 3 weeks plus tislelizumab 200 mg intravenously once every 3 weeks
- Arm B: Tislelizumab 200 mg intravenously once every 3 weeks combined with cCRT for 4 cycles, followed by tislelizumab 200 mg intravenously once every 3 weeks
- Arm C: cCRT only for 4 cycles

Randomization will be stratified by disease stage (I/II versus III) by the American Joint Committee on Cancer staging system, 8th edition.

The chemotherapy regimen is cisplatin 75 mg/m^2 on Day 1 of each cycle for 4 cycles. If the patient is unable to tolerate the 1-day administration of cisplatin 75 mg/m^2, at the investigator's discretion (eg, patients had concurrent superior vena cava syndrome) cisplatin 25 mg/m^2 dosed on Days 1, 2, and 3 is allowed. Etoposide is administered at 100 mg/m^2 on Days 1, 2, and 3 for 4 cycles. Dose adjustment is allowed to address potential renal, hematologic, or other toxicities after the first cycle.

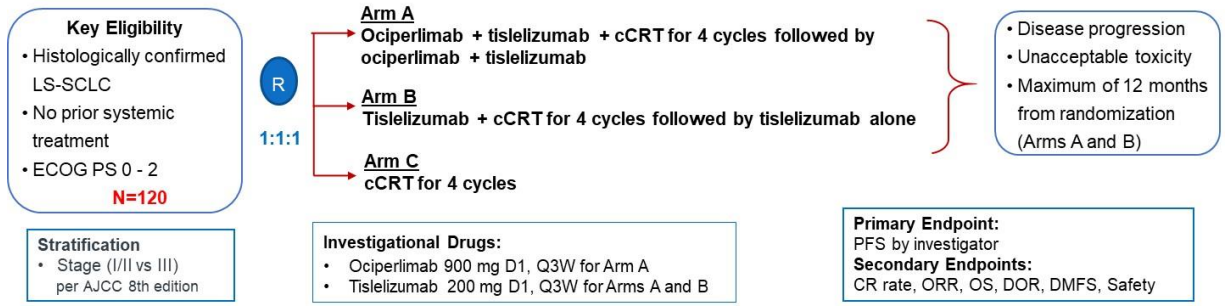
If cisplatin is contraindicated or not tolerated, carboplatin and etoposide will be the alternative regimen (Section 5.2.2.1). Carboplatin at a dose of area under the plasma or serum concentration-time curve 5 (AUC 5) should be administered as an intravenous infusion once every 3 weeks on Day 1 of each cycle for 4 cycles and etoposide 100 mg/m^2 should be administered on Days 1, 2, and 3 of each cycle for 4 cycles.

For Arm A and Arm B, investigational drug(s) (ociperlimab plus tislelizumab [Arm A] or tislelizumab alone [Arm B]) will be given starting on Cycle 1 Day 1 (C1D1) before chemotherapy and continued for a duration of up to 12 months (a maximum of 17 cycles of treatment) or until disease progression according to RECIST v1.1, unacceptable toxicity, death, or another discontinuation criterion is met, whichever occurs first.

Radiation therapy (RT) should start early within cycle 1 or 2 of systemic therapy. The total dose of RT will be 60 to 70 Gy, given in once-daily fractions over 6 to 7 weeks.

Prophylactic cranial irradiation (PCI) is permitted at the investigator's discretion. The preferred total dose for PCI to the whole brain is 25 Gy in 10 daily fractions.

Study Schema



Study Assessments:

Tumor Assessments:

Tumor imaging will be performed ≤ 28 days before randomization. During the study, tumor imaging will be performed at approximately 12 weeks (± 7 days) from the date of randomization (an additional tumor assessment is allowed if clinically indicated), then every 6 weeks (± 7 days) for the next 54 weeks, and then every 12 weeks (± 7 days) thereafter based on RECIST v1.1.

Administration of study treatment will continue for up to 12 months (17 cycles maximum) for Arms A and B and for 4 cycles for Arm C, or until disease progression as assessed by the investigator according to RECIST v1.1, unacceptable toxicity, death, or another discontinuation criterion is met, whichever occurs first.

A patient who discontinues study treatment early for reasons other than disease progression (eg, toxicity) will continue to undergo tumor assessments following the original schedule until disease progression according to RECIST v1.1, withdrawal of consent, loss to follow-up, start of a new anticancer therapy, death, or study termination, whichever occurs first.

In Arms A and B, treatment with ociperlimab plus tislelizumab or with tislelizumab alone beyond the initial investigator-assessed, RECIST v1.1-defined disease progression is permitted provided that the patient has investigator-assessed clinical benefit and is tolerating the study drug(s). The following criteria must be met in order to treat patients who may continue to benefit from study drugs after disease progression:

- Absence of clinical symptoms and signs of disease progression (including clinically significant worsening of laboratory values).
- Stable Eastern Cooperative Oncology Group (ECOG) Performance Status (≤ 2).
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, cord compression) that requires urgent alternative medical intervention.
- Investigators must obtain written informed consent for treatment beyond radiologic disease progression and inform patients that this practice is not considered standard in the treatment of cancer.

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

Safety Assessments:

Patients will be evaluated for any AEs and serious adverse events (SAEs) occurring up to 30 days after the last dose of study treatment (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 ociperlimab or tislelizumab, regardless of initiation of a new anticancer therapy. All treatment-related SAEs will be recorded by the investigator after treatment discontinuation until patient death, withdrawal of consent, or loss to follow-up, whichever occurs first. All study treatment-related SAEs will be followed until they resolve to baseline or ≤ Grade 1, the investigator

assesses the AE as stable and unlikely to improve, the patient is lost to follow-up, or the patient withdraws consent, whichever occurs first.

Safety assessments will also include laboratory values (eg, hematology, clinical chemistry, coagulation, urinalysis), vital signs, electrocardiograms (ECGs), ECOG Performance Status, and physical examinations.

Patient-Reported Outcomes:

Patient-reported outcomes will be collected using the EORTC QLQ-C30 and QLQ-LC13 questionnaires will be completed at predose on Day 1 of every cycle from Cycle 1 (baseline) through Cycle 4, and then to coincide with scheduled tumor assessments (every 6 weeks [± 7 days]) until the EOT Visit (Arms A, B, and C).

Safety Monitoring Committee:

A Safety Monitoring Committee (SMC) consisting of qualified investigators who are taking part in the study will be implemented to support the study and structure the scientific input. The SMC will conduct safety assessments at the following timepoints:

- After approximately 6 patients (≥ 2 patients per arm) have completed 2 cycles of study treatment
- After approximately 18 patients (≥ 6 patients per arm) have completed 2 cycles of study treatment or no later than 6 months after the first SMC evaluation, whichever occurs first
- After the scheduled SMC assessments, the SMC will review data approximately every 6 months for the first 18 months of the study and yearly thereafter

The SMC could review data more frequently if indicated or requested by the medical monitor or SMC based on ongoing safety monitoring of patients on study. The SMC may recommend study modifications including early termination of the study due to safety concerns. Full details of the SMC procedures and processes can be found in the SMC Charter.

Enrollment may continue during these SMC safety reviews.

The study will be conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines.

Duration of Patient Participation:

Duration of treatment will be up to 12 months for Arms A and B (17 cycles maximum), including approximately 3 months (4 cycles) for concurrent administration of chemoradiotherapy, and approximately 3 months (4 cycles) for Arm C. Each patient's study course will include:

- Screening period of up to 28 days before randomization
- Treatment for durations described above or until disease progression (or any other reasons for discontinuation before progression)
- Safety Follow-up Visit to occur within 30 days (± 7 days) after the last dose of study treatment

Survival follow-up information will be collected every 3 months after the Safety Follow-up Visit until death, withdrawal of consent, loss to follow-up, or study completion. The end of study is defined as the timepoint when the final data for the study has been collected, which is after the last study patient has made the final visit to the study location. The duration from the first enrolled patient to the final analysis for PFS is estimated to be approximately 30 months.

Study Population:

The study will enroll approximately 120 patients (randomized at a 1:1:1 ratio) who meet the inclusion/exclusion criteria outlined below.

Key Eligibility Criteria:

Key Inclusion 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 or cytologically confirmed diagnosis of LS-SCLC that is considered unresectable and can be safely treated with definitive radiation doses. Patients must not have received prior treatment for LS-SCLC. Patients must submit qualified archival tumor tissue with an associated pathology report or agree to a tumor biopsy. All patients are also required to have measurable disease per RECIST v1.1 within 28 days before randomization, an ECOG Performance Status ≤ 2, life expectancy ≥ 12 weeks, and adequate organ function. For full inclusion criteria, see Section 4.1.

Key Exclusion Criteria:

Patients will not have mixed SCLC histology (except for mixed SCLC with neuroendocrine carcinoma origin) and will not have received surgical resection for LS-SCLC. Patients must not 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. For full exclusion criteria, see Section 4.2.

Investigational Product, Dose, and Mode of Administration:

- Ociperlimab will be administered at a dose of 900 mg intravenously once every 3 weeks on Day 1 of each cycle
- Tislelizumab will be administered at a dose of 200 mg intravenously once every 3 weeks on Day 1 of each cycle

Reference Therapy, Dose, and Mode of Administration:

Allowed chemotherapy regimens:

- Cisplatin plus etoposide
  - Cisplatin 75 mg/m^2 should be administered as an intravenous infusion once every 3 weeks on Day 1 of each cycle for 4 cycles; If the patient is unable to tolerate the 1-day administration of cisplatin 75 mg/m^2, at the investigator's discretion (eg, patients had concurrent superior vena cava syndrome)
  - cisplatin 25 mg/m^2 dosed on Days 1, 2, and 3 is allowed.
  - Etoposide (100 mg/m^2) should be administered as an intravenous infusion on Days 1, 2, and 3 of each cycle for 4 cycles.
- Carboplatin plus etoposide. To be used if cisplatin is contraindicated. Also, patients will be allowed to switch from cisplatin to carboplatin if they exhibit intolerance to cisplatin after completing ≥ 1 cycle of cisplatin treatment (Section 5.2.2.1)
  - Carboplatin at a dose of AUC 5 should be administered as an intravenous infusion once every 3 weeks on Day 1 of each cycle for 4 cycles.

– Etoposide (100 mg/m^2) should be administered as an intravenous infusion on Days 1, 2, and 3 of each cycle for 4 cycles.

Thoracic radiation therapy (TRT):

- Once-daily fractions for 6 to 7 weeks for a total dose of 60 to 70 Gy

Statistical Methods:

Analysis sets:

The ITT Analysis Set includes all randomized patients. Patients will be analyzed according to their randomized treatment arm. This will be the primary analysis set for all efficacy analysis.

The Safety Analysis Set includes all patients who have received ≥ 1 dose of any component of study drug; it will be the analysis set used for the safety analyses.

The PK Analysis Set includes all patients who receive ≥ 1 dose of tislelizumab/ociperlimab per the protocol and for whom any quantifiable postbaseline PK data are available.

The ADA Analysis Set, which includes all patients who receive ≥ 1 dose of tislelizumab/ociperlimab and for whom both baseline and ≥ 1 postbaseline ADA result are available.

The Biomarker Analysis Set includes all patients who have ≥ 1 evaluable biomarker measurement; it will be used for the biomarker analysis.

Efficacy analysis:

The efficacy endpoints including PFS, CR rate, ORR, DOR, and OS will be summarized by arm in the ITT Analysis Set. The efficacy endpoints will be compared in Arm A versus Arm C and Arm B versus Arm C. These analyses are descriptive and exploratory; no formal testing was designed for this study.

The primary endpoint is PFS assessed by investigators. PFS per investigator is defined as the time from the date of randomization to the date of the first documented disease progression as assessed by the investigator according to RECIST v1.1 or death from any cause, whichever occurs first. Kaplan-Meier methodology will be used to estimate median or other quartiles of PFS along with its 95% confidence interval (CI); constructed using Brookmeyer and Crowley method). Kaplan-Meier curves will be constructed to provide a visual description of the PFS distribution. Event-free rate at selected timepoints will be estimated with 95% CI estimated using Greenwood formula. The hazard ratio (HR) for PFS for each comparison (ie, Arm A versus Arm C, Arm B versus Arm C) will be estimated using a stratified Cox regression model. The 95% CI for the HR will be provided. Unstratified analysis will also be presented.

CR rate is the proportion of patients who had a CR as assessed by the investigator per RECIST v1.1 in all randomized patients with measurable disease at baseline. Patients without any postbaseline assessment will be considered as nonresponders. CR rate and its Clopper-Pearson 95% CI will be calculated for each arm. The comparison of CR rate between arms will be evaluated using the Cochran-Mantel-Haenszel (CMH) X^2 test with the actual stratification factors as strata. Odds ratio and the difference in CR rate, as well as their 2-sided 95% CIs, will be calculated.

ORR is the proportion of patients who had a CR or PR as assessed by the investigator per RECIST v1.1 in all randomized patients with measurable disease at baseline. Patients without any postbaseline assessment will be considered as nonresponders. Similar methodology used to evaluate CR rate will be applied to the analysis of ORR.

DOR is defined for patients with an objective response as the time from the date of the first documented objective response to the date of documented disease progression as assessed by the investigator using RECIST v1.1 or death from any cause, whichever occurs first. Only patients who have achieved objective responses will be included in the analysis of DOR. Similar methodology used

to evaluate PFS will be applied to the analysis of DOR.

DMFS is defined as the time from the date of randomization to the date of the first documented distant metastasis as assessed by the investigator per RECIST v1.1 or death from any cause, whichever occurs first. Similar methodology used to evaluate PFS will be applied to the analysis of DMFS.

OS is defined as the time from the date of randomization to the date of death from any cause. OS will be analyzed in the ITT Analysis Set. Data for patients who are not reported as having died at the time of analysis will be censored at the date the patient was last known to be alive. Data for patients who do not have postbaseline information will be censored at the date of randomization. Similar methodology used to evaluate PFS will be applied to the analysis of OS.

HRQoL is defined as changes from baseline in PRO measures. Summary statistics (mean, standard deviation, median, and range) of the postbaseline scores and the changes from baseline will be reported for the EORTC QLQ-C30 and QLQ-LC13 questionnaires. Line charts depicting the mean changes (and standard errors) over time from the baseline assessment will be provided for each treatment arm. The clinically meaningful changes postbaseline and a mixed model analysis will be performed using the global health status, physical function and fatigue domains of QLQ-C30, and dyspnoea, coughing, haemotysis and pain in chest, pain in arms and shoulders and peripheral neuropathy domains of QLQ-LC13. Completion and compliance rates will be summarized at each timepoint by treatment arm. Only patients in the ITT Analysis Set with a nonmissing baseline assessment and ≥ 1 in-study nonmissing postbaseline assessment will be included in the analyses.

Safety analysis:

Safety will be assessed by monitoring and recording of all AEs graded by NCI-CTCAE v5.0. Safety will also be assessed by laboratory values (eg, hematology, clinical chemistry, coagulation, urinalysis), vital signs, ECGs, ECOG Performance Status, and physical examinations. Descriptive statistics will be used to analyze all safety data overall and by arm in the Safety Analysis Set.

Pharmacokinetic Analysis:

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

Immunogenicity Analysis:

The anti-ociperlimab and anti-tislelizumab antibody 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.

Biomarker Analysis

Raw biomarker data will be normalized to adjust for batch effect, if applicable, for any biomarker analyses. Receiver operating characteristics curves will be generated and AUC will be calculated based on a logistic regression model to evaluate the association between continuous biomarkers and ORR. Youden Index-based optimal cutoffs or/and clinically meaningful cutoffs will be used to divide the biomarker-evaluable population into subgroups. Logistic regression and Cox regression will be used to evaluate the prognostic and predictive effects of the biomarkers on response and survival with treatment, biomarker status, and their interaction as the main factors. The potential utility of ctDNA level change as a surrogate predictor of efficacy and the mechanisms of resistance will also be assessed.

Sample size:

This study is not designed to make explicit power and type I error consideration but rather to obtain preliminary efficacy and safety data for ociperlimab plus tislelizumab and tislelizumab monotherapy for patients with untreated LS-SCLC. This study will enroll approximately 120 subjects into 3 arms,

with approximately 40 patients in each arm. The contribution of tislelizumab to the efficacy results will be demonstrated by descriptive analysis of PFS, ORR, and DOR in the comparison of Arm B versus Arm C. The contribution of adding ociperlimab will be demonstrated by similarly descriptive analysis in the comparison of Arm A versus Arm B. With a sample size of 40 patients in each arm, the binomial probabilities of detecting ≥ 1 TEAEs with a frequency of 5% and 1% are approximately 0.87 and 0.33, respectively. The final analysis for PFS is estimated to happen approximately 30 months after the enrollment of the first patient.

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
ADA	antidrug antibody
AE	adverse event
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma or serum concentration-time curve
cCRT	concurrent chemoradiotherapy
CR	complete response
CT	computed tomography
ctDNA	circulating tumor DNA
DMFS	distant metastasis-free survival
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EOT	End-of-Treatment
EP	etoposide plus cisplatin
ES-SCLC	extensive-stage small cell lung cancer
HBV	hepatitis B virus
HCV	hepatitis C virus
HRQoL	health-related quality of life
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
ITT	Intent-to-Treat

Abbreviation	Definition
LS-SCLC	limited-stage small cell lung cancer
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
PCI	prophylactic cranial irradiation
PD-1	programmed cell death protein-1
PD-L1	programmed cell death ligand-1
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcomes
PT	preferred term
PVR	poliovirus receptor
QLQ-LC13	Quality of Life Questionnaire Lung Cancer 13
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
RT	radiation therapy
SAE	serious adverse event
SCLC	small cell lung cancer
SMC	Safety Monitoring Committee
SOC	system organ class
TEAE	treatment-emergent adverse event
TIGIT	T-cell immunoglobulin and ITIM domain
TMB	tumor mutational burden
TNM	Tumor size, Lymph nodes affected, Metastases
ULN	upper limit of normal

1. INTRODUCTION

1.1. Background Information on Limited-Stage Small Cell Lung Cancer

Lung cancer was the most commonly diagnosed cancer and the leading cause of cancer-related death (Bray et al 2018) in the world for many years. As of 2020, the newest data from Globocan showed that lung cancer is the second most common cancer worldwide with approximately 2.2 million new diagnoses and 1.8 million deaths globally. In China, lung cancer is the leading cause of cancer-related death in both men and women, with an estimated 610,200 deaths and an estimated 733,300 new cases in the year 2015 (Chen et al 2016).

Small cell lung cancer (SCLC) is an aggressive form of lung cancer that accounts for approximately 15% of all lung cancers (PDQ Adult Treatment Editorial Board [NSCLC] 2020). Histologically, it is a high-grade neuroendocrine tumor, which originates from neuroendocrine cells in the bronchial epithelium. The disease typically presents as bulky symptomatic masses, and mediastinal involvement is common. There is a strong association between smoking and SCLC; nearly all cases of SCLC are attributable to cigarette smoking. An important prognostic factor for SCLC is the extent of disease progression. At the time of diagnosis, approximately 30% of patients with SCLC will have tumors confined to the hemithorax of origin, the mediastinum, or the supraclavicular lymph nodes, which can be safely encompassed within a radiation field; these patients are designated as having limited-stage SCLC (LS-SCLC). Patients with disease beyond the ipsilateral hemithorax, including malignant pleural or pericardial effusion or hematogenous metastases, are designated as having extensive-stage SCLC (ES-SCLC). The Veterans Administration (VA) Study Group's 2-stage classification scheme has historically been used to define the extent of disease progression in patients with SCLC and is often used for clinical decision-making. The National Comprehensive Cancer Network (NCCN) SCLC Panel adopted a combined approach for staging SCLC using both the American Joint Committee on Cancer (AJCC) Tumor size, Lymph nodes affected, Metastases (TNM) staging system and the VA classification scheme for SCLC. When the TNM classifications are applied to the VA system, LS-SCLC is defined as stage I to III (T any, N any, M0), excluding T3-4 due to multiple lung nodules that are too extensive or that have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan. ES SCLC is defined as stage IV (T any, N any, M1a/b/c) or T3-4 due to multiple lung nodules that cannot be safely treated with definitive radiation therapy (RT). The TNM system is useful for selecting patients who are eligible for surgery and for radiation treatment planning. Clinical research studies normally recommend the TNM system because it allows for more precise assessments of prognosis and specific therapy.

SCLC clinically differentiates itself from the more prevalent non-small cell lung cancer (NSCLC) by having rapid doubling time, high growth rate, and early appearance of widespread metastases. In addition, even if a majority of patients are sensitive to initial chemotherapy and RT, most of them have rapid occurrence of tumor relapse or metastasis within months of completing initial therapy. A long period of disease-free survival is rare and there have not been significant improvements in the management of resistance to subsequent second-line therapies. Despite some notable progress over the past few decades, the prognosis for patients with LS-SCLC remains unsatisfactory, with median survival times of 16 to 30 months and 2-year survival rates of 44% to 56%. The median survival ranges from 8 to 13 months for patients with

ES-SCLC and the 2-year survival rate is approximately 5% (Murray et al 1993; Turrisi et al 1999; Faivre-Finn et al 2017; Lally et al 2007).

1.2. Current Treatment of Limited-Stage Small Cell Lung Cancer and Unmet Clinical Needs

1.2.1. Concurrent Chemoradiotherapy With or Without Prophylactic Cranial Irradiation as First-Line Therapy for Limited-Stage Small Cell Lung Cancer

Patients with LS-SCLC are a heterogeneous population who have early (TNM stages I-II) and locally advanced (TNM stage III) tumors. The treatment for all stages of LS-SCLC can be briefly categorized as resectable therapy and unresectable therapy.

Briefly, the NCCN guidelines state that surgery with lobectomy and mediastinal nodal sampling is recommended only for patients with stage I to IIA (T1-2, N0) SCLC in whom mediastinal staging has confirmed that mediastinal lymph nodes are not involved. Note that fewer than 5% of patients with SCLC have true stage I to IIA disease. In most patients with SCLC, survival rates are much lower due to aggressive malignant characteristics and more advanced disease with lymph node involvement. There is a paucity of prospective evidence in very early stage SCLC; most of the data regarding the role of surgery in SCLC are from retrospective reviews. For patients with medically inoperable cT1-2 N0 disease, concurrent chemoradiotherapy (cCRT) has been the historical standard. Considering the encouraging results in early-stage NSCLC, stereotactic ablative radiotherapy (SABR) is increasingly being utilized for well-staged medically inoperable SCLC (Verma et al 2017).

The current standard of care for most patients with advanced LS-SCLC is cCRT with etoposide plus cisplatin (EP) along with thoracic radiation therapy (TRT). Patients who have attained a complete or partial response to initial therapy can be considered for prophylactic cranial irradiation (PCI).

EP is the most commonly used initial combination chemotherapy regimen for patients with LS-SCLC. In clinical practice, carboplatin is used as a substitute for cisplatin to reduce the risk of emesis, neuropathy, and nephropathy. However, the use of carboplatin carries a greater risk of myelosuppression. According to a meta-analysis of individual patient data from 4 randomized studies comparing cisplatin-based versus carboplatin-based regimens in patients with SCLC, which included 32% of 663 patients with limited-stage disease, no significant difference was observed in efficacy outcomes (Rossi et al 2012).

TRT improves local control rates by 25% in patients with limited-stage disease and is associated with improved survival (Pignon et al 1992; Warde and Payne 1992). The current standard of care in patients with LS-SCLC is based on a randomized controlled trial that compared once-daily (45 Gy in 25 fractions over 5 weeks) to twice-daily (45 Gy in 30 fractions over 3 weeks) RT delivered concurrently with EP, showing the superiority of twice-daily RT in terms of survival (Turrisi et al 1999). However, there has been a lack of consensus regarding the routine use of twice-daily RT, despite its superiority, due to concerns regarding toxicity and logistical issues. More recently, the CONVERT trial (Faivre-Finn et al 2017) compared twice-daily RT (45 Gy in 30 fractions over 3 weeks) to a higher dose of RT delivered once daily (66 Gy in 33 fractions over 6.5 weeks), both given concurrently with chemotherapy; overall survival (OS) outcomes did

not significantly differ between the 2 groups. This trial supports once-daily RT concurrently with chemotherapy as a standard of care for LS-SCLC. For once-daily RT, the recommended schedule is once daily up to a total dose of 60 to 70 Gy.

Several systematic reviews and meta-analyses of the timing of RT in LS-SCLC have reported that early concurrent RT results in a small but significant improvement in OS when compared with late concurrent or sequential RT. Concurrent chemoradiotherapy where RT starts with an early cycle (1st or 2nd) of chemotherapy is more effective compared with delayed-start RT or sequential chemoradiotherapy. Early RT yielded better survival than delayed RT (eg, at Cycle 4 of chemotherapy), about 10% improvement in survival rate at 2 years (Fried et al 2004).

In SCLC with early and extensive metastatic spread, intracranial metastases occur in more than 50% of patients. The role of PCI in SCLC has evolved over time; PCI confers an OS benefit in patients with LS-SCLC and is considered the standard of care. In a meta-analysis (Aupérin et al 1999) comparing PCI versus no PCI in 987 patients in 7 clinical trials, the data demonstrated that PCI reduced the risk of brain metastasis by 54% and improved the 3-year survival rate by 5.4%.

In general, little significant progress has been made in the treatment of SCLC for more than 3 decades, with the exception of the approval of atezolizumab and durvalumab in combination with EP chemotherapy in the first-line setting for patients with ES-SCLC. LS-SCLC has the same characteristics of high metastatic potential and invariable recurrence after initial treatment as ES-SCLC. Despite several current clinical trials to investigate novel treatment paradigms for LS-SCLC, there are no approved novel agents, including immunotherapy, for LS-SCLC. There is thus a significant unmet clinical need for new agents with novel mechanisms of action and nonoverlapping toxicity that can be combined with established treatments.

1.2.2. Anti-PD-1/PD-L1 Therapy for Limited-Stage Small Cell Lung Cancer

Immunotherapy with checkpoint inhibitors and antibodies against programmed cell death protein-1 (PD-1) and its ligand, programmed cell death ligand-1 (PD-L1), is an active area of research. In cancer tissues, PD-1 is upregulated on tumor-infiltrating lymphocytes, while PD-L1 is expressed on many types of cancer cells. Cancer cells express PD-L1 to escape immune surveillance via ligation to PD-1 expressed in an adaptive immune response (Pardoll 2012).

SCLC has a strong association with smoking and consequently has a high load of somatic mutations induced by tobacco carcinogens. Importantly, the high tumor mutational burden (TMB) of SCLC might provide opportunities for therapeutic intervention, owing to its positive correlation with response to immune checkpoint therapy, which has been demonstrated in the CheckMate-032 trial (Antonia et al 2016). TMB is defined as the total number of nonsynonymous mutations within a tumor genome and can be considered as a surrogate for the load of neoantigens expressed by the tumor. Of note, in the IMpower-133 trial, a blood-based TMB measurement did not correlate with outcomes with the addition of atezolizumab; so, prospective confirmation is needed (Horn et al 2018). Little is known about the best way to assess TMB, and available data suggest that it may behave as a continuum biomarker and that a cutoff may be identified.

