CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 3, Randomized, Open-Label Study to Compare Ociperlimab (BGB-A1217) Plus Tislelizumab (BGB-A317) Versus Durvalumab in Patients With Locally Advanced, Unresectable, PD-L1-Selected Non-Small Cell Lung Cancer Whose Disease Has Not Progressed After Concurrent Chemoradiotherapy
Protocol Number:	BGB-A317-A1217-301 (AdvanTIG-301)
Phase:	3
Investigational Products:	Ociperlimab and Tislelizumab
Proposed Indication(s):	Non-Small Cell Lung Cancer
EudraCT:	2020-004656-14
Sponsor:	BeiGene, Ltd. c/o BeiGene USA, Inc. 2955 Campus Drive, Suite 200 San Mateo, CA 94403 USA
Sponsor Medical Monitor:	[redacted] Telephone: [redacted] Email: [redacted]
Original Protocol Version 0.0:	23 September 2020
Amendment 1.0:	16 April 2021
Amendment 2.0:	21 April 2022

FINAL PROTOCOL APPROVAL SHEET

A Phase 3, Randomized, Open-Label Study to Compare Ociperlimab (BGB-A1217) Plus Tislelizumab (BGB-A317) Versus Durvalumab in Patients With Locally Advanced, Unresectable, PD-L1-Selected Non-Small Cell Lung Cancer Whose Disease Has Not Progressed After Concurrent Chemoradiotherapy

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INVESTIGATOR SIGNATURE PAGE

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Protocol Identifier: BGB-A317-A1217-301 (AdvanTIG-301)

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 Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd., or one of its subsidiaries.

Instructions for Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name and address of the center in which the study will be conducted.

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

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

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SYNOPSIS

Name of Sponsor/Company:	BeiGene, Ltd.	
Investigational Product(s):	Ociperlimab (BGB-A1217) and tislelizumab (BGB-A317)	
Protocol Identifier:	**BGB-A317-A1217-301 (AdvanTIG-301)**	
The context below in the synopsis applies to study conduction since Protocol Amendment (PA) 2.0 implementation only, unless specified otherwise.		
Title of Study:	A Phase 3, Randomized, Open-Label Study to Compare Ociperlimab (BGB-A1217) Plus Tislelizumab (BGB-A317) Versus Durvalumab in Patients With Locally Advanced, Unresectable, PD-L1-Selected Non-Small Cell Lung Cancer Whose Disease Has Not Progressed After Concurrent Chemoradiotherapy	
Planned Number of Patients:	Approximately 700 patients in total	
Study Centers:	Approximately 235 centers globally	
Study Duration:	Prescreening (archival or fresh tumor tissue collected prior to cCRT for evaluation of programmed cell death protein ligand-1[PD-L1] status; up to 120 days), screening (up to 28 days), treatment (immunotherapy until a maximum of 12 months, or disease progression, intolerable toxicity, or treatment discontinuation for other reasons), safety follow-up (approximately 30, 60, 90, and 120 days after the last dose of study treatment), and survival follow-up (approximately every 3 months ± 14 days after the Safety Follow-up Visit).	**Phase**: 3

Study Objectives and Endpoints:

Primary:

Objectives	Endpoints
Compare progression-free survival (PFS) as assessed by the Independent Review Committee (IRC) per Response Evaluation Criteria in Solid Tumors (RECIST) Version (v) 1.1 in ociperlimab plus tislelizumab (Arm A) versus durvalumab (Arm C) among patients with Local Advanced Non-Small Cell Lung Cancer (LA NSCLC) whose disease has not progressed after concurrent chemoradiotherapy (cCRT) and with PD-L1 ≥ 50%	PFS by the IRC, defined as the time from the date of randomization to the date of first documentation of disease progression as assessed by the IRC per RECIST v1.1 or death, whichever occurs first

Compare PFS as assessed by the IRC per RECIST v1.1 in ociperlimab plus tislelizumab (Arm A) versus durvalumab (Arm C) among patients with LA NSCLC whose disease has not progressed after cCRT and with PD-L1 ≥ 1%	

Secondary:

Objectives	**Endpoints**
Compare overall survival (OS) in Arm A versus Arm C among patients with PD-L1 ≥ 50%	OS defined as the time from the date of randomization until the date of death due to any cause
Compare OS in Arm A versus Arm C among patients with PD-L1 ≥ 1%	
Evaluate overall response rate (ORR) and duration of response (DOR) as assessed by both the IRC and investigators in Arm A versus Arm C among patients with PD-L1 ≥ 50% and ≥ 1%	ORR, defined as the proportion of patients who achieve a complete response (CR) or partial response (PR) assessed by both the IRC and investigators per RECIST v1.1
	DOR, defined as the time from the first determination of a confirmed objective response as assessed by both the IRC and investigators per RECIST v1.1 until the first documentation of disease progression or death, whichever occurs first
Evaluate time to death or distant metastasis (TTDM) in Arm A versus Arm C among patients with PD-L1 ≥ 50% and ≥ 1%	TTDM, defined as the time from the date of randomization until the first date of distant metastasis as assessed by both the IRC and investigators, or death. Distant metastasis is defined as any new lesion that is outside of the radiation field per RECIST v1.1 or proven by biopsy
Evaluate PFS2 in Arm A versus Arm C among patients with PD-L1 ≥ 50% and ≥ 1%	PFS2, defined as the time from randomization to the disease progression after next line of treatment, or death from any cause, whichever occurs first

Evaluate safety and tolerability in 3 treatment arms among patients with PD-L1 ≥ 50% and ≥ 1%	Safety and tolerability, defined as adverse events (AEs) (using NCI-CTCAE v5.0), laboratory tests, vital signs, Eastern Cooperative Oncology Group (ECOG) Performance Status, physical examinations, concomitant medications, and dose modifications
Compare the impact of treatments on patient health-related quality of life (HRQoL) in Arm A versus Arm C among patients with PD-L1 ≥ 50% and PD-L1 ≥ 1%	HRQoL, measured via patient-reported outcomes (PROs) using European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13 (EORTC QLQ-LC13), and the 5-Level EuroQol 5-Dimension (EQ-5D-5L)
Characterize the pharmacokinetics (PK) of ociperlimab and tislelizumab	Serum concentrations of ociperlimab and tislelizumab at specified timepoints
Assess host immunogenicity to ociperlimab and tislelizumab	Immunogenic responses to ociperlimab and tislelizumab evaluated through detection of anti-drug antibodies
Evaluate the association of PD-L1 and T-cell immunoglobulin and ITIM domain (TIGIT) expression with clinical efficacy to ociperlimab plus tislelizumab or tislelizumab or durvalumab only	PD-L1 and TIGIT expression in archival and/or fresh tumor tissues before study treatment or at disease progression/reoccurrence, and their association with clinical efficacy

Exploratory:

Objectives	**Endpoints**
Evaluate PFS, ORR, DOR, TTDM by the IRC and investigators per RECIST v1.1 and OS, PFS2, and HRQoL in Arm A versus Arm B among patients with PD-L1 ≥ 50% and ≥ 1%	PFS, ORR, DOR, TTDM by IRC and investigators per RECIST v1.1; OS, PFS2, HRQoL

Evaluate the potential association of exploratory biomarkers with response or resistance to ociperlimab plus tislelizumab or tislelizumab or durvalumab only, and with patient prognosis	Status of exploratory biomarkers including but not limited to the expression of CD226, CD155, and CD112, gene expression profiling (GEP), circulating tumor DNA (ctDNA), tumor mutation burden (TMB), microsatellite instability (MSI), gene mutation profiles, extracellular vesicle (EVs), and tumor-infiltrating lymphocytes (TILs) in archival and/or fresh tumor tissues and blood before and after study treatment, and the association between these biomarkers and clinical efficacy, disease status, response, and resistance mechanisms
Evaluate patient-reported global impression of severity (PGI-S) and patient-reported treatment side-effect burden (PRTSE)	PGI-S and PRTSE
Evaluate the efficacy of patients who have finished definitive cCRT treatment and received at least 1 consolidation treatment among patients enrolled under PA 1.0	PFS by investigators

Study Design

This is an open-label, randomized, multicenter, Phase 3 study to compare the efficacy and safety of anti-T-cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif (ITIM) domains (anti-TIGIT) monoclonal antibody ociperlimab plus tislelizumab versus durvalumab in patients with unresectable LA NSCLC whose disease has not progressed after definitive, platinum-based cCRT and with PD-L1 expression on ≥ 1% of tumor cells (TC) as assessed by the central lab using the VENTANA PD-L1 (SP263) assay.

The primary endpoints are PFS by the IRC per RECIST v1.1 in the PD-L1 ≥ 50% Analysis Set in Arm A and Arm C, and PFS by the IRC per RECIST v1.1 in the PD-L1 ≥ 1% Analysis Set in Arm A and Arm C. Patients with histologically or cytologically confirmed, unresectable LA NSCLC whose disease has not progressed after cCRT and with PD-L1 ≥ 1% are eligible.

Approximately 700 patients will be randomized in a 3:1:3 ratio to receive the study treatment in the following 3 arms:

- Arm A: ociperlimab (900 mg intravenously [IV]) combined with tislelizumab (200 mg IV) every 3 weeks (Q3W)
- Arm B: tislelizumab 200 mg IV Q3W
- Arm C: durvalumab 10 mg/kg IV once every 2 weeks (Q2W) (or 1500 mg every 4 weeks [Q4W] where the dosage has been approved by the local health authority)

Study drugs will be given starting from Cycle 1 Day 1 (C1D1) and continued for up to 12 months, or until progressive disease (PD) per RECIST v1.1, unacceptable toxicity, or death, or until another discontinuation criterion is met, whichever occurs first.

Randomization will be stratified by age (< 65 years versus ≥ 65 years), PD-L1 expression on TC (≥ 50% versus < 50%), and histology (squamous versus nonsquamous). The ITT and PD-L1 ≥ 50% populations are defined as patients with PD-L1 expression on ≥ 1% and ≥ 50% of TC, respectively, with membrane positivity for PD-L1 at any intensity above background staining as determined using the VENTANA PD-L1 (SP263) assay.

The PD-L1 expression status will be closely monitored. For enrolled patients with PD-L1 1% to 49% of TC will be stopped as necessary through Interactive Response Technology (IRT) upon reaching around 50% to ensure that the population reflects the natural PD-L1 expression prevalence.

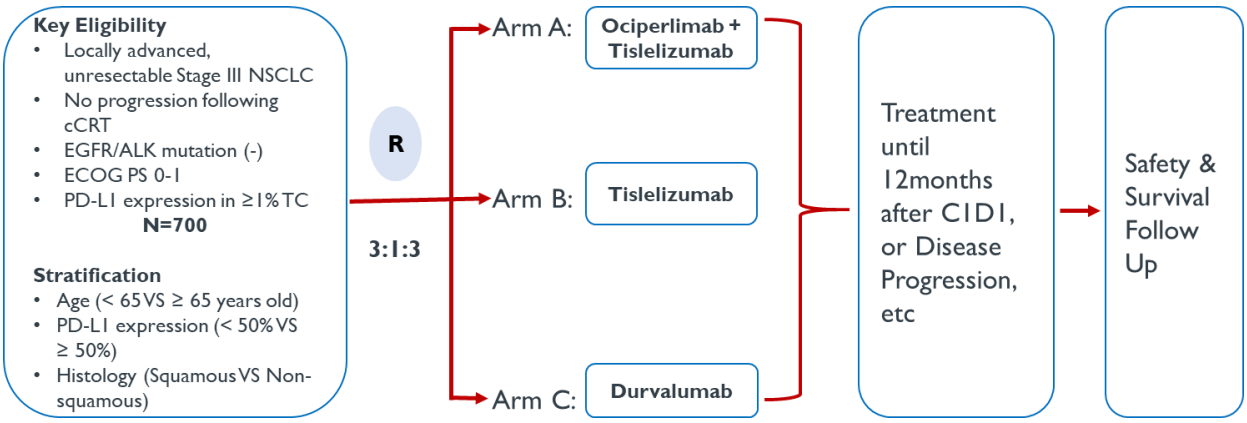
Safety and efficacy will be monitored by an Independent Data Monitoring Committee (IDMC). The IDMC may recommend study modification including early termination of the study due to safety concerns, or for evidence of compelling efficacy at a preplanned interim analysis. There is 1 planned interim analysis in this study for superiority. Full details of the interim analysis can be found in Section 9.8. The first IDMC safety assessment will be conducted after approximately 42 patients (approximately 18 patients each for Arm A and C, approximately 6 patients for Arm B) have been randomized and treated for ≥ 30 days from C1D1 or no later than 6 months after the first patient enrolled. The subsequent IDMC safety assessment will be conducted as determined by the IDMC, or approximately every 6 months thereafter. Full details of the IDMC procedures and processes can be found in the IDMC charter. Enrollment may continue during these IDMC safety reviews.

The study conduct will be overseen by a Steering Committee (SC) composed of selected investigators.

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

The study schema is summarized as below (Figure 1).

Figure 1: Study Schema



Abbreviations: *ALK*, anaplastic lymphoma kinase; C1D1, Cycle 1 Day 1; cCRT, concurrent chemoradiotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; *EGFR*, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death protein ligand-1; R, randomization; TC, tumor cells; TIGIT, T-cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain.

Note, the study was initially implemented with Protocol Amendment 1.0 (PA 1.0, dated on 16 Apr 2021). In the PA 1.0, patients with newly diagnosed, histologically confirmed, unresectable locally advanced NSCLC and evaluable PD-L1 expression all comers were enrolled; cCRT was given within the study. In Protocol Amendment 2.0 (PA 2.0, date 21 Apr 2022), the enrollment of the target population has been revised into patients with unresectable locally advanced NSCLC whose disease has not progressed after definitive, platinum-based cCRT and with PD-L1 expression on ≥ 1% of TC as assessed by the central lab; cCRT was given outside of the study; the eligibility criteria have been updated to reflect the study patient population changes. The enrollment of PA 1.0 will be stopped before PA 2.0 implementation. Patients recruited into the study prior to PA 2.0 will not be included in the primary and secondary analysis but would be included in exploratory analysis defined by PA 2.0.

For all patients randomized with PA 1.0 (defined as Concurrent Part of the study):

Patients who are still on study treatment will be informed of the substantial change from PA 1.0 to PA 2.0, the rationale for this change, and the following treatment options. Investigators will discuss the local available standard-of-care with the patients, and patients have the right to discontinue from the assigned study treatment and receive standard-of-care treatment outside of the study proposed by their physician. However, after discussion of benefit-risk of the study treatment with the treating physician, patients who are still willing to continue the assigned study treatment will be offered the assigned treatment until PA 1.0 defined treatment discontinuation point.

All patients (including those who choose to stop the assigned study treatment) are requested to continue the study for follow-up visits unless the study discontinuation criterion is met.

The care of patients enrolled with PA 1.0, including but not limited to treatment, safety management, and visits, will follow the details in Appendix 17, which are mostly consistent with those defined in PA 1.0 except for minor updates.

Study Assessments:

Tumor Assessment:

Tumor imaging will be performed ≤ 28 days before randomization. During the study, tumor imaging will be performed approximately every 9 weeks (± 7 days) from randomization, for the first 54 weeks and every 12 weeks (± 7 days) thereafter based on RECIST v1.1. 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.

Administration of study drugs will continue for up to 12 months, or until PD as assessed by investigator per RECIST v1.1, unacceptable toxicity, death, or another discontinuation criterion is met, whichever occurs first. Once PD is assessed by investigators, the IRC is required to complete central image review and convey the results to the investigator as soon as possible. If the investigator-assessed PD is NOT confirmed by IRC, the medical monitor will discuss the findings with the investigator and the study treatment is recommended to continue as long as this is considered to be in the best interest of the patient. In the situation where the investigator believes the patient must urgently begin subsequent systemic therapy without waiting for confirmation of PD by IRC, the investigator must contact the medical monitor to inform them of the plan to urgently discontinue study treatment.

A patient who discontinues study treatment for reasons other than PD assessed by the IRC (eg, toxicity, PD by the investigator but not confirmed by the IRC, completion of the 12-month treatment) will continue to undergo tumor assessments following the original plan until the patient experiences PD by

the IRC per RECIST v1.1, withdraws consent, is lost to follow-up, dies, or until the study terminates, whichever occurs first.

If at the investigator's discretion a patient could continue to benefit from ociperlimab and tislelizumab combination treatment or tislelizumab or durvalumab after PD assessed by the IRC or investigator per RECIST v1.1, the patient may continue their assigned treatment. The criteria must be met in order to treat patients who may continue to benefit from study treatment after PD are detailed in Section 3.4. The decision to continue study treatment beyond initial PD assessed by the IRC or investigator per RECIST v1.1 must be agreed upon with the medical monitor and documented in the study records.

Tumor assessments should continue as planned in patients receiving study drug(s) beyond initial PD per RECIST v1.1 assessed by the IRC or investigator. Tumor assessments in such patients should continue until study treatment discontinuation.

Safety assessment:

Patients will be evaluated for any adverse events (AEs) and serious adverse events (SAEs) (all severity grades, per NCI-CTCAE v5.0). After main informed consent has been signed but prior to the administration of the study drug(s), only SAEs should be reported. After initiation of the study drug(s), all AEs and SAEs, regardless of relationship to the study drug(s), will be reported until either 30 days after the last dose of study treatment or the initiation of a new anticancer therapy, whichever occurs first. Immune-related AEs (serious or non-serious) should be reported until 90 days after the last dose of ociperlimab, tislelizumab, or durvalumab, 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 and SAEs (only SAEs in case of screen failure subjects) 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. All AEs, treatment emergent or otherwise, will be presented in patient data listings. SAEs, deaths, TEAEs with Grade 3 or above, treatment-related TEAEs, TEAEs that led to treatment discontinuation, dose interruption or dose delay, and imAEs will be summarized.

Key Inclusion and Exclusion Criteria (Full Details in Section 4):

Key Inclusion criteria:

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

- Histologically or cytologically confirmed, unresectable locally advanced Stage III NSCLC (AJCC Cancer Staging Manual 2017, derived from International Association for the Study of Lung Cancer [IASLC]) prior to cCRT.
- Have completed ≥ 2 cycles of platinum-based chemotherapy concurrent with radiotherapy. For patients who are recovering from toxicities associated with the prior treatment, the first dose of study drug(s) may be delayed by up to 42 days from the end of the cCRT. It is recommended to screen the patients within 14 days after the completion of cCRT.
- Have not experienced PD following definitive, platinum-based cCRT.
- Agree to provide archival tissue (formalin-fixed paraffin-embedded block containing tumor [preferred] or approximately 6 to 15 freshly cut unstained slides) or fresh biopsy (if archival tissue is not available) for prospective central evaluation of PD-L1 levels and retrospective

analysis of other biomarkers. PD-L1 status will be assessed centrally in either a previously obtained archival tumor tissue or fresh tissue obtained from a biopsy collected prior to the first dose of cCRT via VENTANA PD-L1 (SP263) assay. Only patients with PD-L1 expression on ≥ 1% of TC are eligible.

Exclusion criteria:

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

- Prior therapy with an anti-programmed cell death-1(PD-1), anti-PD-L1, anti-PD-L2, anti-T-cell immunoglobulin and ITIM domain (TIGIT), or any other antibody or drugs specifically targeting T-cell co-stimulation or checkpoint pathways.
- Diagnosed with NSCLC that harbors an epidermal growth factor receptor (EGFR)-sensitizing mutation, anaplastic lymphoma kinase (ALK) gene translocation, ROS1 gene translocation, or RET gene rearrangement.
- Distant metastasis identified by imaging assessment and/or other examinations after definitive, platinum-based cCRT.
- Have received chemotherapy and radiotherapy with ≤ 1 cycle overlap for LA NSCLC.
- Have received systemic anticancer treatment besides the specified cCRT.
- Any unresolved toxicity CTCAE > Grade 2 from the prior cCRT. Patients with irreversible toxicity that is not reasonably expected to be exacerbated by study treatment may be included (eg, hearing loss) after consultation with the medical monitor.
- Any grade pneumonitis from prior cCRT.
- Active autoimmune diseases or history of autoimmune diseases that may relapse.
- Any active malignancy ≤ 2 years before the first dose of study drug(s) except for the specific cancer under investigation in this study and any locally recurring cancer that has been treated curatively.
- Any conditions that required systemic treatment with either corticosteroids (> 10 mg daily of prednisone [in Japan, prednisolone] or equivalent) or other immunosuppressive medication ≤ 14 days before the first dose of study drug(s).
- History of interstitial lung disease, non-infectious pneumonitis, or uncontrolled lung diseases including pulmonary fibrosis, acute lung diseases, etc.
- Infections (including tuberculosis infection, etc) that required systemic antibacterial, antifungal, or antiviral therapy within 14 days before the first dose of study drug(s).
- A history of severe hypersensitivity reactions to other monoclonal antibodies or history of hypersensitivity to the ingredients of tislelizumab or ociperlimab.
- Receipt of any immunotherapy (eg, interleukin, interferon, thymosin [not approved in Japan], etc) or any investigational therapies within 14 days or 5 half-lives (whichever is longer) before the first dose of study treatment.

Test Product, Dose and Mode of Administration

Ociperlimab, 300 mg/15 mL, 900 mg Q3W administered by intravenous infusion.

Tislelizumab, 100 mg/10 mL, 200 mg Q3W administered by intravenous infusion.

Durvalumab, 120 mg/2.4 mL (50 mg/mL) and 500 mg/10 mL (50 mg/mL), 10 mg/kg Q2W (or 1500 mg Q4W where the dosage has been approved by the local health authority) administered by intravenous infusion.

Statistical Methods

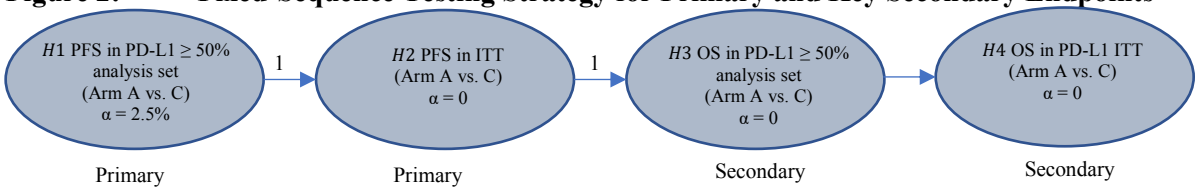
Analysis Sets

- The ITT Analysis Set includes all randomized patients with PD-L1 expression on ≥ 1% of TC. Patients will be analyzed according to the treatment assigned at randomization. This will be one of the primary analysis sets for demography and efficacy analyses.
- The PD-L1 ≥ 50% Analysis Set is a subset of the ITT Analysis Set including patients with PD-L1 ≥ 50% of TCs as determined using the VENTANA PD-L1 (SP263) assay. Patients will be analyzed according to the treatment assigned at randomization. This will be the other primary analysis set for demography and efficacy analyses.
- The Safety Analysis Set (SAS) includes all randomized patients who receive ≥ 1 dose of study drug(s). This will be the primary analysis set for all safety analyses.
- PD-L1 ≥ 50% Safety Analysis Set is a subset of the Safety Analysis Set including patients with PD-L1 ≥ 50%. This will be analysis set for the safety analyses in patients with PD-L1 ≥ 50%.
- The PK Analysis Set includes all patients who receive any dose of any component of study drugs per the protocol and for whom any postdose PK data are available.
- The Immunogenicity Analysis Set includes all patients who receive any dose of any component of study drugs and for whom both baseline antidrug antibody (ADA) and at least 1 postbaseline ADA result are available.

Analysis Methods:

The familywise type I error will be strongly controlled at 1-sided level of 0.025. PFS analysis in Arm A versus Arm C will be carried out in the PD-L1 ≥ 50% Analysis Set first. A formal statistical test of PFS in the ITT Analysis Set will be performed only if the PFS analysis in the PD-L1 ≥ 50% Analysis Set is statistically significant favoring ociperlimab + tislelizumab. If the null hypothesis for PFS in Arm A versus Arm C in the ITT Analysis Set is rejected, the secondary endpoint OS in the PD-L1 ≥ 50% and ITT Analysis Sets in Arm A versus Arm C will be tested sequentially. There is 1 interim analysis planned at around 75% information fraction of PFS events in each analysis set across Arm A and Arm C. See Figure 2 for the fixed-sequence testing strategy diagram of the study.

Figure 2: Fixed-Sequence Testing Strategy for Primary and Key Secondary Endpoints



Abbreviations: ITT: Intent-To-Treat; PFS, progression-free survival; OS, overall survival.