PD-L1 expression shows a statistically significant association with response to checkpoint inhibitors in NSCLC, but the same has not been observed in SCLC. A meta-analysis (Acheampong et al 2020) including 2792 patients from 27 studies showed large inter-study

differences in the rates of PD-L1 expression in SCLC tumors, with rates varying from 0% to 82.8%. The pooled estimate of PD-L1 expression was 22.0% (after removing outlying studies), which is consistent with the low prevalence of PD-L1 expression in this disease. Although the meta-analysis indicated that expression of PD-L1 appears to confer longer OS in SCLC patients, the correlation was not statistically significant, a result that is also consistent with previous reports (Zhang et al 2017).

Strategies targeting the PD-1 pathway alone or in combination with other anticancer agents, including chemotherapy, RT, or anti-cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) agents, have been tested in the front-line setting as maintenance therapy or as late-line palliative treatment.

Until now, as for checkpoint inhibitor monotherapy, the United States Food and Drug Administration (US FDA) has approved pembrolizumab and nivolumab monotherapies as the third-line or later-line treatment in pretreated ES-SCLC. In the KEYNOTE-028 trial (Ott et al 2017), pembrolizumab showed a response rate of 33.3%, with a median duration of response (DOR) of 19.4 months, a median progression-free survival (PFS) of 1.9 months, and median OS of 9.7 months for patients with PD-L1-expressing tumors (tumor proportion score ≥ 1% as measured using the 22C3 antibody). In the KEYNOTE-158 trial (Chung et al 2019), pembrolizumab showed an overall response rate (ORR) of 18.7%, median PFS of 2.0 months, and median OS of 9.1 months regardless of PD-L1 expression. Nivolumab demonstrated similar efficacy in the CheckMate 032 study for treating patients with metastatic SCLC whose cancer had progressed after platinum-based chemotherapy and ≥ 1 other line of therapy (Antonia et al 2016). Other single agents tested as monotherapies include durvalumab for pretreated SCLC, where it showed an ORR of 9.5% and median OS of 4.8 months (Goldman et al 2018) and atezolizumab tested in a randomized study compared with cCRT, where atezolizumab did not increase ORR or PFS (Pujol et al 2019).

Based on the observed anticancer activity and survival benefit of checkpoint inhibitor monotherapy in SCLC, anti-PD-1/PD-L1 antibodies are being investigated in combination with chemotherapy or cCRT in SCLC.

In the past several decades, only atezolizumab and durvalumab, PD-L1 inhibitors, have been approved by the US FDA for use in the first-line setting for patients with ES-SCLC. The IMpower133 study demonstrated improvements in PFS and OS when atezolizumab was added to first-line chemotherapy and continued into the maintenance phase. The median PFS by investigator was 5.2 months with atezolizumab combined with cCRT compared with 4.3 months with cCRT alone; the median OS was 12.3 months versus 10.3 months, respectively. The rate of Grade 3 or 4 adverse events (AEs) was similar in both groups (56%) (Horn et al 2018). The CASPIAN study also showed durvalumab plus chemotherapy significantly improved median OS compared with the chemotherapy arm (13.0 versus 10.3 months; HR0.73, 95%CI: 0.59–0.91; p = 0.0047) (Paz-Ares et al 2019).

Given the positive results of trials adding immunotherapy to standard of care treatment in stage III NSCLC (Antonia et al 2018) and ES-SCLC, an ongoing question is whether immunotherapy could improve survival in the limited-stage setting.

There are currently several studies, either planned or active, that are investigating the role of checkpoint inhibitors in limited-stage disease; these studies include two therapeutic models:

checkpoint inhibitors to complement standard cCRT as sequential consolidation therapy, and incorporation of checkpoint inhibitors in the standard concurrent regimen. These ongoing clinical trials are included in the list of currently ongoing studies shown in Table 1.

Table 1: Ongoing PD-1 Pathway-Targeting Immunotherapy Studies in Limited-Stage Small Cell Lung Cancer

	IO + cCRT	IO + cCRT	IO after cCRT	IO after cCRT	IO after cCRT	IO after cCRT
Study name	NRG-LU005 (NCT03811002)	NCT02402920	ADRIATIC (NCT03703297)	ML41257 (NCT04308785)	STIMULI (NCT02046733)	ACHILES (NCT03540420)
Sponsor	NCI	Merck	AstraZeneca	Roche	Bristol-Myers Squibb	Roche
Phase	Phase 2/3	Phase 1	Phase 3	Phase 2	Phase 2	Phase 2
Study design	Randomized, open-label	Open-label	Randomized, double-blind	Randomized, open-label	Randomized, open-label	Open-label
Target enrollment	506	80	600	242	264	212
Inclusion	Must have 1 pre-registration cycle of chemotherapy	LS-SCLC, ES-SCLC	After 4 cycles of cCRT	After 4 cycles of cCRT	After 4 cycles of cCRT	After 4 cycles of cCRT
Study treatment	• cCRT + atezolizumab for 3 cycles followed by atezolizumab (17 cycles; 1 year) • cCRT for 3 cycles followed by observation	LS-SCLC: pembrolizumab + cCRT for 4 cycles followed by pembrolizumab for 12 cycles	• Durvalumab + placebo for 4 cycles followed by durvalumab for 2 years • Durvalumab + tremelimumab for 4 cycles followed by durvalumab for 2 years • Placebo for 4 cycles followed by placebo maintenance	• 2 cycles chemotherapy + atezolizumab for 12 months • 2 cycles chemotherapy + placebo	• Nivolumab + ipilimumab for 4 cycles followed by nivolumab for 12 months	• Atezolizumab for 12 months
Primary endpoint	Phase 2: PFS Phase 3: OS	Safety	PFS + OS	PFS + OS	PFS + OS	2-year survival
Status	Recruiting (US only)	Recruiting (US only)	Recruiting (global, including China and US)	Not yet recruiting (China only)	Ongoing (AUS, EU)	Recruiting (EU)
Start to estimated primary completion	28 May 2019 to Dec 2026	22 Jul 2015 to 31 July 2023	27 Sep 2018 to Feb 2024	NA to Sep 2022	28 Jul 2014 to Dec 2020	31 Jul 2018 to Dec 2023

Abbreviations: AUS, Australia; cCRT, concurrent chemoradiotherapy; ES-SCLC, extensive-stage small cell lung cancer; EU, European Union; IO, immuno-oncology; LS-SCLC, limited-stage small cell lung cancer; NA, not applicable; NCI, National Cancer Institute; OS, overall survival; PD-1, programmed cell death protein-1; PFS, progression-free survival, US, United States.

The STIMULI trial did not meet its primary endpoint of improving PFS with nivolumab and ipilimumab consolidation after cCRT, the study closed early in 2019 due to slow accrual (Peters et al 2020). Another clinical trial testing the role of immunotherapy is the Phase 3, randomized, double-blind, international ADRIATIC study sponsored by AstraZeneca (ClinicalTrials.gov Identifier: NCT03703297). This is a 3-arm studying evaluating the efficacy of durvalumab or durvalumab with tremelimumab compared with placebo for consolidation in patients with LS-SCLC that has not progressed after cCRT. The primary endpoints of this Phase 3 study are PFS and OS.

Overall, there are no approved novel agents/immunotherapy in LS-SCLC. Even if there is a high response in initial cCRT, most responses are transient, and most patients experience disease recurrence after a few months. Relapsed SCLC is often resistant to second-line therapies. Median survival ranges from 15 to 20 months for LS-SCLC. Because of the dismal prognosis and relative resistance to salvage therapies, there is an urgent need for therapeutic innovations with novel mechanisms of action and nonoverlapping toxicity, which can be combined with established treatments to manage this disease.

1.3. Background Information on Ociperlimab (BGB-A1217)

1.3.1. Nonclinical Summary

1.3.1.1. Pharmacology

Ociperlimab (BGB-A1217) is a humanized immunoglobulin G (IgG) 1 monoclonal antibody against T-cell immunoglobulin and ITIM domain (TIGIT) under clinical development for the treatment of human malignancies.

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 characterization. Ociperlimab has shown antitumor activity in both the GL261 mouse glioma tumor model and the CT26.WT mouse colon cancer model in humanized TIGIT knock-in mice. In the MC-38 mouse colon cancer model in humanized TIGIT knock-in mice, ociperlimab in combination with anti-mouse PD-1 significantly inhibited tumor growth compared with either therapy alone.

Ociperlimab has the constant region of a wild-type human immunoglobulin G1 (IgG1) to enable Fc-mediated effector functions. Ociperlimab has demonstrated competent binding to C1q and all Fc gamma receptors (FcγRs) and induces antibody-dependent cellular cytotoxicity (ADCC) against a TIGIT-overexpressing cell line, but no ADCC or complement-dependent cytotoxicity against primary T cells in cell-based assays.

Refer to the Ociperlimab (BGB-A1217) Investigator's Brochure for detailed information regarding pharmacology studies.

1.3.1.2. Toxicology

Humanized TIGIT knock-in mice containing human TIGIT gene and cynomolgus monkeys were selected for nonclinical safety evaluation of ociperlimab based on the homology of the TIGIT amino acid sequence, binding affinity, and efficacy studies.

Ociperlimab demonstrated a comparable binding affinity in TIGIT receptor occupancy assays with CD3+ splenocytes from humanized TIGIT knock-in mice compared with CD3+ human peripheral blood mononuclear cells (with EC_{50} of 48.8 ng/mL versus 63.2 ng/mL, respectively). In addition, ociperlimab showed a significant inhibition of GL261 tumor growth in humanized TIGIT knock-in mice at a dose of ≥ 0.4 mg/kg via weekly intraperitoneal dosing.

The toxicity and safety profile of ociperlimab was characterized in a 4-week repeated-dose toxicology study in humanized TIGIT knock-in mice and a 13-week repeated-dose toxicology study in cynomolgus monkeys. Ociperlimab was also evaluated in a 4-week repeated-dose study in humanized TIGIT knock-in mice with subcutaneous MC-38 tumors. The cynomolgus monkey was considered the relevant species for toxicity studies based upon the target sequence homology and cross-species TIGIT-binding activities of ociperlimab.

No apparent toxicity was noted in monkeys following repeated dosing at 10, 30, or 100 mg/kg once every 2 weeks for 13 weeks. The toxicokinetic profile in the monkey study showed that systemic exposure appeared to be dose proportional with no sex difference. No accumulation was observed over the 13-week dosing period in monkeys. No immunotoxicity was apparent as no changes in clinical pathology or histopathology were observed. Positive antidrug antibodies (ADAs) against ociperlimab were observed in 6/10, 3/10, and 4/10 animals during the dosing period, and 3/4, 2/4, and 2/4 animals during the recovery period, at dose levels of 10, 30, and 100 mg/kg, respectively. The anti-ociperlimab antibodies showed a rapid clearance of ociperlimab in serum in a few individual animals but did not appear to have an effect on the overall systemic exposure (area under the plasma or serum concentration-time curve [AUC]) or toxicity assessment.

No specific binding of ociperlimab was noted with normal human tissues. A variety of factors might contribute to the negative results, including negligible target expression in normal tissues (Yang 2016; Human Protein Atlas) and sensitivity of the immunohistochemistry method.

No significant increase in cytokine release was observed from an in vitro cytokine release assay following treatment of nonactivated peripheral blood mononuclear cells with ociperlimab when compared with human IgG. The results suggest that ociperlimab has potentially low probability of causing acute cytokine release syndrome.

Overall, no apparent toxicity was noted in the monkey toxicity study. No unexpected tissue cross-reactivity was found in human or monkey tissues. The toxicokinetic profile showed dose-proportional increases in systemic exposure without apparent accumulation or sex difference. Immunogenicity was observed without apparent immunotoxicity or effect on the systemic exposure. The no-observed-adverse-effect level (NOAEL) of ociperlimab was 100 mg/kg in the 13-week monkey toxicity study. The safety profile of ociperlimab is considered adequate to support first-in-human dosing.

Refer to the Ociperlimab (BGB-A1217) Investigator's Brochure for detailed information regarding toxicology studies.

1.3.2. Prior Clinical Experience With Ociperlimab

As of 16 June 2020, a Phase 1 study (BGB-900-105) was investigating the safety/tolerability, pharmacokinetics (PK), and preliminary antitumor activity of ociperlimab in combination with

tislelizumab with or without chemotherapy in patients with unresectable locally advanced or metastatic solid tumors.

Patients enrolled in Study BGB-900-105 were treated with escalating doses of ociperlimab (50, 150, 450, or 900 mg) in combination with tislelizumab 200 mg once every 3 weeks; all patients cleared the dose-limiting toxicity (DLT) period without DLTs. The maximum tolerated dose was not reached and the recommended Phase 2 dose (RP2D) was determined to be 900 mg ociperlimab in combination with 200 mg tislelizumab once every 3 weeks. The most commonly reported treatment-emergent adverse events (TEAEs; Table 2) were fatigue (3 out of 11 patients) and diarrhoea and aspartate aminotransferase (AST) increased (2 patients each out of 11 patients). Most TEAEs were Grade 1 or Grade 2, with the exception of three Grade 3 TEAEs of atrial flutter, pericardial effusion malignant and dyspnea, which were serious and deemed not related to study drugs (1 patient each).

Treatment-related TEAEs (ociperlimab, tislelizumab, or both) occurred in 3 patients and included influenza, AST increased, and dry skin in 1 patient; abdominal pain, dry eye, and diarrhea in 1 patient; and fatigue in 1 patient. All treatment-related TEAEs were Grade 1. No infusion reactions were reported.

The study is currently enrolling patients at the RP2D. Ociperlimab continues to appear to be safe and well-tolerated. Preliminary results also show that 100% receptor occupancy was achieved at 50 mg.

Refer to the Ociperlimab (BGB-A1217) Investigator's Brochure for detailed information regarding clinical experience with ociperlimab.

Table 2: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity (Safety Analysis Set)

System Organ Class Preferred Term	Tislelizumab 200 mg				Total
	Ociperlimab 50 mg (N = 1) n (%)	Ociperlimab 150 mg (N = 3) n (%)	Ociperlimab 450 mg (N = 4) n (%)	Ociperlimab 900 mg (N = 3) n (%)	(N = 11) n (%)
Patients with ≥ 1 TEAE	**1 (100.0)**	**3 (100.0)**	**3 (75.0)**	**1 (33.3)**	**8 (72.7)**
Gastrointestinal disorders	**1 (100.0)**	**1 (33.3)**	**2 (50.0)**	**0 (0.0)**	**4 (36.4)**
Diarrhoea	0 (0.0)	1 (33.3)	1 (25.0)	0 (0.0)	2 (18.2)
Abdominal pain	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (9.1)
Constipation	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (9.1)
Dry mouth	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)
General disorders and administration site conditions	**1 (100.0)**	**0 (0.0)**	**1 (25.0)**	**1 (33.3)**	**3 (27.3)**
Fatigue	1 (100.0)	0 (0.0)	1 (25.0)	1 (33.3)	3 (27.3)
Musculoskeletal and connective tissue disorders	**0 (0.0)**	**1 (33.3)**	**1 (25.0)**	**1 (33.3)**	**3 (27.3)**
Back pain	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	1 (9.1)
Flank pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	1 (9.1)

System Organ Class Preferred Term	Tislelizumab 200 mg				Total (N = 11) n (%)
	Ociperlimab 50 mg (N = 1) n (%)	Ociperlimab 150 mg (N = 3) n (%)	Ociperlimab 450 mg (N = 4) n (%)	Ociperlimab 900 mg (N = 3) n (%)	
Groin pain	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (9.1)
Infections and infestations	**1 (100.0)**	**0 (0.0)**	**1 (25.0)**	**0 (0.0)**	**2 (18.2)**
Influenza	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)
Otitis externa	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (9.1)
Investigations	**1 (100.0)**	**1 (33.3)**	**0 (0.0)**	**0 (0.0)**	**2 (18.2)**
Aspartate aminotransferase increased	1 (100.0)	1 (33.3)	0 (0.0)	0 (0.0)	2 (18.2)
Nervous system disorders	**1 (100.0)**	**0 (0.0)**	**1 (25.0)**	**0 (0.0)**	**2 (18.2)**
Neuralgia	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)
Somnolence	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (9.1)
Respiratory, thoracic, and mediastinal disorders	**0 (0.0)**	**1 (33.3)**	**1 (25.0)**	**0 (0.0)**	**2 (18.2)**
Cough	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (9.1)
Dyspnoea	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	1 (9.1)
Skin and subcutaneous tissue disorders	**1 (100.0)**	**0 (0.0)**	**0 (0.0)**	**1 (33.3)**	**2 (18.2)**
Drug eruption	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	1 (9.1)
Dry skin	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)
Blood and lymphatic system disorders	**0 (0.0)**	**0 (0.0)**	**1 (25.0)**	**0 (0.0)**	**1 (9.1)**
Anaemia	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (9.1)
Cardiac disorders	**1 (100.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (9.1)**
Atrial flutter	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)
Ear and labyrinth disorders	**0 (0.0)**	**1 (33.3)**	**0 (0.0)**	**0 (0.0)**	**1 (9.1)**
Ear discomfort	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	1 (9.1)
Eye disorders	**0 (0.0)**	**0 (0.0)**	**1 (25.0)**	**0 (0.0)**	**1 (9.1)**
Dry eye	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (9.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0 (0.0)**	**0 (0.0)**	**1 (25.0)**	**0 (0.0)**	**1 (9.1)**
Cancer pain	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (9.1)
Pericardial effusion malignant	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (9.1)
Psychiatric disorders	**0 (0.0)**	**1 (33.3)**	**0 (0.0)**	**0 (0.0)**	**1 (9.1)**
Confusional state	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	1 (9.1)

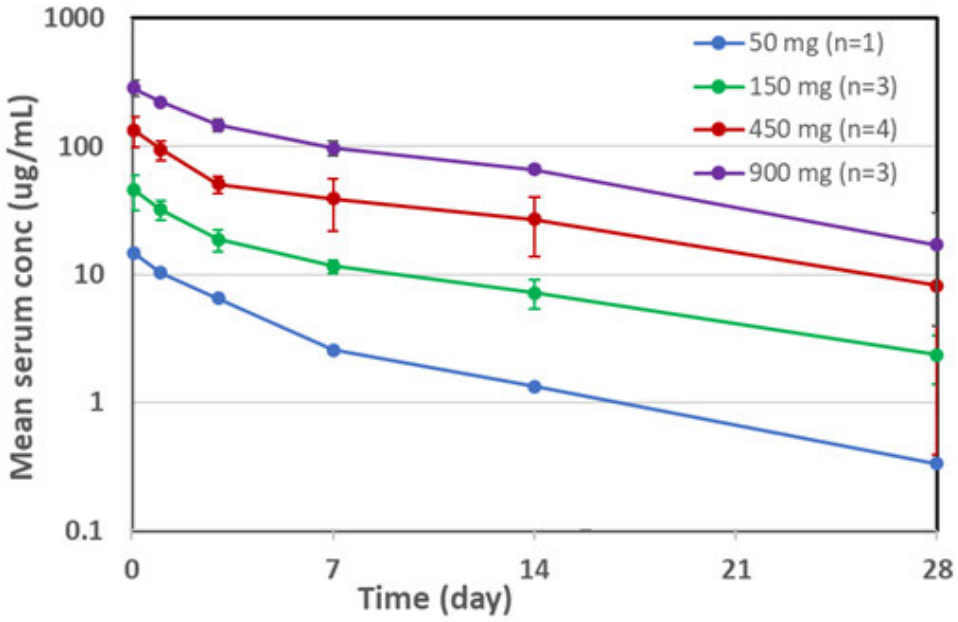
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, total patients treated; NCI-CTCAE v5.0, National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0; TEAE, treatment-emergent adverse event.
Notes: A patient with multiple occurrences of an AE is counted only once in the AE category. MedDRA Version 22.0 was used to code AEs. AEs were graded using NCI-CTCAE v5.0. Events are sorted in descending order of the number of patients for System Organ Class and Preferred Term in the Total column.

1.3.3. Ociperlimab Clinical Pharmacology and Pharmacodynamics

As of the data cutoff date of 16 June 2020, preliminary PK data of ociperlimab are available from a total of 11 patients treated with ociperlimab at the 50 mg (n = 1), 150 mg (n = 3), 450 mg (n = 4), and 900 mg (n = 3) dose levels in combination with tislelizumab 200 mg in the dose-escalation portion of Study BGB-900-105. Ociperlimab serum concentrations declined in a biexponential manner after intravenous infusion and ociperlimab exposures (maximum observed concentration and AUC) increased approximately dose-proportionally from 50 mg to 900 mg (Figure 1).

Peripheral TIGIT receptor occupancy data were available for 11 enrolled patients treated with ociperlimab at the 50 mg (n = 1), 150 mg (n = 3), 450 mg (n = 4), and 900 mg (n = 3) dose levels in Study BGB-900-105. Complete TIGIT receptor occupancy (100%) was observed on CD8, CD4, natural killer (NK), and T regulatory cells in peripheral blood at all the tested dose levels.

Figure 1: Cycle 1 Mean (± SD) Serum Concentration-Time Profiles of Ociperlimab in Study BGB-900-105



Abbreviations: conc, concentration; n, number of patients; SD, standard deviation.

1.4. Background Information on Tislelizumab

1.4.1. Pharmacology

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

Tislelizumab acts by binding to the extracellular domain of human PD-1 with high specificity and affinity (K_D = 0.15 nM). It competitively blocks the binding of 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 dose-dependently enhance the functional activity of human T cells and pre-activated primary peripheral blood mononuclear cells. Tislelizumab has also demonstrated in vivo antitumor activity in several allogeneic xenograft models, in which peripheral blood mononuclear cells were coinjected with human cancer cells (A431 [epidermoid carcinoma]) or tumor fragments (BCCO-028 [colon cancer]) into immunocompromised mice.

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

Please refer to the Tislelizumab Investigator's Brochure 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, repeated-dose toxicology study in cynomolgus monkeys. Cynomolgus monkey was the only relevant species based on the target sequence homology and binding activity.

Overall, no apparent toxicity was noted in the mice or monkey toxicity studies. No tissue cross-reactivity was found in either human or monkey tissues, nor was any effect on cytokine release observed in the human whole-blood assay. The toxicokinetic profile showed 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, AdvanTIG-204.

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

1.4.3. Clinical Pharmacology

Population PK analysis was conducted using data from 798 patients with solid tumors or classical Hodgkin lymphoma who received doses of 0.5, 2.0, 5.0, and 10 mg/kg once every 2 weeks, 2.0 and 5.0 mg/kg once every 3 weeks, and 200 mg once every 3 weeks. The PK of

tislelizumab was best characterized using a 3-compartmental linear population PK model with linear clearance mechanisms. No time-varying clearance was observed in tislelizumab PK. The typical estimates of clearance (CL), central volume (V_c), and peripheral volumes (V_2, V_3) were 0.164 L/day, 2.92 L, 0.928 L, and 1.39 L, respectively, with moderate inter-individual variability in CL (32.2%), V_c (16.7%), V_2 (56.6%), and V_3 (94.2%). The volume of distribution at steady state (V_{ss}) was 5.238 L, which is typical of monoclonal antibodies with limited distribution and consistent with a standard IgG monoclonal antibody (Deng et al 2012; Dirks and Meibohm 2010; Keizer et al 2010; Ryman and Meibohm 2017). Based on population PK analysis, tislelizumab PK was characterized by a terminal half-life of approximately 25.5 days.

Although tumor size, albumin, and tumor type were significant covariates on CL and body weight, sex, and tumor type were significant covariates on V_c, these covariates are not expected to have a clinically relevant impact on tislelizumab exposure. Exposure-response analysis indicated a lack of clinically significant exposure-response relationships for ORR and safety endpoints across a variety of advanced solid tumors and classical Hodgkin lymphoma for tislelizumab. Population PK analysis supports fixed dosing across different ethnic groups.

1.4.4. Prior Clinical Experience With Tislelizumab

As of 20 May 2020, 1181 patients with solid tumors had been treated with tislelizumab monotherapy in 5 clinical studies.

A pooled monotherapy analysis was conducted to provide a comprehensive review of the tislelizumab safety profile. Patients included in this analysis (N = 1181) had a median age of 60.0 years, with 67.1% of them being male. Median treatment exposure duration was 3.7 (range: 0.1 to 55.3) months and median study follow-up duration was 9.9 (range: 0.1 to 58.9) months.

Refer to the Tislelizumab Investigator's Brochure for more detailed information on tislelizumab safety data when given as monotherapy or in combination with chemotherapy.

1.4.4.1. Treatment-Emergent Adverse Events Assessed as Related to Tislelizumab

Of the 1181 patients with solid tumors treated with tislelizumab monotherapy, 788 (66.7%) experienced ≥ 1 treatment-related TEAE. The most commonly occurring TEAEs (≥ 5% of patients) assessed as related to tislelizumab irrespective of grade were AST increased (136 patients, 11.5%), alanine aminotransferase (ALT) increased (125 patients, 10.6%), hypothyroidism (106 patients, 9.0%), rash (97 patients, 8.2%), and pruritus and fatigue (95 patients each, 8.0%).

A total of 167 patients (14.1%) experienced at least 1 ≥ Grade 3 TEAE assessed as related to tislelizumab. The most frequent ≥ Grade 3 TEAEs that occurred in ≥ 1% of the patients were AST increased (21 patients, 1.8%), ALT increased (17 patients, 1.4%), and anaemia (13 patients, 1.1%).

1.4.4.2. Treatment-Emergent Serious Adverse Events

Of the 1181 patients with solid tumors treated with tislelizumab monotherapy, 415 (35.1%) experienced ≥ 1 treatment-emergent serious adverse event (SAE). The most commonly occurring treatment-emergent SAEs (irrespective of relationship to study drug) were pneumonia (41 patients, 3.5%), and pyrexia and ascites (15 patients each, 1.3%).

A total of 107 patients (9.1%) experienced ≥ 1 tislelizumab-related treatment-emergent SAE. The most common treatment-emergent SAEs deemed related to tislelizumab were pneumonitis (11 patients, 0.9%); AST increased (6 patients, 0.5%); and colitis, ALT increased, and pyrexia (5 patients each, 0.4%). All other tislelizumab-related treatment-emergent SAEs occurred in < 5 patients.

1.4.4.3. Immune-Mediated Adverse Events

Anti-PD-1 therapies are known to cause immune-mediated adverse events (imAEs) in some patients and therefore have been defined as adverse events (AEs) of special interest (AESI) in tislelizumab clinical studies and as such are being monitored closely.

Immune-mediated AEs are consistent with an immune-related mechanism or immune-related component for which noninflammatory etiologies (eg, infection or tumor progression) have been ruled out. Immune-mediated AEs can include events with an alternate etiology that were exacerbated by the induction of autoimmunity. There is a potential temporal relationship between the initiation of tislelizumab treatment and the onset of an imAE that spans a window of days to several months.

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

Of the 1113 patients with solid tumors included in the pooled analysis of imAEs, 233 (20.9%) experienced ≥ 1 imAE of any grade. The most commonly occurring imAEs of any grade were hypothyroidism (69 patients, 6.2%), hyperthyroidism (37 patients, 3.3%), and rash (34 patients, 3.1%). A total of 52 patients (4.7%) experienced at least 1 ≥ Grade 3 imAE. The most commonly occurring ≥ Grade 3 imAEs were ALT increased (9 patients, 0.8%) and AST increased and pneumonitis (7 patients each, 0.6%).

1.4.4.4. Infusion-Related Reactions

Infusion-related reactions, including high-grade hypersensitivity reactions, following administration of tislelizumab are uncommon. Of the 1181 patients treated with tislelizumab monotherapy, 45 (3.8%) experienced ≥ 1 infusion-related reaction of any grade. The most commonly occurring infusion-related reactions of any grade were infusion-related reactions (28 patients, 2.4%), pyrexia (10 patients, 0.8%), and nausea (4 patients, 0.3%). Two patients (0.2%) had ≥ Grade 3 infusion-related reactions and all other events occurred in single instances; these included rash, flushing, hypotension, and spinal pain.

1.4.4.5. Liver Laboratory Abnormalities

Of the 932 patients with solid tumors included in the analysis of drug-induced liver injury, 34 patients (3.6%) experienced increases in ALT or AST levels > 5 x upper limit of normal (ULN) but ≤ 10 x ULN, 11 patients (1.2%) had ALT or AST elevations >10 x ULN but ≤ 20 x ULN, and 1 patient (0.1%) had ALT or AST elevations > 20 x ULN. Bilirubin elevation > 2 x ULN was observed in 43 patients (4.6%).

Concomitant ALT/AST and bilirubin elevation in the absence of alkaline phosphatase increases were observed in 2 patients (0.2%). These patients had diagnoses of advanced metastatic gastric or liver cancer and both presented with extensive hepatic involvement and confirmed hepatic disease progression at the time of the observed abnormalities in liver laboratory values; these cases therefore did not meet the criteria for Hy's law.

1.4.4.6. Fatal Adverse Events

Out of 1181 patients treated with tislelizumab monotherapy who were included in the analysis, 18 patients (1.5%) experienced a fatal AE ≤ 30 days after the last study drug dose. A total of 9 patients (0.8%) experienced fatal AEs that were deemed related to tislelizumab, including hepatic failure (2 patients, 0.2%); and large intestinal obstruction, pneumonitis, respiratory arrest, respiratory failure, hepatitis acute, brain oedema, and death (1 patient each, 0.1%).

1.4.5. Efficacy Assessment of Tislelizumab

Efficacy data are available from 2 of the ongoing Phase 1 monotherapy studies in solid tumors, BGB-A317_Study_001 and BGB-A317-102, which are summarized below (data cut-off 20 May 2019) and from a Phase 3 combination study, BGB-A317-304, in NSCLC (data cut-off 06 December 2019; Wang et al 2020).

Study BGB-A317_Study_001 is a Phase 1a/1b study consisting of a dose-escalation phase (1a) and a dose-expansion phase (1b) designed to establish the maximum tolerated dose and schedule, determine the RP2D, and investigate the preliminary efficacy of tislelizumab in previously treated patients with select tumor types.

The RP2D and schedule for tislelizumab was determined to be 200 mg administered once every 3 weeks. Across all disease cohorts (N = 441), 5 patients (1.1%) experienced a CR and 55 patients (12.5%) had a confirmed PR, yielding an ORR of 13.6%. Stable disease was observed in 142 patients (32.2%). The disease control rate was 45.8% (95% CI: 41.1, 50.6) and clinical benefit rate (CBR) was 26.5% (95% CI: 22.5, 30.9).

Study BGB-A317-102 is a nonrandomized, Phase 1/2 study of tislelizumab monotherapy evaluating the activity and safety of tislelizumab at the RP2D and schedule of 200 mg given once every 3 weeks in previously treated Chinese patients with select advanced solid tumors. It showed the recommended dose of tislelizumab 200 mg every 3 weeks was generally well tolerated and demonstrated a manageable safety profile in Chinese patients with advanced solid tumors. Preliminary antitumor activities were observed in the overall patient population and across multiple indications. Across all tumor types, the ORR was 17.0% (51 patients; 95% CI:12.9%, 21.7%). There was 1 patient with a confirmed CR, who was diagnosed with squamous cell carcinoma of the larynx. The CBR (CR + PR + durable stable disease ≥ 24 weeks) was 32% and the DCR was 44.7%.

Study BGB-A317-206 (data on file) was investigating tislelizumab in combination with chemotherapy as first-line treatment in patients with lung cancer. One of the cohorts enrolled 17 ES-SCLC patients who were treated with tislelizumab combined with etoposide plus cisplatin or carboplatin for 4-6 cycles followed by tislelizumab maintenance treatment. As of 25 Feb 2019, the confirmed ORR was 76.5% (95% CI: 50.1, 93.2) and the disease control rate was

88.2% (95% CI: 63.6, 98.5). The median DOR was 6.5 months and the median PFS was 6.9 months (95% CI: 4.90,10.09).

1.5. Study Rationales

1.5.1. Rationale for Combination of Ociperlimab and Tislelizumab in the Treatment of Limited-Stage Small Cell Lung Cancer

SCLC is typically characterized by high TMB, unstable *TP53* and *RB1* genes, and high mutation rate of the DNA damage response pathway. However, SCLC has lower PD-L1 expression than other lung cancers. Certain advances have been made in the use of immune checkpoint inhibitors for the treatment of SCLC. Combination of first-line immune checkpoint inhibitors with chemotherapy for ES-SCLC has shown improved clinical benefit. Besides atezolizumab, which has been approved in combination with standard chemotherapy, durvalumab combined with EP has also shown significant survival improvement and long-term clinical benefit in the CASPIAN trial (Paz-Ares et al 2019). Pembrolizumab also demonstrated significantly improved PFS in the KEYNOTE 604 study (Rudin et al 2020). However, the role of PD-1/PD-L1 antibodies in LS-SCLC has not been determined. Further investigations on novel strategies of immune checkpoint inhibitors combined with other agents may be helpful in overcoming the treatment challenges in SCLC. Other agents that may be investigated for the treatment of SCLC include those that target immune checkpoints other than PD-1/PD-L1 or those that modulate the immune metabolism of the tumor microenvironment.

TIGIT is a receptor found on the surface of NK cells, T regulatory cells, and activated T cells, and it has a high-affinity ligand CD155, also known as poliovirus receptor (PVR) (Hu et al 2020). Upregulation of TIGIT expression in tumor infiltrating lymphocytes has been reported in NSCLC (Tassi et al 2017). Blockade of the TIGIT receptor has been shown both in vitro and in vivo to rescue functionally “exhausted” T cells (Johnston et al 2014).

A recent study using SCLC samples showed that PVR, an immune checkpoint protein expressed on tumor cells, is highly expressed in SCLC cell lines and tumor tissues (Yu et al 2018). According to the same group, PVR mediates the inhibition of T cells by competitively binding to TIGIT, which indicates that the PVR-TIGIT pathway may be a promising target for immunotherapy in SCLC and also highlights the potential for the combination of checkpoint blocking agents (eg, PD-L1) for improved SCLC immunotherapy.

Although targeting TIGIT could eliminate immune suppression by reactivating T effector cells and NK cells, TIGIT blockade alone (ie, ociperlimab monotherapy) is unlikely to result in an effective antitumor response according to existing anti-TIGIT clinical data.

Ociperlimab and tislelizumab have nonoverlapping anticancer mechanisms and are likely to have synergistic and/or added activity. Therefore, the combination use of ociperlimab and tislelizumab concurrent with standard cCRT is designed to evaluate the effect of ociperlimab in combination with tislelizumab in maximizing the potential therapeutic benefit while simultaneously achieving clinical benefit for patients.

1.5.2. Rationale for the Selection of Ociperlimab Dose

Ociperlimab doses ranging from 50 mg to 900 mg administered once every 3 weeks, in combination with 200 mg of tislelizumab once every 3 weeks, were explored in the ongoing Phase 1/1b Study BGB-900-105. All the tested ociperlimab dose levels cleared the DLT window without any significant safety or tolerability events. Ociperlimab exposures increased in an approximately dose-proportional manner (Ociperlimab (BGB-A1217) Investigator's Brochure). As of 07 August 2020, the maximum administered ociperlimab dose of 900 mg was selected as the RP2D.

Complete TIGIT receptor occupancy was observed in circulating T cells and NK cells in peripheral blood at all the tested doses in the BGB-900-105 study. However, since the correlation between TIGIT receptor occupancy in peripheral blood and receptor occupancy in tumor tissues is unknown, quantitative systems pharmacology modeling was performed to predict the occupancy in tumor tissues. Preliminary results show that near complete TIGIT receptor occupancy in tumor tissues is predicted at doses ≥ 450 mg. Due to the lack of information on the impact of immunogenicity on the ociperlimab PK and based on the emerging safety and tolerability data, a dose of 900 mg was selected. This dose level is expected to increase the likelihood of efficacious concentrations and saturation of TIGIT receptors in tumor tissues completely over the entire dosing interval. The absence of any dose-dependent safety events in the ongoing study additionally supports the selection of this dose for further evaluation. The preliminary ociperlimab PK data from the ongoing BGB-900-105 study indicate a lack of a significant relationship between ociperlimab exposure and the patient's body weight and support the selection of a fixed dose for ociperlimab.

1.5.3. Rationale for Selection of Tislelizumab Dose

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

Rates of treatment-related AEs and SAEs observed in patients receiving 2 mg/kg and 5 mg/kg once every 2 weeks and once every 3 weeks were comparable, suggesting no clear dose-dependence across these regimens. Additionally, PK data also showed no relationship between exposure and treatment-emergent imAEs (Wu et al 2019a; Wu et al 2019b).

Confirmed response rates in patients treated with tislelizumab once every 3 weeks were favorable compared with those in patients treated once every 2 weeks. While there are differences in response rates between dose levels, this is more likely a reflection of the small sample size and patient heterogeneity than of dose response.

Clearance of tislelizumab was not dependent on body weight, and the observed serum exposure of a 200 mg dose fell between the serum exposures observed after 2 mg/kg and 5 mg/kg doses. Therefore, clinical activity with a manageable and tolerable safety profile is expected to be maintained in patients receiving tislelizumab 200 mg once every 3 weeks.

Exposure-response analysis indicated a lack of clinically significant exposure-response relationships for ORR and safety endpoints across a variety of advanced solid tumors and classical Hodgkin lymphoma for tislelizumab. These findings support the use of the 200 mg once every 3 weeks dose regimen for pivotal studies.

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

1.5.4. Rationale for Chemoradiotherapy as the Component of the Combination Treatment

Platinum-based chemotherapy is the standard of care for first-line therapy in LS-SCLC. The platinum agents most commonly used are cisplatin and carboplatin, which are often combined with the non-platinum agent etoposide. The addition of RT to standard combination chemotherapy improves both local control and OS. Early cCRT is recommended for patients with LS-SCLC based on the longer survival time reported in patients treated concurrently compared with the survival times for those treated sequentially. For the comparator arm and the 2 study arms in this study, cCRT represents the current standard of care. Patients will receive 4 cycles of EP (or carboplatin plus etoposide if cisplatin is contraindicated or not tolerated) concurrent with RT as backbone treatment.

1.5.5. Rationale for Combination of Concurrent Chemoradiotherapy and Immunotherapy

The rationale for immunotherapy in combination with cCRT has been shown in a multitude of preclinical studies, including xenograft models of some solid tumors (Deng et al 2014). Both chemotherapy and RT can upregulate major histocompatibility complex class I antigens, increase tumor antigen release, drive a polyclonal T-cell response, enhance CD8þ T-cell infiltration, limit T-cell exhaustion, modulate the immune environment, provoke an interferon gamma response, and upregulate the expression of PD-L1 (Gandhi et al 2018; Kordbacheh et al 2018), which could make such tumors sensitive to a PD-1/PD-L1-directed therapy. In this setting, chemotherapy and RT act as priming agents for immunotherapy; elimination of cancer cells by chemotherapy and/or RT triggers release of antigens, which can turn poorly immunogenic or immunosuppressive tumors into an immunogenic environment (Vanneman and Dranoff 2012).

The PACIFIC trial was the first randomized Phase 3 study to clinically validate these findings. This is a global Phase 3 trial of the anti-PD-L1 agent, durvalumab, being compared with placebo as consolidation therapy following ≥ 2 cycles of platinum-based chemotherapy administered concurrently with RT without progression in patients with unresectable stage III NSCLC. The trial demonstrated that median PFS was significantly longer with durvalumab than with placebo (median PFS 16.8 months versus 5.6 months, stratified HR for disease progression or death 0.52), with a similar safety profile in the 2 groups (Antonia et al 2017).

In SCLC, both the IMpower133 (Horn et al 2018) and the CASPIAN (Paz-Ares et al 2019) trials reported that the addition of an immune checkpoint inhibitor to chemotherapy modestly improved survival. The BGB-A317-206 study that is investigating tislelizumab in combination with chemotherapy has also demonstrated confirmed anticancer activity and was well tolerable as first-line treatment for patients with ES-SCLC (see Section 1.4.5). Although immune checkpoint inhibition in combination with chemotherapy demonstrated clinical benefits, survival curves separated late in randomized trials, and patients who would benefit could not be identified. Given that radiation to a primary tumor leads to tumor-antigen release and a tumor-

specific adaptive immune response, which is enhanced by immune-stimulating agents, it is possible that the addition of RT to a chemotherapy and immune checkpoint inhibitor regimen could make SCLC more immunogenic. As for LS-SCLC, the result from a Phase 1/2 trial of pembrolizumab combined with cCRT for patients with LS-SCLC showed that cCRT and pembrolizumab was well tolerated and yielded favorable outcomes, providing a basis for randomized studies (Welsh et al 2020).

More insight into the biological mechanisms underlying treatment resistance is needed to improve patient outcome. Combination with PD-1/PD-L1 and TIGIT blockade might rescue functionally "exhausted" T cells and result in a durable control of cancer. This trial will evaluate whether the addition of an anti-PD-1 therapy and anti-TIGIT therapy to combined modality therapy can benefit patients with LS-SCLC.

In addition, improvement in antitumor effects has been observed preclinically when RT is given concurrently with or immediately after anti-PD-L1 rather than sequentially (Dovedi et al 2014). However, sequential delivery of checkpoint inhibitors did not improve response to RT at local or distant sites (Dovedi et al 2017). The results of the PACIFIC trial, which suggested that the OS was better when durvalumab was given within 2 weeks after the end of cCRT, was consistent with preclinical data (Antonia et al 2017). Therefore, the earlier introduction of tislelizumab + ociperlimab given simultaneously with cCRT may lead to further enhancement of immune-mediated antitumor efficacy.

As a novel immunotherapy combination, anti-PD-L1 plus anti-TIGIT given concurrently with RT has been evaluated in a mouse model (Grapin et al 2019). The experiment compared the tumor response during treatment with anti-PD-L1 plus anti-TIGIT plus RT with single agent therapy plus RT or RT alone. In the CT26 model, 3 x 8 Gy hypofractionated RT was dramatically more effective in combination with anti-TIGIT and anti-PD-L1 therapy, with a CR rate of 90% (9/10 mice) compared with that of 20% (2/10 mice), 30% (3/10 mice), and 0% (0/10 mice) for anti-TIGIT, anti-PD-L1, and RT alone, respectively. A CR with anti-TIGIT and anti-PD-L1 therapy in combination with 18 x 2 Gy normofractionated RT was observed in 7/12 (58.3%) mice compared with 3/12 (25%), 8/12 (66.7%), and 1/10 (10%) mice for anti-TIGIT, anti-PD-L1, and RT alone with the same fractionated RT, respectively.

Based on those preclinical and clinical supportive data, this study is designed to study cCRT combined with anti-PD-1 or anti-PD-1 plus anti-TIGIT therapies to investigate the addition of immunotherapy to cCRT in LS-SCLC. Ideally, these therapeutic strategies will continue to improve long-term survival and quality of life for patients with LS-SCLC.

1.5.6. Rationale for Chemotherapy Regimens

Four cycles of EP is the standard of care of systemic therapy for patients with LS-SCLC. It has been widely applied for initial treatment in LS-SCLC for over 3 decades. In clinical practice, carboplatin is used as a substitute for cisplatin to reduce the risk of emesis, neuropathy, and nephropathy. However, it also carries a greater risk of myelosuppression. During systemic therapy concurrent with RT, EP is recommended (category 1) as the preferred regimen. In this study, patients in each cohort will receive 4 cycles of EP; if cisplatin is contraindicated or not tolerated, carboplatin may be used.

1.5.7. Rationale for Radiation Therapy Dose

The total dose of RT will be 60 to 70 Gy in once-daily fractions given within 6 to 7 weeks, which is a standard RT procedure according to NCCN SCLC Panel recommendations. The RT dose in LS-SCLC therapy may be given as a once-daily or twice-daily regimen; both regimens have shown improved survival outcome for patients with LS-SCLC and there is no significant difference between the 2 options. The Phase 3 CONVERT trial compared total doses of 66 Gy with once-daily fractionation and 45 Gy with twice-daily fractionation in 547 patients with LS-SCLC; OS outcomes did not significantly differ between the 2 groups.

Based on this study, the higher doses of 60 to 70 Gy with once-daily fractionation became another acceptable option (Miller et al 2003; Roof et al 2003; Bogart et al 2004). The once-daily regimen was selected for this study because the twice-daily regimen carries some concerns about tolerance, presents logistic issues for the RT department, and is inconvenient for patients.

The PCI regimen was standardized at 25 Gy in 10 fractions in patients with LS-SCLC who have a good response to initial therapy. It became a component of the standard of care based on a meta-analysis (Aupérin et al 1999) that reported decreased incidence of brain metastases (relative risk = 0.46, $p < 0.001$) and a 5.4% absolute improvement in 3-year OS (20.7% versus 15.3%) with the addition of PCI.

1.5.8. Rationale for Biomarker Strategy

Biomarker assays will be performed using patient-derived tumor tissue(s) and/or blood samples to evaluate the predicative biomarkers associated with tislelizumab plus ociperlimab. These biomarkers will include but not limit to gene expression profile, tissue- or blood-based gene mutations and TMB/microsatellite instability (MSI), PD-L1/TIGIT/CD155/CD226 expression, and SCLC subtyping (ASCL1/NEUROD1/POU2F3/YAP1).

Despite the progress in clinical treatment of SCLC using anti-PD-1/PD-L1 inhibitors, predictive biomarkers for SCLC clinical efficacy are yet to be well-established and biomarker research for LS-SCLC is very scarce. PD-L1 expression is under investigation in ES-SCLC immunotherapy and its correlation with clinical efficacy has not been well-established, which might be due to different scoring algorithms and combination treatment regimens. In Keynote 158, improved ORR was observed in the PD-L1 combined positive score ≥ 1 subgroup treated with pembrolizumab monotherapy for second-line or further-line treatment of SCLC (Chung et al 2018). Other studies investigating PD-L1 tumor cell expression or immune cell expression showed no association with clinical benefit (Hellmann et al 2017). More data are needed to further evaluate the predictive power of PD-L1 expression using different scoring algorithms in SCLC. Another potential predictive biomarker reported in SCLC immunotherapy was tissue and blood TMB. Improved ORR was observed in the Checkmate 032 trial in TMB-high SCLC patients treated with nivolumab (Antonia et al 2016). However, in the IMpower 133 trial, no correlation of TMB with OS was observed in patients with SCLC treated with atezolizumab plus chemotherapy (Horn et al 2018). The predictive value of TMB will be further evaluated in the current study. Moreover, there is a lack of evidence indicating whether genetic mutations could have a correlation with the benefit of immunotherapy in patients with SCLC. SCLC is characterized by relatively high TIGIT and PVR expression and high PVR expression is correlated with poor prognosis (Yu et al 2018). The expression of TIGIT pathway molecules including TIGIT, CD226, CD155, and CD112 will be measured to explore their

relationship with clinical response to ociperlimab plus tislelizumab. Other immune-related factors will also be assessed in this study, including immune-related gene expression and tumor infiltrating immune cells, which could reflect the status of the tumor immune microenvironment in SCLC and potentially unveil the mechanisms of response or resistance to immunotherapy. Moreover, 4 molecular subtypes of SCLC have been increasingly clearly defined (A/N/P/I) in recent years, and SCLC-I subtype is characterized by an inflamed tumor microenvironment, suggesting its sensitivity to immunotherapy (Gay et al 2019). Therefore, SCLC subtyping and its correlation with immunotherapy response will also be explored.

1.6. Benefit-Risk Assessment

Tislelizumab monotherapy and in combination with chemotherapy have shown meaningful antitumor activity and manageable safety profiles in various types of tumors including ES-SCLC. Other immune checkpoint inhibitors combined with first-line chemotherapy have also shown improved efficacy in ES-SCLC in both the IMpower 133 trial (Horn et al 2018) and the CASPIAN trial (Paz-Ares et al 2019). Based on increased evidence for the combination of immunotherapy and RT, the synthetic anticancer activity of immunotherapy has been proven by preclinical and clinical data. Checkpoint inhibitors with cCRT have provided favorable benefit-risk profiles in the PACIFIC trial for patients with unresectable stage III NSCLC (Antonia et al 2017). Earlier treatment with potentially more effective treatment options might further improve the clinical benefit.

As discussed earlier, there is extensive evidence supporting TIGIT's role in regulating immune response and the interaction between the TIGIT and PD-1 pathways has been shown to promote tumor immune escape. The clinical efficacy demonstrated for tislelizumab and preliminary results with an anti-TIGIT/anti-PD-L1 competitor combination suggest that ociperlimab has the potential to improve and/or extend the therapeutic benefits of tislelizumab in the treatment-naïve setting. The novel therapeutic strategy of using ociperlimab and tislelizumab combined with cCRT seeks to augment the current modest improvement in SCLC, especially in LS-SCLC, which still only has cCRT as the standard initial therapy.

PD-1 blockade by tislelizumab has been evaluated in more than 1350 patients with a safety and efficacy profile similar to what has been reported for other anti-PD-1/PD-L1 therapies such as nivolumab and pembrolizumab. Based on the mechanism(s) of action and the nonclinical and preliminary clinical data, the combined blockade of TIGIT and PD-1 by ociperlimab and tislelizumab, respectively, is expected to result in immune-mediated toxicities similar to what has been observed with tislelizumab alone. Preliminary safety results from the CITYSCAPE trial (N = 135) support this hypothesis and demonstrate that patients treated with the anti-TIGIT/anti-PD-L1 combination experienced < 10% increase in overall and Grade 3 or 4 TEAEs compared with patients treated with anti-PD-1 and placebo (Rodriguez-Abreu et al 2020).

As for the safety profile of immunotherapy combined with cCRT, the Phase 3 PACIFIC trial and the Phase 2 trials NICOLAS (Peters et al 2019) and DETERRED (Lin et al 2020) have released preliminary safety data of anti-PD-1/PD-L1 administered at the same time as cCRT. Most of AEs were Grade 1 or 2 and all immune-mediated toxicities were reversible with steroids and supportive care.

The risk of augmented safety signals, as has been shown for other anti-PD-1-based immuno-oncology combinations, still remains. Therefore, the European Society for Medical Oncology and the American Society for Clinical Oncology have established a monitoring plan to monitor, diagnose, and manage imAEs. A Safety Monitoring Committee (SMC) will be established to regularly monitor the safety of ociperlimab plus tislelizumab and tislelizumab alone in combination with cCRT (Section 10.1).

Given the unmet medical need and limited treatment options in this indication, the benefit/risk assessment for this study is favorable, based on strong scientific rationale indicating that the blockade of PD-1 pathway with or without the blockade of the TIGIT pathway combined with standard cCRT may result in enhanced antitumor activity as compared with cCRT alone without a major increase in the risk of immune-mediated toxicities.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

- To compare progression-free survival (PFS) between Arm A (ociperlimab plus tislelizumab plus cCRT) and Arm C (cCRT only) and between Arm B (tislelizumab plus cCRT) and Arm C as assessed by the investigator according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) in the Intent-to-Treat (ITT) Analysis Set

2.1.2. Secondary Objectives

- To compare the following between Arm A and Arm C and between Arm B and Arm C as assessed by the investigator according to RECIST v1.1 in the ITT Analysis Set:
  - Complete response (CR) rate
  - Overall response rate (ORR)
  - Duration of response (DOR)
  - Overall survival (OS)
  - Distant metastasis-free survival (DMFS)
- To evaluate the correlation of PD-L1 and TIGIT expression with ORR, PFS, and OS
- To evaluate the safety and tolerability of ociperlimab combined with tislelizumab plus cCRT and tislelizumab plus cCRT

2.1.3. Exploratory Objectives

- To explore prognostic and predictive effects of tissue- and blood-based biomarkers on efficacy and their association with mechanisms of resistance
- To evaluate health-related quality of life (HRQoL)
- To assess the utility of circulating tumor DNA (ctDNA) level change as a surrogate marker for efficacy
- To assess the PK of ociperlimab and tislelizumab
- To assess the immunogenicity of ociperlimab and tislelizumab

2.2. Study Endpoints

2.2.1. Primary Endpoint

- PFS, defined as the time from the date of randomization to the date of the first documented disease progression as determined by the investigator per RECIST v1.1 or death from any cause (whichever occurs first), in the ITT Analysis Set of Arms A, B, and C

2.2.2. Secondary Endpoints

- CR rate, defined as the proportion of patients who had CR as assessed by the investigator per RECIST v1.1, in the ITT Analysis Set of Arms A, B, and C
- ORR, defined as the proportion of patients who had CR or partial response (PR) as assessed by the investigator per RECIST v1.1, in the ITT Analysis Set of Arms A, B, and
- DOR, defined as the time from the date of the first occurrence of a documented objective response to the date of documented disease progression as determined by the investigator per RECIST v1.1 or death from any cause (whichever occurs first), in the ITT Analysis Set of Arms A, B, and C
- OS, defined as the time from the date of randomization to the date of death due to any cause in the ITT Analysis Set, in the ITT Analysis Set of Arms A, B, and C
- DMFS, defined as the time from the date of randomization to the date of the first documented distant metastasis as assessed by the investigator per RECIST v1.1 or death from any cause (whichever occurs first), in the ITT Analysis Set of Arms A, B, and C
- ORR, PFS, and OS in subgroups based on PD-L1 and TIGIT expression levels
- The incidence and severity of treatment-emergent adverse events (TEAEs) graded according to National Cancer Institute-Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v5.0).

2.2.3. Exploratory Endpoints

- Biomarkers from patient-derived tumor tissue(s) and/or blood samples obtained before, during, and/or after treatment including but not limited to gene expression profile, tissue- or blood-based gene mutations and TMB/MSI, CD155/CD226 expression, SCLC subtyping (ASCL1/NEUROD1/POU2F3/YAP1)
- HRQoL assessment using 2 patient-reported outcomes (PROs) including the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and its lung cancer module Quality of Life Questionnaire Lung Cancer 13 (QLQ-LC13)
- The ctDNA level change before, during, and after treatment as a surrogate marker for efficacy
- Serum concentrations of ociperlimab and tislelizumab at specified timepoints
- Assessment of immunogenicity of ociperlimab and tislelizumab by determining the incidence of ADAs

3. STUDY DESIGN

3.1. Summary of Study Design

This is a Phase 2, multicenter, randomized, 3-arm, open-label study to investigate the preliminary efficacy and safety of ociperlimab plus tislelizumab plus cCRT followed by ociperlimab plus tislelizumab (Arm A) and tislelizumab plus cCRT followed by tislelizumab only (Arm B) compared with cCRT only (Arm C) in patients with previously untreated LS-SCLC.

The primary endpoint is investigator-assessed PFS in the ITT Analysis Set for the comparisons of Arm A versus Arm C and Arm B versus Arm C.