Primary Efficacy Analysis

PFS comparison in Arm A versus Arm C in the PD-L1 ≥ 50% and ITT Analysis Sets:

The null hypothesis to be tested: HR (A vs C) ≥ 1

against the alternative: HR (A vs C) < 1

The primary efficacy analyses of PFS will be performed using a stratified log-rank test, stratified by stratification factors at randomization (age, PD-L1 expression [for the ITT Analysis Set only], and histology) in the PD-L1≥ 50% and ITT analysis sets.

PFS distribution will be estimated using the Kaplan-Meier method in the PD-L1 ≥ 50% and ITT Analysis Sets.

The median PFS and the cumulative probability of PFS at every 3 months including PFS-6m and PFS-12m if estimable, will be calculated for each treatment arm and presented with 2-sided 95% CIs. Kaplan-Meier survival probabilities for each arm will be plotted over time.

The treatment effect will be estimated by fitting a Cox regression model to the PFS including the treatment arm as a factor and stratification factors at randomization (age, PD-L1 expression [in the ITT Analysis Set only], and histology) as strata. From this model, the HR of PFS will be estimated and presented with a 2-sided 95% CI.

Key Secondary Efficacy Analysis

OS comparison in Arm A versus Arm C in the PD-L1 ≥ 50% and ITT Analysis Sets:

The null hypothesis to be tested: HR (A vs C) ≥ 1

against the alternative: HR (A vs C) < 1

The primary efficacy analyses of OS will be performed using a stratified log-rank test, stratified by stratification factors at randomization (age, PD-L1 expression [for ITT only] and histology). OS test in the PD-L1 ≥ 50% and ITT Analysis Sets will be conducted sequentially at a 1-sided significance level of 0.025, after both null hypotheses of PFS are rejected.

OS distribution will be estimated using the Kaplan-Meier method in the PD-L1 ≥ 50% and ITT Analysis Sets. The treatment effect will be estimated by fitting a Cox regression model to OS, similar to the analyses in PFS.

Other Secondary Efficacy Analysis

ORR by both the IRC and investigators per RECIST v1.1 in both the PD-L1 ≥ 50% and ITT Analysis Sets will be summarized, in Arm A versus Arm C. Two-sided 95% CIs of ORR will be calculated using the Clopper-Pearson method in the ITT Analysis Set. The odds ratio for ORR between treatment arms

will be calculated using the Cochran-Mantel-Haenszel (CMH) method adjusting for stratification factors at randomization (age, PD-L1 expression [for the ITT Analysis Set only], and histology), and its 2-sided 95% CIs will be calculated. The Mantel-Haenszel common risk difference in ORR will be estimated, with its 95% CI constructed by a normal approximation and Sato's variance estimator. The proportion for each of the response categories including CR will be presented by treatment arm.

DOR will be analyzed among the responders in the PD-L1 ≥ 50% and ITT Analysis Sets based on assessment by the IRC and investigators, in Arm A versus Arm C. All the censoring rules for PFS primary analysis would be applied to DOR as well.

TTDM by both the IRC and investigators per RECIST v1.1 in the PD-L1 ≥ 50% and ITT Analysis Sets in Arm A versus Arm C will be analyzed.

HRQoL will be analyzed and compared in Arm A versus Arm C in the PD-L1 ≥ 50% and ITT Analysis Sets via the postbaseline scores of EORTC QLQ-C30's Global Health Status/QoL (GHS), functional scales and symptom scales and symptoms single item scores, EORTC QLQ-LC13's index scores and symptoms scales and single item scores, and EQ-5D-5L descriptive scale scores as well as the Visual Analogue Scale (VAS) scores. Observed values and changes from baseline will be summarized using descriptive statistics.

A mixed model repeated measure (MMRM) will be performed using prespecified PRO endpoints of global health status/QoL (GHS), physical function, and fatigue domains of QLQ-C30, and dyspnea, coughing, hemoptysis and pain in chest, pain in arms and shoulders and peripheral neuropathy domains of QLQ-LC13 to evaluate and compare changes from baseline in Arm A and Arm C in pre-specified key clinical visits Week 25 and 43.

Time to deterioration in the PRO endpoint scales will be estimated using the Kaplan-Meier method, with predefined deterioration thresholds, in Arm A and Arm C.

PD-L1 and TIGIT expression will be evaluated before, after study treatment, or at disease progression/reoccurrence, and their association with clinical efficacy will be assessed when appropriate and data allow.

Safety Analysis

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

Verbatim description of AEs will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA) terms and graded per NCI-CTCAE v5.0. All treatment-emergent AEs (TEAEs) will be summarized. A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug(s) up to 30 days following last dose of study drug(s) or initiation of a new anticancer therapy, whichever occurs first. Immune-mediated AEs (imAEs) will be identified from all AEs that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug(s) and up to 90 days from the last dose of study drug(s), regardless of whether or not the patient starts a new anticancer therapy. If an imAE occurs outside of the above mentioned TEAE window, it will not be classified as a TEAE. All imAEs will be reported separately. All AEs, treatment emergent or otherwise, will be presented in patient data listings. SAEs, deaths, ≥ Grade 3 TEAEs, treatment-related TEAEs, TEAEs that led to treatment discontinuation or dose modification, and imAEs will be summarized.

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

Pharmacokinetic Analyses

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

Additional PK analyses may be conducted as appropriate.

Sample Size

The sample size calculation is based on the number of events regarding primary efficacy analyses of PFS between Arm A and Arm C for comparisons in both the PD-L1 ≥ 50% and ITT Analysis Sets. Exponential distribution is assumed for PFS. To demonstrate efficacy with regard to PFS, the estimates of the number of events required are based on the following assumptions:

- The randomization ratio for Arm A versus Arm B versus Arm C is 3:1:3.
- A steady-state enrollment rate of 20 patients per month and an enrollment ramp-up duration of 12 months.
- PFS evaluation dropout rate of 5% per 12 months.
- The prevalence of patients with PD-L1 ≥ 50% of TC in the ITT Analysis Set is approximately 50%. Enrollment of patients with PD-L1 < 50% on TCs might be stopped, if necessary, to ensure that the population reflects the natural PD-L1 expression prevalence.
- Sequential testing procedure is implemented to control the overall alpha at a 2.5% one-sided level. PFS analysis in Arm A versus Arm C in the PD-L1 ≥ 50% Analysis Set will be performed first, and PFS analysis in Arm A versus Arm C in the ITT Analysis Set will be carried out only if the PFS analysis in the PD-L1 ≥ 50% Analysis Set yields a statistically significant between-arm difference favoring Arm A.
- One interim analysis is planned when approximately 75% of the final PFS events have occurred for each PFS primary endpoint, using Lan-DeMets O'Brien-Fleming approximation spending function.
- Median PFS in Arm C within both the PD-L1 ≥ 50% and ITT Analysis Sets is 24.9 months.

Table 1 below summarizes the statistical assumption and power in the sample size calculation in Arm A and Arm C; and the total sample size of the study would be 700.

Table 1: Statistical Assumptions, Sample Size, and Power

1-sided alpha	Analysis Set	HR (A vs C)	mPFS in A	mPFS in C	Accrual Duration	Sample size in A+C	# Events at FA in A+C	Power

0.025	PD-L1 ≥ 50%	0.6	41.5	24.9	41.3	300	141	85.2%
0.025	ITT	0.7	35.6	24.9	41.3	600	288	85.1%

Abbreviation: A: Arm A; C: Arm C; FA: final analysis, mPFS: median Progression-free Survival.

Sample size and power is calculated using EAST (Version 6.5) and R (Version 4.1.2).

Interim Analyses

There is 1 planned interim analysis for this study, using Lan-DeMets O'Brien-Fleming approximation spending function (Lan and DeMets 1983).

The interim analysis of PFS primary analysis will be performed at a later time when the target number of events in either the PD-L1 ≥ 50% or in ITT Analysis Sets is reached, which is approximately 106 events in the PD-L1 ≥ 50% Analysis Set and 216 events in the ITT Analysis Set (75% of the target number of PFS events in each analysis set) in Arm A and Arm C, approximately 45 months after the first patient randomized. The final analysis of PFS will take place after approximately 141 and 288 PFS events have been observed in the 2 analysis sets, respectively, and approximately 56 months after the first patient is randomized. Event number and stopping boundaries in p-value for primary analyses of PFS are shown in Table 2. The boundaries will be updated according to the actual numbers of events in the interim and final analyses, using the above pre-specified alpha spending function.

Table 2: Event Number and Testing Boundaries of Interim Analyses and Final Analysis

Analysis Set	**Type of Analysis**	**# Events**	**p-value for Efficacy IA**	**Approximate HR Threshold for Efficacy**	**Probability of Crossing Efficacy Boundary Under Alternative Hypothesis**
PD-L1 ≥ 50%	IA	106	0.0097	0.635	61.5%
	FA	141	0.0221	0.713	85.2%
ITT	IA	216	0.0097	0.727	61.1%
	FA	288	0.0221	0.789	85.1%

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
ADAs	antidrug antibodies
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BOR	best overall response
CD	cluster of differentiation
CK	creatine kinase
CK-MB	creatine kinase cardiac muscle isoenzyme
CR	complete response
cCRT	concurrent chemoradiotherapy
CT	computed tomography
ctDNA	circulating tumor DNA
DLT	dose-limiting toxicity
DOR	duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture (system)
EOT	End-of-Treatment (Visit)
EVs	Extracellular vesicle
FDG	fluorine-18 [F-18] fluorodeoxyglucose
GCP	Good Clinical Practice
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBV	hepatitis B virus
HCV	hepatitis C virus
ICF	informed consent form
IEC	Independent Ethics Committee
imAE	immune-related adverse event
IRB	Institutional Review Board
ITT	Intent-to-Treat (Analysis Set)
LA NSCLC	locally advanced non-small cell lung cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MSI	microsatellite instability
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NK	natural killer
BGB-A1217	Ociperlimab
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PD	progressive disease
PD-1	programmed cell death protein-1
PD-L1	programmed cell death protein-ligand 1
PET	positron-emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response

Abbreviation	Definition
PTV	planning target volume
PVR	poliovirus receptor
RECIST	Response Evaluation Criteria in Solid Tumors
RT	radiotherapy
SAE	serious adverse event
SOC	System Organ Class
SpO_2	percutaneous arterial oxygen saturation
T3	Triiodothyronine
T4	Thyroxine
TEAE	treatment-emergent adverse event
TC	tumor cells
TIGIT	T-cell immunoglobulin and ITIM domain
BGB-A317	tislelizumab
TIL	tumor-infiltrating lymphocyte
TMB	tumor mutation burden
TTDM	time to death or distant metastasis
ULN	upper limit of normal

1. INTRODUCTION

1.1. Background Information

1.1.1. Background Information on Non-Small Cell Lung Cancer

Lung cancer is the most common cancer worldwide with approximately 2.3 million new diagnoses and 1.8 million deaths in 2020, which corresponds to the highest incidence among cancers and the highest cancer-related mortality. In 2020, an estimated 477,534 new cases of lung cancer were diagnosed in Europe, 253,537 in North America, and 1.3 million in Asia. Approximately 1.1 million deaths in Europe, 384,176 in North America, and 159,641 in Asia were related to lung cancer (World Health Organization 2020). In China in 2015, lung cancer was 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 (Chen et al 2016). Worldwide, lung cancer is one of the most common types of cancers and it is more common in men than women, representing 16.8% of all cancers in men and 8.8% of all cancers in women. Non-small cell lung cancer (NSCLC) originates from the epithelial cells of the lung and accounts for 80% to 85% of all lung cancers. There are 3 main histological subtypes of NSCLC, adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, which constitute 40%, 25%, and 10% of lung cancers, respectively (PDQ Adult Treatment Editorial Board [NSCLC] 2020).

The prognosis for patients with lung cancer is relatively poor. However, the prognosis depends greatly on the stage at which the cancer is detected. Currently, lung cancer staging is performed worldwide according to the eighth edition of tumor, lymph node, and metastasis (TNM) Classification of Malignant Tumors (American Joint Committee on Cancer [AJCC] 2017). If lung cancer is diagnosed in its earliest stages, cure is possible through surgery or chemoradiotherapy. Unfortunately, cases of lung cancer are most often detected relatively late in the illness, which makes a cure less likely. About one-third of patients with NSCLC present with locally advanced (LA) Stage III disease, which includes patients with involvement of locoregional mediastinal lymph nodes or mediastinal organs, etc., with 5-year survival rates of 36% for Stage IIIA, 26% for Stage IIIB, and 13% for Stage IIIC (American Cancer Society 2018). Some patients with Stage IIIA disease can undergo resection and have improved survival compared with those with unresectable tumors.

1.1.2. Current Treatment of Locally Advanced, Unresectable Non-Small Cell Lung Cancer

1.1.2.1. Concurrent Chemoradiotherapy

Concurrent chemoradiotherapy (cCRT) has been the backbone of previously untreated standard of care for patients with unresectable LA Stage III NSCLC (National Comprehensive Cancer Network [NCCN] 2021; European Society for Medical Oncology [ESMO] guidelines 2020). Combined modality treatment with chemotherapy and radiation was shown to be superior to radiotherapy (RT) alone (Rolland et al 2007). The positive outcomes for cCRT have been shown in multiple studies. A meta-analysis from the mid-1990s using updated data on individual patients from 52 randomized clinical trials (NSCLC Collaborative Group 1995) and a subsequent meta-analysis of platinum-based chemotherapies from 1764 patients (Aupérin et al 2006) demonstrated that adding sequential or concurrent chemotherapy to radiotherapy improved

survival in patients with LA NSCLC. When concurrent versus sequential chemoradiotherapy was compared directly in data for 1205 patients from 6 clinical trials, there was a significant benefit with cCRT on overall survival (OS) (HR 0.84; 95% confidence interval [CI]: 0.74, 0.95; p = 0.004), with an absolute benefit of 5.7% (from 18.1% to 23.8%) at 3 years and 4.5% (from 10.6% to 15.1%) at 5 years. For progression-free survival (PFS), the HR was 0.90 (95% CI: 0.79, 1.01; p = 0.07). Concurrent treatment decreased locoregional progression (HR 0.77, [95% CI: 0.62, 0.95], p = 0.01), although distant progression was not different between concurrent treatment and sequential treatment (HR 1.04, [95% CI: 0.86, 1.25], p = 0.69). Concurrent chemoradiotherapy increased acute esophageal toxicity, but there was no significant difference regarding acute pulmonary toxicity (Aupérin et al 2010).

Induction and consolidation chemotherapy have also been studied to improve outcomes for patients with unresectable Stage III NSCLC. Induction chemotherapy showed high incidence for neutropenia with no improvement in OS (Vokes et al 2007). Consolidation chemotherapy has also not been shown to have any impact on OS compared with cCRT alone (Tsujino et al 2013). Therefore, cCRT is considered a standard of care for patients with unresectable LA Stage III NSCLC.

Multiple chemotherapy regimens have been used in combination with radiation for the treatment of Stage III NSCLC. Most regimens are combinations of cisplatin with either pemetrexed, etoposide, vinblastine, or vinorelbine. Few studies have been conducted comparing these chemotherapy regimens, and no chemotherapy regimen has been clearly demonstrated to be better than others. Of the chemotherapy doublets that have comparative evidence, cisplatin in combination with either pemetrexed or etoposide has been studied in Stage III NSCLC population. The PROCLAIM multinational trial (Senan et al 2016) endeavored to establish whether cisplatin plus pemetrexed is superior to cisplatin plus etoposide when given concurrently with standard RT at 60-66 Gray (Gy), followed by a consolidation phase. OS was not superior with cisplatin plus pemetrexed than with cisplatin plus etoposide (median OS, 26.8 months versus 25.0 months; p = 0.831). Both arms exhibited low incidences of Grade 3 or 4 pneumonitis (< 3%), with no significant differences between arms in treatment discontinuations due to drug-related adverse events (AEs) or drug-related deaths. The PROCLAIM study therefore establishes that outcomes with cisplatin with either pemetrexed or etoposide when used in cCRT with conventional RT are similar. As an alternative to cisplatin in combination with pemetrexed doublet chemotherapy regimen, carboplatin is recommended by the NCCN guidelines as well (NCCN 2021). Carboplatin with paclitaxel given weekly during radiation is another cCRT option recommended by the NCCN guidelines (NCCN 2021). This regimen has been evaluated in several studies (Belani et al 2005; Vokes et al 2007; Yamamoto et al 2010; Bradley et al 2015) and is commonly used as the treatment for unresectable LA Stage III NSCLC in the US and other countries globally. Weekly carboplatin plus paclitaxel was used as the chemotherapy regimen in the RTOG 0617 study that evaluated standard versus high doses of radiation to be given concurrently with chemotherapy (Bradley et al 2015). A Phase 3 trial of concurrent thoracic radiation in unresectable Stage III NSCLC found that weekly carboplatin plus paclitaxel was superior to second-generation chemotherapy regimens such as mitomycin plus vindesine, weekly irinotecan plus carboplatin, or cisplatin, or carboplatin as a single agent with RT (Yamamoto et al 2010). Of note, in the Phase 3 PACIFIC study, which evaluated the anti-programmed cell death protein ligand-1 (anti-PD-L1) inhibitor durvalumab compared with placebo after cCRT, carboplatin with paclitaxel was the most common chemotherapy regimen

chosen by the investigator, administered to 33.9% of the patients in the intent-to-treat (ITT) population (Antonia et al 2017). Besides carboplatin plus paclitaxel, cisplatin plus docetaxel was also recommended by the Chinese Society of Clinical Oncology (CSCO) Guidelines (CSCO 2021) and Japan Lung Cancer Society (JLCS) Guidelines (JLCS 2020). For patients > 70 years of age, the JLCS also recommended a single-agent carboplatin regimen (JLCS 2020).

In an attempt to improve outcomes, higher doses of radiation have been studied in combination with chemotherapy. Approximately 60 Gy in 1.8- to 2-Gy fractions has been previously established as the standard conventional radiation dose in Stage III NSCLC in the RTOG 7301 study (Bradley et al 2015). Subsequently, the RTOG 0617 study has shown that 74 Gy regimen showed no superiority to 60 Gy regimen in efficacy (Bradley et al 2015). In fact, the median OS was 28.7 months for 60 Gy cohort versus 20 months for 74 Gy cohort. Local relapse rates were also lower in the 60 Gy cohort. Thus, the accepted standard of care is approximately 60 Gy in 2-Gy fractions (NCCN 2021; ESMO 2020).

Of note, the aforementioned patients with Stage III NSCLC who were treated with cCRT regimens as standard of care include patients with epidermal growth factor receptor (EGFR) sensitizing mutations or anaplastic lymphoma kinase (ALK) gene translocations. (NCCN 2021; ESMO 2020). EGFR and ALK targeted agents are not utilized as upfront therapy for patients with Stage III NSCLC and are still being investigated in trials such as the Radiation Thoracic Oncology Group (RTOG) 1306 study (Berman and Simone 2016).

1.1.2.2. Anti-PD-1/PD-L1 Therapy

Anti-PD-1 therapy has emerged as an effective treatment for patients with tumors expressing varying degrees of PD-L1 (Hanna et al 2017). Anti-PD-1 and anti-PD-L1 therapies target the programmed death receptor pathway of T lymphocytes, and this checkpoint has been found to be activated in cancers, allowing tumors to evade the host immune system.

1.1.2.2.1. PACIFIC Study

In the LA NSCLC setting, the potential benefits of checkpoint blockade when given sequentially following completion of cCRT have been demonstrated in the PACIFIC trial (Antonia et al 2018; Gray et al 2020). This is a global Phase 3 trial of the anti-PD-L1 therapy, durvalumab, compared with placebo as consolidation therapy following 2 or more cycles of platinum-based chemotherapy administered concurrently with RT without progression in patients with unresectable Stage III NSCLC. Patients who were able to complete chemoradiotherapy and who remained progression free at the timepoint of completion of chemoradiotherapy were randomized within 1 to 42 days after completing at least 2 cycles of platinum-based chemotherapy (containing etoposide, vinblastine, vinorelbine, a taxane, or pemetrexed) administered concurrently with definitive RT of 54 to 66 Gy. The trial demonstrated that median PFS (mPFS) was significantly longer with durvalumab than that with placebo (mPFS, 16.9 months versus 5.6 months; stratified HR for disease progression or death, 0.55 [95% CI: 0.45, 0.68]) (Spigel et al 2022). Enrollment was not restricted to any threshold for the level of PD-L1 expression, and results showed that the PFS benefit was observed in both baseline PD-L1 expression subgroups (HR 0.44 [95% CI: 0.29, 0.67] for PD-L1 ≥ 25% and 0.64 [95% CI: 0.48, 0.86] for PD-L1 < 25%). The safety profile of durvalumab in this population was consistent with that of other immunotherapies and with its known safety profile as monotherapy

in patients with more advanced disease (Stage IIIB or IV NSCLC) (Antonia et al 2018). Although the incidences of some adverse events of any cause, including pneumonitis or radiation pneumonitis, were increased with both durvalumab and placebo in this study, this was expected after definitive chemoradiotherapy. In addition, pneumonitis or radiation pneumonitis in patients who received durvalumab was mostly low grade, and the incidence of clinically important grade 3 or 4 events was well balanced between groups (3.4% in the durvalumab group and 2.6% in the placebo group) and lower than that in other studies in the same disease context (Hanna et al 2008; Gandara et al 2003).

In February 2018, based on the results of the PACIFIC study, durvalumab was approved by the United States Food and Drug Administration (US FDA) for the treatment of patients with unresectable Stage III NSCLC whose cancer had not progressed after concurrent chemoradiotherapy (US FDA News Release 2018), followed by the approvals from Pharmaceuticals and Medical Devices Agency in Japan (PMDA) (AZ news 2018), the European Medicines Agency (EMA) (ESMO 2020), the National Medical Products Association (NMPA) of China (AZ news 2019), etc. However, the approval of EMA was restricted to baseline PD-L1 ≥ 1% population based on a post hoc subgroup analysis result that OS benefit varies from PD-L1 expression (HR 0.53 [95% CI: 0.36, 0.77] for PD-L1 ≥ 1% and 1.36 [95% CI, 0.79 to 2.34] for PD-L1 < 1%). Durvalumab thus became the first immunotherapy approved to reduce the risk of disease progression in this setting and led to a change in the treatment for Stage III patients, with the recommendation as consolidation therapy after concurrent chemoradiotherapy (ESMO 2020, NCCN 2021). As of the data cutoff date of 11 Jan 2020, with the median follow-up duration of 34.2 months, the median OS with durvalumab was 47.5 months versus 29.1 months with placebo (stratified HR 0.72 [95% CI: 0.59, 0.89]). The 12-, 24-, 36-, 48-, and 60-month OS rates with durvalumab and placebo were 83.1% versus 74.6%, 66.3% versus 55.3%, 56.7% versus 43.6%, 49.6% versus 36.3%, and 42.9% versus 33.4%, respectively (Spigel et al 2022).

With the improvement in PFS and OS, the PACIFIC study set a new benchmark of standard-of-care for LA Stage III NSCLC; however, there are still some caveats to this study. There is some uncertainty as to whether all patients enrolled in this study underwent appropriate evaluations for optimal staging, and whether this trial included patients with occult Stage IV disease (Copur et al 2018).

In the post hoc subgroup analyses of the PACIFIC study, patients with EGFR-sensitizing mutations showed an inferior trend of PFS (HR 0.82 [95% CI: 0.39, 1.71]) and OS (HR 0.85 [95% CI: 0.37, 1.97]) than those without EGFR-sensitizing mutations (PFS HR 0.52 [95% CI: 0.41, 0.65]) and OS (HR 0.66 [95% CI: 0.52, 0.84]), although the number of enrolled patients with EGFR-sensitizing mutations was relatively small (29 in the durvalumab arm and 14 in the placebo arm). Patients with nonsquamous histology seemed to benefit more in terms of PFS than those with squamous histology (HR 0.48 [95% CI: 0.37, 0.63] versus HR 0.71 [95% CI: 0.54, 0.94]), with the difference in the OS subgroup analysis HR 0.62 (95% CI: 0.47, 0.81) versus HR 0.82 (95% CI: 0.61, 1.09); the conclusion of benefit by subgroup of histology is to be further explored in a well pre-specified stratified study (Spigel et al 2022).

1.1.2.2.2. GEMSTONE-301 Study

Following PACIFIC, Phase 3 Study GEMSTONE-301 also provided evidence that the patients with unresectable stage III NSCLC who had not progressed from CRT could benefit from

consolidation anti-PD-L1 therapy, sugemalimab, versus placebo up to a treatment duration of 24 months. As of 8 Mar 2021, with the median follow-up 14.3 (6.4 to 19.4) months and 13.7 (7.1 to 18.4) months in the sugemalimab arm and placebo arm, respectively; mPFS was significantly longer with sugemalimab than that with placebo (9.0 months [95% CI: 8.1,14.1] vs 5.8 months [95% CI: 4.2, 6.6]; stratified HR was 0.64 [95% CI: 0.48, 0.85], p = 0.0026). OS data is not mature yet at the data cutoff date. Preliminary OS data showed that median OS was not reached (NR) (95% CI: NR, NR) in the sugemalimab arm versus 24.1 months (95% CI: 16.5, NR) in the placebo arm; stratified HR was 0.44 [95% CI: 0.27, 0.73], p = 0.0009). Different from PACIFIC Study, the GEMSTONE-301 Study included around one third of patients who received sequential CRT (sCRT) as well. The stratified subgroup analysis revealed the benefit trend for both cCRT and sCRT subgroups: for the cCRT subgroup, the mPFS of sugemalimab versus placebo was 10.5 versus 6.4 months (HR 0.66 [95% CI: 0.44, 0.99]); for the sCRT subgroup, the mPFS of sugemalimab versus placebo was 8.1 months versus 4.1 months (HR 0.59 [95% CI: 0.39, 0.91]). In terms of safety profile, Grade 3 or 4 treatment-related adverse events occurred in 22 (9%) of 255 patients in the sugemalimab arm versus 7 (6%) of 126 patients in the placebo arm; the most common being pneumonitis or immune-mediated pneumonitis (7 [3%] of 255 patients in the sugemalimab arm vs 1 [< 1%] of 126 patients in the placebo arm). Treatment-related serious adverse events occurred in 38 (15%) patients in the sugemalimab arm and 12 (10%) in the placebo arm. Treatment-related deaths were reported in 4 (2%) of 255 patients (pneumonia in 2 patients, pneumonia with immune-mediated pneumonitis in 1 patient, and acute hepatic failure in 1 patient) in the sugemalimab arm, and none in the placebo arm (Zhou et al 2022). The safety profile of sugemalimab in the GEMSTONE-301 Study was tolerable and consistent with the known safety profile of anti-PD-1/PD-L1 following CRT in this setting (Antonia et al 2018).

1.1.2.3. Unmet Medical Needs

Until recently, cCRT was the standard of care for patients with LA NSCLC with reported 5-year survival rates between 16% and 32%. In 2018, supported by the result of PACIFIC study (Antonia et al, 2017), durvalumab was approved by the US FDA (US FDA News Release 2018), PMDA (AZ news 2018),and China NMPA (AZ news 2019) for the treatment of patients with locally advanced, unresectable NSCLC whose disease did not progress after cCRT irrespective of PD-L1 expression. In Europe, durvalumab was approved by EMA for patients with locally advanced, unresectable NSCLC whose disease did not progress after cCRT with PD-L1 expression on ≥ 1% of tumor cells (TC) (ESMO 2020).

However, most patients still suffered from disease recurrence with an 18-month PFS rate of 44.2%, and most patients still died with a 57% survival rate at 3 years in the PACIFIC study (Antonia et al, 2017). As such, there is still a high unmet medical need for this patient population.

1.2. Compound

1.2.1. Ociperlimab as a TIGIT Inhibitor

Immune surveillance plays a critical role in cancer prevention. However, in situations where tumors develop resistance mechanisms to suppress the host immune system, tumors eventually grow out of control (Schreiber et al 2011; Swann and Smyth 2007). One such resistance

mechanism is the up-regulation of immune checkpoint receptors, such as programmed cell death-1 (PD-1) and T-cell immunoglobulin and ITIM domain (TIGIT) (Johnston et al 2014; Chauvin et al 2015; Pardoll 2012).

Ociperlimab is a humanized immunoglobulin G (IgG) 1 monoclonal antibody binding to TIGIT under clinical development for the treatment of human malignancies.

TIGIT (also known as VSIG9, VSTM3, or WUCAM) is a 26 kDa type I transmembrane glycoprotein and an immune checkpoint receptor, a member of the poliovirus receptor (PVR)/nectin family that plays an important role in promoting T-cell exhaustion in both chronic viral infections and tumor escape from immune surveillance (Yu et al 2009; Boles et al 2009; Stanietsky et al 2009; Levin et al 2011; Johnston et al 2014). TIGIT was initially discovered in a genomic search for genes specifically expressed in T cells that had a protein domain that consisted of inhibitory signaling motifs. The genes and cDNAs coding for TIGIT were cloned and characterized in mouse and human (Yu et al 2009). Mature human TIGIT contains 223 amino acid residues (National Center for Biotechnology Information 2018). Its extracellular domain consists of amino acid residues 1 through 120, and the transmembrane domain and cytoplasmic C-terminal tail comprises residues 121 through 223.

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

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

TIGIT is also expressed on $FoxP3^+$ regulatory T (Treg) cells, especially in tumor tissues (Joller et al 2014; Kurtulus et al 2015). TIGIT-positive Treg cells demonstrated greater suppressive functions when compared with TIGIT-negative Tregs, with higher expression of effector molecules, such as IL-10, granzymes, and Fgl2 (Joller et al 2014). A high TIGIT/CD226 ratio in Tregs is associated with increased Treg frequencies in tumors and poor clinical outcomes upon immune checkpoint blockade (Fourcade et al 2018). Some studies have also shown that TIGIT suppresses immune responses mediated by dendritic cells by binding with PVR, especially in enhancement of IL-10 production and inhibition of IL-12 production (Yu et al 2009).

As an immune “checkpoint” molecule, TIGIT initiates inhibitory signaling in immune cells when engaged by its ligands, PVR (CD155) and poliovirus receptor–related 2 (PVR-L2) (CD112, or

nectin-2). These ligands are primarily expressed on antigen-presenting cells and tumor cells (Casado et al 2009; Stanietsky et al 2009; Yu et al 2009; Levin et al 2011). The binding affinity of TIGIT to PVR (equilibrium dissociation constant [K_D]: ~1 nM) is much higher than to PVR-L2 and whether the TIGIT: PVR-L2 interaction is functionally relevant in mediating inhibitory signals remains to be determined. The co-stimulatory receptor, CD226, binds to the same ligands with lower affinity (K_D: ~100 nM) but delivers positive signals and enhances the cytotoxicity of T cells and NK cells (Bottino et al 2003; Stanietsky et al 2009). High affinity binding of TIGIT to PVR could compete off CD226-PVR interaction, thereby reducing the activation of T cells or NK cells (Stanietsky et al 2009).

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

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

In mouse models, Fc with effector functions is critical for TIGIT antibody-mediated antitumor activity (College of American Pathologist (CAP) guidelines 2018; Argast et al 2018; Leroy et al 2018). In CT26.WT mouse colon cancer model, anti-mouse TIGIT antibody of mIgG2a isotype (antibody-dependent cellular cytotoxicity enabling) demonstrated potent antitumor activity as monotherapy or in combination with anti-PD-1 antibody. In contrast, anti-TIGIT antibody with Fc devoid of effector functions did not show any of the antitumor efficacies in the same model, indicating that Fc-mediated effector functions are required for TIGIT antibody-mediated antitumor effects. Additionally, the observed efficacy was associated with an increased activity of effector T cells ($CD8^+$ and $CD4^+$) and also with Treg depletion within the tumor microenvironment. Argast and colleagues (College of American Pathologist (CAP) guidelines 2018; Argast et al 2018) also observed that effector functions were critical for TIGIT

antibody-induced in vivo efficacy. Waight and colleagues (Waight et al 2018), reported the interaction of anti-TIGIT with FcγR on antigen-presenting cells enhanced antigen-specific T cell responses and antitumor activity.

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

1.2.1.1. Nonclinical

1.2.1.1.1. Pharmacology

Ociperlimab binds to the extracellular domain of human TIGIT with high specificity and affinity (K_D = 0.135 nM), as demonstrated by target-binding assays and surface plasmon resonance characterization. It competitively blocks TIGIT binding to PVR. In in vitro cell-based assays, ociperlimab "in a dose dependent manner": "consistently and dose dependently enhances the functional activities of activated human peripheral blood mononuclear cells (PBMCs)". Additionally, ociperlimab has shown antitumor activities 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 enhanced tumor growth inhibition compared with either therapy alone.

Ociperlimab has the constant region of a wild-type human IgG1 to enable the Fc-mediated effector functions. Ociperlimab has demonstrated competent binding to complement 1q (C1q) and all FcγRs, including FcγRI, FcγRIIA, FcγRIIB, and FcγRIIIA, in in vitro binding assays, and induces antibody-dependent cellular cytotoxicity against TIGIT-overexpressing cell line, but no antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity against primary T cells in cell-based assays.

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

1.2.1.1.2. 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 TIGIT amino acid sequence, binding affinity, and efficacy studies. Cynomolgus monkeys were the most relevant species based on the homology sequence of TIGIT, although it demonstrates a relatively lower ociperlimab-binding affinity compared to human TIGIT (with EC50 756-fold weaker). Ociperlimab does not bind to mouse TIGIT due to the significant sequence divergence between human and mouse TIGIT; however, ociperlimab demonstrates a comparable binding affinity in

TIGIT receptor occupancy assays with $CD3^+$ splenocytes from humanized TIGIT knock-in mice compared to $CD3^+$ human PBMCs (with EC50 of 48.8 ng/mL versus 63.2 ng/mL, respectively). In addition, ociperlimab shows significant inhibition of GL261 tumor growth in humanized TIGIT knock-in mice at a dose of 0.4 mg/kg and above via weekly intraperitoneal dosing.

The toxicity and safety profile of ociperlimab was characterized in a 4-week repeat dose toxicology study in humanized TIGIT knock-in mice and a 13-week repeat dose toxicology study in cynomolgus monkeys. These toxicity studies were conducted following Good Laboratory Practice regulations. Furthermore, ociperlimab was evaluated in a 4-week repeat dose study in humanized TIGIT knock-in mice with subcutaneous MC-38 tumors. The dose levels spanned from the intended human therapeutic doses to 10-fold higher in the 4-week mouse studies and 20-fold higher in the 13-week monkey study. 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. The tissue cross-reactivity was evaluated in the normal frozen tissues from humans. The cytokine release responses were also evaluated using fresh human PBMCs.

No apparent toxicity was noted in humanized mice after repeated dosing of ociperlimab at either 5 or 50 mg/kg weekly for 4 weeks, nor in monkeys following repeated dosing at 10, 30, or 100 mg/kg once every 2 weeks for 13 weeks. The toxicokinetic profile was characterized in both the mouse and monkey studies and the systemic exposure appeared to be dose proportional with no gender difference in either study. A trend of accumulation was noted after repeated doses in mice, however, 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 in these studies. Immunogenicity with positive antidrug antibodies (ADAs) against ociperlimab was noted in several mice dosed at 5 and 50 mg/kg over the 4 weeks; however, with the exception of one animal with strong ADA response at 5 mg/kg dose, most of these animals showed weak ADA signal or were proved to have false positive results. In monkeys, positive 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 during the recovery period, at 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 concentration-time curve [AUC]) or toxicity assessment.

The tissue cross reactivity of ociperlimab was evaluated in frozen normal human tissues using an immunohistochemistry method, with appropriate positive and negative controls. 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 2019) and sensitivity of the immunohistochemistry method.

No significant increase in cytokine release was observed from an in vitro cytokine release assay following treatment of non-activated PBMCs with ociperlimab when compared to human IgG. The results suggested that ociperlimab had potentially low risks of causing acute cytokine release syndrome.

Overall, no apparent toxicity was noted in the monkey or transgenic mice toxicity studies. No unexpected tissue cross reactivity was found in human or monkey tissues. The toxicokinetic profile was well characterized with dose-proportional increases in systemic exposure without

apparent accumulation or sex difference. Immunogenicity was observed without apparent immunotoxicity or effect on the systemic exposure. The no observed adverse effect level (NOAEL) of ociperlimab was 50 mg/kg in the 4-week mouse study and 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 Investigator's Brochure for detailed information regarding toxicology studies.

1.2.1.2. Clinical Experience

1.2.1.2.1. Clinical Experience From Other TIGIT Inhibitors

To date, Phase 1 and 2 clinical studies have been initiated for several TIGIT antibodies. Initial clinical data include data released for OncoMed's Etigilimab (Mettu et al 2022), Merck's vibostolimab (Golan et al 2018; Niu et al 2020; Ahn et al 2020), Genentech/Roche's tiragolumab (Cho et al 2021), and iTeos Therapeutics' EOS-448 (Van den Mooter et al 2021).

The combination of anti-PD-1/PD-L1 antibody and anti-TIGIT antibody is further being explored in NSCLC. The most compelling data currently available includes the study of tiragolumab (anti-TIGIT Ab) in combination with atezolizumab and the study of vibostolimab (anti-TIGIT Ab) monotherapy or combined with pembrolizumab.

The CITYSCAPE study is randomized Phase 2 trial designed to assess preliminary efficacy between tiragolumab in combination with atezolizumab versus atezolizumab. It showed impressive improvement in both ORR and PFS in the ITT (tumor proportion score [TPS] ≥ 1%) population compared to atezolizumab alone, with an even greater magnitude of improvement seen in the PD-L1 TPS ≥ 50% subgroup. An analysis of the safety of tiragolumab plus atezolizumab showed the combination were well tolerated. The safety profile was similar to atezolizumab alone, and while immune-mediated adverse events (imAEs) were more frequent with tiragolumab plus atezolizumab, most imAEs were primarily Grade 1-2 (mostly IRR and rash) and were manageable. Based on these observed efficacy and safety results, Genentech/Roche is conducting an ongoing Phase 3 study (SKYSCRAPER-01) in first-line treatment for patients with NSCLC expressing PD-L1 TPS ≥ 50% (NCT04294810) (Rodriguez-Abreu et al 2020; Cho et al 2021).

The study of Vibostolimab (anti-TIGIT antibody) (NCT02964013) in combination with pembrolizumab enrolled patients with advanced metastatic NSCLC who were untreated or had experienced disease progression on prior therapies. This combination showed encouraging antitumor activity and tolerable safety. For patients who were untreated or previously treated with chemotherapy but naïve to anti-PD-1/PD-L1 therapy, the ORR rate was 24%, whereas limited activity was observed for vibostolimab alone and vibostolimab in combination with pembrolizumab (ORR 2% and 5% respectively) in patients with NSCLC whose disease had already progressed on prior anti-PD-1/PD-L1 therapy in (Niu et al 2020; Ahn et al 2020). Though it is acknowledged that this result should be interpreted with caution due to the small sample size, the result indicated that vibostolimab plus pembrolizumab are efficacious in anti-PD-1/PD-L1 naïve NSCLC patients.

All the data above support further development of anti-TIGIT antibody in combination with existing therapeutic modalities.

1.2.1.2.2. Preliminary Safety

As of the data cutoff date of 28 July 2021, a total of 133 patients received ociperlimab treatment in Study AdvanTIG-105 and Study AdvanTIG-202. In Study AdvanTIG-105, 900 mg ociperlimab was administered as monotherapy in 9 patients in Cohort 1A (dose verification in China). A total of 76 patients have been enrolled and treated with ociperlimab at doses of 50, 150, 450, 900, or 1800 mg in combination with tislelizumab 200 mg and have cleared the dose-limiting toxicity (DLT) period without DLTs in the Phase 1 dose-escalation part of the study. There were 25 patients from the Dose-Expansion Cohorts 1, 2, 4, 6, 7, and 9 were treated with ociperlimab in combination with tislelizumab 200 mg and chemotherapies. In Study AdvanTIG-202, 23 patients have been treated with ociperlimab at a flat dose of 900 mg in combination with tislelizumab 200 mg in Cohort 1. Ociperlimab continues to appear to be safe and well-tolerated up to and including at the 900 mg dose level.

As of the data cutoff date of 28 July 2021, of the 133 patients in the Safety Analysis Set, 117 (88%) patients experienced ≥ 1 treatment-emergent adverse events (TEAEs) and 77 (57.9%) patients experienced ≥ 1 TEAEs related to ociperlimab. TEAEs ≥ Grade 3 in severity were reported in 53 of 133 (39.8%) patients, and 8 (6.0%) patients experienced ≥ Grade 3 TEAEs related to ociperlimab. Serious TEAEs were reported in 47 (35.3%) patients, and 7 (5.3%) of these were considered related to ociperlimab. TEAEs leading to ociperlimab discontinuation were reported in 9 (6.8%) patients. TEAEs leading to death were reported in 6 (4.5%) patients, but none of these events were assessed as related to ociperlimab. No TEAEs were considered to be DLT events.

Please refer to the Ociperlimab Investigator's Brochure for detailed safety information.

1.2.1.2.3. Clinical Pharmacology

Preliminary pharmacokinetic (PK) data are available from a total of 51 patients treated with ociperlimab at the 50 mg, 150 mg, 450 mg, 900 mg, and 1800 mg dose levels in combination with tislelizumab 200 mg in the dose-escalation and dose-verification portions of Study AdvanTIG-105. Ociperlimab serum concentrations decreased in a biexponential manner after treatment administration. The mean elimination half-life ranged from 7.1 to 10.5 days. In Cycle 1, ociperlimab exposures (area under the concentration-time curve [AUC] and maximum observed serum concentration [C_{max}]) increased approximately dose-proportionally from the 50 mg to the 1800 mg dose levels.

As of 23 July 2021, peripheral TIGIT receptor occupancy data were available for 32 enrolled patients treated with ociperlimab at the 50 mg (n = 1), 150 mg (n = 3), 450 mg (n = 6), 900 mg (n = 16), and 1800 mg (n = 6) dose levels in Study BGB-900-105. Complete TIGIT receptor occupancy (100%) was observed on CD8, CD4, and Treg cells in peripheral blood at all the tested dose levels.

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

1.2.1.2.4. Efficacy

The first-in-human Study AdvanTIG-105 evaluating the efficacy of ociperlimab in combination with tislelizumab in advanced solid tumors is still ongoing. Efficacy data from Study AdvanTIG-105 (as of the data cutoff date of 21 February 2021) were presented at the 2021 meeting of the American Society of Clinical Oncology. A total of 26 evaluable patients received ociperlimab (dose range: 50 to 900 mg) in combination with tislelizumab 200 mg. One patient was treated with ociperlimab 50 mg, 3 with ociperlimab 150 mg, 6 with ociperlimab 450 mg, and 16 with ociperlimab 900 mg. Partial response (PR) was observed in 2 patients (1 receiving ociperlimab 450 mg and 1 receiving ociperlimab 900 mg). Stable disease was observed in 9 patients (1 receiving ociperlimab 150 mg, 3 receiving ociperlimab 450 mg, and 5 receiving ociperlimab 900 mg). The longest duration of stable disease was 54 weeks (a patient receiving ociperlimab 150 mg). Three patients (2 receiving ociperlimab 450 mg and 1 receiving ociperlimab 900 mg) had a > 30% reduction in target lesions. More follow-up data will be updated in further updates to the Ociperlimab Investigator's Brochure.

1.2.2. Tislelizumab as a PD-1 Inhibitor

1.2.2.1. Pharmacology

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

Tislelizumab acts by binding to the extracellular domain of human PD-1 with high specificity as well as high affinity (dissociation constant [KD] = 0.15 nM). It competitively blocks binding efforts by both PD-L1 and programmed cell death protein ligand-2 (PD-L2), thus inhibiting PD-1-mediated negative signaling in T cells. In in vitro cell-based assays, tislelizumab was observed to enhance the functional activity of human T cells and pre-activated primary PBMCs consistently and dose-dependently. Tislelizumab has also demonstrated in-vivo antitumor activity in several allogeneic xenograft models, in which PBMCs were co-injected with human cancer cells (A431 [epidermoid carcinoma]) or tumor fragments (BCCO-028 [colon cancer]) into immunocompromised mice.

Tislelizumab is an IgG4-variant antibody to gamma fragment crystallizable region (Fc) receptors (FcγR) such as FcγRI and FcγRIIIA, and it has very low binding affinity to C1q, a subunit of complement 1. In vitro assays with tislelizumab suggest either low or no antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), or complement-dependent cytotoxicity (CDC) effects in humans (Labrijn et al 2009). Tislelizumab was specifically engineered to abrogate these potential mechanisms of T-cell clearance and potential resistance to anti-PD-1 therapy.

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

1.2.2.2. 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. Tissue cross-reactivity was evaluated in normal frozen tissues from both

humans and monkeys. The cytokine release assays were conducted using fresh human whole blood cells. The pivotal toxicology studies were conducted following Good Laboratory Practice (GLP) regulations. The single-dosing regimens spanned from the intended human doses to 10-fold higher than the maximum of the intended human doses, and the repeated-dosing regimens spanned to 3-fold higher than the maximum of the intended human doses. Cynomolgus monkey was the only relevant species based on the target sequence homology and binding activity.

Overall, no apparent toxicity was noted in mice or monkey toxicity studies. No tissue cross-reactivity was found in either human or monkey tissues, nor was any effect on cytokine release observed in the human whole-blood assay. The toxicokinetic profile was well characterized, with dose proportional increases in systemic exposure without apparent accumulation or sex difference. Immunogenicity was observed without apparent immunotoxicity or effect on the systemic exposure. The No Observed Adverse Effect Level (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-301.

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

1.2.2.3. Clinical Pharmacology

Based on pooled data from 2596 patients across 12 clinical studies, the PK of tislelizumab was best characterized using a 3-compartmental linear population PK model with linear clearance mechanisms. No time-varying clearance was observed in tislelizumab PK. The C_{max} and AUC increased in a nearly dose-proportional manner from 0.5 mg/kg to 10 mg/kg. The terminal $t_{1/2}$ was estimated to be approximately 23.8 days, and the steady state is expected to be reached in 12 weeks.

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

1.2.2.4. Prior Clinical Experience With Tislelizumab

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

1.2.2.4.1. Pooled Safety Assessment of Tislelizumab

1.2.2.4.1.1. Pooled Safety Assessment of Monotherapy Studies

As of 20 May 2021, 1992 patients with solid tumors had been treated with tislelizumab monotherapy in 7 clinical studies, and 158 patients treated in 3 hematologic malignancy studies.

Solid tumor studies with tislelizumab monotherapy include the following: BGB-A317_Study_001 (Phase 1a/1b study in Advanced Solid Tumors), BGB-A317-102 (Phase 1/2 study in advanced solid tumors), BGB-A317-204 (Phase 2 study in locally advanced or metastatic urothelial bladder cancer), BGB-A317-208 (Phase 2 study in previously treated unresectable hepatocellular carcinoma), BGB-A317-209 (Phase 2 study in previously-treated locally advanced unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch

repair deficient [dMMR] solid tumors), BGB-A317-302 (Phase 3 study in advanced unresectable/metastatic esophageal squamous cell carcinoma), and BGB-A317-303 (Phase 3 study in non-small cell lung cancer).

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

Pooled Demographics and Baseline Characteristics

As of 20 May 2021, a pooled monotherapy analysis was conducted to provide a comprehensive review of the tislelizumab safety profile. Patients included in this analysis (N = 1992) had a median age of 60.0 years with 72.1% of them being male. Median duration of treatment exposure was 4.1 months (range: 0.1 to 41.5 months) and median duration of study follow-up was 11.5 months (range: 0.1 to 58.9 months).

Treatment-Related Adverse Events

Of the 1992 patients in the solid tumor group within the pooled monotherapy studies, 1391 (69.8%) experienced ≥ 1 treatment-related TEAE. The most commonly occurring TEAEs (≥ 5% of patients) assessed as related to tislelizumab irrespective of grade were aspartate aminotransferase (AST) increased (250 patients, 12.6%), ALT increased (242 patients, 12.1%), hypothyroidism (197 patients, 9.9%), anaemia (186 patients, 9.3%), rash (159 patients, 8.0%), pruritus (142 patients, 7.1%), fatigue (138 patients, 6.9%), decreased appetite (115 patients, 5.8%), blood bilirubin increased (111 patients, 5.6%), and diarrhoea (103 patients, 5.2%).

Further, 269 of the 1992 patients (13.5%) 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 (25 patients, 1.3%), and ALT increased and anaemia (20 patients, 1.0% each).

Treatment-Emergent and Related Serious Adverse Events

A total of 706 of the 1992 patients (35.4%) in the solid tumor group within the pooled monotherapy studies experienced ≥ 1 treatment-emergent serious adverse events (SAE). The most commonly occurring treatment-emergent SAEs (irrespective of relationship to study drug) were pneumonia (95 patients, 4.8%), pneumonitis (33 patients, 1.7%), dysphagia (23 patients, 1.2%), and pleural effusion and pyrexia (20 patients, 1.0% each).