Approximately 120 patients will be randomized in a 1:1:1 ratio to receive the study treatment in the following 3 arms:

- Arm A: Ociperlimab 900 mg intravenously once every 3 weeks plus tislelizumab 200 mg intravenously once every 3 weeks combined with cCRT for 4 cycles, followed by ociperlimab 900 mg intravenously once every 3 weeks plus tislelizumab 200 mg intravenously once every 3 weeks
- Arm B: Tislelizumab 200 mg intravenously once every 3 weeks combined with cCRT for 4 cycles, followed by tislelizumab 200 mg intravenously once every 3 weeks
- Arm C: cCRT only for 4 cycles

Randomization will be stratified by disease stage (I/II versus III) by the AJCC staging system, 8th edition.

The chemotherapy regimen is cisplatin 75 mg/m^2 on Day 1 of each cycle for 4 cycles. If the patient is unable to tolerate the 1-day administration of cisplatin 75 mg/m^2, at the investigator's discretion (eg, patients had concurrent superior vena cava syndrome), cisplatin 25 mg/m^2 dosed on Days 1, 2, and 3 is allowed. Etoposide is administered at 100 mg/m^2 on Days 1, 2, and 3 for 4 cycles. Dose adjustment is allowed to address potential renal, hematologic, or other toxicities after the first cycle.

If cisplatin is contraindicated or not tolerated (Section 5.2.2.1), carboplatin and etoposide will be the alternative chemotherapy regimen. Carboplatin at a dose of area under the plasma or serum concentration-time curve 5 (AUC 5) should be administered as an intravenous infusion once every 3 weeks on Day 1 of each cycle for 4 cycles and etoposide 100 mg/m^2 should be administered on Days 1, 2, and 3 of each cycle for 4 cycles.

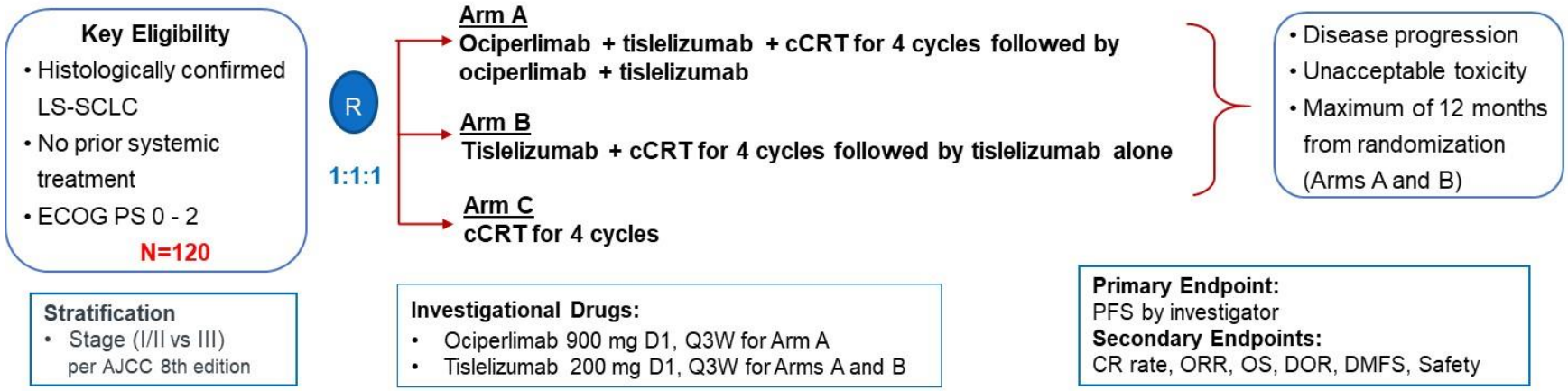
For Arm A and Arm B, investigational drug(s) (ociperlimab plus tislelizumab [Arm A] or tislelizumab alone [Arm B]) will be given starting on Cycle 1 Day 1 (C1D1) before chemotherapy and continued for a duration of up to 12 months (a maximum of 17 cycles of treatment) or until disease progression according to RECIST v1.1, unacceptable toxicity, death, or another discontinuation criterion is met, whichever occurs first.

RT should start early within cycle 1 or 2 of systemic therapy. The total dose of RT will be 60 to 70 Gy, given in once-daily fractions over 6 to 7 weeks.

PCI is permitted at the investigator's discretion. The preferred total dose for PCI to the whole brain is 25 Gy in 10 daily fractions.

The study design schematic is presented in Figure 2.

Figure 2: Study Schema



Abbreviations: AJCC, American Joint Committee on Cancer; cCRT, concurrent chemoradiotherapy; CR, complete response; D1, Day 1; DMFS, distant metastasis-free survival; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; LS-SCLC, limited-stage small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; Q3W, once every 3 weeks; R, randomization.

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

3.2. Screening Period

Screening evaluations will be performed within 28 days before randomization. Patients who agree to participate in this study will sign the informed consent form (ICF) before undergoing any screening procedure. Patients who are suspected to have concurrent serious respiratory illness or exhibit significant respiratory symptoms unrelated to underlying cancer will also take a pulmonary function test (refer to Section 7.1.5 and Appendix 1 for details). Screening evaluations may be repeated as needed within the screening period; the investigator is to assess preliminary patient eligibility according to the latest screening assessment results.

Archival tumor tissue must be collected for the purpose of biomarker analysis. If no archival samples are available, a fresh tumor biopsy at baseline is required. Refer to Section 7.7 for details.

3.3. Treatment Period

After completing all screening activities, eligible patients will be randomized in a 1:1:1 ratio to receive either ociperlimab plus tislelizumab plus cCRT followed by ociperlimab plus tislelizumab (Arm A), tislelizumab plus cCRT followed by tislelizumab only (Arm B), or cCRT only (Arm C). Randomization will be stratified according to stage (stage I/II versus stage III).

Patients will receive open-label treatment with one of the following:

- Arm A: Ociperlimab 900 mg intravenously once every 3 weeks plus tislelizumab 200 mg intravenously once every 3 weeks combined with cCRT for 4 cycles, followed by ociperlimab 900 mg intravenously once every 3 weeks plus tislelizumab 200 mg intravenously once every 3 weeks
- Arm B: Tislelizumab 200 mg intravenously once every 3 weeks combined with cCRT for 4 cycles, followed by tislelizumab 200 mg intravenously once every 3 weeks
- Arm C: cCRT only for 4 cycles

For Arm A and Arm B, investigational drug(s) will be given starting on Cycle 1 Day 1 (C1D1) before chemotherapy and continued for a duration of up to 12 months, or until disease progression per RECIST v1.1, unacceptable toxicity, death, or another discontinuation criterion is met, whichever occurs first.

In Arms A and B, treatment with ociperlimab plus tislelizumab or with tislelizumab alone beyond the initial investigator-assessed, RECIST v1.1-defined disease progression is permitted provided that the patient has investigator-assessed clinical benefit and is tolerating study drug. Specific requirements for patients with disease progression to be able to continue treatment with ociperlimab and tislelizumab are described in Section 7.5.

During the study, tumor imaging will be performed at approximately 12 weeks (± 7 days) from the date of randomization (an additional tumor assessment is allowed if clinically indicated), then every 6 weeks (± 7 days) for the next 54 weeks, and then every 12 weeks (± 7 days) thereafter based on RECIST v1.1. Tumor response will be assessed by investigators. Details are provided in Section 7.5.

Safety will be assessed throughout the study by monitoring AEs/SAEs (toxicity grades assigned per NCI-CTCAE v5.0 and laboratory results. Vital signs, physical examinations, Eastern Cooperative Oncology Group (ECOG) Performance Status change, electrocardiogram (ECG) results, and other examinations will also be used for safety assessment. Safety assessments are further detailed in Section 7.4 and the Schedule of Assessments (Appendix 1).

3.4. End of Treatment/Safety Follow-up

The End-of-Treatment (EOT) Visit and Safety Follow-up Visit are planned to be conducted when the investigator determines that study treatment will no longer be used. The EOT Visit should be conducted within 7 days after the decision to discontinue study treatment or upon completion of study treatment. If routine laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the planned EOT or Safety Follow-up Visit, these tests need not to be repeated. Tumor assessment is not specifically required at the EOT or Safety Follow-up Visit and should follow the regular tumor evaluation schedule detailed in Section 7.5. However, in some cases, the time window of tumor assessment might overlap with the EOT and/or Safety Follow-up Visit.

Patients who discontinue study treatment for any reason will be asked to return to the clinic for the Safety Follow-up Visit, which is required to be conducted 30 days (± 7 days) after the last dose/last day of study treatment (including cCRT), or initiation of new anticancer therapy, whichever occurs first.

For Arms A and B, patients should return to the site or telephone contacts with patients should be conducted to assess imAEs and concomitant medications (if appropriate, ie, associated with an imAE or is a new anticancer therapy) at 60 and 90 days (± 7 days) after the last dose of ociperlimab or tislelizumab, regardless of whether patients start a new anticancer therapy. If patients report a suspected imAE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated.

The EOT Visit may be used as the Safety Follow-up Visit if it occurred 30 days (± 7 days) after the last dose of study treatment, eg, at an EOT Visit right after a response assessment showed disease progression resulting in patient discontinuation. Patients who discontinue study treatment or complete study treatment before disease progression will have their tumors assessed as outlined in Section 7.5. If the EOT Visit is used as the Safety Follow-up Visit, the assessment that has been performed at the EOT Visit does not need to be repeated.

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

Patients who discontinue or complete study treatment before disease progression will need to undergo tumor assessments as outlined in Section 7.5.

For patients who have disease progression during the study, an optional biopsy will also be taken at the EOT or Safety Follow-up Visit from accessible tumor sites, which could be used for exploratory study including, but not limited to, study of the resistance mechanism. If feasible, any follow-up biopsy should be ideally taken from the same tumor lesion as the baseline biopsy. Written informed consent is required before fresh tumor biopsies.

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

3.5. Survival Follow-up

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

3.6. Discontinuation From the Study Treatment or From the Study

3.6.1. Patient Discontinuation From Study Treatment

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

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

- Radiographic disease progression 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)
- Patient noncompliance
  Investigative site staff should first counsel patients who are significantly noncompliant (eg, missing 2 treatment cycles) on the importance of study drug compliance and drug accountability. The investigator may, in consultation with the medical monitor, discontinue patients from treatment who are consistently noncompliant.
- Completion of study treatment

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

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

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

3.7. End of Study

The end of study is defined as the timepoint when the final data point is collected from the last patient in the study. This is when the last patient 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 and Safety Follow-up Visit.

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

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

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

4. STUDY POPULATION

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

4.1. Inclusion Criteria

Each patient eligible to participate in this study must meet all 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 (or the legal age of consent in the jurisdiction in which the study is taking place) on the day of signing the informed consent form
3. Patient has pathologically (histologically or cytologically) proven diagnosis of small cell lung cancer
4. Has limited-stage disease (stage Tx, T1-T4, N0-3, M0; AJCC staging, 8th edition), and can be safely treated with definitive radiation doses. Note: Patients with stage T3-4 disease due to multiple lung nodules that are too extensive or that have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan are ineligible
5. Patient has not received any prior treatment for LS-SCLC
6. Patient has measurable disease as assessed according to RECIST v1.1 that is appropriate for selection as a target lesion for repeat measurement, as determined by local site investigator/radiology review
7. Patients must agree to provide an archival tumor tissue with an associated pathology report or agree to perform a fresh tumor biopsy during screening (formalin-fixed paraffin-embedded block or approximately 15 unstained slides [8 slides minimum])

   Note: If < 8 unstained slides are available, a discussion with the sponsor is required
8. ECOG Performance Status ≤ 2 assessed within 7 days before the first administration of study intervention
9. Patients must have a life expectancy of ≥ 12 weeks
10. Adequate organ function as indicated by the following screening laboratory values obtained within 7 days before randomization:
    a. Absolute neutrophil count ≥ 1.5 x 10^9/L, platelets ≥ 100 x 10^9/L, hemoglobin ≥ 90 g/L. Note: Patients must not have undergone a blood transfusion or received growth factor support ≤ 14 days before sample collection at screening
    b. International normalized ratio or prothrombin time ≤ 1.5 x ULN
    c. Activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN
    d. Serum total bilirubin ≤ 1.5 x ULN (total bilirubin must be < 3 x ULN for patients with Gilbert's syndrome)
    e. AST and ALT ≤ 2.5 x ULN
    f. Calculated creatinine clearance (CrCl) ≥ 45 mL/min (Cockcroft-Gault formula) (Appendix 12)

11. 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 ociperlimab and tislelizumab in Arm A or tislelizumab in Arm B, or ≥ 180 days after the last dose of radiotherapy or chemotherapy (except for cisplatin), or ≥ 14 months after the last dose of cisplatin, whichever occurs later; and have a negative urine or serum pregnancy test ≤ 7 days before randomization. See Appendix 9.
12. Non-sterile 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 ociperlimab and tislelizumab in Arm A or tislelizumab in Arm B, or ≥ 180 days after the last dose of radiotherapy or chemotherapy (except for cisplatin), or ≥ 11 months after the last dose of cisplatin, whichever occurs later.
    - A sterile male is defined as one for whom azoospermia has been previously demonstrated in a semen sample examination as definitive evidence of infertility.
    - Males with known "low sperm counts" (consistent with "sub-fertility") are not to be considered sterile for purposes of this study.

4.2. Exclusion Criteria

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

1. Mixed small cell lung cancer histology. Note: mixed SCLC with the component of neuroendocrine carcinoma origin is considered eligible
2. Have received surgical resection for LS-SCLC
3. Any patient for whom the tumor is considered resectable by surgery or stereotactic body radiation therapy/stereotactic ablative radiotherapy should be considered ineligible
4. Is expected to require any other form of antineoplastic therapy while on study.
5. Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-TIGIT, or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways
6. Receipt of interleukin, interferon, thymosin, or any investigational therapies within 14 days or 5 half-lives (whichever is longer) before randomization
7. Patient's radiation treatment plans are likely to encompass a volume of whole lung receiving ≥ 20 Gy in total (V20) of > 38% of lung volume. Prior tangent fields for breast cancer with minimal overlap with target volumes are allowed per approval of the principal investigators
8. Active autoimmune diseases or history of autoimmune diseases that may relapse

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

a. Controlled type I diabetes
b. Hypothyroidism (provided it is managed with hormone replacement therapy only)
c. Controlled celiac disease
d. Skin diseases not requiring systemic treatment (eg, vitiligo, psoriasis, alopecia)

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

9. Any active malignancy ≤ 2 years before 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)
10. Any condition that required systemic treatment with either corticosteroids (> 10 mg daily of prednisone or equivalent) or other immunosuppressive medication ≤ 14 days before randomization

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

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

11. 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
12. History of interstitial lung disease, non-infectious pneumonitis or uncontrolled lung diseases including pulmonary fibrosis, acute lung diseases, etc. Patients with significantly impaired pulmonary function or who require supplemental oxygen at baseline must undergo an assessment of pulmonary function at screening (see Section 7.1.5)
13. Infection (including tuberculosis infection, etc) requiring systemic antibacterial, antifungal, or antiviral therapy within 14 days before randomization
    Note: Antiviral therapy is permitted for patients with hepatocellular carcinoma or chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection.
14. Untreated chronic hepatitis B or chronic HBV carriers with HBV DNA > 500 IU/mL (or > 2500 copies/mL) at screening
    Note: Inactive hepatitis B surface antigen (HBsAg) carriers and those with treated and stable hepatitis B (HBV DNA < 500 IU/mL or < 2500 copies/mL) can be enrolled. Patients with detectable hepatitis B surface antigen (HBsAg) or detectable HBV DNA should be managed per treatment guidelines. Patients receiving antiviral therapy at screening should have been treated for > 2 weeks before randomization.
15. Patients with active hepatitis C
    Note: Patients with a negative HCV antibody test at screening or a 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 testing positive for HCV antibody. Patients receiving antiviral therapy at screening should have been treated for > 2 weeks before randomization.

16. Known history of HIV infection
17. Any major surgical procedure ≤ 28 days before randomization (except for placement of vascular access). Patients must have recovered adequately from the toxicity and/or complications from the intervention before randomization
18. Prior allogeneic stem cell transplantation or organ transplantation
19. Any of the following cardiovascular risk factors:
    a. Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living, ≤ 28 days before randomization
    b. Pulmonary embolism ≤ 28 days before randomization
    c. Any history of acute myocardial infarction ≤ 6 months before randomization
    d. Any history of heart failure meeting New York Heart Association Classification III or IV (Appendix 6) ≤ 6 months before randomization
    e. Any event of ventricular arrhythmia ≥ Grade 2 in severity ≤ 6 months before randomization
    f. Any history of cerebrovascular accident ≤ 6 months before randomization
    g. Uncontrolled hypertension that cannot be managed by standard anti-hypertension medications ≤ 28 days before randomization
    h. Any episode of syncope or seizure ≤ 28 days before randomization
20. A history of severe hypersensitivity reactions to other monoclonal antibodies
21. A history of allergic reactions to cisplatin, carboplatin, other platinum-containing compounds, or etoposide.
22. Patients with toxicities (as a result of prior anticancer therapy) which have not recovered to baseline or stabilized, except for AEs not considered a likely safety risk (eg, alopecia, neuropathy and specific laboratory abnormalities)
23. Was administered a live vaccine ≤ 28 days before randomization
    Note: Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed.
24. Underlying medical conditions (including laboratory abnormalities) or alcohol or drug abuse or dependence that will be unfavorable for the administration of study drug, or affect the explanation of drug toxicity or AEs, or result in insufficient or impaired compliance with study conduct
25. Women who are pregnant, breastfeeding, or planning to get pregnant during the study.
26. Concurrent participation in another therapeutic clinical study

5. STUDY TREATMENT

5.1. Formulation, Packaging, and Handling

5.1.1. Ociperlimab

Ociperlimab is a monoclonal antibody formulated for intravenous injection in a single-use vial (20 mL glass vial, USP Type I) containing a total of 300 mg antibody in 15 mL of buffered isotonic solution as available. 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 condition as 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 (BGB-A1217) Investigator's Brochure for other details regarding ociperlimab.

5.1.2. Tislelizumab

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

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

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

Refer to the pharmacy manual for details regarding intravenous administration, accountability, and disposal. Please also refer to the Tislelizumab Investigator's Brochure for other details regarding tislelizumab.

5.1.3. Chemotherapy

Management (ie, handling, storage, administration, and disposal) of cisplatin, carboplatin, and etoposide will be in accordance with the relevant local guidelines and/or prescribing information/summary of product characteristics.

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

5.2. Dosage, Administration, and Compliance

Dosing schedules for all treatment arms, broken out by individual arm, are provided in Table 3. The first dose of study drug is to be administered within 3 business days of randomization.

C1D1 is defined as the day of the administration of the first dose of ociperlimab or tislelizumab. Ociperlimab and tislelizumab and will be given starting from C1D1 in the cCRT phase and continued for a duration of up to 12 months after C1D1. During the cCRT phase, ociperlimab and tislelizumab should be administered before chemotherapy; in case the logistical circumstances do not allow for all of the intravenous study drugs (including ociperlimab, tislelizumab, and platinum-based doublet chemotherapy) to be administered on the same day, ociperlimab and tislelizumab administration on the same day should be guaranteed and then chemotherapy should start as soon as possible within the following 3 days. For Arm C (cCRT only), C1D1 is defined as the day of administration of the first dose of chemotherapy.

All patients will be monitored continuously for AEs. Treatment modifications (eg, dose delay, reduction, interruption, or discontinuation) will be based on specific laboratory and AE criteria, as described in Section 5.5.

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

Study drug	Dose		Frequency of administration	Route of administration	Duration of treatment
Ociperlimab	900 mg		Day 1 of each cycle (3-week cycles)	Intravenous	See Section 3.3
Tislelizumab	200 mg		Day 1 of each cycle (3-week cycles)	Intravenous	See Section 3.3
Cisplatin + Etoposide	Cisplatin	75 mg/m^2	75 mg/m^2: Day 1 of each cycle If the patient is unable to tolerate the 1-day administration of cisplatin 75 mg/m^2, at the investigator's discretion cisplatin 25 mg/m^2 dosed on Days 1, 2 and 3 is allowed. (3-week cycles)	Intravenous	First 4 cycles
	Etoposide	100 mg/m^2	Days 1, 2, and 3 of each cycle (3-week cycles)	Intravenous	First 4 cycles
Carboplatin + Etoposide	Carboplatin	AUC 5	Day 1 of each cycle (3-week cycles)	Intravenous	First 4 cycles
	Etoposide	100 mg/m^2	Days 1, 2, and 3 of each cycle (3-week cycles)	Intravenous	First 4 cycles

Abbreviation: AUC, area under the plasma or serum concentration-time curve.

5.2.1. Ociperlimab and Tislelizumab

In Arm A, tislelizumab 200 mg followed by ociperlimab 900 mg will be administered on Day 1 of each cycle (once every 3 weeks). In Arm B tislelizumab 200 mg will be administered on Day 1 of each cycle (once every 3 weeks),

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

The initial 2 infusions for Arms A and B (Day 1 of Cycles 1 and 2) will be delivered over 60 (± 5) minutes each for ociperlimab and tislelizumab (Table 4); if these infusions are well tolerated, then the subsequent infusions may be administered over 30 (± 5) minutes, which is the shortest time period permissible for infusion. Ociperlimab and tislelizumab and must not be concurrently administered with any other drug (refer to Section 6).

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 consistent with approved institutional procedures.

At the end of the infusion period, the line will be flushed with enough normal saline to make sure the complete doses of ociperlimab and tislelizumab are administered.

As a routine precaution, after infusion of tislelizumab followed by ociperlimab (Arm A) and tislelizumab (Arm B) on Day 1 of Cycles 1 and 2, patients must be monitored in an area with resuscitation equipment and emergency agents for ≥ 120 minutes. From Cycle 3 onwards, a ≥ 60-minute monitoring period in an area with resuscitation equipment and emergency agents is required (Table 4).

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

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

Table 4: Administration of Ociperlimab and Tislelizumab and Monitoring Time

Arm	Cycle	Ociperlimab in combination with tislelizumab or tislelizumab alone [a]
Arm A	Cycle 1 Day 1	Tislelizumab infusion over 60 (± 5) minutes followed by ociperlimab infusion over 60 (± 5) minutes Patient monitoring for ≥ 120 minutes
	Cycle 2 Day 1	Tislelizumab infusion over 60 (± 5) minutes followed by ociperlimab infusion over 60 (± 5) minutes Patient monitoring for ≥ 120 minutes
	Cycle 3 Day 1 onwards	Tislelizumab infusion over 30 (± 5) minutes followed by ociperlimab infusion over 30 (± 5) minutes Patient monitoring for ≥ 60 minutes
Arm B	Cycle 1 Day 1	Tislelizumab infusion over 60 (± 5) minutes Patient monitoring for ≥ 120 minutes
	Cycle 2 Day 1	Tislelizumab infusion over 60 (± 5) minutes Patient monitoring for ≥ 120 minutes
	Cycle 3 Day 1 onwards	Tislelizumab infusion over 30 (± 5) minutes Patient monitoring for ≥ 60 minutes

[a] There is no required monitoring period between tislelizumab infusion and ociperlimab infusion.

5.2.2. Chemotherapy

5.2.2.1. Cisplatin + Etoposide

Cisplatin 75 mg/m^2 will be administered on Day 1 for 4 cycles. If the patient is unable to tolerate the 1-day administration of cisplatin 75 mg/m^2, at the investigator's discretion (eg, patients had concurrent superior vena cava syndrome) cisplatin 25 mg/m^2 dosed on Days 1, 2, and 3 is allowed. Etoposide 100 mg/m^2 will be administered on Days 1, 2, and 3 of each of the first 4 cycles by intravenous infusion.

For cisplatin, all patients should receive adequate hydration (including pretreatment hydration) and diuretics. Urinary output > 2000 mL must be maintained in the 24 hours following the infusion.

For etoposide, extravasation of infusion should be avoided.

Additional premedications should be administered as per standard practice.

If a patient is contraindicated for cisplatin, carboplatin plus etoposide is the alternative chemotherapy regimen. Also, patients will be allowed to switch from cisplatin to carboplatin if they exhibit intolerance to cisplatin after completing ≥ 1 cycle of cisplatin treatment (Section 5.2.2.2).

Contraindication or intolerance to cisplatin is indicated if the patient has a history of allergy or hypersensitivity to cisplatin, has had intolerable toxicity to cisplatin, has met Hy's law criteria after receiving cisplatin-containing treatment, or has blood creatinine clearance < 60 mL/min.

5.2.2.2. Carboplatin + Etoposide

If patients have contraindication or intolerance to cisplatin, carboplatin will be used in the chemotherapy regimen in place of cisplatin.

Carboplatin at a dose of AUC 5 will be administered on Day 1 and etoposide 100 mg/m^2 will be administered on Days 1, 2, and 3 of each of the first 4 cycles by intravenous infusion.

Carboplatin dose should be calculated before each dose using actual weight if the patient's body weight changes by more than 10% from baseline (or the newly referred body weight) and current serum creatinine level according to local prescribing information and local practice.

5.2.3. Thoracic Radiation Therapy

Before enrolling a patient in this study, the radiation oncologist will evaluate the thoracic CT scan or MRI to ensure that the treatment volumes are unlikely to significantly exceed the specified normal tissue constraints and that it is feasible to administer the RT dose at the range as allowed in the protocol for a patient. A patient will be excluded if his/her radiation treatment plans are likely to encompass a volume of the whole lung receiving ≥ 20 Gy in total (V20) of more than 38% of lung volume. All patients will receive RT using either a standardized 3-dimensional conformal RT technique or intensity-modulated radiotherapy or volumetric modulated arc therapy on a linear accelerator delivering a beam energy of ≥ 6 MV.

RT should start early within cycle 1 or 2 of systemic therapy. The total dose of RT will be 60 to 70 Gy to the initial primary tumor target volume and be delivered once daily over 6 to 7 weeks.

While 60 to 70 Gy in 6 to 7 weeks is the target dose of radiation, concern about patient tolerance discovered during treatment planning or delivery, for example, a V20 exceeding that recommended in the protocol, may dictate that a lower dose be administered after consulting with sponsor medical monitor. Definitive RT will be considered as receiving a minimum of 56 Gy to the planning target volume (PTV).

Contouring of normal tissues and organs for radiotherapy planning will be in accordance with the NCCN guideline or local institutional guidelines.

5.2.3.1. Radiation Dose Specifications

Patients will receive treatment for 5 days per week, in once-daily fractions, to a target dose of 60 to 70 Gy in 6 to 7 weeks. Normalization of the treatment plan will cover 95% of the PTV with the prescription dose. The minimum PTV dose should ideally not fall below 93% of the prescription dose. All radiation doses will be calculated with inhomogeneity corrections that take into account the density differences within the irradiated volume (ie, air in the lung and bone). The maximum and minimum point doses (within the PTV) will be reported.

For patients with LS-SCLC who experience tumor shrinkage with chemotherapy, treating all involved nodal stations (at time of diagnosis) and post-chemotherapy lung parenchymal tumor is recommended.

Organs at Risk

Normal tissue constraints are prioritized in Table 5 for treatment planning.