A total of 209 of the 1992 patients (10.5%) experienced ≥ 1 tislelizumab-related treatment-emergent SAE. The most common treatment-emergent SAE deemed related to tislelizumab was pneumonitis (31 patients, 1.6%). All other tislelizumab-related treatment-emergent SAEs occurred in ≤ 1% of patients.

Immune-Mediated Adverse Events

Of the 1912 patients in the adjudicated solid tumor group within the pooled monotherapy studies, 286 patients (15.0%) experienced ≥ 1 imAE of any grade. The most commonly occurring imAEs of any grade were hypothyroidism (115 patients, 6.0%), pneumonitis (41 patients, 2.1%), immune-mediated lung disease (14 patients, 0.7%), rash (13 patients, 0.7%), and ALT increased and hyperthyroidism (12 patients, 0.6% each). A total of 73 patients (3.8%) had ≥ 1 imAE that was ≥ Grade 3 in severity. The most commonly occurring imAEs that were ≥ Grade 3 in severity

were pneumonitis (15 patients, 0.8%) and interstitial lung disease (7 patients, 0.4%) (Tislelizumab Investigator's Brochure).

Infusion-Related Reactions

Infusion-related reactions, including high-grade hypersensitivity reactions, following tislelizumab administration are common.

Of the 1992 patients in the solid tumor group within the pooled monotherapy studies, 58 patients (2.9%) experienced ≥ 1 infusion-related reaction of any grade. The most commonly occurring infusion-related reactions of any grade were infusion-related reactions (28 patients, 1.4%); pyrexia (17 patients, 0.9%); rash (5 patients, 0.3%); and hypotension, nausea, and pruritus (3 patients, 0.2% each). There were 5 patients (0.3%) with ≥ Grade 3 infusion-related reactions. The most common ≥ Grade 3 infusion-related reaction was infusion-related reaction (2 patients, 0.1%). All other ≥ Grade 3 infusion-related reactions occurred in 1 patient each.

Fatal Adverse Events

A total of 163 patients (8.2%) within the solid tumor studies had died within 30 days of the last dose of study treatment as of 20 May 2021. The causes of death for these patients were adverse events (54 patients, 2.7%), disease under study (52 patients, 2.6%), disease progression (50 patients, 2.5%), and other (7 patients, 0.4%).

1.2.2.4.1.2. Pooled Safety Assessment of Combination Studies With Chemotherapy

A pooled analysis of combination studies with tislelizumab and chemotherapy was conducted to provide a comprehensive safety assessment separately from other combination therapy studies. (Tislelizumab Investigator's Brochure). As of 20 May 2021, a total of 544 patients were treated with tislelizumab in combination with chemotherapy in 4 studies, including BGB-A317-205 (Phase 2 study in esophageal, gastric, or gastroesophageal junction carcinoma), BGB-A317-206 (Phase 2 study in lung cancer), BGB-A317-304 (Phase 3 study in nonsquamous NSCLC), and BGB-A317-307 (Phase 3 study in squamous NSCLC).

Of the 544 patients in the pooled chemotherapy combination studies, 543 (99.8%) experienced ≥ 1 TEAE and 472 patients (86.8%) experienced ≥ 1 TEAE considered related to tislelizumab treatment. A total of 192 patients (35.3%) experienced at least one ≥ Grade 3 TEAE considered related to tislelizumab. SAEs were reported in 225 patients (41.4%) and 104 patients (19.1%) experienced a serious tislelizumab-related TEAE. A total of 24 patients (4.4%) experienced a TEAE leading to death.

1.2.2.4.2. Efficacy Assessment of Tislelizumab

As of 20 May 2021, efficacy data in patients with NSCLC are available from 6 of the ongoing monotherapy studies in solid tumors, BGB-A317_Study_001, Study BGB-A317-102, Study BGB-A317-203, Study BGB-A317-204, Study BGB-A317-207, and Study BGB-A317-208 (Tislelizumab Investigator's Brochure; Lu et al 2020; Wang J et al 2020).

1.2.2.4.2.1. Efficacy Assessment of Monotherapy Studies

Study BGB-A317_Study_001

Study BGB-A317_Study_001 is a 2-stage study consisting of a Phase 1a dose-escalation (0.5 to 10 mg/kg) and dose-finding component with 3 parts (2 and 5 mg/kg given either once every 2 weeks or Q3W, and a fixed dose of 200 mg given Q3W) to establish the maximum tolerated dose (MTD), if any, and a recommended Phase 2 dose (RP2D), which is followed by a Phase 1b component to investigate efficacy in select tumor types at the RP2D to further evaluate safety and tolerability of tislelizumab. Indication-specific cohorts included esophageal (EC), gastric (GC), hepatocellular (HCC), and non-small cell lung (NSCLC) cancer. Efficacy data from BGB-317_Study_001 were published in Desai et al 2020 (data cutoff May 2019).

The patients with NSCLC (n = 49) enrolled to Study_001 were treated at the 2 or 5 mg/kg dose every 2 weeks and every 3 weeks dosing schedules (97% received the 5 mg/kg dose every 3 weeks). Among these 49 patients with NSCLC, the ORR was 12.2% ([95% CI: 4.63%, 24.77%], all PR), the disease control rate (DCR) (CR + PR + SD) was 59.2% (95% CI: 44.21%, 73.0%), and the clinical benefit rate (CBR) (CR + PR + ≥ 24 weeks of SD) was 34.7% (95% CI: 21.67%, 49.64%). The median time to initial response was 91.0 days (range: 62 to 189 days). As of the cutoff date of 26 August 2020, the median duration of response (DOR) for these patients was not reached; 6 of 49 patients with an objective response to tislelizumab had an ongoing response at the time of cutoff date. The median PFS was 4.2 months (95% CI: 2.1, 7.8 months). The median OS was 11.5 months (95% CI, 9.3 to 32.8 months).

Study BGB-A317-102

Study BGB-A317-102 is a non-randomized, Phase 1/2 study of tislelizumab monotherapy in Chinese patients with advanced solid tumors. Phase 1 includes a dose verification substudy and a substudy of PK evaluation of the products derived from 2 manufacturing processes and scales. Phase 2 evaluates the activity and safety of tislelizumab at its RP2D of 200 mg given Q3W in indication-specific expansion cohorts. Efficacy data from Study BGB-A317-102 were published in Shen et al 2020 (data cutoff 01 December 2018).

Among the 56 patients with NSCLC enrolled to Study 102 and treated with tislelizumab 200 mg Q3W IV, the ORR (CR + PR) was 17.9% (95% CI, 8.9% to 30.4%, all PR), the DCR (CR + PR + SD) was 55.4% (95% CI, 41.5% to 68.7%), and the CBR (CR + PR + ≥ 24 weeks of SD) was 30.4% (95% CI, 18.8% to 44.1%). As of the cutoff date of 31 May 2020, median DOR for these patients was not reached; 10 of 56 patients with an objective response to tislelizumab had an ongoing response. The median PFS was 4.0 months (95% CI, 2.1 to 8.1 months). The estimated 6-month and 12-month PFS event-free rates were 40% (95% CI, 30% to 50%) and 30% (95% CI, 20% to 40%), respectively. The median OS was not yet evaluable. The estimated 6-month and 12-month OS event free rates were 70% (95% CI, 60% to 80%) and 60% (95% CI, 40% to 70%), respectively.

Study BGB-A317-303

RATIONALE 303 is a Phase 3 randomized, open-label, multicenter global clinical trial to evaluate the efficacy and safety of tislelizumab compared with docetaxel in the second- or third-line setting in patients with LA or metastatic NSCLC whose disease has progressed on a prior platinum-based chemotherapy.

A total of 805 patients were randomized 2:1 to either the tislelizumab arm or the docetaxel arm in 10 countries. The study met its primary endpoint of OS in the ITT population and in patients with PD-L1 expression ≥ 25% population at interim analysis with a data cutoff date of 10 Aug 2020. Compared with docetaxel, OS was significantly longer with tislelizumab (stratified HR 0.64 [95% CI, 0.527 to 0.778]; p < 0.0001); median OS was 17.2 months and 11.9 months in tislelizumab and docetaxel arm, respectively. Benefit of OS in patients with PD-L1 expression ≥ 25% receiving tislelizumab versus docetaxel was also observed (stratified HR 0.52 [95% CI, 0.384 to 0.713]; p < 0.0001); median OS was 19.1 months and 11.9 months in tislelizumab and docetaxel arm, respectively. Among the secondary endpoints in ITT population, median PFS was reported as 4.1 months versus 2.6 months (HR 0.64, p < 0.0001); ORR was 21.9% versus 7.1%; DCR was 55.7% versus 42.2%; and DOR was 13.5 months versus 6.2 months (HR 0.31, p < 0.0001) for the tislelizumab and docetaxel arm, respectively (Zhou et al 2021).

1.2.2.4.2.2. Efficacy Assessment of Combination Studies With Chemotherapy

Study BGB-A317-206

Study BGB-A317-206 is a multi-cohort, Phase 2 study of tislelizumab in combination with standard chemotherapy as first-line treatment in Chinese patients with LA or metastatic lung cancer. In the cohort of nonsquamous NSCLC, patients were treated with tislelizumab 200 mg plus pemetrexed-cisplatin or carboplatin (n = 16). In the cohort of squamous NSCLC, patients were treated with tislelizumab 200 mg plus paclitaxel-cisplatin or carboplatin (n = 15). In the cohort of squamous NSCLC, patients were treated with tislelizumab plus gemcitabine-cisplatin or carboplatin (n = 6). Across treatment arms, confirmed ORRs ranged from 43.8% to 80%. The median PFS time ranging from 7.0 months to not reached (NR). OS data is not yet mature for all cohorts until data cutoff of 30 June 2019 (Wang et al 2020).

Study BGB-A317-304

Study BGB-A317-304 is a Phase 3, 2-arm, randomized, multicenter study to compare the efficacy and safety of tislelizumab combined with cisplatin or carboplatin plus pemetrexed (Arm A) versus cisplatin or carboplatin plus pemetrexed (Arm B) as first-line treatment in 334 patients with stage IIIB or IV nonsquamous NSCLC (confirmed EGFR wildtype and without ALK rearrangement).

A total of 334 patients were randomized, and Study BGB-A317-304 met its primary endpoint of PFS at interim analysis with a data cutoff date of 23 January 2020. Compared with the chemotherapy-only arm, PFS as assessed by the IRC was significantly longer with tislelizumab in combination with chemotherapy (stratified HR = 0.645 [95% CI, 0.462 to 0.902]; p = 0.0044); median PFS by IRC was 9.7 months in Arm A and 7.6 months in Arm B. Similar median PFS results were observed for Arm A versus Arm B (HR = 0.561 [95% CI, 0.411 to 0.767]; p = 0.0001) when assessed by investigators. With more than 75% of the patients censored in both arms, median OS was not reached in either arm. Higher ORR by IRC (57.4% versus 36.9%) and DCR by IRC (89.2% versus 81.1%) were observed in the tislelizumab plus chemotherapy arm compared with chemotherapy alone. Among 128 responders with tislelizumab combination therapy, median DOR by IRC was 8.5 months (95% CI, 6.80 to 10.58 months); in the 41 patients who achieved a response with chemotherapy alone, median DOR by IRC was 6.0 months (95% CI, 4.99 months to not evaluable). At time of data cutoff, > 62% of patients were censored in each arm, suggesting DOR by IRC was not fully mature in either arm (Lu et al 2020).

Study BGB-A317-307

Study BGB-A317-307 is a phase 3, 3-arm, open-label, randomized, multicenter study to compare the efficacy and safety of tislelizumab combined with carboplatin and either paclitaxel (Arm A) or nab-paclitaxel (Arm B) versus paclitaxel plus carboplatin alone (Arm C) as first-line treatment in 360 patients with stage IIIB or IV squamous NSCLC.

A total of 360 patients were randomized, and Study BGB-A317-307 has been fully enrolled and met its primary endpoint of PFS at interim analysis with a data cutoff date of 06 December 2019. Median PFS was 7.6 months (95% CI, 6.0 to 9.8 months) and 7.6 months (95% CI, 5.8 to 11.0 months) in Arms A and B, respectively, both of which were significantly longer than the median PFS in Arm C (5.5 months, [95% IC, 4.2 to 5.7]). With a median study follow-up time of 8.6 months, median OS had not been reached. ORR was 73% (95% CI, 63.6% to 80.3%) and 75% (95% CI, 66.0% to 82.3%) in Arms A and B, respectively, and higher compared with Arm C (50% [95% CI, 40.4% to 58.8%]). DCR was 88% (95% CI, 80.2% to 92.8%) and 91% (95% CI, 84.1% to 95.3%) in Arms A and B, respectively, and higher compared with Arm C (80% [95% CI, 71.9% to 86.9%]). Similarly, DOR was longer in both tislelizumab-containing arms compared with chemotherapy alone (8.2 months [95% CI, 5.0 to NE] for Arm A, 8.6 months [95% CI, 6.3 months to NE] for Arm B and 4.2 months [95% CI, 2.8 to 4.9 months] for Arm C) (Wang J et al 2020).

1.3. Study Rationale

As described earlier, despite the wealth of evidence supporting TIGIT's role in promoting tumor immune tolerance, the available clinical data of TIGIT blockade alone hasn't shown an effective antitumor response, compared with the increased antitumor response signal observed with anti-TIGIT plus anti-PD-1/PD-L-1 combination (see Section 1.2.1). Therefore, the clinical development of ociperlimab focuses on rational combinations, such as with tislelizumab. Taking this into account, the study of the combination of ociperlimab and tislelizumab is designed to evaluate the effect of ociperlimab in combination with tislelizumab in maximizing the patient's potential therapeutic benefit and to characterize the safety and efficacy of this combination.

1.3.1. Rationale for the Dose Selection

1.3.1.1. Rationale for the Selection of Ociperlimab Dose

The ociperlimab dose of 900 mg once every 3 weeks (Q3W) combined with tislelizumab 200 mg Q3W was selected as the RP2D for further investigations based on clinical safety, tolerability, PK, and pharmacodynamic data from the ongoing Phase 1/1b Study AdvanTIG-105.

Complete TIGIT receptor occupancy was observed in circulating T cells in peripheral blood at all the tested doses of ociperlimab in Study AdvanTIG-105. However, the correlation between TIGIT receptor occupancy in the periphery and in tumor tissues is unknown. In a previous Phase 1 study of tiragolumab, another anti-TIGIT antibody, complete peripheral receptor occupancy was reached at the 30 mg dose level, but the clinical dose of 600 mg was determined as the RP2D, which was 20-fold higher than 30 mg (Bendell et al 2020). Similarly, although complete peripheral receptor occupancy was observed at the 50 mg dose level of ociperlimab, the RP2D of 900 mg is approximately 20-fold higher than the dose of 50 mg. As of 12 May 2021, a total of 3 patients were assessed to have a confirmed partial response, 1 patient

each in the 450 mg, 900 mg, and 1800 mg cohorts. Ociperlimab exposure in all 3 patients with a partial response was consistent with that expected at the 900 mg dose level. The confirmed DCR observed in the 450 mg, 900 mg, and 1800 mg cohorts were 60%, 64.3% and 60%, respectively.

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

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

1.3.1.2. Rationale for the Selection of Tislelizumab Dose

The dose of 200 mg intravenously Q3W was selected based on safety, efficacy, and PK assessments in the first-in-human study BGB-A317_Study_001. A wide range of doses were investigated in this study, including 2 mg/kg and 5 mg/kg on schedules of once every 2 weeks (Q2W) and once every 3 weeks (Q3W). For the Q3W schedule, a fixed dose of 200 mg was also investigated, and it was ultimately selected for the following reasons:

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

Compared with a once every 2 weeks schedule, a once every 3 weeks schedule allows for more convenient integration with common chemotherapeutic regimens and increases patient convenience.

1.3.2. Rationale for Combination of Ociperlimab and Tislelizumab in the Treatment of Non-Small Cell Lung Cancer

Upregulation of TIGIT expression in TILs has been reported in NSCLC (Tassi et al 2017). Blockade of a TIGIT receptor alone or in combination with PD-1/PD-L1 blockade has been shown both in vitro and in vivo to rescue functionally "exhausted" T-cells (Johnston et al 2014; Chauvin et al 2015). In mouse models, TIGIT blockade in combination with anti-PD-1/PD-L1 antibodies demonstrated significantly better antitumor efficacy than either monotherapy (Johnston et al 2014; Dixon et al 2018). Preclinical studies have also indicated that platinum-

based chemotherapy elicits tumor $CD8^+$ T-cell infiltration and sensitizes tumors to immune checkpoint blockade therapy, which results in a durable control of cancer (Pfirschke et al 2016).

The Cancer Genome Atlas (TCGA) dataset showed upregulation of TIGIT and PVR expression in tumor samples than in normal samples in both adenocarcinoma lung cancer and squamous cell lung cancer. The TCGA RNAseq dataset showed that patients with NSCLC with low expression of PVR have longer survival than those with high PVR expression ($p = 0.0082$). This is consistent with the important role of the TIGIT/PVR signaling pathway in the immune tolerance to cancer (Section 1.2.1). In addition, increased expression of TIGIT and PD-1 in human NSCLC suggests potential synergy of combination of an anti-TIGIT antibody and anti-PD-1 antibody can have a potential synergic effect (Solomon and Garrido-Laguna 2018).

Clinically, treatment with anti-TIGIT antibody in combination with anti-PD-1/PD-L1 therapy has the potential to be more efficacious than anti-PD-1/PD-L1 in metastatic NSCLC without prior checkpoint inhibitor therapy. The combination of tiragolumab plus atezolizumab resulted in an ORR of 38.8%, PFS of 5.6 months and OS of 23.2 months ORR of 20.6%, PFS of 3.9 months and OS of 14.5 months with placebo plus atezolizumab in first-line Stage IV NSCLC patients with PD-L1 TPS ≥ 1% (Cho et al 2021). Similarly, the vibostolimab plus pembrolizumab combination resulted in an unconfirmed and confirmed ORR of 29% and 24%, respectively, in patients who were untreated or had been treated with at least 1 line of platinum-containing chemotherapy who had not previously received anti-PD-1/PD-L1 therapy. However, in patients with NSCLC who had experienced prior anti-PD-1/PD-L1 treatment, both the unconfirmed and confirmed ORR for vibostolimab plus pembrolizumab combination were 5%, and were not superior to the ORR with vibostolimabalone (unconfirmed and confirmed ORR 7% and 2% respectively) (Niu et al 2020; Ahn et al 2020).

The safety profiles of both the tiragolumab plus atezolizumab and vibostolimab plus pembrolizumab combinations were tolerable. The imAE rate with the tiragolumab plus atezolizumab combination was higher than that with placebo plus atezolizumab (76.1% versus 47.1%), but most of the imAEs were manageable Grade 1 or 2 events of infusion-related reactions, including rash. the incidence rate of TRAE of any grade was slightly higher with the vibostolimab plus pembrolizumab combination than with vibostolimab monotherapy, (71% versus 59%); however, the incidence rate of ≥ Grade 3 TRAE was similar for the 2 arms (15% versus 13%), indicating that most of the TRAEs in the combination arm are Grade 1 or 2 (Cho et al 2021; Rodriguez-Abreu et al 2020; Niu et al 2020; Ahn2020).

As mentioned in Section 1.2.1.2.2, Study AdvanTIG-105 showed the preliminary safety for ociperlimab plus tislelizumab was consistent with that of other anti-TIGIT plus anti-PD-1/PD-L1 treatment, with no MTD reached and no DLT events occurred during the treatment period for each dose level. Ociperlimab plus tislelizumab appeared to be well-tolerated at all administered dose levels. Adding ociperlimab to tislelizumab will likely further enhance the overall clinical activity of the anti-PD-1/PD-L1 therapy and prevent progression/disease-related death in LA Stage III NSCLC in the front line.

1.3.3. Rationale for Durvalumab as the Comparator

The rationale for using durvalumab as the comparator is based on the PFS and OS benefit demonstrated in the PACIFIC study (Antonia et al 2018; Gray et al 2020; Faivre-Finn et al 2020). The study reported that median PFS was significantly longer with durvalumab than with

placebo (median PFS 16.9 months versus 5.6 months, stratified HR for disease progression or death 0.55), with an acceptable safety profile in the durvalumab group (Antonia et al 2018). In February 2018, durvalumab was approved by the US FDA for the treatment of patients with unresectable Stage III NSCLC whose cancer had not progressed after chemoradiation (US FDA News Release 2018); this approval was also followed by approvals from the PMDA (AZ news 2018), EMA (ESMO 2020), NMPA (AZ news 2019), etc. This immunotherapy thus became the first treatment approved to reduce the risk of NSCLC progression in this setting and led to a change in the treatment for patients with Stage III disease, with the recommendation that anti-PD-L1 consolidation therapy be offered after cCRT (NCCN 2021). As of the data cutoff date of 11 Jan 2020, with the median duration of follow-up of 34.2 months, the median OS with durvalumab was 47.5 months versus 29.1 months with placebo (stratified HR = 0.72 [95% CI, 0.59 to 0.89]). The 12-, 24-, 36-, 48-, and 60-month OS rates with durvalumab and placebo were 83.1% versus 74.6%, 66.3% versus 55.3%, 56.7% versus 43.6%, 49.6% versus 36.3%, and 42.9% versus 33.4%, respectively (Spigel et al 2022).

1.3.4. Biomarker Strategy Rationale

Biomarker analyses including but not limited to the analyses of PD-L1 expression, TIGIT pathway molecules, gene expression profiling (GEP), circulating tumor DNA (ctDNA), tumor mutation burden (TMB), microsatellite instability (MSI), gene mutation profiles, extracellular vesicle (EVs) and TILs will be performed in the study treatment of ociperlimab plus tislelizumab and tislelizumab or durvalumab monotherapy, to explore the predictive, prognosis biomarkers and potential mechanisms of resistance.

PD-L1 was expressed in TC and TILs in advanced NSCLC and its expression level showed correlation with clinical efficacy of anti-PD-1 treatment in multiple studies (Topalian et al 2012; Herbst et al 2014; Borghaei et al 2015; Fehrenbacher et al 2016; Herbst et al 2016; Rosenberg et al 2016). PD-L1 immunohistochemistry (IHC) assays, 22C3 and SP263 pharmDx, were approved as the companion diagnostic (CDx) assay to identify NSCLC patients for treatment with KEYTRUDA (pembrolizumab) monotherapy (Herbst et al 2016). The PACIFIC study was not designed to evaluate durvalumab versus placebo based on archival tumor PD-L1 expression and 37% patients were not PD-L1 expression evaluable, but the results of the exploratory analyses support treatment benefit with durvalumab versus placebo in all subgroups including PD-L1 expression in terms of PFS, ORR etc. On the other hand, post-hoc analysis of PD-L1 expression showed a larger PFS benefit in patients with PD-L1 ≥ 1% than in those with PD-L1 < 1% (PFS HR, 0.47 vs 0.80). The OS benefit was mainly driven by the PD-L1 ≥ 1% subgroup (HR = 0.61, 95% CI ,0.44 to 0.85), while there was no treatment benefit in PD-L1 < 1% subgroup (HR = 1.15, 95% CI, 0.75 to1.75) (Spigel et al 2022). Based on this ad-hoc analysis from the PACIFIC study, PD-L1 IHC SP263 pharmDx assay also received CE-IVD certification in Europe to identify patients with Stage III NSCLC with PD-L1 ≥ 1% in TC for durvalumab maintenance therapy after CRT, which indicates PD-L1 expression is probably a predictive biomarker for anti-PD-1/PD-L-1 treatment in LA NSCLC.

However, the predictive role of PD-L1 in identifying patients with LA NSCLC who could benefit from combination treatment with dual-immunotherapeutic agents for maintenance therapy after cCRT is still not well-explored. In the CITYSCAPE study, patients with NSCLC with PD-L1 ≥ 50% in TC derived significant benefit from atezolizumab (anti-PD-L1) plus

tiragolumab (anti-TIGIT) than patients with PD-L1 1-49% (PFS HR 0.29 versus 1.07, OS HR 0.23 versus 1.16), suggesting that PD-L1 is a predictive biomarker for treatment co-targeting the PD-1 and TIGIT pathways (Cho et al 2021). In this study, patients with NSCLC with PD-L1 ≥ 50% in TC will be randomized to 3 different treatment arms and PD-L1 ≥ 50% was designed to be one of the stratification factors to balance the 3 treatment arms and to explore the association of PD-L1 expression with clinical efficacy.

Neither the randomized Phase 3 Study PACIFIC nor GEMSTONE-301 has revealed the prevalence of patients with unresectable Stage III NSCLC whose tumors express PD-L1 ≥ 50% in the PD-L1 ≥ 1% population. In 2 retrospective analyses of unresectable Stage III NSCLC studies, the proportion of PD-L1 ≥ 50% population was reported to be 63% and 58% (IHC assay 22C3), respectively (Desilets et al 2020; Kartolo ea al 2021). Referring to data in the first-line NSCLC treatment, the prevalence of PD-L1 ≥ 50% population was 43%, 52% (nonsquamous only), and 41% (squamous only) (IHC assay 22C3) in CITYSCAPE, KEYNOTE-189, and KEYNOTE-407, respectively (Cho et al 2021; Gadgeel et al 2020; Paz-Ares et al 2020); however, in another 2 first-line randomized controlled trials (RCT), Rationale-304 (nonsquamous) and Rationale-307 (squamous), this prevalence was both reported to be 58%, and in the second or third line RCT (Rationale-303), this prevalence was reported to be 50% (IHC SP263) (Lu et al 2020; Wang et al 2020; Zhou et al 2021). Based on the data above, the enrollment of patients in this study with PD-L1, 1% to 49% will be stopped upon reaching around 50% to ensure that the prevalence of the enrolled population is close to the natural PD-L1 expression.

In addition to PD-L1 expression, TMB, MSI, abundance and location of TILs, and tumor and immune-related gene expression profile are a few factors associated with response to immunotherapies including anti-PD-1 antibodies in different cancers (Vilain et al 2017; Goodman et al 2017; Gandara et al 2018; Jiang et al 2018). In melanoma patients, high TIGIT/CD226 ratio on Treg cells correlated with poor clinical outcome upon treatment with anti-PD-1 or anti-PD-L1 antibodies. Additionally, a higher frequency of $TIGIT^+$ T cells among $PD\text{-}1^+CD8+$ T cells were associated with hyperprogressive disease during PD-1/PD-L1 blockade, and these patients showed a lower survival rate (Kim et al 2019). These results suggested that signaling through TIGIT pathway in tumor tissues might contribute to resistance to current immune checkpoint inhibitors targeting PD-1 or PD-L1 (Fourcade et al 2018). Therefore, the expression of TIGIT pathway molecules including TIGIT, CD226, CD155, CD112, as well as PD-L1, ctDNA, TMB, MSI, TILs, EVs, and gene expression profile will be studied, and their relationship with clinical response to study treatment will be further assessed to explore potential predictive biomarkers.

Besides biomarkers that have the potential to predict clinical efficacy, mechanisms of resistance to immunotherapeutics are also not well understood and need more exploration. Identification of somatic mutations or gene expression profiles that are associated with disease progression or acquired resistance to study treatment may increase the understanding of disease pathobiology and help in collecting biological evidence for combination strategies.

1.4. Benefit-Risk Assessment

Study AdvanTIG-301 compares the combination of tislelizumab plus anti-TIGIT monoclonal antibody ociperlimab versus durvalumab in patients with locally advanced, unresectable NSCLC

who have been treated with cCRT and whose disease has not progressed. As discussed above, there is extensive evidence supporting TIGIT's role in regulating immune response as well as the interaction between the TIGIT and PD-1 pathways in promoting tumor immune escape (Section 1.2.1, Section 1.3.2). Combined with the clinical efficacy that has been demonstrated for tislelizumab as PD-1 inhibitor (Section 1.2.2), the data strongly suggest that ociperlimab has the potential to improve and/or extend the therapeutic benefits of tislelizumab, especially in the anti-PD-1/PD-L1 treatment-naïve settings.

As discussed earlier (Section 1.2.1.1.2, Section 1.2.1.2, Section 1.3.1, and Section 1.3.2), based upon the mechanism(s) of action, nonclinical as well as 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. Although there is the risk of observing augmented safety signals as has been shown for other anti-PD-1 based immuno-oncology combinations, a comprehensive algorithm derived from the European Society for Medical Oncology and American Society for Clinical Oncology, has been established to monitor, diagnose, as well as manage such immune-related toxicities (Specific Appendix 10). It is important to note that peripheral effector T cells typically do not express TIGIT, which contrasts with TILs stimulated by the antigens in tumor microenvironment. Therefore, the combination provides an opportunity to specifically augment the activity of effector T-cells in the tumor rather than periphery and/or nontumor tissue (Johnston et al 2014).

Blockade of the PD-1 pathway has demonstrated strong antitumor efficacy either alone or in combination with standard of care in multiple cancer indications. As discussed in Section 1.2.1.2 and Section 1.2.2.4, PD-1 blockade by tislelizumab has been evaluated in more than 1992 patients with a safety and efficacy profile similar to what has been reported for other anti-PD-(L)1 therapies.

As shown specifically in Appendix 1, a comprehensive monitoring plan will be utilized to monitor patient safety. The subsequent safety data will be continuously analyzed by the sponsor's study team and in consultation with investigator(s) as needed. Refer to Section 1.2.1.2, Section 1.2.2.4, and Section 8 for information regarding additional safeguards and considerations related to potential risk.

In addition, available data from clinical trials of other anti-PD-1/PD-L1 antibodies, including tislelizumab, durvalumab, sugemalimab, and pembrolizumab, have demonstrated favorable benefit/risk ratio. Available data indicates that tislelizumab has a tolerable safety profile and very promising antitumor activity when administered in patients with advanced lung cancer. Also, studies PACIFIC, GEMSTONE-301, and LUN14-179 have released a consistent and favorable benefit/risk profile of anti-PD-1/PD-L1 single agent administered following concurrent chemoradiotherapy (Section 1.1.2.2; Durm et al 2020). When further adding another immunotherapy agent to consolidation therapy following cCRT based on anti-PD-1/PD-L1 therapy, eg anti-CD73 and anti-NKG2A, the interim analysis of Study COAST indicated that no new safety signals identified in the arms of dual immunotherapy agents while promising efficacy data was observed (COAST 2021).

In summary, there is strong scientific rationale that the combined blockade of the TIGIT pathway and PD-1/PD-L1 pathway following standard chemoradiotherapy may result in enhanced

antitumor activity and benefit more patients as compared with anti-PD-1/PD-L1 monotherapy without a major increase in the risk of immune-related toxicities.

An Independent Data Monitoring Committee (IDMC) will be established to regularly monitor the safety of ociperlimab, tislelizumab, and durvalumab.

1.5. Study Conduct

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

2. STUDY OBJECTIVES AND ENDPOINTS

The study objectives and endpoints defined in this section apply to the patients enrolled since Protocol Amendment (PA) 2.0 implementation only, unless otherwise specified. The same rules apply to the following sections in this protocol.

2.1. Study Objectives and Endpoints

Table 3: Primary Objectives and Endpoints

Objectives	Endpoints
Compare progression-free survival (PFS) as assessed by the Independent Review Committee (IRC) per Response Evaluation Criteria in Solid Tumors (RECIST) Version (v) 1.1 in ociperlimab plus tislelizumab (Arm A) versus Durvalumab (Arm C) among patients with locally advanced non-small cell lung cancer (LA NSCLC) whose disease has not progressed after concurrent chemoradiotherapy (cCRT) and with PD-L1 ≥ 50%	PFS by the IRC, defined as the time from the date of randomization to the date of first documentation of disease progression assessed by the IRC per RECIST v1.1 or death, whichever occurs first
Compare PFS as assessed by the IRC per RECIST v1.1 in ociperlimab plus tislelizumab (Arm A) versus Durvalumab (Arm C) among patients with LA NSCLC whose disease has not progressed after cCRT and with PD-L1 ≥ 1%	

Table 4: Secondary Objectives and Endpoints

Objectives	Endpoints
Compare overall survival (OS) in Arm A versus Arm C among patients with PD-L1 ≥ 50%	OS defined as the time from the date of randomization until the date of death due to any cause
Compare OS in Arm A versus Arm C among patients with PD-L1 ≥ 1%	
Evaluate overall response rate (ORR) and duration of response (DOR) as assessed by both the IRC and investigators in Arm A	ORR, defined as the proportion of patients who achieve a complete response (CR) or partial response (PR) assessed by both the IRC and investigators per RECIST v1.1

Objectives	Endpoints
versus Arm C among patients with PD-L1 ≥ 50% and ≥ 1%	DOR, defined as the time from the first determination of a confirmed objective response assessed by both the IRC and investigators per RECIST v1.1 until the first documentation of disease progression or death, whichever occurs first
Evaluate time to death or distant metastasis (TTDM) in Arm A versus Arm C among patients with PD-L1 ≥ 50% and ≥ 1%	Time to death or distant metastasis (TTDM), defined as the time from the date of randomization until the first date of distant metastasis assessed by both the IRC and investigators, or death. Distant metastasis is defined as any new lesion that is outside of the radiation field per RECIST v1.1 or proven by biopsy.
Compare PFS2 in Arm A versus Arm C among patients with PD-L1 ≥ 50% and ≥ 1%	PFS2, defined as the time from randomization to the disease progression after next line of treatment, or death from any cause, whichever occurs first
Evaluate safety and tolerability in 3 treatment arms among patients with PD-L1 ≥ 50% and ≥ 1%	Safety and tolerability, defined as AEs (using NCI-CTCAE v5.0), laboratory tests, vital signs, ECOG Performance Status, physical examinations, concomitant medications, and dose modifications
Compare impact of treatments on patient health-related quality of life (HRQoL) in Arm A versus Arm C among patients with PD-L1 ≥ 50% and ≥ 1%	HRQoL, measured via patient-reported outcomes (PROs) using EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L questionnaires
Characterize the pharmacokinetics (PK) of ociperlimab and tislelizumab	Serum concentrations of ociperlimab and tislelizumab at specified timepoints
Assess host immunogenicity to ociperlimab and tislelizumab	Immunogenic responses to ociperlimab and tislelizumab evaluated through detection of antidrug antibodies

Objectives	Endpoints
Evaluate the association of PD-L1 and TIGIT expression with clinical efficacy to ociperlimab plus tislelizumab or tislelizumab or durvalumab only	PD-L1 and TIGIT expression in archival and/or fresh tumor tissues before study treatment or at disease progression/reoccurrence, and their association with clinical efficacy

Table 5: Exploratory Objectives and Endpoints

Objectives	Endpoints
Evaluate PFS, ORR, DOR by the IRC and investigators per RECIST v1.1 and OS, TTDM, PFS2 and HRQoL in Arm A versus Arm B among patients with PD-L1 ≥ 50% and ≥ 1%	PFS, ORR, DOR, TTDM, by the IRC and investigators per RECIST v1.1; OS, PFS2, HRQoL
Evaluate the potential association of exploratory biomarkers with response or resistance to ociperlimab plus tislelizumab or tislelizumab or durvalumab only, and with patient prognosis	Status of exploratory biomarkers including but not limited to the expression of CD226, CD155, and CD112, gene expression profiling (GEP), circulating tumor DNA (ctDNA), TMB, MSI, gene mutation profiles, extracellular vesicle (EVs), and TILs in archival and/or fresh tumor tissues and blood before and after study treatment, and the association between these biomarkers and clinical efficacy, disease status, response, and resistance mechanisms
Evaluate patient-reported global impression of severity (PGI-S) and patient-reported treatment side-effect burden (PRTSE)	PGI-S and PRTSE
Evaluate the efficacy in patient who finished definitive cCRT treatment and received at least 1 consolidation treatment among patients enrolled under PA 1.0	PFS by investigators

2.2. Definition of Primary Estimand

2.2.1. Primary Estimand 1 – PFS benefit in patients with LA NSCLC who have not progressed after cCRT and with PD-L1 ≥ 50%

The primary scientific question of interest is: Does ociperlimab in combination with tislelizumab prolong time to death/progression (PFS) compared to durvalumab in patients with unresectable

LA NSCLC whose disease has not progressed after cCRT and with PD-L1 ≥ 50% (no subsequent anticancer therapy after assigned therapy).

The primary estimand is described by the following attributes:

1. Treatment of interest:
   The experimental treatment consists of ociperlimab 900 mg combined with tislelizumab 200 mg Q3W for a maximum of 12 months. The standard of care treatment consists of durvalumab 10 mg/kg Q2W (or 1500 mg Q4W where the dosage has been approved by the local health authority) for a maximum of 12 months.
2. Population:
   Patients with unresectable LA NSCLC whose disease has not progressed after cCRT and whose tumors express PD-L1 on ≥ 50% of TC.
3. Primary variable:
   Progression-free survival (PFS), defined as the time from the date of randomization to the date of the first documented tumor progression assessed by Independent Review Committee IRC per RECIST v1.1, or death, whichever occurs first.
4. Handling of intercurrent events:
   - Anticancer therapy, subsequent to assigned therapy, that is started before IRC-assessed PD: PFS will be censored at the last adequate disease assessment before the subsequent anticancer therapy (hypothetical strategy)
   - Discontinuation of treatment: tumor assessment and survival data collected after discontinuation of study treatment will be used for analysis (treatment policy strategy)
   - Death due to COVID-19: death due to COVID-19 will be considered as part of PFS events (composite strategy)
   - COVID-19 infection: any incidence of COVID-19 infection will be ignored (treatment policy strategy)
5. Population-level summary: HR and its 95% CI for PFS comparing ociperlimab + tislelizumab versus durvalumab, estimated using a Cox regression model stratified by age (< 65 years versus ≥ 65 years), and histology (squamous versus nonsquamous).

2.2.2. Primary Estimand 2 – PFS benefit in patients with LA NSCLC whose disease has not progressed after cCRT and with PD-L1 ≥ 1%

The primary scientific question of interest is: Does ociperlimab in combination with tislelizumab prolong time to death/progression (PFS) compared to durvalumab in patients with unresectable LA NSCLC whose disease has progressed after cCRT and with PD-L1 ≥ 1% (no subsequent anticancer therapy after assigned therapy).

The attributes of Primary Estimand 2 are the same as Primary Estimand 1, except that the population consists of patients with PD-L1 expression on ≥ 1%; and for HR calculation, the

stratification factors in Cox model include age (< 65 years versus ≥ 65 years), PD-L1 expression in TC (≥ 50% versus < 50%), and histology (squamous versus nonsquamous).

2.3. Definition of Key Secondary Estimand

2.3.1. Key Secondary Estimand 1 – OS benefit in patients with LA NSCLC whose disease has not progressed after cCRT and with PD-L1 ≥ 50%

The scientific question of interest is: Does ociperlimab in combination with tislelizumab prolong time to death (OS) compared to durvalumab in patients with unresectable LA NSCLC whose disease has not progressed after cCRT and with PD-L1 expression on ≥ 50%, regardless of whether to receive subsequent anticancer therapy after assigned therapy.

The key secondary estimand 1 is described by the following attributes:

1. Treatment of interest is the same as those in the primary estimand.
2. Population:

   Patients with unresectable LA NSCLC whose disease has not progressed after cCRT and with PD-L1 expression on ≥ 50% of TC.
3. Primary variable:
   Overall survival defined as the time from the date of randomization to the date of death due to any cause.
4. Handling of intercurrent events:
   - Anticancer therapy, subsequent to assigned therapy, started prior to death: any incidence will be ignored, ie, any death or patients' data collected after the new anticancer therapy will be considered for analysis (treatment policy strategy)
   - Discontinuation of treatment: any death or patients' data collected after the discontinuation of treatment will be considered for analysis (treatment policy strategy)
   - Any unforeseen intercurrent events: OS will take into account all deaths and any patients' data after any unforeseen intercurrent events (treatment policy)
5. Population-level summary: HR of OS and its 95% CI for OS comparing ociperlimab + tislelizumab versus durvalumab, estimated using a Cox regression model stratified by age (< 65 years versus ≥ 65 years), and histology (squamous versus nonsquamous).

2.3.2. Key Secondary Estimand 2 – OS benefit in patients with LA NSCLC whose disease has not progressed after cCRT and with PD-L1 ≥ 1%

The attributes of this estimand are the same as Key Secondary Estimand 1, except that the population consists of patients with PD-L1 expression on ≥ 1%, and for HR calculation, the stratification factors in Cox model include age (< 65 years versus ≥ 65 years), PD-L1 expression in TC (≥ 50% versus < 50%), and histology (squamous versus nonsquamous).

3. STUDY DESIGN

3.1. Summary of Study Design

This is an open-label, randomized, multicenter, Phase 3 study to compare the efficacy and safety of ociperlimab plus tislelizumab (Arm A) versus durvalumab (Arm C) in patients with unresectable, PD-L1 selected LA NSCLC whose disease has not progressed after cCRT.

Patients who have diagnosed with histologically or cytologically confirmed, unresectable LA Stage III NSCLC with PD-L1 ≥ 1% of TC and whose disease has not progressed after definitive, platinum-based cCRT are eligible. Approximately 700 patients will be enrolled and randomized in a 3:1:3 ratio to Arm A, Arm B, or Arm C in this study. Randomization will be stratified by age (< 65 years versus ≥ 65 years), PD-L1 expression in TC (≥ 50% versus < 50%), and histology (squamous versus nonsquamous).

The PD-L1 expression status will be closely monitored. For enrolled patients with PD-L1, 1% to 49% of TC will be stopped as necessary through Interactive Response Technology (IRT) when the prevalence for this population reaches around 50%. This will ensure that the population reflects the natural PD-L1 expression prevalence.

During the treatment period, in Arm A, patients will receive ociperlimab 900 mg combined with tislelizumab 200 mg Q3W. In Arm B, patients will receive tislelizumab 200 mg Q3W. In Arm C, patients will receive durvalumab 10 mg/kg Q2W (or 1500 mg Q4W where the dosage has been approved by a local health authority). Patients in all 3 arms will receive study treatment for a maximum of 12 months, or until PD per RECIST v1.1, unacceptable toxicity, death, or another discontinuation criterion is met, whichever occurs first.

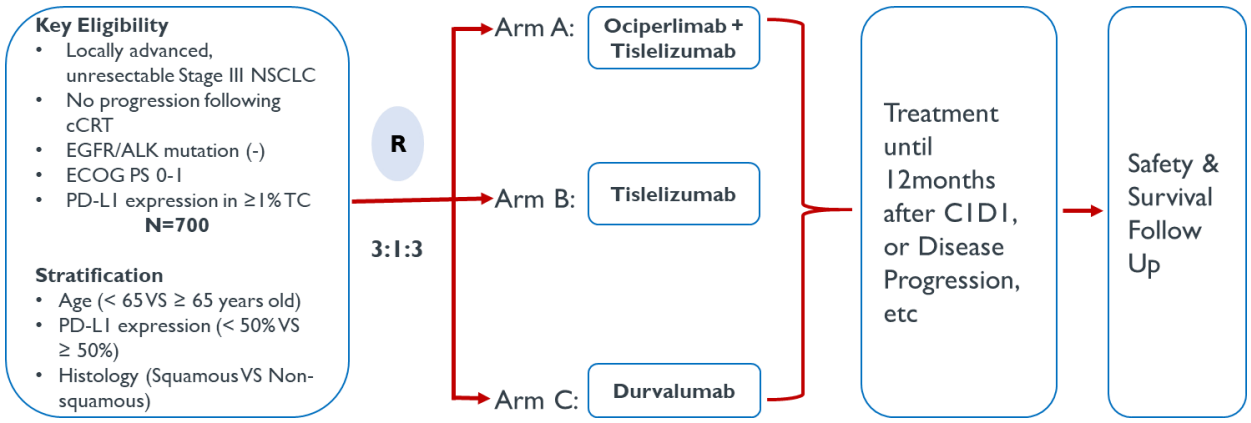
End-of-Treatment (EOT) Visit, Safety Follow-up Visit, and Survival Follow-up Visit will be conducted to monitor patient status and collect data beyond study treatment.

Safety and efficacy will be monitored by an IDMC. There is 1 planned interim analysis in this study for superiority. Please refer to details in Section 10.2 and Section 9.8, respectively.

The study conduct will be overseen by a Steering Committee (SC) composed of selected investigators. Please refer to details in Section 10.3.

The study design schema is presented in Figure 3.

Figure 3: Study Schema



Abbreviations: *ALK*, anaplastic lymphoma kinase; C1D1, Cycle 1 Day 1; cCRT, concurrent chemoradiotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; *EGFR*, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death protein ligand-1; R, randomization; TC, tumor cells; TIGIT, T-cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain.

For all study procedures see Section 7 and Appendix 1.

Note, the study was initially implemented with Protocol Amendment 1.0 (dated on 16 Apr 2021, PA 1.0). In the PA 1.0, patients with newly diagnosed, histologically confirmed, unresectable LA NSCLC and evaluable PD-L1 expression all comers were enrolled; cCRT was given within the study. In Protocol Amendment 2.0 (date 21 Apr 2022, PA 2.0), the enrollment of the target population has been revised into patients with unresectable LA NSCLC whose disease has not progressed after definitive, platinum-based cCRT with PD-L1 expression on ≥ 1% of TC as assessed by the central lab; cCRT was given outside of the study; the eligibility criteria have been updated to reflect the patient population change. The enrollment of PA 1.0 will be stopped before PA 2.0 implementation. Patients recruited into the study prior to PA 2.0 will not be included in the primary and secondary analysis but would be included in exploratory analysis defined by PA 2.0.

For all patients randomized with PA 1.0 prior to PA 2.0 implementation (defined as the Concurrent Part of the study):

Patients who are still on study treatment will be informed of the substantial change from PA 1.0 to PA 2.0, the rationale for this change, and the following treatment options. Investigators will discuss the local available standard-of-care with the patients, and patients have the right to discontinue from the assigned study treatment and receive standard-of-care treatment outside of the study proposed by their physician. However, after discussion of benefit-risk of the study treatment with the treating physician, the patients who are still willing to continue the assigned study treatment will be offered the assigned treatment until PA 1.0 defined treatment discontinuation point.

All patients (including those who chooses to stop assigned study treatment) are requested to continue in the study for follow-up visits unless the study discontinuation criterion is met.

The care of the patients enrolled under PA 1.0, including but not limited to treatment, safety management and visits, will follow the details in Appendix 17, which are mostly consistent with those defined in PA 1.0, except for minor updates.

3.2. Prescreening

All patients will undergo prescreening for central evaluation of PD-L1 status up to 120 days before randomization. PD-L1 status will be determined centrally in either a previously obtained archival tumor tissue or fresh tissue obtained from a biopsy collected prior to the initiation of cCRT. A separate prescreening informed consent must be obtained.

Archival tumor tissue must be collected for the purpose of PD-L1 evaluation and other exploratory biomarker analysis. If no archival samples are available, a fresh tumor biopsy prior to the first dose of CRT is mandatory (Section 7.8).

EGFR, ALK, RET, and ROS1 mutational status, if known, will also be collected at this time.

Patients with nonsquamous NSCLC and unknown EGFR mutational status will be required to have a tissue-based EGFR test performed either locally or centrally, or endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) based EGFR test performed locally during prescreening. Patients found to have EGFR sensitizing mutations will not be eligible.

3.3. Screening Period

Patients with PD-L1 ≥ 1% of TC and with no EGFR-sensitizing mutations or known ALK, RET, or ROS1 mutation will then proceed to screening. 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. Screening evaluations may be repeated as needed within the screening period; the investigator is to assess preliminary patient eligibility according to the latest screening assessment results.

3.4. Treatment Period

After completing all prescreening and screening activities, eligible patients will be randomized in a 3:1:3 ratio to 3 arms (Arm A, Arm B, and Arm C). Randomization will be stratified by age (< 65 years versus ≥ 65 years), PD-L1 expression in TC (≥ 50% versus < 50%), and histology (squamous versus nonsquamous).

Patients will receive open-label treatments as follows:

- Arm A: Ociperlimab 900 mg Q3W combined with tislelizumab 200 mg Q3W intravenously up to 12 months, or until PD per RECIST v1.1, unacceptable toxicity, death, or until another discontinuation criterion is met
- Arm B: Tislelizumab 200 mg intravenously Q3W up to 12 months, or until PD per RECIST v1.1, unacceptable toxicity, death, or until another discontinuation criterion is met
- Arm C: Durvalumab 10 mg/kg intravenously Q2W (or 1500 mg Q4W where the dosage has been approved by a local health authority) up to 12 months, or until PD per RECIST v1.1, unacceptable toxicity, death, or until another discontinuation criterion is met

Radiological assessment of tumor-response status will be performed approximately every 9 weeks (± 7 days) after randomization, for the first 54 weeks, and every 12 weeks (± 7 days) thereafter based on RECIST v1.1. Tumor response will be assessed by both the IRC and the investigator. 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. Details are provided in Section 7.6.