Table 5 Normal Tissue Dose-Volume Constraints for Conventionally Fractionated Radiation Therapy with Concurrent Chemotherapy [a]

Organ at risk	Constraints in 30–35 fractions
Spinal cord	Max ≤ 50 Gy
Lung	V20 ≤ 35%–40%[b,c]; MLD ≤ 20 Gy [d]
Heart	V50 ≤ 25%; Mean ≤ 20 Gy
Esophagus	Mean ≤ 34 Gy; Max ≤105% of prescription dose; V60 ≤ 17%; contralateral sparing is desirable
Brachial plexus	Max ≤ 66 Gy

Abbreviations: DLCO, diffusing capacity of the lung;; FEV1, forced expiratory volume in 1 second; Gy, Gray; max, maximum; MLD, mean lung dose; NCCN, National Comprehensive Cancer Network; OAR, organ at risk; PFT, pulmonary function test

[a] These constraints represent doses that generally should not be exceeded, based on a consensus survey of NCCN Member Institutions. Because the risk of toxicity increases progressively with dose to normal tissues, a key principle of radiation treatment planning is to keep normal tissue doses "as low as reasonably achievable" while adequately covering the target. The doses to any given organ at risk should typically be lower than these.

[b] Use V20 < 35%, especially for the following: elderly ≥ 70 years, and poor PFTs (such as FEV1 or DLCO < 50% normal). Use more conservative limits with a diagnosis or radiologic evidence of idiopathic pulmonary fibrosis (IDP)/usual interstitial pneumonia (UIP) (the tolerance of these patients is lower though not well characterized).

[c] Vxx = % of the whole OAR receiving ≥ xx Gy

[d] MLD, being the volumes of both lungs minus the gross tumor volume

5.2.3.2. Variations of Dose Prescription

The variations in dose prescription are described below, and also summarized in Table 6 (NCCN 2021).

Per Protocol: ≥ 99% of the PTV receives at least 93% of the prescribed dose, and no volume ≥ 1 cm^3 within the PTV receives > 110% of the prescribed dose, and no more than a contiguous volume of 1 cm^3 outside the PTV receives a maximum of 110% of the prescribed dose, and the percent volume of both lungs (excluding PTV) receiving a dose of 5 Gy or higher (V5) is ≤ 60%.

Variation Acceptable: Deviations of this magnitude are not desirable but are acceptable. Between < 99% but ≥ 95% of the PTV receives at least 93% of the prescribed dose, or a contiguous volume of > 1 cm^3 within the PTV receives > 110% but ≤ 115% of the prescribed dose, or a contiguous volume of >1cm^3 outside the PTV receives > 110% but ≤ 115% of the prescribed dose, or V5 is > 60% but ≤62%.

Table 6: Summary of Dose Prescription Variations

	Per Protocol	Acceptable Variation

PTV volume coverage	≥ 99% of PTV receives at least 93% of prescribeddose	≥ 95% but < 99% of PTV receives at least 93% of prescribed dose
Excessive dose within PTV	No contiguous volume > 1 cm^3 within the PTV receives > 107%of prescribed dose	> 1 cm^3 contiguous volume within PTV receives > 107% but ≤ 110% of prescribed dose
Excessive dose outside PTV	No contiguous volume > 1 cm^3 outside PTVreceives > 105% of prescribed dose	> 1 cm^3 contiguous volume outside PTVreceives > 105% but ≤ 107% of prescribed dose
Spinal Cord	D_{max} ≤ 50 Gy	50 Gy < D_{max} ≤ 52 Gy
Excessive Lung V5/V20 /meandose	V5 ≤60% V20 ≤ 38% Mean dose ≤ 20 Gy	V5 > 60% but ≤ 62%
Heart	V50 ≤ 25% Mean dose ≤ 20 Gy	25% < V50 ≤ 33% 20 Gy < Mean dose ≤22Gy
Esophagus	Mean dose ≤ 34 Gy D_{max} ≤105% of prescription dose; V60 ≤ 17%; contralateral sparing is desirable	34 Gy < Mean dose ≤ 36 Gy V60 ≤ 19%; contralateral sparing is desirable
Brachial Plexus	D_{max} ≤ 66 Gy	D_{max} ≤ 68 Gy

Abbreviations: D_{max}, Maximum dose; Gy, Gray; PTV, planning target volume; Vxx, percentage of the whole organ at risk receiving ≥ xx Gy

5.2.3.3. Localization, Simulation, and Immobilization

Each patient will be positioned in an institution-specific immobilization device in the treatment position on a flat table. All planning CT scans should be performed in the treatment position using the same immobilization device for setup as is used at the linear accelerator. Optimal immobilization is critical for this protocol in order to ensure reproducibility of the daily setup. Either a conventional (non-4D CT) treatment planning CT study or a 4-dimensional computed tomography (4DCT) will be performed. Conventional CT scans will be performed during quiet, uncoached respiration while the patient undertakes a normal respiration, using at least 5-mm slices through the entire target volume. The whole thorax (cricoid to L2) should be covered using < 1 cm slices in order to generate dose-volume histograms to be calculated of the lungs, spinal cord, heart, and esophagus. A treatment planning FDG-PET/CT scan (or FDG-PET alone) with the patient in the treatment position can be used for treatment planning. Where a PET/CT is obtained in the treatment position, the CT from this study may be used as the planning CT scan.

The gross tumor volume (GTV), internal target volume (ITV) and PTV will be defined on all appropriate slices (see definitions in Section 5.2.3.4). Intravenous contrast (if no contraindication exists) during the planning CT is optional, provided that a recent diagnostic chest CT was done with contrast to delineate the major blood vessels. If not, intravenous contrast can be administered during the planning CT, if this is considered necessary in the view of the radiation oncologist. If contrast is used, the densities can be overridden or the contrast scan could be registered to a non-contrast scan for planning purposes. Acceptable methods of accounting for tumor motion include design of the PTV to cover the excursion of the lung primary cancer and nodes during breathing such as an ITV approach, breath-holds (eg, Eleckta ABC device), or respiratory gating (for example, Varian RPM system).

During patient treatment, daily image guided radiation therapy (IGRT) using orthogonal X-ray, cone beam CT, CT on rails, or MR guidance must be used for all patients, regardless of radiation techniques. Daily image guidance that allows for 3D shifts is the minimum requirement for this trial. Most advanced imaging techniques can be utilized as long as they also allow for 3D shifts. The setup margin in this trial is tied to the use of daily image guidance. Registering anatomy using soft tissue will be most effective for localization. Other soft tissues in the lung such as the carina can help for mediastinal alignment. Fiducial markers can be used for localization as needed. Any linear shifts seen that are ≥2 mm should be applied prior to treatment.

5.2.3.4. Radiation Treatment Planning

Three-Dimensional Conformal Radiotherapy (3DCRT)

The PTV is to be treated with any combination of coplanar or noncoplanar 3D conformal fields shaped to deliver the specified dose while restricting the dose to the normal tissues. The treatment plan used for each patient will be based on an analysis of the volumetric dose, including dose-volume histogram analyses of the PTV and critical normal structures. Each field is to be treated daily.

Intensity Modulated Radiation Therapy (IMRT)

The use of IMRT is recommended, provided that the institution has been using this technique for treating lung cancer for at least 6 months before study activations, as IMRT results in a greater proportion of out of target lung receiving radiation outside the PTV.

Detailed Specification

Target volumes: the definitions of volumes will be in accordance with the ICRU 50 (1999) for 3DCRT and ICRU 83 (2010) for IMRT.

GTV: The primary tumor and clinically positive lymph nodes seen on the planning CT (> 1 cm short axis diameter) or pre-treatment PET scan (SUV > 3) will constitute the GTV. This volume(s) may be disjointed. In the event of a collapsed lobe or lung segment, the use of PET to distinguish tumor from fluid/atelectasis is encouraged.

CTV: The CTV is defined to be the GTV plus a 0.5 cm margin as appropriate to account for microscopic tumor extension. The CTV should be adjusted to not expand into other organs such as esophagus, heart, major blood vessels, or bone unless clinically indicated. If an ITV approach is used, then the ITV plus 0.5 cm margin forms the CTV.

PTV: The PTV will be equal to the CTV plus 0.5 cm setup margin in all directions.

5.2.4. Prophylactic cranial irradiation (PCI)

For patients with stage II-III LS-SCLC who are less than 70 years of age with good performance status (ECOG 0 to 2), without impaired neurocognitive function, and attain a complete or partial response to initial systemic therapy, PCI is recommended.

The preferred dose for PCI to the whole brain is 25 Gy in 10 daily fractions. The decision for PCI administration should be made according to investigator's discretion and local institutional guidelines.

Only standard prophylactic whole brain radiation therapy is allowed in the trial. Memantine may be used for prevention of brain irradiation-induced cognitive toxicity at the investigator's discretion.

During the PCI treatment period (about 2 weeks), the immunotherapy, including tislelizumab monotherapy and the combination of ociperlimab plus tislelizumab, will be temporarily suspended.

5.3. Incorrect Administration or Overdose

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

AEs associated with an overdose or incorrect administration of study drug will be recorded on the AE eCRF. Any SAEs associated with an overdose or incorrect administration must be reported within 24 hours of awareness via the SAE reporting process described in Section 8.6.2. 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, cisplatin, carboplatin, and etoposide) will be provided by the sponsor or sourced by the site and reimbursed by the sponsor, as required by local or country-specific guidance. The investigational site will acknowledge receipt of IMPs. Any damaged shipments will be replaced.

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

5.5. Dose Delay or Modification

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

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

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

5.5.1. Dose Delay or Modification for Ociperlimab or Tislelizumab

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

If a dose delay is required, ociperlimab and tislelizumab will be delayed for Arm A (ie, ociperlimab and tislelizumab must both be delayed in Arm A and, if applicable, restarted at the same time) and tislelizumab will be delayed in Arm B.

Ociperlimab and tislelizumab in Arm A or tislelizumab in Arm B may be temporarily suspended if the patient experiences a toxicity that is considered related to ociperlimab or tislelizumab and requires a dose to be withheld. Investigational drug(s) should resume as soon as possible after the AEs recover to baseline or Grade 1, whichever is more severe, except for AEs that, in the opinion of the investigator, are not considered a safety risk to the patient. If a treatment delay is due to laboratory results worsening, eg, 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 the administration of the study drug(s) can resume within ≤ 10 days, the drug(s) should be administered in the current cycle. If the study drug needs to be withheld for > 10 days, it should be omitted from the current cycle and administration should continue at the start of the next cycle. If the patient is unable to resume ociperlimab plus tislelizumab or tislelizumab alone ≤ 12 weeks after the last dose of study treatment, then the patient should be discontinued from treatment. If the patient is not able to resume ociperlimab plus tislelizumab or tislelizumab alone ≤ 12 weeks after the last dose for unforeseen non-drug-related reasons, continued treatment may be allowed if approved by the medical monitor.

If imAEs are persistent without any improvement for >12 weeks, permanent discontinuation of the study drugs should be considered. In Arm A, the treatment discontinuation in response to imAEs should be applied to both ociperlimab and tislelizumab because the causality of imAEs 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 the study drugs is permitted only in patients who are deemed to be deriving clinical benefit per the opinion of the investigator following agreement between the investigator and the medical monitor.

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

If one component of chemotherapy is discontinued permanently during the first 4 cycles of treatment for reasons other than disease progression, the other component of chemotherapy may be continued per the guidelines in the study protocol and as per local practice. Ociperlimab plus tislelizumab (Arm A) or tislelizumab alone (Arm B) may continue as indicated.

If both components of the chemotherapy are withheld because of toxicity for > 6 weeks, chemotherapy should be discontinued; ociperlimab plus tislelizumab or tislelizumab alone may be continued if the toxicity resulting in chemotherapy discontinuation is not considered by the investigator to be related to ociperlimab plus tislelizumab or tislelizumab alone. Exceptions based on clinical benefit require the prior approval of the medical monitor.

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

5.5.2. Dose Delay, Interruption, or Modifications for Radiation Therapy

Investigators will be advised to suspend the use of chemotherapy and/or ociperlimab plus tislelizumab or tislelizumab alone given with RT if they believe that continuing administration of chemotherapy and/or ociperlimab plus tislelizumab or tislelizumab alone will compromise delivery of full-dose RT in a timely manner.

Reversible or permanent alopecia, bone marrow toxicity, esophagitis, and skin pigmentation are expected side effects of RT. Radiation-induced myocarditis and spinal cord injury rarely occur at doses lower than 50 Gy. Radiographic evidence of radiation-induced changes and subsequent fibrosis of the lung may occur within lung volumes receiving ≥ 20 Gy. It is essential to spare as much normal lung as possible in order to avoid symptomatic lung injury.

- In case of radiation dose delay due to machine breakdown or public holidays or any dose delay of RT up to 7 days, radiation should be completed to the prescribed doses. Total number of fractions and elapsed days should be carefully reported.
- During the cCRT phase, esophagitis is managed according to Appendix 13 and Appendix 14 with regard to RT. During this cCRT period, chemotherapies and/or ociperlimab plus tislelizumab or tislelizumab alone should be withheld if the investigator believes that continued use will jeopardize the delivery of full-dose RT and RT is to be continued. Retreatment with chemotherapies and/or ociperlimab plus tislelizumab or tislelizumab alone is permitted if there is resolution of the esophagitis to ≤ Grade 2.
- If Grade 4 esophagitis related to RT, chemotherapies, or ociperlimab plus tislelizumab or tislelizumab alone occurs, RT, chemotherapies, and/or ociperlimab plus tislelizumab or tislelizumab alone should be held until resolution of the esophagitis to ≤ Grade 2.
- During the cCRT phase, in case of Grade 3 or Grade 4 radiation pneumonitis/lung infiltrates related to RT, the recommendation is to hold RT, chemotherapies and ociperlimab plus tislelizumab or tislelizumab alone. Retreatment with RT, chemotherapies and ociperlimab plus tislelizumab or tislelizumab alone is acceptable if symptoms resolve to ≤ Grade 1 or are controlled on prednisolone ≤ 10 mg/day (or equivalent corticosteroids). Discontinue study treatment if symptoms persist with corticosteroid treatment.

Radiation toxicities will be assessed according to NCI-CTCAE v5.0 criteria and reported per Section 8.3. Note that radiation toxicities can arise more than 90 days after the completion of RT.

Esophagitis

The first symptoms of acute esophagitis usually start in the second or third week of RT, commonly at the dose of 18.0 to 21.0 Gy of standard fractionated RT (Wei et al 2006), and include a sensation of difficult swallowing (dysphagia). This may progress to painful swallowing of food and saliva (odynophagia) and later to constant pain not necessarily related to swallowing. In severe cases, patients may not be able to swallow at all and may require intravenous hydration, feeding through a gastric tube and, in rare cases, parenteral nutrition. Symptomatic esophagitis is common with combined modality therapy (Werner-Wasik 2005) and it does not constitute a reason to delay RT or chemotherapy, provided oral intake is sufficient to maintain hydration. Symptoms of acute esophagitis may persist for 1 to 3 weeks after completion of RT. If CTCAE Grade 4 esophagitis occurs and treatment is delayed, every effort should be made to limit the radiation dose delay to 3 treatment days or less. Patients requiring hospitalization, placement of a feeding tube in the stomach, or intravenous feedings because of esophagitis may have their treatment dose delayed in order to allow for healing of the esophageal mucosa.

Recommended dose modifications of the chemotherapy regimens in cases of Grade 3 or 4 esophagitis are presented in Appendix 13.

Information regarding esophagitis grading according to NCI-CTCAE v5.0 and management of radiation esophagitis through diet and medications is presented in Appendix 14.

Pneumonitis

Pneumonitis has been reported in association with use of anti-PD-L1/anti-PD-1 antibodies. It is also seen in 5% to 15% of patients irradiated for breast, lung, and mediastinal tumors. Thus, pneumonitis may be immune-related or as a result of late toxicity to RT. The risk of developing radiation pneumonitis is directly related to the volume of irradiated lung, the amount of radiation given, and the use of cCRT. Additional risk factors include comorbid lung disease, poor baseline pulmonary function testing, and low performance status.

Symptoms of radiation pneumonitis, including low-grade fever, congestion, dry cough, pleuritic chest pain, and a sensation of chest fullness, usually develop 1 to 3 months after completion of RT. Diagnosis is difficult, often complicated by comorbid conditions and radiation injury to adjacent structures (eg, esophagus, pericardium). Prednisone, in dosages of at least 50 to 60 mg per day for 1 week followed by an extended taper, has been shown to abate symptoms and improve lung function. Bronchodilators and supplemental oxygen may be necessary.

5.5.3. Dose Delay, Interruption, or Modifications for Chemotherapy

Dose modifications for chemotherapy should be performed per applicable local prescribing information and per local practice according to the investigator's clinical judgment. Recommended dose modifications for key chemotherapy toxicities are outlined in Appendix 13. If chemotherapy-related toxicities warrant a dosing delay, chemotherapy administration may restart as soon as is feasible. Chemotherapy may be delayed up to 3 weeks to allow sufficient time for recovery. Upon recovery, chemotherapy is recommended to be administered according to the dose as described in Appendix 13.

These serve as guidelines and do not replace investigator judgment and applicable local label recommendations if more stringent.

Baseline body weight is used to calculate the required chemotherapy doses. Dose modifications are required if the patient's body weight changes by ≥ 10% from baseline (or the new reference body weight). Chemotherapy doses should not be modified for any body weight change of < 10%.

Reduction of one chemotherapy agent and not the other agent is appropriate if, in the opinion of the investigator, the toxicity is clearly related to one of the treatments. If, in the opinion of the investigator, the toxicity is related to the combination of both chemotherapy agents, both drugs should be held/modified according to recommended dose modifications.

Study drug-related toxicities must be resolved to baseline or Grade 1 (whichever is more severe) before administering the next dose, except for alopecia or ≤ Grade 2 fatigue or neuropathy. A maximum of 2 dose reductions for each chemotherapeutic agent, except for carboplatin, are permitted. Only 1 dose reduction is permitted for carboplatin. Once the dose has been decreased, it should remain reduced for all subsequent administrations or further reduced if necessary. There will be no dose escalations in this study. If additional reductions are required, that chemotherapeutic agent must be discontinued.

The interval between the start of 2 consecutive chemotherapy regimens should be ≥ 3 weeks. If chemotherapy-related toxicities warrant a dosing delay, chemotherapy administration may restart as soon as is feasible. For example, chemotherapy administration can occur during an unscheduled visit and resynchronize with ociperlimab plus tislelizumab or tislelizumab alone at subsequent cycle(s), if possible. Dosing intervals of subsequent cycles of ociperlimab plus tislelizumab or tislelizumab alone may be shortened or extended as clinically feasible to allow for resynchronization, but the time between 2 consecutive doses of ociperlimab plus tislelizumab or tislelizumab alone should be at least 10 days. If clinically appropriate, the investigator may delay all treatment components up to a maximum of 7 days to allow synchronized administration of all agents and realigned dosing of treatment cycles according to the original schedule.

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

SELECTED PRECAUTIONS FOR CHEMOTHERAPY:

- Neutropenia: Fever or other evidence of infection must be assessed promptly and treated aggressively following the local clinical practice and/or the guidelines.
- Renal Toxicity:
    - Nephrotoxicity is common with cisplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside antibiotics.
    - Patients should not be given cisplatin or carboplatin if their creatinine clearance is < 60 mL/min or < 45 mL/min, respectively.
    - Etoposide dosage should be reduced to 75% of dose in patients with a creatinine clearance from 15 to 50 mL/min.
    - Patients will be allowed to switch from cisplatin to carboplatin if patients become ineligible for cisplatin due to toxicity related to cisplatin if they have completed

≥ 1 cycle of cisplatin treatment. Reasons for platinum switch should be documented in source documents and eCRF.

- Ototoxicity and sensory neural damage should be assessed before each cycle. Cisplatin is contraindicated in patients with a preexisting hearing deficit.

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

5.5.4. Criteria for Discontinuing Chemotherapy Regimens

Except where specified above, both chemotherapy drugs in the platinum-based doublet regimen should be discontinued for any of the following:

- Any Grade 4 peripheral neuropathy
- Persistent Grade 3 paresthesia
- Grade 3 or 4 drug-related thrombocytopenia associated with clinically significant bleeding
- Any drug-related liver function test abnormality value that meets any of the following criteria requires discontinuation:
  - AST or ALT > 5 x ULN for > 2 weeks
  - AST or ALT > 10 x ULN or
  - Total bilirubin > 5 x ULN or
  - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Any drug-related AE that recurs after 2 prior dose reductions (1 dose reduction for carboplatin) for the same drug-related AE requires discontinuation of the drug(s).
- Any Grade 3 or 4 drug-related hypersensitivity reaction or infusion reaction requires discontinuation of the drug(s) assessed to be causing the reaction. The drug assessed as not related to the hypersensitivity reaction or infusion reaction may be continued.
- Any Grade 4 AE that the investigator considers related to study drug and inappropriate to be managed by dose reduction(s) requires discontinuation of drug(s). The drug not assessed to be related to the event may be continued.
- If any significant toxicity does not resolve within 21 days, that component will be discontinued.

For toxicities not listed above, the investigator would determine whether the chemotherapy regimen should be discontinued per clinical judgment, patient's well-being, and local standards.

6. PRIOR AND CONCOMITANT THERAPY

6.1. Prior Therapy

The eligibility criteria (Section 4) specify that patients should not have received any prior treatment for LS-SCLC; prior therapies targeting PD-1, PD-L1, PD-L2, TIGIT, T-cell costimulation or checkpoint pathways; immunotherapy (eg, interleukin, interferon, or thymosin); or investigational therapy ≤ 14 days or 5 half-lives (whichever is longer) before randomization.

6.2. Concomitant Therapy

6.2.1. Permitted Concomitant Medications/Procedures

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

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

6.2.1.1. Systemic Corticosteroids

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

6.2.1.2. Hepatitis B Treatment

Patients with active hepatitis B, defined as HBV DNA ≥ 500 IU/mL at screening, must initiate treatment 2 weeks before randomization and continue until 6 months after the last dose of study drug(s). Patients should continue effective antiviral treatment during the study to decrease potential viral re-activation risk. Tenofovir and entecavir are recommended in the American Association for the Study of Liver Disease (AASLD) guideline because patients are unlikely to develop resistance to these drugs with long-term use (Terrault et al 2016; AASLD/IDSA HCV Guidance Panel 2015). The investigator may approve the use of other antiviral agents, if appropriate, following local guidelines. However, interferon-based therapy for hepatitis B is not permitted on study.

Management of prophylactic antiviral therapy for patients with inactive, treated, and stable hepatitis B (HBV DNA < 500 IU/mL) is at the discretion of the investigator, in accordance with local guidance. Such medications must be documented in the patient's chart and recorded in the eCRF. Patients receiving antiviral therapy at screening should be treated for > 2 weeks before randomization and continue treatment during the study and for 6 months after study treatment discontinuation.

6.2.1.3. Hepatitis C Treatment

Patients who are receiving treatment for hepatitis C at screening should remain on continuous, effective antiviral therapy during the study. Investigators can consider treatment with sofosbuvir alone or in combination with other antivirals following the AASLD guideline or local guidelines as appropriate. However, interferon-based therapy for HCV is not permitted on study. Patients who are given antiviral therapy must initiate treatment > 2 weeks before randomization.

6.2.2. Prohibited Concomitant Medications/Procedures

Live vaccines ≤ 28 days before randomization and ≤ 60 days after the last dose of study drug(s) are prohibited.

The following medications are prohibited during screening, through the EOT Visit or disease progression, whichever occurs later:

- Any concurrent anticancer therapy, including chemotherapy, hormonal therapy, immunotherapy, standard anticancer agents, or investigational anticancer agents
- Any investigational anticancer therapy
- Herbal remedies for the treatment of cancer or Chinese patent medicines with approval from the China National Medical Products Administration (NMPA) for use as anticancer treatment (regardless of cancer type)
- Herbal remedies with immune-stimulating properties (eg, mistletoe extract) or that are known to potentially interfere with liver or other major organ functions (eg, hypericin)

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

6.2.3. Restricted Concomitant Medications/Procedures

The following medications are restricted during screening and through the EOT Visit:

- 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. In addition, use of inhaled and intranasal corticosteroids is permitted
- Patients should not abuse alcohol or other drugs during the study
- Use of potentially hepatotoxic drugs in patients with impaired hepatic function should be carefully monitored

6.3. Potential Interactions Between 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 small molecule drug products is very low because ociperlimab and tislelizumab are therapeutic monoclonal

antibodies. Additionally, ociperlimab and tislelizumab are unlikely to have an effect on drug-metabolizing enzymes or transporters because they are expected to be degraded into amino acids and recycle into other proteins.

7. STUDY ASSESSMENTS AND PROCEDURES

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

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

7.1. Screening

Screening evaluations will be performed within 28 days before randomization. Patients who agree to participate will sign the ICF before undergoing any screening procedure. The screening period begins on the first day a screening procedure is conducted. Screening evaluations may be repeated as needed within the screening period; the investigator is to assess patient eligibility according to the latest screening assessment results.

Results of standard-of-care tests or examinations performed 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 unless otherwise indicated.

Procedures conducted during the Screening Visit only are described in this section. Patients who are suspected or known to have concurrent serious respiratory illness or exhibit significant respiratory symptoms unrelated to underlying cancer should take a pulmonary function test (refer to Appendix 1 for details) based upon the treatment physician's judgement. For the description of other assessments that are conducted during screening, as well as throughout the study, refer to Safety Assessments (Section 7.4), Tumor and Response Evaluations (Section 7.5) and Biomarkers (Section 7.7) sections. The PK sampling schedule is shown in Appendix 1.

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

7.1.1. Informed Consent and Screening Log

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

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

7.1.2. Patient Numbering

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

7.1.3. Demographic Data and Medical History

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

Medical history includes any history of clinically significant disease, surgery, or cancer; reproductive status (ie, of childbearing potential or no childbearing potential); history of alcohol consumption and tobacco (ie, former or current or never); and all medications (eg, prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 28 days before randomization.

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

Preexisting AEs at baseline should be recorded as medical history.

7.1.4. Female Patients of Childbearing Potential and Contraception

Childbearing potential is defined as the physiological ability to become pregnant. Refer to Appendix 9 for contraception guidelines and definitions of "women of childbearing potential" and "no childbearing potential."

A 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 before the first dose of study treatment. Urine pregnancy tests will be performed at the timepoints indicated in Appendix 1. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.

7.1.5. Pulmonary Function Tests

Pulmonary function testing including spirometry and assessment of oxygenation, at a minimum, pulse oximetry at rest and with exercise, or alternatively, assessment of diffusion capacity, are to be performed as clinically indicated (eg, patient is having symptoms of lung problems or has medical history of chronic lung disease) during the Screening Period to assist the determination of suitability on the study. Respective test results need to be submitted to the sponsor.

For test results indicative of significantly impaired pulmonary function, eg, resting pulse oximetry < 90% on room air and further desaturation upon exercise, forced expiratory volume (FEV1) < 60% or diffusing capacity of the lungs for carbon monoxide (DLCO) (if performed) < 60% of age- and sex-adjusted predicted performance levels (Pellegrino et al 2005), the medical monitor needs to be consulted to confirm eligibility.

Tests may be repeated as clinically indicated while on study.

7.2. Enrollment

7.2.1. Confirmation of Eligibility

The investigator is responsible for ensuring that each patient meets the eligibility criteria for this study. The investigator will assess and confirm the eligibility of each patient. All results from the screening procedures and relevant medical history must be available before eligibility can be

determined. All inclusion criteria must be met and none of the exclusion criteria may be met. No eligibility waivers will be granted.