Administration of study treatment will continue up to 12 months, or until PD as assessed by the investigator per RECIST v1.1, unacceptable toxicity, or death, or until another discontinuation criterion is met, whichever occurs first. Once PD is assessed by the investigator, the IRC is required to complete central image review and convey the results to the investigator as soon as possible. If the investigator-assessed PD is NOT confirmed by the IRC, the medical monitor will discuss the findings with the investigator and the study treatment is recommended to continue as

long as it is considered to be in the best interest of the patient. In the situation where the investigator believes the patient must urgently begin subsequent systemic therapy without waiting for confirmation of PD by IRC, the investigator must contact the medical monitor to inform them of the plan to urgently discontinue study treatment.

A patient who discontinues study treatment for reasons other than PD by the IRC (eg, toxicity, PD by the investigator, completion of the 12-month treatment) will continue to undergo tumor assessments following the original plan until the patient experiences PD per RECIST v1.1 assessed by the IRC, withdraws consent, is lost to follow-up, dies, or until the study terminates, whichever occurs first.

Study treatment beyond initial PD per RECIST v1.1

If at the investigator's discretion a patient could continue to benefit from the immunotherapy (ociperlimab and tislelizumab combination treatment in Arm A, tislelizumab in Arm B, or durvalumab in Arm C) after PD per RECIST v1.1 assessed by the IRC or investigator, the patient may continue their assigned treatment. The following criteria must be met in order to treat patients who may continue to benefit from study treatment after PD:

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

The decision to continue study treatment beyond initial PD per RECIST v1.1 assessed by the IRC or investigator must be agreed upon with the medical monitor and documented in the study records.

Tumor assessment should continue as planned in patients receiving study treatment beyond initial PD per RECIST v1.1 criteria assessed by the IRC or investigator. Tumor assessment in such patients should continue until study treatment discontinuation.

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

Blood sample must be collected at C1D1 (predose) for biomarker test. Optional blood samples will be collected at C3D1 (predose), C4D1 (predose), and at the EOT Visit after disease progression (Appendix 1). All these blood samples will be collected to explore association of blood-based biomarkers with response, resistance, and prognosis. Written informed consent is required before optional blood samples collection.

Safety will be assessed throughout the study by monitoring AEs/SAEs (toxicity grades assigned per NCI-CTCAE v5.0]) and laboratory results. Vital signs, physical examinations, ECOG Performance Status change, electrocardiogram (ECG) results, and other examinations will also

be used for safety assessment. Safety assessments are further detailed in Section 7.5 and the Schedule of Assessments (Appendix 1).

3.5. End of Treatment

The End-of-Treatment (EOT) Visit is planned when the investigator determines that study treatment will no longer be used.

The date of End of Treatment (EOT) is defined as the date the investigator determines that study treatment will no longer be used. Patients shall have an EOT Visit within 7 days after the date the investigator determines that study treatment will no longer be used, or before the initiation of a new anticancer treatment, whichever occurs first. For Arm A, patients shall have an EOT Visit only if both study drugs were discontinued. However, the EOT Visit may occur later than 7 days for specific circumstances, such as prolonged hospitalization.

See Appendix 1 for assessments to be performed at the EOT.

3.6. Safety Follow-up

The Safety Follow-up Visit is planned when the investigator determines that study treatment will no longer be used.

The date of Safety Follow-up Visit is defined as the date when safety assessments and procedures are performed after the last dose of study treatment for an individual patient.

All patients that discontinue study treatment (both study drugs if in Arm A) will have a Safety Follow-up Visit approximately 30 days (± 7 days) after the last dose of study drug or before the initiation of new anticancer therapy, whichever occurs first. This visit will include the collection of data about AEs and serious adverse events (SAEs) that may have occurred after the patient discontinued the study drug. The investigator or his/her designee will continue to collect information on new anticancer therapy given after the last dose of study drug. In cases where the time window of EOT and Safety Follow-up visit overlap, these two visits can be combined. See Appendix 1 for assessments to be performed at the Safety Follow-up Visit.

Additional Safety Follow up visits at 60, 90, and 120 days (this visit is only required for women of childbearing potential) after the last dose of study drug can be required (in clinic or over the phone, as needed based on assessments required). Patients will be contacted by telephone to assess imAEs and relevant concomitant medication use (ie, those associated with an imAE or any new anticancer therapy). These contacts should be made at 60 days (± 14 days) and 90 days (± 14 days) after the last dose of study treatment regardless of whether the patient starts a new anticancer therapy. For women of childbearing potential (see Appendix 5), an additional visit to perform a pregnancy test will occur at approximately 120 days (± 14 days) after the last dose of study treatment. If a patient reports a suspected imAE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated.

3.7. Survival Follow-up

Patients will be followed for survival follow-up data after discontinuation of study treatment via telephone calls, patient medical records, and/or clinic visits approximately every 3 months

(± 14 days) after the 90-Day Safety Follow-up Visit or as directed by the sponsor until death, loss to follow-up, withdrawal of consent, or end of study by the sponsor.

During the survival follow-up period subsequent anticancer therapy information including medication start date, end date, reason for treatment and date of progression after receiving the subsequent anticancer therapy will be collected.

3.8. Discontinuation From the Study Treatment or From the Study

3.8.1. Discontinuation From Study Treatment

Patients have the right to withdraw from the study or discontinue study treatment at any time for any reason. In addition, the investigator has the right to discontinue a patient from the study treatment at any time. Patients who discontinue study treatment for reasons other than PD should be followed for assessments of antitumor activity (Section 7.6), safety (Section 7.5), and survival (Section 3.7), if possible.

The primary reason for discontinuation from the study treatment should be documented on the appropriate electronic case report form (eCRF).

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

- Radiographic PD per RECIST v1.1
- AE
- Use of any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents [including herbal medicine and patent medicines] for the treatment of cancer) (Section 6.3).
- Patient noncompliance

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

Patients will discontinue from the study treatment for reasons following:

- Patient's decision to withdraw from study treatment
- Any medical condition that the investigator determines may jeopardize the patient's safety, if he or she were to continue the study treatment
- Pregnancy.

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

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

- Patient's withdrawal of consent from study treatment and follow-up
- Death

- Lost to follow-up
- Patients have completed all study assessments

3.9. 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
- A rollover study becomes available

The sponsor will notify each investigator if a decision is made to terminate the study. Should this be necessary, patients who prematurely discontinued from treatment should be seen as soon as possible for an EOT 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 IRBs/IECs of the early termination of the study.

At the end of study, patients who are still in the originally assigned treatment within 12 months after C1D1 and continue to benefit from the treatment at study termination in the opinion of the investigator, will be offered the option to continue treatment in a company-sponsored clinical trial until treatment duration reach 12 months after C1D1 or it is commercially available in the country of the patient's residence.

The sponsor has the right to close a site at any time. The decision will be 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 must meet all of the following inclusion criteria to be considered eligible for participation in this study:

1. Age ≥ 18 years on the day of signing the ICF (or the legal age of consent in the jurisdiction in which the study is taking place).
2. Ability to provide written informed consent and to understand and agree to comply with the requirements of the study and the schedule of assessments.

   Note for sites in France: Patients who are unable to express their consent (adults protected by local law of Article L1121-8 Public Health Code) are not allowed to participate in the study.
3. Patient has histologically or cytologically confirmed, locally advanced, unresectable Stage III NSCLC (AJCC Cancer Staging Manual 2017, derived from IASLC) prior to initiation of cCRT.

   Note: Tumors of mixed non-small cell histology will be categorized by the predominant cell type; if small cell elements are present, the patient is ineligible.
4. Patients must have completed at least 2 cycles of platinum-based chemotherapy concurrent with radiotherapy. For patients who are recovering from toxicities associated with prior treatment, the first dose of study treatment may be delayed by up to 42 days from the end of the cCRT. It is recommended to screen the patients within 14 days after the completion of cCRT.
   a. The platinum-based chemotherapy regimen must contain cisplatin or carboplatin, and may contain one of the following agents: etoposide, vinblastine, vinorelbine, taxane (paclitaxel or docetaxel), or pemetrexed, according to the local standard-of-care regimens. If a patient was receiving a weekly chemotherapy regimen, platinum-based chemotherapy of at least 4 weeks should be completed.
   b. The last dose of chemotherapy must be administered no later than the last dose of radiotherapy. Consolidation chemotherapy is not allowed after radiotherapy; but induction chemotherapy no more than 2 cycles before cCRT is allowed.
   c. Where possible, chemotherapy regimens should be given according to National Comprehensive Cancer Network (NCCN) Guidelines, European Society for Medical Oncology (ESMO) Guidelines, Chinese Society of Clinical Oncology (CSCO) Guidelines, Japan Lung Cancer Society (JLCS) Guidelines, or other local guidelines if applicable.
   d. Patients must have received a total dose of radiation of 60 ± 10% Gy (54 to 66 Gy), as part of the CRT.
   e. The minimum technical standard for radiotherapy is 3D conformal radiotherapy (3D-CRT) with CT planning. Intensity modulated radiotherapy (IMRT) is recommended.

f. RT dose received by organs is recommended to be (the medical monitor needs to be consulted to confirm eligibility for the patients who received higher RT dose for the organs below):

- Spinal cord: max dose ≤ 48 Gy
- Lung: V20 ≤ 35%, mean dose ≤ 20 Gy
- Esophagus: mean dose ≤ 34Gy
- Heart: V50 ≤ 25%, mean dose ≤ 20 Gy

5. Patients must have not experienced PD following definitive, platinum-based cCRT.
6. Agree to provide archival tissue (formalin-fixed paraffin-embedded block containing tumor [preferred] or approximately 6 to 15 freshly cut unstained slides) or fresh biopsy obtained prior to cCRT (if archival tissue is not available) for prospective central evaluation of PD-L1 levels and retrospective analysis of other biomarkers. PD-L1 status will be assessed centrally in either a previously obtained archival tumor tissue or fresh tissue obtained from a biopsy collected prior to the first dose of cCRT via VENTANA PD-L1 (SP263) assay. Only patients with PD-L1 ≥ 1% of TC are eligible.
7. ECOG Performance Status of 0 or 1.
8. Patients must have adequate organ function as indicated by the following screening laboratory values obtained within 7 days before randomization:
   a. Patients must not have required blood transfusion or growth factor support ≤ 14 days before sample collection at screening for the following:
      i. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
      ii. Platelets ≥ 75 x 10^9/L
      iii. Hemoglobin ≥ 90 g/L or ≥ 5.6 mmol /L (Note: Criteria must be met without a transfusion within 14 days of obtaining the sample)
   b. Serum creatinine ≤ 1.5 x upper limit of normal (ULN), or for patients whose serum creatinine > 1.5×ULN, estimated Glomerular Filtration Rate (GFR) by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation or Calculated creatinine clearance (CrCl) by Cockcroft-Gault (CG) equation ≥ 30 mL/min (Appendix 14).
   c. Serum total bilirubin ≤ 1.5 x ULN (total bilirubin must be < 3 x ULN for patients with Gilbert syndrome).
   d. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN.
   e. INR and aPPT ≤ 1.5 x ULN. This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation should be on a stable dose.
9. Female patients of childbearing potential must consent 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 ≥ 90 days after the last dose of durvalumab, and have a negative urine or serum pregnancy test ≤ 7 days before the first dose of any of the study treatment.

10. Nonsterile male patients must consent 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 ≥ 90 days after the last dose of durvalumab
    a. A sterile male is defined as one for whom azoospermia has been previously demonstrated in a semen sample examination as definitive evidence of infertility.
    b. Male patients 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 will be excluded from this study:

1. Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, TIGIT, or any other antibody or drugs specifically targeting T-cell co-stimulation or checkpoint pathways.
2. Diagnosed with NSCLC that harbors an *EGFR*-sensitizing mutation, *ALK* gene translocation, *ROS1* gene translocation or *RET* gene rearrangement.
    a. For nonsquamous and squamous NSCLC, patients with known *EGFR* mutation status, *ALK* translocation, *ROS1* translocation, or *RET* rearrangement who are sensitive to available targeted inhibitor therapy are excluded (Note: If no targeted therapy approved by the local health authority is available for *ROS1* or *RET* mutations, then these patients are eligible).
    b. For nonsquamous NSCLC, patients with unknown *EGFR* mutation status will be required to undergo a tissue-based *EGFR* test locally or at a central laboratory before randomization. An additional ≥ 6 slides are required if *EGFR* mutation status needs to be tested in a central laboratory. Patients with sensitive *EGFR* mutation status will be excluded. Patients with unknown *ALK*, *ROS1*, or *RET* status may be enrolled.
    c. Patients with squamous NSCLC and unknown *EGFR*, *ALK*, *ROS1*, or *RET* status will not be required to be tested before randomization.
3. Distant metastasis identified by imaging assessment and/or other examinations after definitive, platinum-based cCRT.
4. Patients who received chemotherapy and radiotherapy with ≤ 1 cycle overlap for LA NSCLC.
5. Patients who received systemic anticancer treatment besides the specified cCRT.
6. Any unresolved toxicity CTCAE > Grade 2 from the prior cCRT. Patients with irreversible toxicity that is not reasonably expected to be exacerbated by study treatment may be included (eg, hearing loss).
7. Patients with any grade pneumonitis from prior cCRT.
8. Active autoimmune diseases or history of autoimmune diseases that may relapse (Appendix 4).
   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 the first dose of study treatment 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 [in Japan, prednisolone] or equivalent) or other immunosuppressive medication ≤ 14 days before the first dose of study treatment.
    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 [in Japan, prednisolone] 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 the first dose of study treatment.
12. Uncontrollable pleural effusion, pericardial effusion, or ascites requiring frequent drainage (recurrence within 2 weeks of intervention). Note for sites in Germany: patients with malignant pleural or pericardial effusion or ascites are excluded regardless of whether it is uncontrollable or not.
13. History of interstitial lung disease, non-infectious pneumonitis or uncontrolled lung diseases including pulmonary fibrosis, acute lung diseases, etc.
14. Infection (including tuberculosis infection, etc) requiring systemic antibacterial, antifungal, or antiviral therapy within 14 days before the first dose of study treatment.
    Note: Antiviral therapy is permitted for patients with chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection.
15. 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 (defined as patients with positive HBsAg but asymptomatic), treated and stable hepatitis B (HBV DNA < 500 IU/mL or < 2500 copies/mL) can be enrolled. Patients with detectable HBsAg or detectable HBV DNA should be managed per treatment guidelines. Patients receiving antivirals at screening should have been treated for > 2 weeks before enrollment.
16. Patients with active hepatitis C.
    Note: Patients with a negative HCV antibody test at screening or positive HCV antibody test followed by a negative HCV RNA test at screening are eligible. The HCV RNA test

will be performed only for patients testing positive for HCV antibody. Patients receiving antivirals at screening should have been treated for > 2 weeks before enrollment.

17. Known history of HIV infection. Note for sites in Germany and where required by Health Authority or local guidance: An HIV serology test (including antigen and/or antibodies) will be conducted at baseline for the patients with unknown HIV status and patients with positive HIV test will be excluded.
18. Any major surgical procedure ≤ 28 days before the first dose of study treatment. Patients must have recovered adequately from the toxicity and/or complications from the intervention before the first dose of study treatment.
19. Prior allogeneic stem cell transplantation or organ transplantation.
20. 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 the first dose of study treatment.
    b. Pulmonary embolism ≤ 28 days before the first dose of study treatment.
    c. Any history of acute myocardial infarction ≤ 6 months before the first dose of study treatment.
    d. Any history of heart failure meeting New York Heart Association (NYHA) Classification (Appendix 6) III or IV ≤ 6 months before the first dose of study treatment.
    e. Any event of ventricular arrhythmia ≥ Grade 2 in severity ≤ 6 months before the first dose of study treatment.
    f. Any history of cerebrovascular accident ≤ 6 months before the first dose of study treatment.
    g. Uncontrolled hypertension that cannot be managed by standard anti-hypertension medications ≤ 28 days before the first dose of study treatment.
    For France only, specify: systolic pressure ≥ 140 mmHg or diastolic pressure ≥ 90 mmHg on repeated measurements.
    h. Any episode of syncope or seizure ≤ 28 days before the first dose of study treatment.
21. A history of severe hypersensitivity reactions to other monoclonal antibodies or history of hypersensitivity to the ingredients of tislelizumab or ociperlimab.
22. Receipt of any immunotherapy (eg, interleukin, interferon, thymosin [not approved in Japan], etc) or any investigational therapies within 14 days or 5 half-lives (whichever is longer) before the first dose of study treatment.
23. Administration of a live vaccine ≤ 28 days before the first dose of study treatment.
    Note: Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed. For COVID-19 vaccines, non-live vaccines are allowed, including inactivated vaccines; live or live-attenuated vaccines ≤ 28 days before the first dose of stud treatment 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 treatment, or affect the explanation of treatment toxicity or AEs, or result in insufficient or impaired compliance with study conduct.
25. Patients who are pregnant or suspected of being pregnant, breastfeeding, or planning to get pregnant during the study.

Note for sites in Japan: women of breast-feeding that agree to stop breast-feeding prior to screening are allowed to enroll. They cannot breast-feed during the study and for at least 120 days after the last dose of study drugs.

26. Concurrent participation in another therapeutic clinical study.
    Note: Concurrent participation in observational or non-interventional studies is allowed. In addition, patients who have completed active treatment in a clinical study and are in the follow-up period can be enrolled in this study.

5. STUDY TREATMENT

5.1. Formulation, Packaging, and Handling

5.1.1. Ociperlimab

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

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

The study drug must be kept at the temperature 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 Investigator's Brochure for other details regarding ociperlimab.

5.1.2. Tislelizumab

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

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

The study drug must be kept at the temperature condition as specified on the label in the Pharmacy Manual. Refer to the Pharmacy Manual for details regarding intravenous administration, accountability, and disposal. Refer to the Tislelizumab Investigator's Brochure for other details regarding tislelizumab.

5.1.3. Durvalumab

Durvalumab is a monoclonal antibody formulated for intravenous infusion in a single-dose vial, containing a total of 500 mg antibody in 10 mL (or 120 mg antibody in 2.4 mL, 50 mg/mL) clear to opalescent, colorless to slightly yellow solution.

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.

Please refer to the Pharmacy Manual for details regarding administration, accountability, and disposal.

5.2. Dosage, Administration, and Compliance

Planned dosage and dosing frequency for study treatment are presented in Table 6 and Table 7.

For all 3 arms, the first dose of the immunotherapy (ociperlimab and tislelizumab in Arm A, tislelizumab in Arm B, durvalumab in Arm C) is to be administered within 2 business days of randomization. C1D1 is defined as the day of the administration of the first dose of the immunotherapy. Immunotherapy will be given starting from C1D1 and continued for a duration of up to 12 months.

In Arm A, ociperlimab and tislelizumab should be administered on the same day if feasible. If the first dose of ociperlimab and tislelizumab were not administered on the same day for reasons other specified, C1D1 is defined as the day of administration of the first dose of tislelizumab. For Arm B or Arm C, C1D1 is defined as the day of administration of the first dose of tislelizumab or durvalumab, respectively.

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

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

Table 6: Planned Dose, Frequency of Administration, and Route of Administration for Study Drugs

Study drugs	Dose	Frequency of Administration	Route of Administration	Duration of Treatment
Ociperlimab	900 mg	Day 1 of each cycle (21 days)	Intravenous	Refer to Section 3.4
Tislelizumab	200 mg	Day 1 of each cycle (21 days)	Intravenous	Refer to Section 3.4
Durvalumab	10 mg/kg or 1500 mg [a]	Day 1 of each cycle (14 days) or Day 1 of each cycle (28 days)	Intravenous	Refer to Section 3.4

Abbreviation: AUC, area under the concentration-time curve; Q4W, every 4 weeks.
[a] 1500 mg Q4W will be used where the dosage has been approved by a local health authority.

Table 7: Administration of Ociperlimab and Tislelizumab and Monitoring Time

Cycle	Ociperlimab and tislelizumab combination in Arm A	Tislelizumab in Arm B
Cycle 1 Day 1	Tislelizumab infusion for ≥ 60 minutes followed by **Ociperlimab** infusion for ≥ 60 minutes Patient monitoring for ≥ 120 minutes	Tislelizumab infusion for ≥ 60 minutes Patient monitoring for ≥ 60 minutes
Cycle 2 Day 1	Tislelizumab infusion for ≥ 60 minutes followed by	Tislelizumab infusion for ≥ 60 minutes Patient monitoring for ≥ 60 minutes

	Ociperlimab infusion for ≥ 60 minutes Patient monitoring for ≥ 120 minutes	
Cycle 3 Day 1 onwards	Tislelizumab infusion for ≥ 30 minutes followed by **Ociperlimab** infusion for ≥ 30 minutes Patient monitoring for ≥ 60 minutes	Tislelizumab infusion for ≥ 30 minutes Patient monitoring for ≥ 30 minutes

5.2.1. Ociperlimab and Tislelizumab Treatment Administration

Patients will receive tislelizumab 200 mg on Day 1 of each 21-day cycle (ie, Q3W) followed by the administration of ociperlimab 900 mg for Arm A, or patients will receive tislelizumab 200 mg on Day 1 of each 21-day cycle (ie, Q3W) for Arm B.

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

As specified in Table 7, the initial infusion (C1D1 and C2D1) will be delivered for ≥ 60 minutes for each study drug of the immunotherapy in Arm A and Arm B; if this is well tolerated, then the subsequent infusions from Cycle 3 onward may be administered for ≥ 30 minutes for each study drug of the immunotherapy in Arm A and Arm B, which is the shortest period permissible for infusion.

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 the immunotherapy are administered.

As a routine precaution, after infusion of ociperlimab and tislelizumab in Arm A on C1D1 and C2D1, patients will be monitored for ≥ 2 hours in an area with resuscitation equipment and emergency agents; similarly, after infusion of tislelizumab in Arm B on C1D1 and C2D1, patients will be monitored for ≥ 1 hour. From Cycle 3 onward, at least a 60-minute monitoring period is required in an area with resuscitation equipment and emergency agents for Arm A; and for Arm B, the monitoring period is at least 30 minutes.

5.2.2. Durvalumab

Durvalumab 10 mg/kg will be administered by intravenous infusion for ≥ 60 minutes every 2 weeks (or 1500 mg Q4W where the dosage has been approved by a local health authority) for up to 12 months. For the patient whose body weight is < 30 kg, only the regimen of durvalumab 10 mg/kg Q2W is applicable.

Refer to the Pharmacy Manual and local prescribing information of durvaluamb for detailed instructions on drug preparation, storage, and administration.

5.2.3. Supportive Care

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

All patients are strongly suggested to accept nutrition support if there is any indication including (but not limited to): medium-severe dysphagia; weight loss > 5% in 1 month; Body Mass Index (BMI) < 18.5 kg/m^2; scored patient-generated subjective global assessment ≥ 4 score; and food intake is < 60% required for > 3 days.

5.3. Incorrect Administration or Overdose

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

AEs associated with an incorrect administration or overdose of study treatment will be recorded on the AE eCRF. Any SAEs associated with an incorrect administration or overdose must be reported within 24 hours of awareness via the SAE reporting process as described in Section 8.6.2. Supportive care measures should be administered as appropriate.

5.4. Investigational Medicinal Product Accountability

The investigational medicinal products required for completion of this study (ociperlimab, tislelizumab, and durvalumab) will be provided by the sponsor. The investigational site will acknowledge receipt of investigational medicinal products. Any damaged shipments will be replaced.

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

5.5. Dose Modification

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

Every effort should be made to administer the study treatment according to the planned dose and schedule. In the event of significant toxicities, dosing may be delayed based on the guidelines provided below. Reasons for dose modifications or delays, the supportive measures taken, and the outcome will be documented in the patient's chart and recorded in the eCRF. Skipped doses due to reasons others than AE (eg, COVID-19 lockdown, warfare, etc) should be added at the back end to ensure the total duration of treatment in each arm is 12 months or corresponding cycles, ie, a maximum of 17 cycles in Arm A and B, 26 cycles for Q2W regimen and 13 cycles for Q4W regimen in Arm C.

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 Interruption or Delay for Ociperlimab and Tislelizumab

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

If treatment is delayed due to TEAEs, treatment may resume only after the AEs have returned to baseline or ≤ Grade 1 severity except for alopecia or 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.

In Arm A and B, if a dose is delayed for the immunotherapy (ociperlimab and tislelizumab in Arm A, tislelizumab in Arm B) for ≤ 10 days for a planned dosing cycle, the immunotherapy should be administered. If the delay is > 10 days, the patient should skip administration of the immunotherapy and the immunotherapy will be administered on Day 1 of the next planned cycle.

If imAEs are persistent without any improvement for more than 12 weeks, permanent discontinuation of the study treatment 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, re-initiation 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.

Management guidelines for imAEs and infusion-related reactions in patients treated with the immunotherapy are presented in Section 8.7, and Appendix 12.

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

5.5.2. Dose Reductions for Ociperlimab and Tislelizumab

There will be no dose reductions allowed for ociperlimab or tislelizumab in Arm A and Arm B.

5.5.3. Dose Interruption, Delay or Modification for Durvalumab

There will be no dose reductions allowed for durvalumab. Please refer to prescribing information Recommended Dosage Modifications (Appendix 15) approved by US FDA for specific information. Note, in countries/regions other than US, recommended dosage modifications of durvalumab prescribing information approved by local health authority may differ from that approved by US FDA. In these cases, please refer to the recommendations approved by local health authority.

6. PRIOR AND CONCOMITANT THERAPY

6.1. Prior Therapy

Patients should not have received prior therapies targeting PD-1, PD-L1, PD-L2, TIGIT, T-cell costimulation or checkpoint pathways; or immunotherapy (eg, interleukin, interferon, or thymosin) or investigational therapy ≤ 14 days or 5 half-lives (whichever is longer) before the first dose of study treatment; or systemic anticancer treatment besides the specified cCRT.

6.2. Permitted Concomitant Medications/Procedures

Unless noted otherwise, 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, hematopoietic growth factors, red blood cell/platelet transfusions) and in a patient's interest are allowed. Opiates and other medication required for pain management of patients are allowed.

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

Bisphosphonates are permitted during the study for a nonmalignant indication. Use of potentially hepatotoxic drugs in patients with impaired hepatic function is allowed but should be carefully monitored.

Vaccines for COVID-19 are allowed except for any live vaccine (ie, live SARS-CoV-2 virus) that may be developed. Attenuated (vector) COVID-19 vaccines are inactivated vaccines and as such, are permitted. It is recommended to avoid COVID-19 vaccination within 72 hours before or after study drug administration during the first 2 treatment cycles and within 24 hours before or after study drug administration thereafter (ie, from Cycle 3 onwards). Vaccinations are considered a concomitant medication and hence should be entered on the eCRF. The specific COVID-19 vaccine should be recorded instead of generic language, eg, mRNA-1273 vaccine (Moderna), BioNTech vaccine (Pfizer), etc.

6.2.1. Systemic Corticosteroids

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

6.2.2. Hepatitis B Treatment

Patients with active hepatitis B, defined as HBV DNA ≥ 500 IU/mL at screening, must initiate antiviral treatment ≥ 2 weeks before the first dose of study treatment. The patients would not be eligible unless HBV DNA decreases to < 500 IU/mL. If the patients are treated and eligible, antiviral treatment must continue until 6 months after the last dose of study treatment. Patients should continue effective antiviral treatment during the study to decrease potential viral re-activation risk. Tenofovir and entecavir are recommended in the American Association for the Study of Liver Disease (AASLD) guideline because they lack resistance with long-term use

(Terrault et al 2016, AASLD/IDSA HCV Guidance Panel 2015). The investigator may use other antiviral agents, if appropriate, following local guidelines. However, interferon-based therapy for hepatitis B is not permitted on study.

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

6.2.3. Hepatitis C Treatment

Patients with detectable HCV RNA who are receiving treatment at screening must meet the criterion of negative HCV RNA to be eligible. If the patients are treated and eligible, they will remain on continuous, effective antiviral therapy during the study. Investigators can consider treatment with antivirals following the international 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 enrollment and continue treatment during the study and for 6 months after study treatment discontinuation.

6.3. Prohibited Concomitant Medications/Procedures

The following medications are prohibited during the study:

- Any concurrent anticancer therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents including herbal medicine and patent medicines for the treatment of cancer [Appendix 16]).
- Live vaccines within 28 days before the first dose of study treatment and 60 days following the last dose of study treatment.
- Herbal remedies with immune-stimulating properties or that are known to potentially interfere with liver or other major organ functions.

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

6.4. Restricted Concomitant Medications/Procedures

The following medications are restricted during the study:

- Immunosuppressive agents (except to treat a drug-related AE).
- Systemic corticosteroids > 10 mg daily (prednisone [in Japan, prednisolone] or equivalent), except to treat or control a drug-related AE (per protocol) or for short-term use as prophylactic treatment.
- Patients should not abuse alcohol or other drugs during the study.

6.5. Potential Interactions Between the Study Drugs and Concomitant Medications

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

7. STUDY ASSESSMENT AND PROCEDURES

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

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

7.1. Prescreening

All patients will undergo prescreening for central evaluation of PD-L1 status before randomization. PD-L1 status will be determined centrally using either a previously obtained archival tumor tissue or fresh biopsy tissue sample collected prior to the first dose of cCRT. A separate prescreening informed consent must be obtained.

Archival tumor tissue must be collected for the purpose of PD-L1 evaluation and other exploratory biomarker analysis. If no archival samples are available, a fresh tumor biopsy prior to the first dose of cCRT is mandatory (Section 7.8)

EGFR, *ALK*, *ROS1*, and *RET* mutational status, if known, will also be collected at this time.

Only for patients with nonsquamous NSCLC: If EGFR mutational status is unknown, patients with nonsquamous NSCLC will be required to have a tissue-based EGFR test performed either locally or centrally, or EBUS-TBNA based EGFR test locally, at prescreening. Patients found to have EGFR sensitizing mutations will not be eligible.

The following tasks will be performed during the Prescreening Visit:

- Obtain written informed consent (prescreening ICF) to obtain archival tissue or biopsy
- Collect EGFR, ALK, ROS1 and RET mutational status if known; obtain consent to have EGFR mutational status determined if unknown (for patients with nonsquamous NSCLC only)
- Prepare tumor samples and ship to the qualified central lab for analysis as specified in the lab manual

7.2. Screening Period

Screening evaluations will be performed ≤ 28 days before randomization. A patient who agrees to participate in this study will sign the ICF before undergoing any screening assessment. The screening period begins on the first day that a screening assessment is conducted. Screening evaluations may be repeated as needed within the screening period. The investigator is to assess patient eligibility according to the latest screening assessment results.

Results of standard-of-care tests or examinations performed before informed consent has been obtained and ≤ 28 days before randomization may be used for the purposes of screening rather than repeating the standard-of-care tests unless otherwise indicated.

Procedures conducted only during the Screening Visit are described in this section. 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 7.5), Tumor and Response Evaluations (Section 7.6), PK and ADA Assessments (Section 7.7) and Biomarkers (Section 7.8) sections.

Rescreening under limited conditions may be allowed after consultation with the sponsor (eg, when a patient's laboratory result narrowly misses a laboratory criterion and it is correctable and not due to rapidly deteriorating condition or PD). Rescreening is allowed only once. Rescreened patients must provide new informed consent, as described in Section 7.2.1. A new patient number will be assigned as described in Section 7.2.2.

7.2.1. Informed Consent and Prescreening and Screening Log

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

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

7.2.2. Patient Numbering

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

7.2.3. 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 history; reproductive status (ie, of childbearing potential or no childbearing potential); history of and tobacco (ie, former or current or never). Prior or concomitant medications include 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 radiotherapy, 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.

7.2.4. Females of Childbearing Potential and Contraception

Childbearing potential is defined as being physiologically capable of becoming pregnant, ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile. Refer to Appendix 5 for contraception guidelines and definitions of "women of childbearing potential" and "no childbearing potential."

7.2.5. Pulmonary Function Tests

All patients should take a pulmonary function test (refer to Appendix 1 for details) at screening to assist in the determination of eligibility for the study.

Pulmonary function testing includes assessment of spirometry and oxygenation. The assessment of oxygenation should include at least pulse oximetry (percutaneous arterial oxygen saturation, SpO_2) at rest and with exercise; an assessment of diffusion capacity is optional. Respective test results should be submitted to the sponsor.

The medical monitor needs to be consulted to confirm eligibility if test results indicate significantly impaired pulmonary function, eg, resting pulse oximetry < 90% on room air and further desaturation upon exercise, absolute forced expiratory volume (FEV1) value < 1L, FEV1 of age and sex adjusted predicted performance levels < 50%, diffusing capacity of the lungs for carbon monoxide (DLCO) (if performed) < 40% of age and sex adjusted predicted performance levels (Pellegrino et al 2005).

Tests may be repeated as clinically indicated while on study.

Notes for sites in Japan: at each subsequent visits before dosing, an assessment of oxygenation is to be performed including at least SpO_2 at rest and with exercise according to Appendix 1, an assessment of diffusion capacity is optional; a spirometry test may be repeated as clinically indicated.

7.2.6. HIV Serology Test

Note for Germany and where required by Health Authority or local guidance: An HIV serology test (including antigen and/or antibodies) will be conducted at baseline for the patients with unknown HIV status.

7.2.7. COVID-19 Test

A COVID-19 test may be conducted according to local practice.

7.3. Enrollment

7.3.1. Confirmation of Eligibility

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

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

7.3.2. Randomization

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

7.4. Study Drug Dispensation

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

7.5. Safety Assessment

7.5.1. Vital Signs

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

The patient's vital signs are required to be recorded within 60 minutes before, during, and within 30 minutes after completion of infusion of study treatment (ociperlimab and tislelizumab in Arm A, tislelizumab in Arm B, and durvalumab in Arm C). For subsequent infusions, vital signs will be collected within 60 minutes before infusion and, if clinically indicated, during and within 30 minutes after the completion of infusion.

Weight is required to be measured once on the scheduled assessment day and before study treatment if there is any. Height measurements are only required at screening.

Note for sites in Germany: when both ociperlimab and tislelizumab are administered, vital signs are required to be measured at 3 timepoints (within 60 minutes before, during, and within 30 minutes after the completion of infusion) throughout all treatment periods. When tislelizumab alone or durvalumab is administered, the 3-timepoint vital signs are required for the first infusion, and vital signs within 60 minutes before infusion are required at subsequent infusions. Details of vital signs are specified in Appendix 1.

7.5.2. Physical Examinations

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

Patients should be solicited at every visit for any vision changes (eg, blurred/distorted vision, blind spots, change in color vision, photophobia, tenderness/pain, and eyelid swelling) and should be referred to an ophthalmologist if further evaluation is needed.

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

Note for sites in Japan: Bilateral lung auscultation will be performed at screening and subsequent visits as described in Appendix 1.

7.5.3. Eastern Cooperative Oncology Group Performance Status

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

7.5.4. Laboratory Safety Tests

Local and/or central laboratory assessments of clinical chemistry, hematology, coagulation, and urinalysis will be conducted as outlined in Appendix 2 per the timepoints shown in Appendix 1.

If hematology and serum chemistry at screening are not performed within 7 days before the planed C1D1, these tests should be repeated and reviewed before randomization. If a coagulation test was performed and reviewed during screening, it is not mandated to repeat before C1D1 unless the investigator deems it necessary. Hematology, serum chemistry (including liver function tests), creatine kinase (CK) and creatine kinase cardiac muscle isoenzyme (CK-MB) as specified in Appendix 2 should be performed weekly for the first 9 weeks for Arm A and B (equal to 3 cycles), first 8 weeks for Arm C (equal to 4 cycles for Q2W regimen, 2 cycles for Q4W regimen), at the beginning of each subsequent cycle, and the EOT Visit (Appendix 1). After Cycle 1, these laboratory tests are to be performed and reviewed within 48 hours before study treatment administration. Urinalysis is to be conducted during the treatment period only if clinically warranted.

Local laboratory assessments will include the following:

- Hematology (complete blood count [CBC], including hemoglobin, hematocrit, white blood cell [WBC] count [neutrophils and lymphocyte], and platelet count)
- Serum chemistry (glucose, blood urea nitrogen [BUN] or urea, creatinine, sodium, potassium, magnesium, chloride, calcium, phosphorus, direct bilirubin, total bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase [LDH], total protein, albumin)
- Coagulation test (international normalized ratio, prothrombin time, and activated partial thromboplastin time)
- Urine or serum pregnancy test (for women of childbearing potential, including premenopausal women who have had a tubal ligation)
- Urinalysis (complete [including, but not limited to specific gravity, pH, glucose, protein, ketones] and/or microscopic at screening and if clinically indicated)
- Thyroid function testing (thyroid stimulating hormone [TSH], free T3 or total T3, free T4 or total T4).

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

7.5.4.1. Cardiac Enzyme Monitoring

Although immune-mediated myocarditis is a rare complication of immune checkpoint inhibitors, serum CK and CK-MB are monitored in all tislelizumab studies to protect study patients and to quantify the risk of muscle inflammation (see Appendix 1 for the blood collection schedule and Appendix 12 for guidelines for management of suspected immune-mediated myocarditis, respectively). Serum troponins may be substituted per local guideline if used consistently through the study.

Serum CK and CK-MB testing will be implemented for all patients at screening, at scheduled visits during the treatment periods, and at the EOT Visits. In the event that CK-MB fractionation is not available, serum troponins (troponin I and/or T) measurements will be performed instead per local guidelines if used consistently throughout the study.

7.5.5. Electrocardiograms

The ECG recordings will be obtained during screening, and as clinically indicated during the treatment period, and at the EOT 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.

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

7.5.6. Adverse Events

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

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

7.5.7. Hepatitis B and C Testing

Testing will be performed by a central laboratory and/or the local laboratory at screening (and as clinically indicated) and will include HBV/HCV serology (HBsAg, hepatitis B surface antibody [HBsAb], hepatitis B core antibody [HBcAb], and HCV antibody). In the case of positive HBsAg result or positive HCV antibody result, these tests will be followed by viral load assessment (HBV DNA or HCV RNA) at screening.

For patients who have detectable HBV DNA or HCV RNA at screening or upon repeated testing, the respective viral load test will be performed every 12 weeks. A detailed schedule is provided in Appendix 1.

7.6. Tumor and Response Evaluations

Tumor imaging will be performed ≤ 28 days before randomization. Results of standard-of-care tests or examinations performed before obtaining informed consent and ≤ 28 days before randomization may be used for the purposes of screening rather than repeating the standard-of-care tests. During the study, tumor imaging will be performed approximately every 9 weeks (± 7 days) from randomization for the first 54 weeks, and every 12 weeks (± 7 days) thereafter, based on RECIST v1.1. If a tumor assessment is missed or conducted outside of the specified assessment window, all subsequent scans should be conducted according to the planned schedule. Tumor assessments must 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.

Screening assessments must include:

- CT scans (with oral/intravenous contrast, unless contraindicated) of the chest, abdomen, and pelvis; brain imaging by MRI or CT with contrast; and bone scan. Note: If PET/CT is performed at screening, bone scan is not required at screening.
- PET/CT or bone scan should be performed for the whole body, or as sufficient to rule out distant metastases (eg, from skull base to knees).
- If the CT scan portion of PET/CT is with contrast and is of sufficiently high quality, a separate CT scan at screening for the chest, abdomen, and pelvis can be skipped.
- MRI (or CT scan if MRI is contraindicated or not readily available) with contrast of the head is required at screening.
- If the patient's disease stage was confirmed as Stage III NSCLC (AJCC 2017) based on PET/CT or bone scan and brain imaging via MRI or CT with contrast performed before cCRT, these tests are not required to repeat at screening.

If the CT scan portion of FDG-PET/CT is not qualified enough as specified above, screening assessment must include CT scans (with oral/intravenous contrast, unless contraindicated) of the chest, abdomen, and pelvis. At each subsequent assessment, at least CT scans (with oral/intravenous contrast, unless contraindicated) of the chest and abdomen, are included. If contraindication exists, other modalities can be allowed after consultation with the medical monitor (eg, MRI, CT without contrast).

All measurable and evaluable lesions should be assessed and documented at the Screening Visit and reassessed at each subsequent tumor evaluation. The same radiographic procedure used to assess disease sites at screening must be used throughout the study (eg, the same contrast protocol for CT scans).

- If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the study, a noncontrast CT of the chest plus a contrast-enhanced MRI (if possible) of abdomen ± pelvis should be performed.
- If a CT scan for tumor assessment is performed on a PET/CT scanner, the CT acquisition must be consistent with the standards of a diagnostic CT scan.
- MRI (or CT scan if MRI is contraindicated or not readily available) of the head or bone scan or PET/CT is performed if clinically indicated at the discretion of investigator before the discontinuation of tumor assessment.
- At the investigator's discretion, other methods of assessment of target lesion and non-target lesions per RECIST v1.1 may be used.

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

Administration of study treatment will continue for up to 12 months, or until PD as assessed by the investigator per RECIST v1.1, unacceptable toxicity, death; or another discontinuation criterion is met. Once PD is assessed by the investigator, the IRC is required to complete central image review and convey the results to the investigator as soon as possible. If the investigator-

assessed PD is NOT confirmed by the IRC, the medical monitor will discuss the findings with the investigator and the study treatment is recommended to continue as long as this is considered to be in the best interest of the patient. In the situation where the investigator believes the patient must urgently begin subsequent systemic therapy without waiting for confirmation of PD by IRC, the investigator must contact the medical monitor to inform them of the plan to urgently discontinue study treatment.

A patient who discontinues study treatment for reasons other than disease progression assessed by the IRC (eg, toxicity, PD by the investigator, completion of the 12-month treatment) will continue to undergo tumor assessments following the original plan until the patient experiences PD per RECIST v1.1 by the IRC, withdraws consent, is lost to follow-up, dies, or until the study terminates, whichever occurs first.

Study treatment beyond initial PD per RECIST 1.1

If at the investigator's discretion a patient could continue to benefit from ociperlimab and tislelizumab combination treatment or tislelizumab or durvalumab after PD per RECIST v1.1 assessed by the IRC or investigator, the patient may continue their assigned treatment. The following criteria must be met in order to treat patients who may continue to benefit from study treatment after PD:

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

The decision to continue study treatment beyond initial PD per RECIST v1.1 assessed by the IRC or investigator must be agreed upon with the medical monitor and documented in the study records.

Tumor assessment should continue as planned in patients receiving study treatment beyond initial PD per RECIST v1.1 assessed by the IRC or investigator. Tumor assessment in such patients should continue until study treatment discontinuation.

Second Progression

Following the first progression assessed by IRC, patients will be assessed every 12 weeks (± 7 days) for a second progression (using the patient's status at the first progression as reference for assessment of second progression). A patient's second progression status is defined according to local standard clinical practice and may involve any of: objective radiological, symptomatic progression or death. Measurements per RECIST v1.1 will not be collected for assessment of PFS2. The date of PFS2 assessment and investigator's opinion of progression status (progressed or non-progressed) at each assessment will be recorded in the eCRF.

7.7. Pharmacokinetic and Antidrug Antibody Testing

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

PK and ADA assays of ociperlimab and tislelizumab will be managed through a central laboratory. Serum samples will be assayed for ociperlimab and tislelizumab concentrations using validated immunoassays.

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

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

7.8. Biomarker

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

Tissue-based biomarkers, including but not limited to the expression of TIGIT, CD226, CD155, CD112, and PD-L1, GEP, TMB, MSI, gene mutation profiles, and TILs at baseline and at disease progression/reoccurrence will be tested. (Note: For the sites in mainland China, tissues will be obtained to test the expression of TIGIT, CD226, CD155, CD112, and PD-L1, GEP, TMB, MSI, gene mutation profiles, and TILs at baseline and at disease progression/reoccurrence).

Patients are required to provide tumor tissues (archival tumor tissues collected before cCRT [FFPE blocks containing tumor [preferred] or approximately 15 [≥ 6] freshly cut unstained FFPE slides]). If archival tumor tissues are not available, a fresh tumor biopsy is required prior to the first dose of cCRT. Acceptable fresh biopsy samples include core needle biopsies for deep tumor tissue or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.

If clinically feasible, it is highly recommended to obtain a tumor biopsy at the time of disease progression to explore the immune- or tumor-related biomarkers and biological changes that might drive disease progression or acquired resistance to ociperlimab and tislelizumab. Blood samples must be collected at C1D1 (predose) for a blood-based biomarker test. Optional blood will be collected at C3D1 (predose), C4D1 (predose), and at the EOT Visit after the disease progression (Appendix 1). All these blood samples will be collected to explore the association of blood-based biomarkers with response, resistance, and prognosis. (Note: Blood-based

biomarkers, including ctDNA, TMB, MSI, EVs and gene mutational profiles, will be explored in the blood samples which will be collected in the sites in China mainland).

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

7.9. Health-Related Quality of Life

Patients will be asked to complete 5 PROs, that include the EORTC QLQ-C30 (Appendix 7), EORTC QLQ-LC13 (Appendix 8), EQ-5D-5L questionnaires (Appendix 9), PGI-S (Appendix 10), and PRTSE (Appendix 11) before any clinical activities are performed during on-study clinic visits according to the schedule in Appendix 1. The questionnaires will be provided in the patient's preferred language.

7.10. Visit Windows

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

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other events, the visit should be scheduled for the nearest feasible date (the visit window is provided in Appendix 1), with subsequent visits conducted according to the planned schedule every 3 weeks (Arm A and Arm B) or every 2 or 4 weeks (Arm C) from C1D1.

7.11. Unscheduled Visits

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

If an unscheduled visit is necessary to assess toxicity or for suspected PD, 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 Treatment

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, has been observed in animal models treated with ociperlimab. Furthermore, in the absence of activation, peripheral effector T cells do not typically express TIGIT, thereby minimizing any potential negative additive 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 workup procedures for suspected imAEs are provided in Appendix 12.

8.1.2. Risks Associated With Durvalumab

Durvalumab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that binds to PD-L1 and blocks the interaction of PD-L1 with PD-1 and CD80. The PD-L1/PD-1 pathway is involved in peripheral tolerance; therefore, such therapy may increase the risk of imAEs similar to PD-L1/PD-1 class drugs, specifically the induction or enhancement of autoimmune conditions. The risks are immune-mediated pneumonitis, hepatitis, colitis, endocrinopathies, nephritis, dermatologic reactions; and other immune-mediated adverse reactions (incidence of less than 1%) such as aseptic meningitis, hemolytic anemia, immune thrombocytopenic purpura, myocarditis, myositis, and ocular inflammatory toxicity, including uveitis and keratitis. Besides immune-related side effects, and infusion-related reactions are common. Overall infection is also very common.

Refer to the durvalumab prescribing information for details.

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 first dose of the study treatment 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, clinical chemistry, etc), and other assessments including those listed in Appendix 1. In addition, patients will be closely monitored for the development of any signs or symptoms of autoimmune conditions or infection.

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

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

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

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

8.3. Adverse Events

8.3.1. Definitions and Reporting

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

Examples of AEs include:

- Worsening of a chronic or intermittent pre-existing condition, including an increase in severity, frequency, duration, and/or has an association with a significantly worse outcome
- New conditions detected or diagnosed after study treatment administration even though the condition might 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 treatment 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 NCI-CTCAE v5.0.

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

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care, activities of daily living
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

Note: The terms “severe” and “serious” are not synonymous. Severity is a measure of intensity (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 treatment and the occurrence of each AE or SAE using best clinical judgement. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, and other risk factors, and the temporal relationship of the AE or SAE to the study treatment will be considered and investigated. The investigator should consult the Tislelizumab Investigator’s Brochure, Ociperlimab Investigator’s Brochure, durvalumab prescribing information in the determination of his/her assessment.

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always assesses causality for every SAE before transmission of the SAE report to the sponsor because the causality assessment is 1 of the criteria used when determining

regulatory reporting requirements. The investigator may change his/her opinion of causality considering follow-up information, amending the SAE report accordingly.

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

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

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

- There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out
- There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
- There is some evidence to suggest a causal relationship (eg, the AE occurred within a reasonable time after administration of the study treatment[s]). However, the influence of other factors may have contributed to the AE (eg, the patient's clinical condition or other concomitant AEs).

8.3.4. Follow-up of Adverse Events

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

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

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

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

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

8.3.5. Laboratory Test Abnormalities

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

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

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (eg, alkaline phosphatase and bilirubin 5 x ULN associated with cholestasis), only the diagnosis (ie, cholestasis) should be recorded on the AE 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 AE eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

8.4. Definition of a Serious Adverse Event

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

- Results in death
- Is life-threatening

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

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

8.5. Suspected Unexpected Serious Adverse Reaction

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

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

8.6.1. Adverse Event Reporting Period

After the main ICF has been signed, during the screening period, only SAEs should be collected and reported to the sponsor.

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. Immune-mediated AEs (serious or nonserious) should be reported until 90 days after the last dose of ociperlimab, tislelizumab, or durvalumab, regardless of whether the patient starts a new anticancer therapy. All SAEs considered related to the study treatment(s) that are brought to the attention of the investigator should be reported regardless of time since the last dose of treatment.