After a patient is screened and the investigator determines that the patient is eligible, study site personnel will complete the Treatment Eligibility Form (TEF) by transcribing information on inclusion/exclusion criteria, significant medical history, concomitant medications, disease history, pathology diagnosis, information from relevant imaging reports (as applicable), prior anticancer therapies and screening safety laboratory results requested in the TEF.

To confirm eligibility, the TEF will be sent by the site to the medical monitor or designee, via secure transmission, for review during the screening period. Per the patient privacy/confidentiality provisions in this protocol, the TEF should be coded with the patient's screening ID number to protect the patient's personal data in accordance with local laws and regulations and BeiGene requirements (eg, direct identifiers such as names, initials and full date of birth should never be shared, and personal data not specifically required by the protocol should never be included or otherwise provided).

The medical monitor will review the TEF and confirm the investigator has accurately assessed that all inclusion criteria have been met and none of the exclusion criteria apply and communicate their conclusion to the site. If the medical monitor raises concerns about the eligibility of a potential patient or the contents of the TEF, the investigator is responsible for reviewing and responding to the medical monitor's concerns and/or correcting the contents of the TEF, as appropriate. A patient cannot be started on study drug until confirmation of eligibility from the medical monitor or designee is received and filed in the patient's records.

7.2.2. Enrollment/Randomization

Site personnel will access the IRT system to randomize patients to treatment assignment and to enable study drug dispensation. Study treatment must commence within 3 business days after randomization/treatment assignment.

7.3. Study Drug Dispensation

All study drugs will be dispensed and administered as described in Section 5.2.

7.4. Safety Assessments

7.4.1. Vital Signs, Height, and Weight

Vital signs will include measurements of body temperature, pulse rate, and blood pressure (systolic and diastolic).

Vital signs will be assessed in Arms A, B, and C at screening, before study drug administration on Days 1, 8, and 15 in the first 2 cycles for all patients at the beginning of each subsequent cycle, at the EOT Visit, and at the Safety Follow-up Visit (Appendix 1).

The patient's vital signs must be recorded within 60 minutes before, during, and 30 minutes after the first infusion of ociperlimab plus tislelizumab (as a whole infusion) in Arm A or tislelizumab alone in Arm B at each cycle visit for 2 cycles. For subsequent cycles, vital signs will be

collected within 60 minutes before the infusion, if clinically indicated, during and 30 minutes after the infusion.

Pulse rate and blood pressure should be collected while the patient is in a seated position after resting for 10 minutes and before the start of any treatment. Weight will be assessed at screening, before study drug administration on Day 1 of each cycle, at the EOT Visit, and at the Safety Follow-up Visit. Height will be recorded at screening only.

7.4.2. Physical Examinations

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

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

7.4.3. Eastern Cooperative Oncology Group Performance Status

ECOG Performance Status (Appendix 3) will be assessed during the study as outlined in Appendix 1.

7.4.4. Laboratory Safety Tests

Local laboratory assessments of serum chemistry, hematology, coagulation, and urinalysis will be conducted as outlined in Appendix 2.

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

Hematology, serum chemistry (including liver function tests), and coagulation assessments will be performed at the timepoints specified in Appendix 1.

Urinalysis is to be conducted at screening and during the treatment period only if clinically warranted.

Thyroid assessments (free or total triiodothyronine [T3]; free or total thyroxine [T4], and thyroid-stimulating hormone [TSH]) will be performed at the timepoints specified in Appendix 1.

7.4.4.1. Cardiac Enzyme Monitoring

Although immune-related myocarditis is a rare complication of immune checkpoint inhibitors, serum creatinine kinase (CK) and CK cardiac isoenzyme (CK-MB) will be monitored to protect study participants and to quantify the risk of muscle inflammation (see Appendix 1 for the blood collection schedule and Appendix 7 for guidelines for management of suspected immune-related

myocarditis). Serum troponins may be substituted per local guidelines if used consistently throughout the study.

7.4.5. Electrocardiograms

The 12-lead ECG recordings will be obtained during screening, as clinically indicated during the treatment period, at the EOT Visit, and at the Safety Follow-up Visit (Appendix 1).

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

Patients should rest in semirecumbent supine position for ≥ 10 minutes before ECG collection. When coinciding with blood draws at the same timepoint, ECG assessment should be performed before blood draws and study treatment infusions.

7.4.6. Adverse Events

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

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

7.4.7. Hepatitis B and C Testing

Testing will be performed by the local laboratory at screening and will include screening HBV/HCV serology (HBsAg, HBsAb, HBcAb, and HCV antibody). After screening, viral load assessment (HBV DNA and HCV RNA) may be performed if clinically indicated. Patients who have detectable HBV DNA at screening or upon repeat testing will undergo the respective viral load test every 4 cycles (eg, Cycles 4, 8, and 12) (Appendix 1).

7.5. Tumor and Response Evaluations

Tumor imaging will be performed within 28 days before randomization. During the study, tumor imaging will be performed at approximately 12 weeks (± 7 days) from the date of randomization (an additional tumor assessment is allowed if clinically indicated), then every 6 weeks (± 7 days) for the next 54 weeks, and then 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 on the planned schedule.

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

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).

- Imaging of the brain (preferably MRI) at baseline is required for all screened patients. Screening evaluations will be performed within 28 days before randomization and additional evaluations may also be performed as clinically indicated during the study.
- If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the study, a non-contrast CT of the chest plus a contrast-enhanced MRI (if possible) of the abdomen and pelvis should be performed.
- If a CT scan for tumor assessment is performed on a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards of a diagnostic CT scan.
- Bone scans (Technetium-99m [Tc-99m]) or PET should be performed at screening if clinically indicated.
- CT scans of the neck or extremities should be performed at screening only if clinically indicated.
- At the investigator's discretion, other methods of assessment of target lesions and nontarget lesions per RECIST v1.1 may be used.

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

Administration of study treatment will continue until up to12 months after randomization for Arms A and B and for 4 cycles for Arm C, or until disease progression as assessed by the investigator per RECIST v1.1, unacceptable toxicity, death, or another discontinuation criterion is met, whichever occurs first.

A patient who discontinues study treatment early for reasons other than disease progression (eg, toxicity) or completes study treatment will continue to undergo tumor assessments following the original schedule until disease progression per RECIST v1.1, withdrawal of consent, loss to follow-up, the start of a new anticancer therapy, death, or study termination, whichever occurs first.

In Arms A and B, treatment with ociperlimab plus tislelizumab or with tislelizumab alone beyond the initial investigator-assessed, RECIST v1.1-defined disease progression is permitted provided that the patient has investigator-assessed clinical benefit and is tolerating the study drug(s). The following criteria must be met in order to treat patients who may continue to benefit from study drugs after disease progression:

- Absence of clinical symptoms and signs of disease progression (including clinically significant worsening of laboratory values)
- Stable ECOG Performance Status (≤ 2)
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, cord compression) that requires urgent alternative medical intervention
- Investigators must obtain written informed consent for treatment beyond radiologic disease progression and inform patients that this practice is not considered standard in the treatment of cancer

The investigator should obtain written agreement from the sponsor medical monitor on continuing study drug(s) beyond the initial investigator-assessed progression, and the decision must be documented in the study records.

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

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

7.6. Pharmacokinetic and Antidrug Antibody Testing

Checkpoint inhibitor drugs may elicit an immune response. Patients with signs of any potential immune response to ociperlimab or tislelizumab will be closely monitored. Validated screening and confirmatory assays will be employed to detect ADAs at multiple timepoints throughout the study (Appendix 1). The immunogenicity evaluation will utilize a risk-based immunogenicity strategy (Koren et al 2008; Worobec and Rosenberg 2004a; Worobec and Rosenberg 2004b) to characterize ADA responses to ociperlimab and tislelizumab in support of the clinical development program. 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).

The following assessments will be performed at a central laboratory:

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

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

7.7. Biomarkers

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

Patients must agree to provide an archival tumor tissue with an associated pathology report or agree to perform a fresh tumor biopsy during screening (formalin-fixed paraffin-embedded block or approximately 15 unstained slides [8 slides minimum]). Note: If < 8 unstained slides are available, a discussion with the sponsor is required. PD-L1 and TIGIT expression by immunohistochemistry will be tested in the central laboratory and their association with clinical efficacy with be analyzed for the secondary endpoint analysis. In addition to PD-L1 and TIGIT expression, other exploratory predictive biomarkers, including but not limited to gene expression profile, tissue- or blood-based gene mutations and TMB/MSI, CD155/CD226 expression, and SCLC subtyping by the expression of transcription factors

(ASCL1/NEUROD1/POU2F3/YAP1), which may be related to the clinical benefit of ociperlimab and tislelizumab, may also be evaluated. If no archival samples are available, a fresh tumor biopsy at baseline is required. For fresh biopsy specimens, acceptable samples include core needle biopsies for deep tumor tissue or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.

For patients who have confirmed disease progression during the study, optional biopsies will also be taken from accessible tumor sites to obtain samples to explore resistance mechanisms. If feasible, any follow-up biopsy should be ideally taken from the same tumor lesion as the baseline biopsy. Written patient consent is required for fresh tumor biopsies. Biomarker testing for optional biopsy samples will include PD-L1 and TIGIT as well as other exploratory biomarkers.

(Note: for the sites in China mainland, tissue and blood samples will be obtained to test the expression of PD-L1 and TIGIT, gene expression profile, tissue- or blood-based gene mutations and TMB/MSI and ctDNA level change, CD155/CD226 expression, and SCLC subtyping by the expression of transcription factors (ASCL1/NEUROD1/POU2F3/YAP1).

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

Blood samples will be collected at screening and at defined timepoints during treatment as well as at the time of confirmed disease progression (see Appendix 1 for the specified timepoints) for assessment of blood-based tumor mutation profile and ctDNA level change before and after treatment. The association of ctDNA level change with ORR, PFS, and OS will be analyzed to evaluate the potential utility of ctDNA as a surrogate marker for clinical efficacy.

Sample collection and biomarker testing will be performed after relevant regulatory approval.

7.8. Patient-Reported Outcomes

Patients will be asked to complete questionnaires before any clinical activities (including blood draws or imaging scans) are performed during on-study clinic visits according to the schedule in Appendix 1. These questionnaires will include the EORTC-QLQ-C30 (Appendix 10) and its lung cancer module QLQ-LC13 (Appendix 11). The questionnaires will be provided in the patient's preferred language.

7.9. Visit Windows

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

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other event, the visit should be scheduled on the nearest feasible date (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.

7.10. Unscheduled Visits

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

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

8. SAFETY MONITORING AND REPORTING

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

8.1. Risks Associated With Study 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 ociperlimab and tislelizumab and published data on other molecules within the same biologic class.

The PD-L1/PD-1 pathway is involved in peripheral immune tolerance; therefore, such therapy may increase the risk of imAEs, specifically the induction or enhancement of autoimmune conditions. AEs observed with anti-PD-1 therapy are presented in Section 8.7.3. Ociperlimab-mediated TIGIT inhibition may increase the risk of imAEs. However, no apparent immunotoxicity, or toxicity in general, have 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 affect 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 evaluation and management guidelines for suspected imAEs are provided in Appendix 7.

8.1.2. Risks Associated With Chemotherapy

Please refer to Table 7 for the reported toxicity for the respective chemotherapeutic agents. The investigator should refer to the package insert for a complete list of potential side effects.

Table 7: The Summary of the Commonly and Specific Reported Toxicity of the Chemotherapeutic Agents

Agents	Specific toxicity	Common toxicity
Cisplatin	Nephrotoxicity; ototoxicity; peripheral neuropathies	Myelodepression with leukopenia, thrombocytopenia and anemia; infectious complications; nausea/vomiting and other gastrointestinal toxicity; hepatic impairment; fatigue; anorexia; constipation
Carboplatin	Ototoxicity, peripheral neuropathies	
Etoposide	Hypersensitivity reactions; ocular; respiratory; skin; neurologic	

8.1.3. Risks Associated With Radiation Therapy

AEs related to RT include nausea/vomiting, diarrhea, weight loss, fatigue, hematological toxicity, skin erythema, subcutaneous fibrosis, esophagitis, esophageal stricture, esophageal fistula, carditis, myelitis, acute radiation pneumonitis, and late pulmonary fibrosis.

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 TIGIT and PD-L1/PD-1 inhibitors, were considered. Specifically, patients at risk for study-emergent active autoimmune diseases or with a history of autoimmune diseases that may relapse, patients who have undergone allogeneic stem cell or organ transplantation, and patients who have received a live vaccine ≤ 28 days before 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. 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 8), physical examinations, laboratory measurements (hematology, chemistry, etc) and other assessments, including those listed in Appendix 1. In addition, patients will be closely monitored for the development of any signs or symptoms of infections or autoimmune conditions.

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

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

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

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

8.3. Adverse Events

8.3.1. Definitions and Reporting

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

Examples of AEs include the following:

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

When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory results, and diagnostics reports) relative to the AE or SAE. The investigator will then record all relevant information regarding an AE or SAE in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by the sponsor. In this instance, all patient identifiers will be blinded on the copies of the medical records 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 the NCI-CTCAE v5.0.

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

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- 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 (eg, grade of a specific AE, mild [Grade 1], moderate [Grade 2], severe [Grade 3], or life-threatening [Grade 4]), whereas seriousness is classified by the criteria based on the regulatory definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the sponsor to applicable regulatory authorities as described in Section 8.6.2.

8.3.3. Assessment of Causality

The investigator is obligated to assess the relationship between the study drug and the occurrence of each AE or SAE, using best clinical judgment. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of

the AE or SAE to the study drug should be considered and investigated. The investigator should consult the Tislelizumab Investigator's Brochure, Ociperlimab (BGB-A1217) Investigator's Brochure, chemotherapy prescribing information, or radiation manual in the determination of his/her assessment.

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

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

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

8.3.4. Follow-up of Adverse Events

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

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

All AEs and SAEs will be followed until resolution, the condition stabilizes or is considered chronic, the AE or SAE is otherwise explained, the patient is lost to follow-up or the patient withdraws consent. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE.

This may include additional laboratory tests or investigations, histopathological examinations, radiographic imaging, or consultation with other health care professionals.

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

New or updated information should be reported to the sponsor according to the SAE instructions provided by the sponsor within the timeframes 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 significantly worsen during the study. The definition of clinically significant is left to the judgment of the investigator. In general, these are the laboratory test abnormalities or other abnormal assessments that:

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

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

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

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 from

which the patient was at risk of death at the time of the AE. It does not refer to an AE that hypothetically might have caused death if it were more severe.

- Requires hospitalization or prolongation of existing hospitalization.
  Note: In general, hospitalization signifies that the patient was admitted (usually involving at least an overnight stay) to the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.
- Results in disability/incapacity.
  Note: The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect.
- Is considered a significant medical AE by the investigator based on medical judgement (eg, may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

The following are NOT considered to be SAEs:

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

8.5. Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is a serious adverse reaction that is both unexpected (ie, not present in the product's Reference Safety Information) and meets the definition of a serious adverse drug reaction, the specificity or severity of which is not consistent with those noted in the Tislelizumab Investigator's Brochure, Ociperlimab (BGB-A1217) Investigator's Brochure, chemotherapy prescribing information, or radiation manual.

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

8.6.1. Adverse Event Recording Period

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

After initiation of study treatment, all AEs and SAEs, regardless of relationship to study treatment, will be reported until either 30 days after the last dose of study treatment or initiation of new anticancer therapy, whichever occurs first.

For patients in Arm A and Arm B, immune-mediated AEs (serious or nonserious) should be reported until 90 days after the last dose of ociperlimab plus tislelizumab or tislelizumab alone, regardless of whether or not the patient starts a new anticancer therapy.

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

All AEs ongoing at the time of treatment discontinuation which worsen in severity to Grade 5 should be reported regardless of time from treatment stop.

AEs and SAEs should be recorded according to the details in Table 8. For the follow-up period for AEs, see Section 8.3.4. For the definition of TEAEs, see Section 9.3.2.

Table 8: Guidance for Duration of Recording New or Worsening Adverse Events in All Treatment Arms

Event type	Record new or worsening events that occur during this period	
	Begin	End
SAEs [a]	Signing of informed consent	Up to 30 days after last dose, initiation of new anticancer therapy, death, withdrawal of consent, or loss to follow-up, whichever occurs first
Nonserious AEs due to disease progression	Do not record (see Section 8.6.4)	
All nonserious AEs, except those due to PD	First dose of study treatment	Up to 30 days after last dose, initiation of new anticancer therapy, death, withdrawal of consent, or loss to follow-up, whichever occurs first
Immune-related AEs (serious or nonserious)	First dose of study treatment	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, disease progression; 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 9.

Table 9: Timeframes and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

	Timeframe for sending initial/follow-up [a] report	Documentation method	Reporting method
All SAEs	Within 24 hours of first knowledge of the SAE	SAE Report	Electronic submission of SAE form to safety portal [b]

Abbreviations: EDC, electronic data capture; IMP, investigational medicinal product; SAE, serious adverse event.
[a] Report follow-up information that is clinically relevant and pertains to the SAE; this includes, but is not limited to, the following: Update to the SAE, new additional SAE, outcome, seriousness criteria, investigator causality, event start date/date of onset, date of death, relationship to each IMP. Follow-up information will also be reported at the discretion of the investigator if the new or updated information changes the medical assessment of the case.
[b] SAE reports should be submitted to the sponsor's safety database electronically from within the EDC. If the electronic submission is not available for any reason, a paper SAE form should be submitted by email or fax.

8.6.2.2. Completion and Transmission of the Serious Adverse Event Report

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

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

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

The sponsor will provide contact information for SAE receipt.

8.6.2.3. Regulatory Reporting Requirements for Serious Adverse Events

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

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

All SUSARs (as defined in Section 8.5) will be submitted to all applicable regulatory authorities and investigators for 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

Disease progression, which is expected in this study population and is measured as an efficacy endpoint, should not be recorded as an AE term. Similarly, nonserious AEs that are clearly consistent with the pattern of progression of the underlying disease and are considered unequivocally due to disease progression should not be recorded. However, if there is any uncertainty as to whether a nonserious AE is due to disease progression, it should be recorded as an AE. All SAEs and deaths regardless of relatedness to disease progression should be recorded and reported (see Section 8.6.2).

8.6.5. Deaths

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

8.6.6. Pregnancies

If a female patient or the partner of a male patient becomes pregnant while receiving investigational therapy, or within 120 days after the last dose of ociperlimab and tislelizumab in Arm A or tislelizumab in Arm B, or within 180 days after the last dose of radiotherapy or chemotherapy (except for cisplatin), or within 14 months after the last dose of cisplatin (for the female patient), or within 11 months after the last dose of cisplatin (for the partner of the male patient), a pregnancy report form is required to be completed and expeditiously submitted to the sponsor to facilitate outcome follow-up. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow-up will be no longer than 6 to 8 weeks 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 be always reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a patient exposed to the study drug should be recorded and reported as an SAE.

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

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

To determine the reporting requirements for individual SAEs, the sponsor will assess the expectedness of the SAEs using the following Reference Safety Information documents:

- Tislelizumab Investigator's Brochure
- Ociperlimab (BGB-A1217) Investigator's Brochure
- Cisplatin prescribing information
- Carboplatin prescribing information
- Etoposide prescribing information

8.6.8. Assessing and Recording Immune-Mediated Adverse Events

Because treatment with anti-PD-1 therapy 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 90 days after the last dose of study treatment.

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

An extensive list of potential imAEs appears in Table 11. All conditions similar to those listed should be evaluated to determine whether they are imAEs, based on a similar diagnostic process to those reactions that are presented in more detail in Appendix 7.

8.6.9. Recording Infusion-Related Reactions

The symptoms of infusion-related reactions may include, but are not limited to, fever, chills/rigor, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness, or hypertension. Severe reactions may include acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, or cardiogenic shock. Each individual sign and symptom of an infusion-related reaction should be recorded 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 ociperlimab and tislelizumab (Arm A) and tislelizumab (Arm B) on Day 1 of Cycles 1 and 2, patients must be monitored for ≥ 120 minutes afterward in an area with resuscitation equipment and emergency agents. From Cycle 3 onward, a ≥ 60-minute monitoring period is required in an area with resuscitation equipment and emergency agents.

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

8.7.1. Managing Infusion-Related Reactions

Patients should be closely monitored for infusion-related reactions. Immediate access to an Intensive Care Unit (ICU) or equivalent environment and appropriate medical therapy (including

epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen) must be available to treat infusion-related reactions.

Treatment modifications for symptoms of infusion-related reactions due to study drug(s) are provided in Table 10.

Table 10: Treatment Modifications for Symptoms of Infusion-Related Reactions Due to Study Drug(s)

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

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

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

NCI-CTCAE Grade 1 or 2 infusion-related reaction: Proper medical management should be instituted as indicated per the type of reaction. This includes, but is not limited to, an antihistamine (eg, diphenhydramine or equivalent), antipyretic (eg, paracetamol or equivalent),

and if considered indicated, oral or intravenous glucocorticoids, epinephrine, bronchodilators, and oxygen. In the next cycle, patients should receive oral premedication with an antihistamine (eg, diphenhydramine or equivalent) and an antipyretic (eg, paracetamol or equivalent), and they should be closely monitored for clinical signs and symptoms of an infusion-related reaction.

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

8.7.2. Severe Hypersensitivity Reactions and Flu-Like Symptoms

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

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

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

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

8.7.3. Immune-Mediated Adverse Events

Immune-mediated AEs are of special interest in this study. If the events listed below or similar events occur, the investigator should exclude alternative explanations (eg, combination drugs, infectious disease, metabolic, toxin, disease progression, or other neoplastic causes) with appropriate diagnostic tests 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 11. All conditions similar to those listed should be evaluated in patients receiving ociperlimab or tislelizumab to determine whether they are immune mediated.

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

Table 11: Examples of Immune-Mediated Adverse Events

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

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

Recommendations for managing imAEs are detailed in Appendix 7.

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

9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

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

9.1. Statistical Analysis

9.1.1. Randomization Methods

As discussed in Section 7.2.2, patients will be randomized using the IRT system for this study by permuted block stratified randomization with a stratification factor of disease stage (stage I/II versus stage III).

9.1.2. Analysis Sets

The ITT Analysis Set includes all randomized patients. Patients will be analyzed according to their randomized treatment arm. This will be the primary analysis set for all efficacy analysis.

The Safety Analysis Set includes all patients who have received ≥ 1 dose of any component of study drug; it will be the analysis set for the safety analyses.

The PK Analysis Set includes all patients who receive ≥ 1 dose of tislelizumab/ociperlimab per the protocol and for whom any quantifiable postbaseline PK data are available.

The ADA Analysis Set, which includes all patients who receive ≥ 1 dose of tislelizumab/ociperlimab and for whom both baseline and ≥ 1 postbaseline ADA result are available.

The Biomarker Analysis Set includes all patients who have ≥ 1 evaluable biomarker measurement; it will be used for biomarker analysis.

9.1.3. Patient Disposition

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

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

9.1.4. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics of the ITT population will be summarized using descriptive statistics. Continuous variables include age, weight, vital signs, and time since initial cancer diagnosis. Categorical variables include gender, ECOG Performance Status, geographical region, country, race, disease stage, smoking history, and PET-CT done or not done.

9.1.5. Prior and Concomitant Medications

Concomitant medications will be coded using the WHO Drug Dictionary drug codes. Concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical (ATC) code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class in the Clinical Study Report (CSR) for this protocol. Prior medications will be defined as medications that were stopped before the day of the first dose of study drug. Concomitant medications will be defined as medications that 1) were started before the first dose of study drug and were continuing at the time of the first dose of study drug, or 2) were started on or after the date of the first dose of study drug up to 30 days after the patient's last dose (as of the Safety Follow-up Visit). In addition, telephone contacts with patients should be conducted to assess imAEs and concomitant medications (if appropriate, ie, associated with an imAE or is a new anticancer therapy) at 60 and 90 days (± 7 days) after the last dose of study drugs regardless of whether or not the patient starts a new anticancer therapy.

9.2. Efficacy Analyses

The efficacy endpoints including PFS, CR rate, ORR, DOR, and OS will be summarized by arm in the ITT Analysis Set. The efficacy endpoints will be compared in Arm A versus Arm C and Arm B versus Arm C. These analyses are descriptive and exploratory; no formal testing was designed for this study.

9.2.1. Primary Efficacy Analysis

The primary endpoint is PFS as assessed by investigators. PFS per investigator is defined as the time from randomization to the first documented disease progression as assessed by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first. Kaplan-Meier methodology will be used to estimate median or other quartiles of PFS along with its 95% confidence interval (CI; constructed using the Brookmeyer and Crowley method). Kaplan-Meier curves will be constructed to provide a visual description of PFS distribution. Event-free rate at selected timepoints will be estimated with 95% CI using Greenwood formula. The hazard ratio (HR) for PFS for each comparison (ie, Arm A versus Arm C, Arm B versus Arm C) will be estimated using a stratified Cox regression model. The 95% CI for the HR will be provided. Unstratified analysis will also be presented.

Subgroup analysis of primary endpoint of PFS per investigator will be conducted to determine whether the treatment effect is consistent across various subgroups. Subgroup factors include but are not limited to PD-L1 expression in tumor cells (clinical meaningful cutoffs), TIGIT expression level (clinical meaningful cutoffs), region, race, disease stage, gender, and age.

9.2.2. Secondary Efficacy Analysis

Complete Response Rate

CR rate is the proportion of patients who had a CR as assessed by investigator per RECIST v1.1 in all randomized patients with measurable disease at baseline. Patients without any postbaseline assessment will be considered nonresponders. CR rate and its Clopper-Pearson 95% CI will be calculated for each arm. The comparison in CR rate between arms will be evaluated using the

Cochran-Mantel-Haenszel (CMH) X^2 test with the actual stratification factors as strata. Odds ratio and the difference in CR rate, as well as their 2-sided 95% CIs, will be calculated.

Overall Response Rate

ORR is the proportion of patients who had a CR or PR as assessed by the investigator per RECIST v1.1 in all randomized patients with measurable disease at baseline. Patients without any postbaseline assessment will be considered nonresponders. Similar methodology used to evaluate CR rate will be applied to the analysis of ORR.

Duration of Response

DOR is defined for patients with an objective response as the time from the first documented objective response to documented disease progression as assessed by the investigator using RECIST v1.1, or death from any cause, whichever occurs first. Only patients who have achieved objective responses will be included in the analysis of DOR. Similar methodology used to evaluate PFS will be applied to the analysis of DOR.

Overall Survival

OS is defined as the time from randomization to death from any cause. OS will be analyzed in the ITT Analysis Set. Data for patients who are not reported as having died at the time of analysis will be censored at the date the patients were last known to be alive. Data for patients who do not have postbaseline information will be censored at the date of randomization. Similar methodology used to evaluate PFS will be applied to the analysis of OS.

Distant Metastasis-Free Survival

DMFS is defined as the time from the date of randomization to the date of the first documented distant metastasis as assessed by the investigator per RECIST v1.1, or death from any cause, whichever occurs first. Similar methodology used to evaluate PFS will be applied to the analysis of DMFS.

The distant metastasis includes separate tumor nodule(s) in a contralateral lobe, tumor with pleural or pericardial nodules or malignant pleural or effusion pericardial, single extrathoracic metastasis in a single organ (including involvement of a single nonregional node), and multiple extrathoracic metastases in a single organ or in multiple organs.

ORR, PFS, and OS in PD-L1 and TIGIT Subgroups

Clinically meaningful cutoffs of PD-L1 and TIGIT expression level will be selected to divide the biomarker-evaluable patients into subgroups. ORR, PFS, and OS analysis by PD-L1 and TIGIT expression subgroups will be performed to investigate the predictive value of these biomarkers.

9.2.3. Exploratory Efficacy Analysis

Biomarker Analysis

Raw biomarker data will be normalized to adjust for batch effect, if applicable, for exploratory statistical analyses. Receiver operating characteristics curves will be generated and AUC will be calculated based on a logistic regression model to evaluate the association between continuous biomarkers and ORR. Biomarker cutoffs (PD-L1 and TIGIT expression levels) used in subgroup analyses will be explored in this study using the Youden method. The cutoffs from the Youden

method or/and clinically meaningful cutoffs will be used in subgroup analyses. Logistic regression and Cox regression will be used to evaluate the prognostic and predictive effects of the biomarkers on response and survival endpoints with treatment, biomarker status, and their interaction as the main factors.

The potential utility of ctDNA level change as a surrogate predictor of efficacy and the mechanisms of resistance will also be assessed.

Health-Related Quality of Life

Summary statistics (mean, standard deviation, median, and range) of the postbaseline scores and changes from baseline will be reported for the EORTC QLQ-C30 and QLQ-LC13 questionnaires. Line charts depicting the mean changes (and standard errors) over time from the baseline assessment will be provided for each treatment arm. The clinically meaningful changes postbaseline and a mixed model analysis will be performed using the global health status, physical function and fatigue domains of QLQ-C30, and dyspnoea, coughing, haemotysis and pain in chest, pain in arms and shoulders and peripheral neuropathy domains of QLQ-LC13. Completion and compliance rates will be summarized at each timepoint by treatment arm. Only patients in the ITT Analysis Set with a nonmissing baseline assessment and ≥ 1 in-study nonmissing postbaseline assessment will be included in the analyses.

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, coagulation, urinalysis), vital signs, ECGs, and physical examinations will also be used to assess safety. Descriptive statistics will be used to analyze all safety data overall and by arm in the Safety Analysis Set.

9.3.1. Extent of Exposure

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

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

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

9.3.2. Adverse Events

The AE verbatim descriptions (investigator's description from the eCRF) will be classified into standardized medical terminology using MedDRA. AEs will be coded according to MedDRA (Version 22.0 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 drug and up to 30 days after study treatment discontinuation or initiation of new anticancer therapy, whichever occurs first. The TEAE classification also applies to imAEs that are recorded up to 90 days after discontinuation of

ociperlimab or tislelizumab, regardless of whether the patient starts a new anticancer therapy. Only those AEs that were treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in patient data listings.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by SOC and 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 more than 1 TEAE within a specific SOC and PT.

The number (percentage) of patients with TEAEs will also be summarized by relationship to the study drug. Treatment-related AEs include those events considered by the investigator to be related to a study drug or with missing assessment of the causal relationship.

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

9.3.3. Laboratory Analyses

Clinical laboratory (eg, hematology, serum chemistry, 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 provided. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) for laboratory parameters and their changes from baseline will be calculated. Laboratory values will be summarized by visit and by worst postbaseline visit.

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

9.3.4. Vital Signs

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

9.3.5. Pulmonary Function Test

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

9.4. Pharmacokinetic Analysis

Ociperlimab and tislelizumab serum concentration data will be tabulated and summarized by the visit/cycle at which these concentrations are collected. Descriptive statistics will include means, medians, ranges, and standard deviations, as appropriate. Additional PK analyses may be conducted as appropriate.

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 clinical study report.

9.5. Immunogenicity Analysis

The anti-ociperlimab antibody and anti-tislelizumab antibody 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 and will be reported separately from the main study report.

9.6. Sample Size Consideration

This study is not designed to make explicit power and type I error considerations but rather to obtain preliminary efficacy and safety data for ociperlimab plus tislelizumab and tislelizumab monotherapy for patients with untreated LS-SCLC. This study will enroll approximately 120 subjects into 3 arms with approximately 40 patients in each arm. The contribution of tislelizumab to the efficacy results will be demonstrated by descriptive analysis of PFS, ORR, and DOR in the comparison of Arm B versus Arm C. The contribution of adding ociperlimab will be demonstrated by similarly descriptive analysis in the comparison of Arm A versus Arm B. With a sample size of 40 patients in each arm, the binomial probabilities of detecting 1 or more TEAEs with a frequency of 5% and 1% are approximately 0.87 and 0.33, respectively. The final analysis for PFS is estimated to happen approximately 30 months after the enrollment of the first patient.

9.7. Interim Analyses

No interim analyses are planned.

10. STUDY COMMITTEES AND COMMUNICATION

10.1. Safety Monitoring Committee

An SMC consisting of qualified investigators who are taking part in the study will be implemented to support the study and structure the scientific input. The SMC will conduct safety assessments at the following timepoints:

- After approximately 6 patients (≥ 2 patients per arm) have completed 2 cycles of study treatment
- After approximately 18 patients (≥ 6 patients per arm) have completed 2 cycles of study treatment or no later than 6 months after the first SMC evaluation, whichever occurs first
- After the scheduled SMC assessments, the SMC will review data approximately every 6 months for the first 18 months of the study and yearly thereafter

The SMC could review data more frequently if indicated or requested by the medical monitor or the SMC based on ongoing safety monitoring of patients on study. The SMC may recommend study modifications including early termination of the study due to safety concerns. Full details of the SMC procedures and processes can be found in the SMC Charter.

Enrollment may continue during these SMC safety reviews.

10.1.1. Study Safety Stopping Criteria

During the ongoing trial, early stopping for safety will be assessed according to a prespecified stopping rule. The early stopping rule will be based on the number of patients who experience ≥ Grade 3 pneumonitis, serious TEAE with life-threatening outcome, or TEAE leading to death. If the patients have more than one AEs as defined above, the patients will be counted only once. If the early stopping boundary is met, enrollment will be suspended to wait for the recommendation of the SMC. Based on the SMC recommendation, the sponsor may choose to:

1. terminate the treatment arm or arms meeting the stopping rule;
2. amend the protocol to improve the benefit/risk for patients;
3. continue without any changes.

The stopping rule is established by using the Bayesian approach proposed by Thall, Simon, and Estey (Thall et al 1995). The sponsor may consider terminating the treatment arm if the posterior probability of the AE rate of greater than 30% is at least 80% for that treatment arm. Noninformative prior of Beta (1,1) is used to calculate the Bayesian posterior probability. Two evaluations of early stopping are planned in accordance with the scheduled SMC review.

1. The first one is planned when approximately 18 patients (≥ 6 patients per arm) have completed 2 cycles of study treatment. Based on the prespecified early stopping rule, the early stopping boundary is observing ≥ 3 patients with the above AEs among 6 patients in Arm A or Arm B.
2. The second one is planned approximately 6 months later after the first early stopping review or when approximately 60 patients (≥ 20 patients per arm) have completed 2

cycles of study treatment, whichever is earlier. Based on the prespecified early stopping rule, the early stopping boundary is observing ≥ 8 patients with the above AEs among 20 patients in Arm A or Arm B.

The stopping boundary will be adjusted according to the actual patients enrolled in Arm A or Arm B at the analysis timing of early stopping evaluation.

Besides the stopping rule with Bayesian approach, the sponsor will further evaluate the trend of the AE rates between experimental arm (Arm A or Arm B) and control arm (Arm C). The safety evaluation will be continued by regular SMC review after the two stopping rule review. An ad-hoc SMC review will be triggered for further safety evaluation if necessary to address emerging safety concerns.

11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

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

11.1. Access to Information for Monitoring

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

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

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 access to records, facilities, and personnel to representatives of a regulatory agency or the sponsor for the effective conduct of any inspection or audit.

12. QUALITY ASSURANCE AND QUALITY CONTROL

12.1. Regulatory Authority Approval

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

12.2. Quality Assurance

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

12.3. Study Site Inspections

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

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

12.4. Drug Accountability

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

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

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 patient. The study will also comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

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

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

13.2.1. Protocol Amendments

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

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

13.3. Informed Consent

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

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

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

Patients must reconsent to the most current version of the ICFs (or to a significant new information/findings addendum in accordance with applicable laws and IRB/IEC policy) during their participation in the study. 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 dataset transmitted to any sponsor location.

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

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

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

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

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

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

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 interests of the 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 the clinical investigators with the sponsor that could affect reliability of data submitted to health authorities are identified and disclosed by the sponsor. Investigators are responsible for providing information about their financial interests before participation in the study and for updating this information if any relevant changes occur during the study and for 1 year after completion of the study (ie, last patient, last visit).

14. DATA HANDLING AND RECORD KEEPING

14.1. Data Collection and Management Responsibilities

14.1.1. Data Entry in the Electronic Case Report Form

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

14.1.2. Data Collection

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

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

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

14.1.3. Data Management/Coding

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

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

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

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

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

14.2. Data Integrity and In-house Blinding

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 system. In addition, the central imaging vendor will perform the central imaging review without knowledge of treatment arm assignment. Although the study is open-label, 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 to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least 1 of the following 2 categories: 1) investigator's study file, and/or 2) patient clinical source documents.

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

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

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 there is an acceptable backup of these reproductions and that an acceptable quality control process exists for making these reproductions.

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

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

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

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

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 sponsor.

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

14.5. 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). Note that an abbreviated report may be prepared in certain cases.

The results of this study will be published or presented at scientific meetings in a timely, objective, and clinically meaningful manner that is consistent with good science, industry and regulatory guidance and the need to protect the intellectual property of the sponsor, regardless of the outcome of the study. The data generated in this clinical study are the exclusive property of the sponsor and are confidential. As this is a multicenter study, the first publication or disclosure of study results shall be a complete, joint multicenter publication or disclosure coordinated by the sponsor. Thereafter, any secondary publications will reference the original publication(s). Authorship will be determined by mutual agreement and all authors must meet the criteria for authorship established by the International Committee of Medical Journal Editors Uniform Requirements for Manuscripts or stricter local criteria (International Committee of Medical Journal Editors 2018).

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

publication/presentation may be requested by the sponsor to allow for patent filings in advance of the publication/presentation.

14.6. Study and Study Center Closure

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

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

In addition, the sponsor reserves the right to suspend the enrollment or prematurely discontinue this study either at a single study center or at all study centers at any time for any reason. Potential reasons for suspension or discontinuation include but are not limited to safety or ethical issues or noncompliance with this protocol, GCP, the sponsor's written instructions, the clinical study agreement, or applicable laws and regulations. If the sponsor determines such action is needed, the sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. When feasible, the sponsor will provide advance notification to the investigator of the impending action before it takes effect.

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

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

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

14.7. Information Disclosure and Inventions

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

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

All information provided by the sponsor and all data and information generated by the study center as part of the study (other than a patient's medical records) are the sole property of the sponsor and will be kept confidential by the investigator and other study center personnel.

This information and data will not be used by the investigator or other study center personnel for any purpose other than conducting the study without the prior written consent of the sponsor.

These restrictions do not apply to the following:

- Information that becomes publicly available through no fault of the investigator or study center personnel
- Information that is necessary to disclose in confidence to an IEC/IRB solely for the evaluation of the study
- Information that is necessary to disclose to provide appropriate medical care to a patient
- Study results that may be published as described in Section 14.5

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

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APPENDIX 1. SCHEDULE OF ASSESSMENTS

Assessment	Screening [a]	Treatment Cycles				EOT Visit [b]	Safety Follow-up Visit	60-Day and 90-Day Follow-up [c]	Survival Follow-up [d]
		Cycles 1 to 2			≥ Cycle 3 and up to Cycle 17 (approximately 12 months)				
Days (Window)	**-28 to -1**	**1 (+ 3) [e]**	**8 (±3)**	**15 (±3)**	**1 (±3)**	**0 to 7 days after last dose**	**30 (±7) days after last dose**	**60 and 90 (±7) days after last dose**	**Every 3 months (±14 days) after Safety Follow-up**
STUDY ENTRY AND GENERAL ASSESSMENTS									
Informed consent [a]	X								
Inclusion/exclusion criteria	X								
Randomization [f]	X								
Medical history (including cancer history) [g]	X								
Demographics [g]	X								
Prior /concomitant medication evaluation [g]	Continuous from ≤ 28 days before randomization until 30 days after the last dose of study treatment								
SAFETY ASSESSMENTS									
AE evaluation [h]	Continuous from informed consent until 30 days after the last dose of study treatment for AEs; 90 days after the last dose of ociperlimab plus tislelizumab or tislelizumab alone for imAEs. 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.								
Physical examination [i]	X	X	X	X	X	X	X		
Vital signs/weight [j]	X	X	X	X	X	X	X		
ECOG Performance Status [w]	X	X			X	X	X		
Height	X								

Assessment	Screening [a]	Treatment Cycles				EOT Visit [b]	Safety Follow-up Visit	60-Day and 90-Day Follow-up [c]	Survival Follow-up [d]
		Cycles 1 to 2			≥ Cycle 3 and up to Cycle 17 (approximately 12 months)				
Days (Window)	**-28 to -1**	**1 (+ 3) [e]**	**8 (±3)**	**15 (±3)**	**1 (±3)**	**0 to 7 days after last dose**	**30 (±7) days after last dose**	**60 and 90 (±7) days after last dose**	**Every 3 months (±14 days) after Safety Follow-up**
Pulmonary function test [k]	Only if clinically indicated								
12-lead ECG [l]	X	Only if clinically indicated				X	X		
Hematology [m]	X	X	X	X	X (also Day 8 [± 3 days] in Cycles 3 and 4) [m]	X	X		
Chemistry [m]	X	X	X		X (also Day 8 [± 3 days] in Cycles 3 and 4) [m]	X	X		
Coagulation laboratory (PT, PTT, INR) [m]	X	X			X	X	X		
Thyroid function [n]	X				Cycles 4, 7, 10, 13, and 16		X		
HBV/HCV test [o]	X	As clinically indicated							
Urinalysis [m]	X	As clinically indicated							
Serum β-hCG pregnancy test [p]	X								
Urine β-hCG pregnancy test [p]	X	X			X	X	X		
EFFICACY ASSESSMENTS									
Tumor assessment CT/MRI	X	Tumor imaging will be performed at approximately 12 weeks (± 7 days) from the date of randomization (an additional tumor assessment is allowed if clinically indicated), then every 6 weeks (± 7 days) for the next 54 weeks, and then every 12 weeks (± 7 days) thereafter based on RECIST v1.1. (Section 7.5).							
Brain MRI with contrast or CT scan, with contrast, of the head	X	Only if clinically indicated							
PRO [q]		X			X	X			

Assessment	Screening [a]	Treatment Cycles				EOT Visit [b]	Safety Follow-up Visit	60-Day and 90-Day Follow-up [c]	Survival Follow-up [d]
		Cycles 1 to 2			≥ Cycle 3 and up to Cycle 17 (approximately 12 months)				
Days (Window)	**-28 to -1**	**1 (+ 3) [e]**	**8 (±3)**	**15 (±3)**	**1 (±3)**	**0 to 7 days after last dose**	**30 (±7) days after last dose**	**60 and 90 (±7) days after last dose**	**Every 3 months (±14 days) after Safety Follow-up**
PHARMACOKINETIC ASSESSEMENTS									
Pharmacokinetics [r]		X			Cycles 5, 9, and 17		X		
Anti-ociperlimab and anti-tislelizumab antibody blood samples [s]		X			Cycles 5, 9, and 17		X		
BIOMARKER ASSESSMENTS									
Archived tumor [t]	X								
Fresh tumor biopsy [t]	X	At the time of disease progression or at EOT Visit (optional)							
Blood [u]		X (C1D1 predose)			C3D1, C5D1, disease progression or EOT Visit				
Investigational Product (s)									
Arm A: ociperlimab + tislelizumab administration [v]		X			X				
Arm B: tislelizumab administration [v]		X			X				
Concurrent CRT (chemotherapy every 3 weeks for 4 cycles)									
Radiation therapy administration [v]		Given once daily for a total dose of 60 to 70 Gy over 6 to 7 weeks							
Chemotherapy [v]		X			X (through Cycle 4)				

Assessment	Screening [a]	Treatment Cycles				EOT Visit [b]	Safety Follow-up Visit	60-Day and 90-Day Follow-up [c]	Survival Follow-up [d]
		Cycles 1 to 2			≥ Cycle 3 and up to Cycle 17 (approximately 12 months)				
Days (Window)	**-28 to -1**	**1 (+ 3) [e]**	**8 (±3)**	**15 (±3)**	**1 (±3)**	**0 to 7 days after last dose**	**30 (±7) days after last dose**	**60 and 90 (±7) days after last dose**	**Every 3 months (±14 days) after Safety Follow-up**
FOLLOW-UP									
Survival status							X	X	X
Disease therapy since IP discontinuation							X	X	X

Abbreviations: ADA, antidrug antibody; AE, adverse event; β-hCG, beta human chorionic gonadotropin; CxDy, Cycle x Day y; cCRT, concurrent chemoradiotherapy; CT, computed tomography; D, day; DLCO, diffusing capacity of the lungs for carbon monoxide; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer-Quality of Life C30 questionnaire; EOT, End of Treatment; FEV, forced expiratory volume; 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; INR, international normalized ratio; IEC, Independent Ethics Committee; IP, investigational product; IRB, Institutional Review Board; IRC, Independent Review Committee; IRT, integrated response technology; QLQ-LC13, Lung Cancer Module of EORTC QLQ-C30; MRI, magnetic resonance imaging; NCI, National Cancer Institute; PK, pharmacokinetics; PR, partial response; PRO, Patient-Reported Outcome; PT, prothrombin time; PTT, partial thromboplastin time; RT, radiation therapy; SAE, serious adverse event; T3, triiodothyronine; T4, thyroxine.

[a] Written informed consent is required before performing any study-specific tests or procedures. Screening evaluations must be completed within 28 days of randomization. Results of standard-of-care tests or examinations performed before obtaining informed consent and within 28 days before randomization may be used for screening assessments rather than repeating such tests.

[b] The EOT Visit (Section 3.4) is to be completed within 7 days after the decision to discontinue study treatment or upon completion of study treatment. 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 specifically required at the EOT Visit. Patients who discontinue study treatment before disease progression confirmed by the investigator will need to undergo tumor assessments as outlined in Section 7.5; however, in some cases, the time window of tumor assessment might overlap with the EOT and/or Safety Follow-up Visit.

[c] The 60-day and 90-day follow-up visits may be completed at the site or by telephone.

[d] Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months after the Safety Follow-up Visit until death, loss to follow-up, withdrawal of consent, or end of study by sponsor. All patients will be followed up for survival and subsequent anticancer therapy information unless a patient requests to be withdrawn from follow-up.

[e] Cycle 1 Day 1 (C1D1) dosing should be initiated within 3 business days of randomization.

[f] Patients will be randomized into Arm A, Arm B, or Arm C via IRT. All patients must receive study treatment within 3 business days of randomization.

[g] Includes age or year of birth, sex, and self-reported race/ethnicity; medical history includes any history of clinically significant disease, surgery, or cancer; cancer history will include an assessment of prior surgery, prior RT, and prior drug therapy including start and stop dates, best response, and reason for discontinuation. Information on radiographic studies performed before study entry may be collected for review by the investigator. Preexisting AEs at baseline should be recorded as medical history. Refer to Section 7.1.3 for additional information.

[h] 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 first administration of study treatment, only SAEs should be recorded. After initiation of study treatment, all AEs and SAEs, regardless of relationship to study treatment, will be reported until either 30 days after last dose of study treatment or initiation of new anticancer therapy, whichever occurs first. For patients in Arm A and Arm B, immune-mediated AEs (serious or nonserious) should be reported until 90 days after the last dose of ociperlimab plus tislelizumab or tislelizumab alone regardless of whether or not the patient starts a new anticancer therapy. All SAEs considered related to the study drug(s) that are brought to the attention of the investigator should be reported regardless of time since the last dose of treatment. Refer to Section 8.6 for additional information.

[i] A complete physical examination will be performed at the Screening Visit. At subsequent visits and as clinically indicated, limited, symptom-directed physical examinations will be performed. Refer to Section 7.4.2 for additional information.

[j] Vital signs collected on study include temperature, pulse rate, and blood pressure (systolic and diastolic). Vital signs will be assessed in Arms A, B, and C at screening, before study drug administration on Days 1, 8, and 15 in the first 2 cycles for all patients, at the beginning of each subsequent cycle, at the EOT Visit, and at the Safety Follow-up Visit (Section 7.4.1). The patient's vital signs should be recorded within 60 minutes before, during, and 30 minutes after the first infusion of ociperlimab plus tislelizumab (as a whole infusion) in Arm A or tislelizumab alone in Arm B at each cycle visit for 2 cycles. For subsequent cycles, vital signs will be collected within 60 minutes before infusion and, if clinically indicated, during and 30 minutes after the infusion. Pulse rate and blood pressure should be collected while the patient is in a seated position after resting for 10 minutes. Weight will be assessed at screening, before study drug administration on Day 1 of each cycle, at the EOT Visit, and at the Safety Follow-up Visit. Height will be recorded at screening only.

[k] Pulmonary function testing, including spirometry and assessment of oxygenation, at a minimum, pulse oximetry at rest and with exercise, or alternatively, assessment of diffusion capacity, is to be performed as clinically indicated during the screening period to assist the determination of suitability on the study. Respective test results need to be submitted to the sponsor. For test results indicative of significantly impaired pulmonary function, eg, resting pulse oximetry < 90% on room air and further desaturation upon exercise, FEV1 < 60% or DLCO (if performed) < 60% of age- and sex-adjusted predicted performance levels (Pellegrino et al 2005), the medical monitor needs to be consulted to confirm eligibility. Tests may be repeated as clinically indicated while on study.

[l] The ECG recordings will be obtained during screening, as clinically indicated during the treatment period, at the EOT Visit, and at the Safety Follow-up Visit. Patients should rest in semirecumbent supine position for ≥ 10 minutes before ECG collection.

[m] Local laboratory assessments of serum chemistry, hematology, coagulation, and urinalysis will be conducted as outlined in Appendix 2. If laboratory tests at screening are not performed within 7 days before the administration of study drug(s) on Day 1 of Cycle 1, these tests should be repeated and reviewed before administration of study drug(s). Hematology and serum chemistry assessments (including liver function tests) are specified in Appendix 2. Hematology assessments should be performed at Day 1 (± 3 days), Day 8 (± 3 days), and Day 15 (± 3 days) of the first 2 cycles, at Day 1 (± 3 days) and Day 8 (± 3 days) of the third and the fourth cycles, on Day 1 (± 3 days) of each subsequent cycle, at the EOT Visit, and at the Safety Follow-up Visit. Serum chemistry assessments (including liver function tests) should be performed on Day 1 (± 3 days) and Day 8 (± 3 days) of the first 4 cycles, on Day 1 (± 3 days) of each subsequent cycle, at the EOT Visit, and at the Safety Follow-up Visit. Coagulation assessments should be performed at screening, on Day 1 (± 3 days) of each cycle, at the EOT Visit, and at the Safety Follow-up Visit. Urinalysis is to be conducted during the treatment period only if clinically warranted. Refer to Section 8.3.5 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.

[n] Analysis of free T3 or total T3, free T4 or total T4, and thyroid-stimulating hormone will be performed by the local study site laboratory. Thyroid function tests will be performed at screening and every 3 cycles (ie, Cycles 4, 7, 10, etc.), and at the Safety Follow-up Visit.

[o] Testing will be performed by the local laboratory at screening and will include screening HBV/HCV serology (HBsAg, HBsAb, HBcAb, and HCV antibody). After screening, viral load assessment (HBV DNA and HCV RNA) may be performed if clinically indicated. Patients who have detectable HBV DNA at screening or upon repeat testing will undergo the respective viral load test every 4 cycles (, Cycles 4, 8, and 12).

[p] 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 before the first dose of study treatment. Urine pregnancy tests will be performed at each cycle before dosing, and at the EOT and Safety Follow-up Visits. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.

[q] To be completed before any clinical activities during on-study site visits. EORTC QLQ-C30 and QLQ-LC13 questionnaires will be completed at predose on Day 1 of every cycle from Cycle 1 (baseline) through Cycle 4, and then to coincide with scheduled tumor assessments (every 6 weeks [± 7 days]) until the EOT Visit (Arms A, B, and C).

[r] PK blood samples will be collected from patients who randomized to receive ociperlimab plus tislelizumab or tislelizumab alone (Arms A and B). Procedures for collection of ociperlimab and tislelizumab PK and ADA samples are described in the Laboratory Manual. Predose (within 60 minutes before starting the first study drug infusion) PK samples (Arm A: 2 samples collected at the same time [1 for ociperlimab, another for tislelizumab]; Arm B: 1 sample for tislelizumab) will be collected on Day 1 of Cycles 1, 2, 5, 9 and 17. Postdose (within 30 minutes after completing the last study drug infusion) PK samples (2 samples collected at the same time [1 sample for ociperlimab; another for tislelizumab] in Arm A; 1 sample for tislelizumab in Arm B) will be collected on Day 1 of Cycles 1 and 5. An additional PK sample is required to be collected at the Safety Follow-up Visit (Arm A: 2 samples collected at the same time [1 for ociperlimab, another for tislelizumab]; Arm B: 1 sample for tislelizumab). Should a patient present with any ≥ Grade 3 imAE, an additional blood PK sample may be taken to determine the serum concentration of ociperlimab and tislelizumab (Arm A: 2 samples collected at the same time [1 for ociperlimab, another for tislelizumab]; Arm B: 1 sample for tislelizumab). These tests are required when it is allowed by local regulations/IRBs/IECs.

[s] ADA blood samples will be collected from patients who randomized to receive ociperlimab plus tislelizumab or tislelizumab alone (Arms A and B). Blood samples will be collected at predose (within 60 minutes before dose) on Day 1 of Cycles 1, 2, 5, 9, 17, and at the Safety Follow-up Visit for ociperlimab and tislelizumab (Arm A: 2 samples collected at the same time [1 for ociperlimab, another for tislelizumab]; Arm B: 1 sample for tislelizumab). 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.

[t] Patients must agree to provide an archival tumor tissue with an associated pathology report or agree to perform a fresh biopsy during screening (formalin-fixed paraffin-embedded block or approximately 15 unstained slides [8 slides minimum]). Note: If < 8 unstained slides are available, a discussion with the sponsor is required. If the baseline archival tumor tissues are not collected during the screening period due to unspecified reasons, archival tissue collection after screening period is applicable. If baseline archival tumor tissue is not available, a fresh biopsy of a tumor lesion at baseline (within 28 days before randomization) is required. Optional biopsies will also be taken for the patients at confirmed disease progression or EOT for the assessment of mechanism of resistance. Written informed consent is required before collecting fresh tumor biopsies. If at any time during the study a patient undergoes a medically indicated procedure that has the likelihood of yielding tumor tissue, any remaining sample or a portion of the sample not necessary for medical diagnosis (leftover tumor tissue) may be obtained for exploratory analysis.

[u] For Arm A and Arm B: Blood samples (about 10 mL at each timepoint) will be collected predose at C1D1, C3D1, C5D1, EOT visit or at the time of confirmed disease progression (whichever occurs first). For Arm C: Blood samples (about 10 mL at each timepoint) will be collected predose at C1D1, C3D1, EOT visit or at the time of confirmed disease progression (whichever occurs first).

[v] The schedule of RT and chemotherapy administrations is detailed in the specific section. The recommendation is to start RT on C1D1 of chemotherapy. Ociperlimab plus tislelizumab or tislelizumab alone should be given intravenously once every 3 weeks. The initial 2 infusions (Cycles 1 and 2) will be delivered over 60 (± 5) minutes, and administration can then occur over 30 (± 5) minutes for subsequent infusions if well-tolerated. Patients must be monitored for 2 hours after infusion of tislelizumab followed by ociperlimab (Arm A) and tislelizumab (Arm B) on Day 1 of Cycles 1 and 2; from Cycle 3 onward, at least a 60-minute monitoring period is required. The first dose will be given on C1D1and subsequent dosing will continue on the scheduled 3-week intervals. The chemotherapy regimens will be given intravenously on a 3-week cycle for the first 4 cycles. On Day 1 of Cycles 1 to 4, chemotherapy drugs will be administered in a sequential manner separately after the infusion of ociperlimab plus tislelizumab or tislelizumab alone; cisplatin 75 mg/m^2 will be administered on Day 1 of each cycle. If the patient is unable to tolerate the 1-day administration of cisplatin 75 mg/m^2, at the investigator's discretion (eg, patients had concurrent superior vena cava syndrome) cisplatin 25 mg/m^2 dosed on Days 1, 2 and 3 is allowed; carboplatin will be administered on Day 1 of each cycle; etoposide will be administered on Days 1, 2, and 3 of each cycle.

[w] ECOG Performance Status will be assessed in Arms A, B, and C at screening, before study drug administration on Day 1 of each cycle, at the EOT Visit, and at the Safety Follow-up Visit.

APPENDIX 2. CLINICAL LABORATORY ASSESSMENTS

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

Abbreviations: CK-MB, creatine kinase cardiac muscle isoenzyme.

[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] Calcium values will be corrected for patients with hypoalbuminemia.

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

APPENDIX 3. EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light 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 4. THE RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) GUIDELINES, VERSION 1.1

Source: Eisenhauer et al 2009.

Definitions

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

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

Measurable Disease

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

- 10 mm by computed tomography (CT) and magnetic resonance imaging (MRI) (no less than double the slice thickness and a minimum of 10 mm). Assumes a scan slice thickness no greater than 5 mm.
- 10 mm caliper measurement by clinical exam (when superficial)
- 20 mm by chest X-ray (if clearly defined and surrounded by aerated lung)

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

Nonmeasurable Disease

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

Bone lesions:

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

- Blastic bone lesions are nonmeasurable.

Cystic lesions:

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

Lesions with prior local treatment:

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

Target Lesions

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

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

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

Nontarget Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as nontarget lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as “present,” “absent,” or in rare cases “unequivocal

progression" (more details to follow). In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (eg, "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

Guidelines for Evaluation of Measurable Disease

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

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

- Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the trial.
- Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scans).
- Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date, and because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.
- Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.
- Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, 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 that are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

- Cytology, histology: These techniques can be used to differentiate between partial response (PR) and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

Response Criteria

Evaluation of Target Lesions

- Complete response: Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm.
- Partial response: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters
- Progressive disease: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: The appearance of one or more new lesions is also considered progression).
- Stable disease: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study
- Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the “sum” of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report form may be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, stable disease, and progressive disease, 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 that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure."
  When this occurs, it is important that a value be recorded on the electronic case report form (eCRF). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat, such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially nonreproducible; therefore, providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that measurement should be recorded, even if it is below 5 mm.
- Lesions that split or coalesce on treatment: When non-nodal lesions "fragment," the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion."

Evaluation of Nontarget Lesions

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

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

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

- When the patient has only nonmeasurable disease: This circumstance arises in some Phase 3 trials when it is not a criterion of trial entry to have measurable disease. The same general concept applies here as noted above; however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in nonmeasurable disease burden. Because worsening in nontarget disease cannot be easily quantified (by definition: if all lesions are truly nonmeasurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in nonmeasurable disease is comparable in magnitude to the increase that would be required to declare progressive disease 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 progressive disease at that point. While it would be ideal to have objective criteria to apply to nonmeasurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

New Lesions

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

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

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

While fluorodeoxyglucose (FDG)-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning

in assessment of progression (particularly possible "new" disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up, is a sign of progressive disease 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 progressive disease. 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 progressive disease will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a preexisting site of disease on CT that is not progressing on the basis of the anatomic images, this is not progressive disease.
- Timepoint Response
- It is assumed that at each protocol-specified time point, a response assessment occurs. The following table provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline:

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
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 patients have nonmeasurable (therefore nontarget) disease only, the following table is to be used:

Nontarget Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Stable disease (Non-CR/non-PD)
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

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

Evaluation of Best Overall Response

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

The best overall response is determined once all the data for the patient is known.

Best response determination in trials where confirmation of CR or PR IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has stable disease at first assessment, PR at second assessment, and progressive disease on last assessment has a best overall response 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 time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has stable disease at first assessment, progressive disease at second and does not meet minimum duration for stable disease, will have a best response of progressive disease. The same patient lost to follow-up after the first stable disease assessment would be considered inevaluable.

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

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

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

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

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

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

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

Confirmation of Measurement/Duration of Response

Confirmation

In nonrandomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure that 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 that 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 the measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

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

Duration of Stable Disease

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

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

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

APPENDIX 5. PREEXISTING IMMUNE DEFICIENCIES OR AUTOIMMUNE DISEASES

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

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

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

APPENDIX 6. NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

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

Adapted from Dolgin 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, p114.

APPENDIX 7. IMMUNE-MEDIATED ADVERSE EVENT EVALUATION AND MANAGEMENT

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

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

- What was the temporal relationship between initiation of tislelizumab or tislelizumab plus ociperlimab and the AE?
- How did the patient respond to withdrawal of tislelizumab or tislelizumab plus ociperlimab?
- Did the event recur when tislelizumab or tislelizumab plus ociperlimab was reintroduced?
- Was there a clinical response to corticosteroids?
- Is the event an autoimmune endocrinopathy?
- Is disease progression or an alternative diagnosis a more likely explanation?

When alternative explanations to autoimmune toxicity have been excluded, the imAE field associated with the AE in the eCRF should be checked. If further diagnostic evaluations change the assessment, the eCRF should be updated accordingly.

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

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

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

Immune-related Toxicity	Diagnostic Evaluation Guideline
Neurological Toxicity	Perform a comprehensive neurological examination and brain MRI for all CNS symptoms; review alcohol history and other medications. Conduct a diabetic screen and assess blood B12/folate, HIV status, TFTs, and consider autoimmune serology. Consider the need for brain/spine MRI/MRA and nerve conduction study for peripheral neuropathy. Consult with a neurologist if there are abnormal findings.
Colitis	Review dietary intake and exclude steatorrhea. Consider comprehensive testing, including the following: FBC, UEC, LFTs, CRP, TFTs, stool microscopy and culture, viral PCR, *Clostridium difficile* toxin, and cryptosporidia (drug-resistant organism). In case of abdominal discomfort, consider imaging, eg, X-ray, CT scan. If a patient experiences bleeding, pain, or distension, consider colonoscopy with biopsy and surgical intervention as appropriate.
Eye Disorders	If a patient experiences acute, new onset, or worsening of eye inflammation; blurred vision; or other visual disturbances, refer the patient urgently to an ophthalmologist for evaluation and management.
Hepatitis	Check ALT/AST/total bilirubin, INR/albumin; the frequency will depend on severity of the AE (eg, daily if Grade 3 to 4; every 2 to 3 days if Grade 2, until recovering). Review medications (eg, statins, antibiotics) and alcohol history. Perform liver screen including hepatitis A/B/C serology, hepatitis E PCR and assess anti-ANA/SMA/LKM/SLA/LP/LCI, iron studies. Consider imaging (eg, ultrasound scan for metastases or thromboembolism). Consult with a hepatologist and consider liver biopsy.
Renal toxicity	Review hydration status and medication history. Test and culture urine. Consider renal ultrasound scan, protein assessment (dipstick/24-hour urine collection), or phase-contrast microscopy. Refer to a nephrologist for further management assistance.
Dermatology	Consider other causes by conducting a physical examination. Consider dermatology referral for skin biopsy.
Joint or muscle inflammation	Conduct musculoskeletal history and perform complete musculoskeletal examination. Consider joint X-ray and other imaging as required to exclude metastatic disease. Perform autoimmune serology and refer to rheumatology for further management assistance. For suspected myositis/rhabdomyolysis/myasthenia, include CK, ESR, CRP, troponin, and consider a muscle biopsy.
Myocarditis	Perform ECG, echocardiogram, CK/CK-MB, troponin (I and/or T), and refer to a cardiologist.

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

Treatment of Immune-Related Adverse Events

- Immune-related AEs can escalate quickly. Study treatment interruption, close monitoring, timely diagnostic work-up, and treatment intervention as appropriate is required.
- Immune-related AEs should improve promptly after introduction of immunosuppressive therapy. If this does not occur, review the diagnosis, seek further specialist advice, and contact the study medical monitor.
- For some Grade 3 toxicities that resolve quickly, rechallenge with study drug may be considered if there is evidence of a clinical response to study treatment, after consultation with the study medical monitor.
- Steroid dosages in the table below are for oral or intravenous (methyl)prednisolone. Equivalent dosages of other corticosteroids can be substituted. For steroid-refractory 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.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3-4 Severe symptoms, hospitalization required	Refer patient to an endocrinologist. If hypothyroid, replace with thyroxine 0.5-1.6 µg/kg/day (for the elderly or those with comorbidities, the suggested starting dose is 0.5 µg/kg/day). Add oral prednisolone 0.5 mg/kg/day for thyroid pain. Thyrotoxic patients require treatment with a beta blocker and may require carbimazole until thyroiditis resolves.	Hold study treatment; resume when resolved/improved to Grade 0-1.
Hypophysitis	**1-2** Mild-moderate symptoms	Refer patient to an endocrinologist for hormone replacement. Add oral prednisolone 0.5-1 mg/kg/day for patients with pituitary inflammation. Taper corticosteroids over at least 1 month. If there is no improvement in 48 hours, treat as Grade 3-4.	Continue study treatment.
	3-4 Severe or life-threatening symptoms	Refer patient to an endocrinologist for assessment and treatment. Initiate pulse intravenous methylprednisolone 1 mg/kg for patients with headache/visual disturbance due to pituitary inflammation. Convert to oral prednisolone and taper over at least 1 month. Maintain hormone replacement according to endocrinologist's advice.	Hold study treatment for patients with headache/visual disturbance due to pituitary inflammation until resolved/improved to ≤ Grade 2. Discontinuation is usually not necessary.
Pneumonitis	**1** Radiographic changes only	Monitor symptoms every 2-3 days. If appearance worsens, treat as Grade 2.	Consider holding study treatment until appearance improves and cause is determined.

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

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

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

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	2 ALT or AST 3-5 x ULN	Recheck LFTs every 48-72 hours. For persistent ALT/AST elevation: consider oral prednisolone 0.5-1 mg/kg/day for 3 days, then taper over 2-4 weeks. For rising ALT/AST: start oral prednisolone 1 mg/kg/day and taper over 2-4 weeks; re-escalate dose if LFTs worsen, depending on clinical judgement.	Hold study treatment; treatment may be resumed when resolved/improved to baseline grade and prednisolone tapered to ≤ 10 mg.
	3 ALT or AST 5-20 x ULN	ALT/AST < 400 IU/L and normal bilirubin/INR/albumin: Initiate oral prednisolone 1 mg/kg and taper over at least 4 weeks. ALT/AST > 400 IU/L or raised bilirubin/INR/low albumin: Initiate intravenous (methyl)prednisolone 2 mg/kg/day. When LFTs improve to Grade 2 or lower, convert to oral prednisolone and taper over at least 4 weeks.	Hold study treatment until improved to baseline grade; reintroduce only after discussion with the study medical monitor.
	4 ALT or AST > 20 x ULN	Initiate intravenous methylprednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 6 weeks.	Discontinue study treatment.
	Worsening LFTs despite steroids: • If on oral prednisolone, change to pulsed intravenous methylprednisolone. • If on intravenous methylprednisolone, add mycophenolate mofetil (MMF) 500 to 1000 mg twice a day. • If worsening on MMF, consider addition of tacrolimus. Duration and dose of steroid required will depend on severity of event.		
Nephritis	**1** Creatinine 1.5 x baseline or > ULN to 1.5 x ULN	Repeat creatinine weekly. If symptoms worsen, manage as per criteria below.	Continue study treatment.

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

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	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.	Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1.
Ocular Toxicity	**1** Asymptomatic eye examination/test abnormality	Consider alternative causes and prescribe topical treatment as required.	Continue study treatment.
	2 Anterior uveitis or mild symptoms	Refer patient to an ophthalmologist for assessment and topical corticosteroid treatment. Consider a course of oral steroids.	Continue study treatment or hold treatment if symptoms worsen or if there are symptoms of visual disturbance.
	3 Posterior uveitis/panuveitis or significant symptoms	Refer patient urgently to an ophthalmologist. Initiate oral prednisolone 1-2 mg/kg and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1; reintroduce only after discussion with the study medical monitor.
	4 Blindness (at least 20/200) in the affected eyes	Initiate intravenous (methyl)prednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks.	Discontinue study treatment.
Pancreatitis	**2** Asymptomatic, blood test abnormalities	Monitor pancreatic enzymes.	Continue study treatment.

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

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3 Severe pain, limited food and fluid intake, daily living activity limited	Admit to hospital for appropriate management. Initiate intravenous (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when symptoms improve to Grade 2 and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1.
	4 Life-threatening complications or dehydration	Admit to hospital for emergency care. Consider intravenous corticosteroids if not contraindicated by infection.	Discontinue study treatment.
Myositis/ Rhabdomyolysis	**1** Mild weakness with/without pain	Prescribe analgesics. If CK is significantly elevated and patient has symptoms, consider oral steroids and treat as Grade 2.	Continue study treatment.
	2 Moderate weakness with/without pain	If CK is 3 x ULN or worse, initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1.
	3-4 Severe weakness, limiting self-care	Admit to hospital and initiate oral prednisolone 1 mg/kg. Consider bolus intravenous (methyl)prednisolone and 1-2 mg/kg/day maintenance for severe activity restriction or dysphagia. If symptoms do not improve, add immunosuppressant therapy. Taper oral steroids over at least 4 weeks.	For Grade 3: Hold study treatment until improved to Grade 0-1. Discontinue upon any evidence of myocardial involvement.

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

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; CHF, congestive heart failure; CK, creatine kinase; CK-MB, creatine kinase cardiac isoenzyme; ECG, electrocardiogram; INR, international normalized ratio; LFT, liver function test; MMF, mycophenolate mofetil; MUGA, multigated acquisition scan; NYHA, New York Heart Association; T4, thyroxine; TB, tuberculosis; TFT, thyroid function test; TSH, thyroid-stimulating hormone; U&E, urea and electrolytes; ULN, upper limit of normal.
[a] If clinically significant cardiac enzyme abnormalities are detected during laboratory assessment and serial cardiac enzyme assessments pose logistical hardship for the patient, then patient hospitalization should strongly be considered until immune-related myocarditis has been ruled out.

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

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

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

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

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

Contraception Guidelines

The Clinical Trials Facilitation Group recommendations related to contraception and pregnancy testing in clinical trials include the use of highly effective forms of birth control (Clinical Trials Facilitation Group 2014). These methods include the following:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with the inhibition of ovulation
  - Oral, intravaginal, or transdermal
- Progestogen-only hormonal contraception associated with the inhibition of ovulation
  - Oral, injectable, implantable
    Note: Oral birth control pills are not considered a highly effective form of birth control, and if they are selected, they must be used with a second, barrier method of contraception such as condoms with or without spermicide.
- An intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
  Note: This is only considered a highly effective form of birth control when the vasectomized partner is the sole partner of the study participant and there has been a medical assessment confirming surgical success.
  - A sterile male is one for whom azoospermia in a semen sample has been demonstrated as definitive evidence of infertility.
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment)
  Note: Total sexual abstinence should only be used as a contraceptive method if it is in line with the patients' usual and preferred lifestyle. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable methods of contraception.

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

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

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

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

- Surgically sterile (ie, through bilateral salpingectomy, bilateral oophorectomy, or hysterectomy)
- Postmenopausal, defined as:
  - ≥ 55 years of age with no spontaneous menses for ≥ 12 months OR
  - < 55 years of age with no spontaneous menses for ≥ 12 months AND with postmenopausal follicle-stimulating hormone (FSH) concentration > 30 IU/mL and all alternative medical causes for the lack of spontaneous menses for ≥ 12 months have been ruled out, such as polycystic ovarian syndrome, hyperprolactinemia, etc.

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

Adapted from Clinical Trials Facilitation Group (CTFG) 2014.

APPENDIX 10. EUROPEAN ORGANISATION FOR RESEARCH AND TREATMENT OF CANCER QUALITY OF LIFE CANCER QUESTIONNAIRE (EORTC-QLQ-C30)

EORTC QLQ-C30 (version 3)

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

Please fill in your initials: ____

Your birthdate (Day, Month, Year): ____

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

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

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

Please go on to the next page

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

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

APPENDIX 11. EUROPEAN ORGANISATION FOR RESEARCH AND TREATMENT OF CANCER QUALITY OF LIFE QUESTIONNAIRE LUNG CANCER (QLQ-LC13)

EORTC QLQ - LC13

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.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

APPENDIX 12. COCKROFT-GAULT FORMULA AND CALVERT FORMULA

CALVERT FORMULA:

FOR SERUM CREATININE CONCENTRATION (SCr) IN MG/DL[a]

Cl_{cr} for males (mL/min) $\quad \frac{(140\text{-age})(\text{weight}^{b})}{(72)(SCr)}$

CL_{cr} for females (mL/min) $\quad \frac{(0.85)(140\text{-age})(\text{weight}^{b})}{(72)(SCr)}$

FOR SERUM CREATININE CONCENTRATION (SCr) IN µMOL/L[a]

Cl_{cr} for males (mL/min) $\quad \frac{(140\text{-age})(\text{weight}^{b})}{(0.81)(SCr)}$

CL_{cr} for females (mL/min) $\quad \frac{(0.85)(140\text{-age})(\text{weight}^{b})}{(0.81)(SCr)}$

a Age in years and weight in kilograms.

b Recommend using ideal body weight if the patient is obese (> 30% over ideal body weight) in calculation of estimated CL_{Cr}. Calculating by actual body weight is acceptable.

(GFR* + 25) x AUC = dose (in mg).

*GFR calculation formula is same as Cl_{Cr} formula as shown above.

APPENDIX 13. DOSE MODIFICATION OF CHEMOTHERAPY

Dose Reduction Level of Etoposide, Cisplatin and Carboplatin

Dose Lever	Etoposide (mg/m^2)[a]	Cisplatin (mg/m^2)[a]	Carboplatin (mg/m^2)[a]
Full Dose	100 mg/m^2, on Days 1, 2, and 3 of each cycle for 4 cycles	75 mg/m^2, on Day 1 of each cycle for 4 cycles If the patient is unable to tolerate the 1-day administration of cisplatin 75 mg/m^2, at the investigator's discretion, cisplatin 25 mg/m^2 dosed on Days 1, 2 and 3 is allowed	AUC 5 on Day 1 of each cycle for 4 cycles
First Dose Reduction (-1 dose level)	75% of initial starting dose	75% of initial starting dose	75% of initial starting dose
Second Dose Reduction [b] (-2 dose level)	50% of initial starting dose	50% of initial starting dose	NA [c]

Abbreviations: AUC, area under the plasma or serum concentration-time curve; NA, not applicable.
[a] Dose reductions may or may not be concomitant, refer to the tables below.
[b] Including the second appearance of the toxicity needs 1 dose reduction. A maximum of 2 dose level reductions are allowed.
[c] Only 1 dose reduction is permitted for carboplatin.

In patients with impaired renal function, the following initial dose modification should be considered based on measured creatinine clearance:

Measured Creatinine Clearance	>50 mL/min	15 to 50 mL/min
Etoposide	100% of dose	75% of dose

Subsequent etoposide dosing should be based on patient tolerance and clinical effect. The minimum dose of etoposide should be 50% of dose.

Recommended Dose Modifications for Hematologic Toxicity

Dose adjustments are based on nadir blood counts since the preceding chemotherapy administration. Dose level adjustments are relative to those of the preceding administration. Recommended dose modifications for hematologic toxicity are provided in the following table.

Chemotherapy Dose Modification for Hematological Toxicity [a]

Adverse event		Treatment
Febrile neutropenia; documented infection		1) The first episode of febrile neutropenia or documented infection will result in antibiotic treatment and 1 dose level reduction in the dose of both drugs. 2) If there is a second episode despite dose reduction, the patient must receive prophylactic antibiotics during the subsequent cycle. 3) If there is a third episode, the chemotherapy will be discontinued.
Neutropenia	Grade 3 ($0.5\text{-}1.0 \times 10^9$/L)	Chemotherapy delay until ≤ Grade 1 ($\geq 1.5 \times 10^9$/L); restart with the full dose
	Grade 4 ($< 0.5 \times 10^9$/L)	Chemotherapy delay until recovered to ≤ Grade 1; 1 dose reduction of all further doses
Thrombo-cytopenia	Grade 1	Chemotherapy delay until recovered to normal; restart with the full dose
	Grade 2 or Grade 3 without bleeding	Chemotherapy delay until recovered to normal; 1 dose reduction of all further doses
	Grade 4	Chemotherapy delay until recovered to normal; 2 dose reduction of all further doses (the lowest dose level)
	Grade 3 or 4 associated with clinically significant bleeding	Discontinue chemotherapy
Recurrence of Grade 3 or 4 after 2 dose reductions (with either neutropenia or thrombo cytopenia)		Discontinue chemotherapy

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

Recommended Dose Modifications for Nonhematologic Toxicities

The dose adjustments of chemotherapy for nonhematologic toxicity are described in the following table. All dose modifications should be made based on the worst grade toxicity.

In general, for ≥ Grade 3 nonhematologic toxicities, chemotherapy should be delayed until resolution to less than or equal to the patient's baseline value before resuming treatment at a reduced dose. However, exceptions may be made for Grade 3 neurotoxicity or esophagitis. In the case of neurotoxicity, the investigator and patient may decide to continue treatment at a reduced dose, with no delay required, as neurotoxicity may not resolve to baseline values. Adjustments for esophagitis are recommended to follow dose modifications as described in the table below.

Chemotherapy Dose Modifications [a] for Nonhematologic Toxicities

Toxicity	Grade	Treatment
Renal toxicity	≥ Grade 1	Delay chemotherapy until recovered to Grade 0 or baseline, change cisplatin to carboplatin, if possible; 1 dose reduction for other drug; if recur, discontinue chemotherapy. Etoposide dosage should be reduced one dose level in patients with a creatinine clearance from 15 to 50 mL/min.
Ototoxicity	Grade 2	1 Reduction of all further doses of cisplatin
	Grade 3-4	Delay chemotherapy until recovered to ≤ Grade 2, change cisplatin to carboplatin
Sensory neuropathy [b, c]	Grade 2	1 Reduction for all further doses of cisplatin
		For carboplatin + paclitaxel regimen, delay paclitaxel until ≤ Grade 1 while continuing carboplatin
	Grade 3	Discontinue cisplatin, change cisplatin to carboplatin; 1 dose reduction for etoposide
		For carboplatin + paclitaxel regimen, discontinue paclitaxel while continuing carboplatin
	Grade 4	Discontinue cisplatin, carboplatin, paclitaxel, and etoposide
Hepatic toxicity (transaminase elevation)	Grade 3 or 4	1 dose reduction for cisplatin and etoposide
Diarrhea	Grade 4	Discontinue chemotherapy
Oral mucositis or stomatitis	≥ Grade 3	Reduction for further doses of etoposide
		Discontinue chemotherapy for Grade 4
Esophagitis [d, e]	≥ Grade 3	Hold chemotherapy until ≤ Grade 2
		Delay chemotherapy at the discretion of investigator for Grade 3; delay chemotherapy for Grade 4
Other organ toxicity	Grade 2	Delay chemotherapy until ≤ Grade 1 or baseline [f]
	Grade 3-4	Delay chemotherapy until recovered to ≤ Grade 1 or baseline [e]; 1 reduction of all further doses

[a] If considered in the best interest of the patient and consistent with local practice, investigators may decide to use supportive measures/treatment and/or secondary prophylaxis instead of dose reductions for the next cycle. The provided triggers for dose modifications are recommendations only.
[b] Delay until resolution of toxicity to baseline value is not required for Grade 3 neurotoxicity.

[c] At the discretion of the attending physician, patients experiencing Grade 3 neurologic toxicity as a transient ischemic attack that has completely resolved may not require dose reduction or discontinuation.
[d] Grade 3 esophagitis will occur in a significant number of patients toward the end of radiation therapy. For patients who experience this event earlier than anticipated in the course of their treatment, the advice would be to hold chemotherapy and assess at weekly intervals. If symptoms do not progress at the time of assessment, chemotherapy can be resumed; chemotherapy can be resumed at 80% of previous dose for both drugs.
[e] Grade 4 esophagitis results in holding chemotherapy until toxicity resolves to ≤ Grade 2, and then chemotherapy may be resumed; chemotherapy can be resumed at 80% of previous dose for both drugs.
[f] Skin reactions, paronychia, alopecia, fatigue, nausea/vomiting, which may have resolved to Grade 2 or baseline.

APPENDIX 14. MANAGEMENT OF RADIATION ESOPHAGITIS

CTCAE Scale: Acute Esophagitis Related to Radiation

Grade	Clinical state
1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
2	Symptomatic; altered eating/swallowing; oral supplements indicated
3	Severely altered eating/swallowing; tube feeding, TPN, or hospitalization indicated
4	Life-threatening consequences; urgent operative intervention indicated
5	Death

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; TPN, total parenteral nutrition.

Dietary and Nutritional Support Recommendations for Acute Radiation Esophagitis

Supportive measure	Recommendation
Dietary modification	• Consider dietician referral • Avoid potentially irritant foods (tobacco, alcohol, coffee, and spicy foods) • Soft, bland diet • Small, frequent meals
Nutritional support	• Liquid meal replacements/supplements • Intravenous hydration • Electrolyte correction • For prolonged symptoms, enteral feeding or total parenteral nutrition may be required, although former is preferred • Antiemetics may be beneficial

Modified from Baker and Fairchild 2016

Recommendations for Medication Management of Radiation Esophagitis

Treatment option	Management of esophagitis
1	Ketoconazole 200 mg PO QD
2	Fluconazole 100 mg PO QD until the completion of radiation
3	Mixture of viscous lidocaine 60 mL + Mylanta (or generic equivalent antacid) 30 mL + sucralfate (1 gm/mL) 10 mL. Take 15 to 30 mL PO q3 to 4 h PRN
4	Ranitidine 150 mg PO BID (or other histamine-2 [H2] receptor blocker or a proton-pump inhibitor such as omeprazole) until completion of radiation
5	Grade 4 esophagitis: hold CRT until Grade 2 or less

Abbreviations: BID, twice daily; CRT, chemoradiotherapy; h, hour; PO, oral; PRN, when necessary; q, every; QD, once daily.