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

Table 8: Guidance for Duration of Recording New or Worsening Adverse Events in 3 Arms

Event Type	Record new or worsening events that occur during this period	
	Begin	**End**
SAEs[a]	Signing of informed consent	Up to 30 days after last dose, initiation of new anticancer therapy, death, withdrawal of consent, or loss to follow-up, whichever occurs first
Nonserious AEs due to PD	Do not record (see Section 8.6.4)	
All nonserious AEs, except those due to PD	First dose of study 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-mediated 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, progressive disease; SAE, serious adverse event.
[a] All SAEs considered related to the study treatment(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: Time Frames and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

	Time frame for sending initial report	Documentation method	Time frame for sending follow-up report	Documentation method	Reporting method
All SAEs	Within 24 hours after first knowledge of the AE	SAE report	As expeditiously as possible	SAE report	Email or fax SAE form or pregnancy form

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

8.6.2.2. Completion and Transmission of the Serious Adverse Event Report

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

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

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

The sponsor will provide contact information for SAE receipt.

8.6.2.3. Regulatory Reporting Requirements for Serious Adverse Events

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

The investigator, or 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, tislelizumab, and durvalumab studies.

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

8.6.3. Eliciting Adverse Events

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

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

8.6.4. Disease Progression

PD, which is expected in this study population and measured as an efficacy endpoint, should not be recorded as an AE term. Similarly, nonserious AEs that are clearly consistent with the pattern of progression of the underlying disease and are considered unequivocally due to 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 AE. If the only information available is death and the cause of death is unknown, then the death is reported as an event (eg, "death," "death of unknown cause," or "death unexplained").

8.6.6. Pregnancies

If a female patient or the female partner of a male patient becomes pregnant while the patient is receiving study treatment or within 120 days after the last dose of ociperlimab and tislelizumab in Arm A or tislelizumab in Arm B, or within 90 days after the last dose of durvalumab in Arm C, a pregnancy report form must be completed and expeditiously submitted to the sponsor to facilitate outcome follow-up. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

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

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

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

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

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

- Tislelizumab Investigator's Brochure
- Ociperlimab Investigator's Brochure
- Durvalumab prescribing information

8.6.8. Assessing and Recording Immune-Mediated Adverse Events

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

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

An extensive list of potential imAEs appears in Section 8.7.3, Table 11. All conditions like those listed should be evaluated to determine whether they are imAEs based on a similar diagnostic process to those reactions that are presented in more detail in Appendix 12.

8.6.9. Recording Infusion-Related Reactions

The symptoms of infusion-related reactions may include but are not limited to fever, chills/rigor, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness, or hypertension. Severe reactions may include acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, or cardiogenic shock. Each individual sign and symptom of an infusion reaction should be recorded each as a separate AE in 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 in Arm A on Day 1 of Cycle 1 and Cycle 2, patients must be monitored for at least 2 hours afterwards in an area with resuscitation equipment and emergency agents; similarly, after infusion of tislelizumab in Arm B on C1D1 and C2D1, patients will be monitored for ≥ 1 hour. From Cycle 3 onward, at least a 60-minute monitoring period is required in an area with resuscitation equipment and emergency agents for Arm A, and for Arm B, the monitoring period is at least 30 minutes.

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

8.7.1. Infusion-Related Reactions

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

Treatment modification for symptoms of infusion-related reactions due to study drugs is provided in Table 10.

Table 10: Treatment Modification for Symptoms of Infusion-Related Reactions Due to Study Drugs

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

NCI-CTCAE grade	Treatment modification for Ociperlimab and Tislelizumab
initial improvement; hospitalization indicated for clinical sequelae.	
Grade 4 – life-threatening Life-threatening consequences; urgent intervention indicated.	Immediately stop the infusion. Proper medical management should be instituted as described in the text following this table. The patient should be withdrawn from the study treatment. Hospitalization is recommended.

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

In Arm A and Arm B, 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. If the patient has a second infusion-related reaction (≥ Grade 2) on the slower infusion rate, the infusion should be discontinued, and the patient should be withdrawn from ociperlimab and tislelizumab treatment.

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

NCI-CTCAE Grade 3 or 4 infusion 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 antihistamine, antipyretic, glucocorticoids, epinephrine, bronchodilators, and oxygen.

8.7.2. Severe Hypersensitivity Reactions and Flu-Like Symptoms

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

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

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

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

8.7.3. Immune-Mediated Adverse Events

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

A list of potential imAEs is shown below in Table 11. All conditions similar to those listed should be evaluated in patients receiving ociperlimab and tislelizumab in Arm A, tislelizumab in Arm B to determine whether they are immune-mediated.

Recommendation for diagnostic evaluation and management of imAEs is based on ESMO and American Society of Clinical Oncology guidelines (Haanen et al 2017; Brahmer et al 2018) and common immune-mediated toxicities are detailed in Appendix 12. For any AEs not included in Appendix 12, refer to the American Society of Clinical Oncology Clinical Practice Guideline (Brahmer et al 2018) for further guidance on diagnostic evaluation and management of immune-mediated toxicities.

Table 11: 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
Musculoskeletal	arthritis; arthralgia; myalgia; myasthenic syndrome/myasthenia gravis; myositis
Blood	anemia; leukopenia; thrombocytopenia

Body system affected	Events
Renal	interstitial nephritis; glomerulonephritis; acute renal failure
Cardiac	pericarditis; myocarditis; heart failure
Neurologic	encephalitis; meningitis; meningoradiculitis; meningoencephalitis; Guillain-Barre syndrome; neuropathy

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

Recommendations for managing imAEs are detailed in Appendix 12.

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

8.7.4. Adverse Events of Special Interest of Durvalumab

Infusion-related reaction, infection, and imAEs are of special interest with durvalumab. Please refer to durvalumab prescribing information which has been approved by local health authority. Appendix 15 provides recommended dosage modifications from the durvalumab prescribing information approved by the US FDA for reference.

9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

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

All the analyses defined in this section apply to the patients enrolled within the updated PA 2.0 only, unless otherwise specified.

9.1. Statistical Analysis

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

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

There are a maximum of 2 PFS analyses for the primary efficacy endpoints. Any additional data for ongoing participants following the final analysis will be further summarized in a final study report.

9.1.1. Randomization Methods

As discussed in Section 7.3.2, patients will be randomized using the IRT system for this study by permuted block stratified randomization with stratification factors of age (< 65 years versus ≥ 65 years), PD-L1 expression on TC (≥ 50% versus < 50%), and histology (squamous versus nonsquamous). The PD-L1 expression status will be closely monitored. Enrollment of patients with expression of PD-L1 1% to 49% of TC will be stopped as necessary through the IRT system upon reaching around 50% to ensure the population are close to the natural PD-L1 expression prevalence.

9.1.2. Analysis Sets

The Intent-to-treat (ITT) Analysis Set includes all randomized patients. Patients will be analyzed according to their treatment assigned at randomization. This will be one of the primary analysis sets for demography and efficacy analyses.

The PD-L1 ≥ 50% Analysis Set is a subset of the ITT Analysis Set including patients with ≥ 50% of TCs with membrane positivity for PD-L1 at any intensity above background staining using VENTANA PD-L1 (SP263) assay. Patients will be analyzed according to their treatment assigned at randomization. This will be the other primary analysis set for demography and efficacy analyses.

The Safety Analysis Set includes all randomized patients who received ≥ 1 dose of study treatment. This will be the primary analysis set for all safety analyses.

PD-L1 ≥ 50% Safety Analysis Set is a subset of the Safety Analysis Set including patients whose PD-L1 ≥ 50%. This will be the analysis set for the safety analyses in patients with PD-L1 ≥ 50%.

The PK Analysis Set includes all patients who received any dose of any component of study treatment per the protocol, for whom any quantifiable postdose PK data are available.

The Immunogenicity Analysis Set includes all patients who received any dose of any component of study treatment for whom both baseline ADA result and at least 1 postbaseline ADA result are available.

9.1.3. Patient Disposition

The number of patients randomized, treated, and discontinued from the study treatment and/or study and those with critical protocol deviations will be counted. The primary reason for study treatment 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) as of 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 will be summarized using descriptive statistics in the ITT Analysis Set. Continuous variables include age, weight, vital signs, time since initial cancer diagnosis, etc. Categorical variables include sex, ECOG Performance Status, region/country, race, etc.

9.1.5. Prior and Concomitant Medications

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

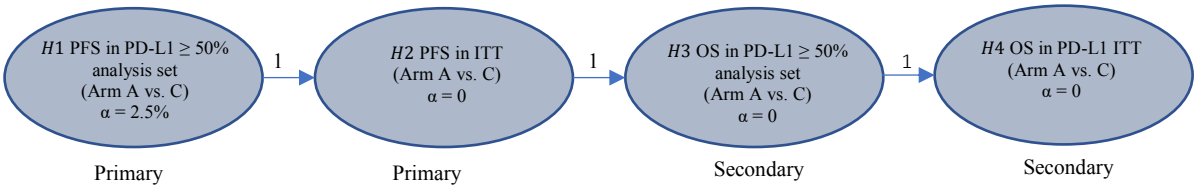
9.2. Efficacy Analyses

The familywise type I error will be strongly controlled at 1-sided level of 0.025. PFS analysis in Arms A and C will be carried out in the PD-L1 ≥ 50% Analysis Set first. A formal statistical test of PFS in the ITT Analysis Set will be performed only if the PFS analysis in the PD-L1 ≥ 50% Analysis Set is statistically significant favoring ociperlimab + tislelizumab. If the null hypothesis for PFS between Arm A and Arm C in the ITT Analysis Set is rejected, the secondary endpoint OS in PD-L1 ≥ 50% and ITT Analysis Sets between Arm A and Arm C will be tested

sequentially. There is one interim analysis planned at around 75% information fraction of PFS events in each analysis set across Arm A and C.

See Figure 4 for the fixed-sequence testing strategy diagram of the study.

Figure 4: Fixed-Sequence Testing Strategy for Primary and Key Secondary Endpoints



Abbreviations: PFS, progression-free survival; OS, overall survival.

9.2.1. Primary Efficacy Analysis

9.2.1.1. Primary Estimand

Primary estimand is defined in Section 2.2.

9.2.1.2. Primary Analysis for Primary Estimand

PFS by IRC comparison between Arm A and Arm C in PD-L1 ≥ 50% and ITT Analysis Set:

The null hypothesis to be tested: HR (A vs C) ≥ 1

against the alternative: HR (A vs C) < 1

The null hypothesis will be tested using a log-rank test, stratified by stratification factors at randomization (age, PD-L1 expression [in ITT Analysis Set only] and histology), in the PD-L1 ≥ 50% and ITT analysis sets sequentially, as described above.

PFS distribution will be estimated using the Kaplan-Meier method in the PD-L1 ≥ 50% and ITT Analysis Set.

The median PFS and the cumulative probability of PFS at every 3 months including PFS-6m and PFS-12m if estimable, will be calculated for each treatment arm and presented with 2-sided 95% CIs. Kaplan-Meier survival probabilities for each arm will be plotted over time.

The treatment effect will be estimated by fitting a Cox regression model to PFS including the treatment arm as a factor and stratification factors at randomization (age, PD-L1 expression [in ITT only] and histology) as strata. From this model, the HR of PFS will be estimated and presented with a 2-sided 95% CI.

9.2.1.3. Handling of Missing Values Not Related to Intercurrent Event

PFS will be censored at the last adequate tumor assessment for the following:

- patients without disease progression or death as of the clinical cutoff date

- patients who, as of the clinical cutoff date, have withdrawn consent for the study or are lost to follow-up
- patients with a PFS event (PD or death) after ≥ 2 missing or non-adequate tumor assessments

PFS will be censored at the date of randomization if no baseline or any post-baseline tumor assessments and without death ≤ 19 weeks after randomization.

The above text follows the PFS censoring rule specified in Tables C1 and C2 of Appendix C of the FDA "Guidance for industry clinical trial endpoints for the approval of non-small cell lung cancer drugs and biologics (2015)" (US FDA 2015).

9.2.1.4. Sensitivity Analyses/Supplementary for Primary Endpoint/Estimand

Sensitivity analyses (eg, unstratified Cox model or PFS per investigator assessment) and supplementary analyses (eg, ignoring subsequent anticancer therapy when driving PFS) may be considered and will be detailed in the SAP.

9.2.2. Efficacy Analysis for Key Secondary Estimand

9.2.2.1. Definition of Key Secondary Estimand

Key secondary estimand in terms of OS is defined in Section 2.3.

9.2.2.2. Primary Analysis for Key Secondary Estimand

OS comparison between Arm A and Arm C in PD-L1 ≥ 50% and ITT Analysis Sets:

The null hypothesis to be tested: HR (A vs C) ≥ 1

against the alternative: HR (A vs C) < 1

The null hypothesis will be tested using a log-rank test, stratified by stratification factors at randomization (age, PD-L1 expression [in ITT only] and histology). OS test in PD-L1 ≥ 50% and ITT analysis set will be conducted sequentially at 1-sided significance level of 0.025, after both null hypotheses of PFS are rejected.

OS distribution will be estimated using the Kaplan-Meier method in the PD-L1 ≥ 50% and ITT Analysis Sets.

The median OS and the cumulative probability of OS at every 6 months including OS-6m and OS-12m if estimable, will be calculated for each treatment arm and presented with 2-sided 95% CIs. Kaplan-Meier survival probabilities for each arm will be plotted over time.

The treatment effect will be estimated by fitting a Cox regression model to the OS times including the treatment arm as a factor and stratification factors at randomization (age, PD-L1 expression [in ITT only] and histology) as strata. From this model, the HR of OS will be estimated and presented with a 2-sided 95% CI.

For patients who are alive by the clinical cutoff date, OS will be censored at the last known alive date. Detailed derivation and imputation rule of last known alive date will be defined in the SAP.

9.2.2.3. Sensitivity Analyses/Supplementary for Key Secondary Endpoint/Estimand

Sensitivity analyses (eg, unstratified Cox model) and supplementary analyses (eg, Max-Combo) may be considered and will be detailed in the SAP.

9.2.3. Other Secondary Efficacy Analysis

Overall Response Rate (ORR)

ORR by both the IRC and the investigator per RECIST v1.1 in both PD-L1 ≥ 50% and ITT Analysis Set will be summarized, between Arm A versus Arm C. Two-sided 95% CI of ORR will be calculated using the Clopper-Pearson method in the ITT analysis set. The odds ratio for ORR between treatment arms will be calculated using the Cochran-Mantel-Haenszel (CMH) method adjusting for stratification factors at randomization (age, PD-L1 expression [in ITT only] and histology), and its two-sided 95% CIs will be calculated. Mantel-Haenszel common risk difference in ORR will be estimated, with its 95% confidence interval constructed by a normal approximation and Sato's variance estimator. The proportion for each of the response categories including CR will be presented by treatment arm.

Duration of Response (DOR)

DOR will be analyzed among the responders in PD-L1 ≥ 50% and ITT Analysis Set based on assessment by the IRC and the investigator, between Arm A versus Arm C. All the censoring rules for PFS primary analysis would be applied to DOR as well.

The Median and other quantiles of DOR and the cumulative probability of DOR at every 3 months if estimable, will be calculated for each treatment arm and presented with 2-sided 95% CIs.

Time to Death or Distant Metastasis (TTDM)

TTDM by both the IRC and the investigator per RECIST v1.1 in PD-L1 ≥ 50% and ITT Analysis Set between Arm A versus Arm C will be analyzed. The detailed censor rule will be defined in the SAP.

Progression-free survival after next line of treatment (PFS2)

PFS2 in PD-L1 ≥ 50% and ITT Analysis Set, between Arm A versus Arm C, will be analyzed similarly as the primary analysis of the primary estimand. The detailed censor rule will be defined in the SAP.

Health-Related Quality of Life (HRQoL)

HRQoL will be analyzed and compared between Arm A versus Arm C in the PD-L1 ≥ 50% and ITT Analysis Sets via the postbaseline scores of EORTC QLQ-C30's Global Health Status/QoL (GHS), functional scales and symptom scores and symptoms single item scores, EORTC QLQ-LC13's index score and symptoms scales and single item scores, and EQ-5D-5L descriptive scale scores as well as the Visual Analogue Scale (VAS) scores. Observed values and changes from baseline will be summarized using descriptive statistics. Compliance rates (adjusted completion rates) will be reported for all the three questionnaires at each PRO data collection timepoint.

A mixed model repeated measure (MMRM) will be performed to evaluate and compare changes from baseline between Arm A and Arm C at the prespecified key visits Week 25 and 43, in the PD-L1 ≥ 50% and ITT Analysis Sets. The prespecified PRO endpoints of GHS used will be physical function, fatigue domains of QLQ-C30, dyspnea, coughing, hemoptysis and pain in chest, pain in arms and shoulders, and peripheral neuropathy domains of QLQ-LC13. The key clinical cycles are clinically justified as they both fall after the first and second scheduled tumor assessments.

Time to deterioration in the PRO endpoints will be estimated using Kaplan-Meier method between Arm A versus Arm B in the PD-L1 ≥ 50% and ITT Analysis Sets. Deterioration thresholds will be based the (Osoba et al 1998) definition and will be derived from the published 10-point EORTC threshold. Other sensitivity analysis would explore a secondary deterioration threshold using an anchor-based meaningful within-patient change (MWPC) framework as needed.

PD-L1 and TIGIT expression

PD-L1 and TIGIT expression will be evaluated before, after study treatment, or at disease progression/reoccurrence, and their association with clinical efficacy will be assessed when appropriate and data allow.

9.2.4. Exploratory Efficacy Analyses

Analyses of PFS, ORR, DOR, TTDM assessed by IRC and investigator per RECIST v1.1, OS, PFS2, and HRQoL in the PD-L1 ≥ 50% and ITT Analysis Sets, will also be conducted between Arm A versus Arm B. The comparisons are descriptive only and aim to evaluate the contribution of Ociperlimab as a component of the study.

Potential predictive markers, including but not limited to CD226, CD155, CD112, GEP, ctDNA, TMB, MSI, gene mutation profiles, EVs and TILs may be assessed when appropriate.

Compliance rates and scores of the PGI-S and PRTSE will be analyzed descriptively.

9.2.5. Subgroup Analyses

Subgroup analysis of PFS and OS will be descriptively conducted to assess the consistency of treatment effect across various subgroups. Details will be provided in the SAP.

9.3. Safety Analyses

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

9.3.1. Extent of Exposure

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

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

Patient data listings will be provided for all dosing.

9.3.2. Adverse Events

The AE verbatim descriptions (investigator's description from the eCRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be coded to MedDRA (Version 24 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 treatment up to 30 days following study treatment discontinuation or initiation of the first new systemic anticancer therapy after the last study treatment, whichever occurs first. Only those AEs that were treatment-emergent will be included in TEAE summary tables. Immune-mediated AEs (imAEs) will be identified from all AEs that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study treatment and up to 90 days from the last dose of study treatment, regardless of whether or not the patient starts a new anticancer therapy. If an imAE occurs outside of the above mentioned TEAE window it will not be classified as a TEAE. All imAEs will be reported separately. All AEs, treatment-emergent or otherwise, will be presented in patient data listings. COVID-19 related AEs will be summarized separately.

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 or higher within an SOC and PT, even if the patient experienced > 1 TEAE within a specific SOC and PT.

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

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

9.3.3. Laboratory Analyses

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

Laboratory parameters that are graded in NCI-CTCAE v5.0 or higher will be summarized by NCI-CTCAE grade. In the summary of laboratory parameters by NCI-CTCAE grade, parameters

with NCI-CTCAE grading in both high and low directions (eg, calcium, glucose, magnesium, potassium, and sodium) will be summarized separately.

9.3.4. Vital Signs

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

9.4. Pharmacokinetic Analyses

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

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

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

9.5. Immunogenicity Analyses

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

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

9.6. Other Exploratory Analyses

Summary statistics will be provided for exploratory biomarkers including but not limited to expression of CD226, CD155, CD112, GEP, ctDNA, TMB, MSI, gene mutation profiles, EVs, and TILs in tumor tissues and/or peripheral blood when appropriate and data allow.

An exploratory analysis of the potential correlation of these tumor tissue or blood-based biomarkers with response, resistance, and prognosis will be performed to understand disease pathobiology and explore potential predictive biomarkers when appropriate and data allow.

Summary of descriptive analysis will be provided for PGI-S and PRTSE in Arm A versus Arm C, among patients with PD-L1 ≥ 50% and ≥ 1%.

Patients randomized under PA 1.0 (Concurrent Part)

Analyses of PFS, ORR, DOR assessed by investigator per RECIST v1.1, OS, TTDM and HRQoL among randomized patients in Concurrent Part. The comparisons across 3 arms are descriptive only. In addition, for patients finish definitive cCRT treatment and receive at least 1 consolidation treatment, their PFS assessed by the investigator, will be analyzed separately.

Safety profile will be assessed among randomized patients who received at least one dose of study treatment in the Concurrent Part.

The cutoff for primary analyses of the Concurrent Part will be approximately 14 months after last patient randomized.

9.7. Sample Size Consideration

The sample size calculation is based on the number of events regarding primary efficacy analyses of PFS between Arm A and Arm C for both comparisons in the PD-L1 ≥ 50% and ITT Analysis Sets. Exponential distribution is assumed for PFS. To demonstrate efficacy with regards to PFS, the estimates of the number of events required are based on the following assumptions:

1. The randomization ratio for Arm A versus Arm B versus Arm C is 3:1:3.
2. A steady-state enrollment rate of 20 patients per month and an enrollment ramp-up duration of 12 months.
3. PFS evaluation dropout rate of 5% per 12 months.
4. The prevalence of PD-L1 ≥ 50% among ITT is approximately 50%. Enrollment of patients with PD-L1 < 50% might be stopped, if necessary, to ensure that the percentage of PD-L1 ≥ 50% is no less than 50% of the ITT analysis set.
5. Sequential testing procedure is implemented to control overall alpha at 2.5% one-sided. PFS analysis between Arm A versus Arm C in the PD-L1 ≥ 50% analysis set will be performed first, and PFS analysis between Arm A versus Arm C in the ITT analysis set will be carried out only if the PFS analysis in the PD-L1 ≥ 50% analysis set is statistically significant favoring Arm A.
6. One interim analysis is planned when approximately 75% of final PFS events have occurred for each PFS primary endpoint, using Lan-DeMets O'Brien-Fleming approximation spending function.
7. Median PFS in Arm C within both PD-L1 ≥ 50% and ITT analysis set is 24.9 months.

Table 12 below summarizes the statistical assumption and power in the sample size calculation in Arm A and C; and the total sample size of the study would be 700.

Table 12: Statistical assumptions, sample size and power

1-sided Alpha	Analysis Set	HR (A vs C)	mPFS in A	mPFS in C	Accrual Duration	Sample Size in A+C	# Events at FA in A+C	Power
0.025	PD-L1 ≥ 50%	0.6	41.5	24.9	41.3	300	141	85.2%
0.025	ITT	0.7	35.6	24.9	41.3	600	288	85.1%

Abbreviation: A: Arm A; C: Arm C; FA: final analysis; vs, versus

Sample size and power is calculated by EAST (Version 6.5) and R (Version 4.1.2). Details of interim analysis will be presented in Section 9.8.

9.8. Interim Analysis

There is 1 planned interim analysis for this study, using Lan-DeMets O'Brien-Fleming approximation spending function (Lan and DeMets 1983).

The interim analysis of PFS primary analysis will be performed at a later time when the target number of events in either the PD-L1 ≥ 50% or ITT Analysis Sets is reached, which is approximately 106 events in the PD-L1 ≥ 50% analysis set and 216 events in the ITT analysis set (75% of the target number of PFS events in each analysis set) among Arms A and C, approximately 45 months after first patient randomized. The final analysis of PFS will take place after approximately 141 and 288 PFS events have been observed in the 2 analysis sets, respectively, and approximately 56 months after the first patient is randomized. Event number and testing boundaries in p-value for primary analyses of PFS are shown in Table 13. The boundaries will be updated according to the actual numbers of events in the interim and final analyses, using the above prespecified alpha spending function.

Table 13: Event number, and Testing Boundaries of Interim Analyses and Final Analysis

Analysis Set	Type of Analysis	# Events	p-value for Efficacy IA	Approximate HR Threshold for Efficacy	Prob of Crossing Efficacy Boundary Under Alternative Hypothesis
PD-L1 ≥ 50%	IA	106	0.0097	0.635	61.5%
	FA	141	0.0221	0.713	85.2%
ITT	IA	216	0.0097	0.727	61.1%
	FA	288	0.0221	0.789	85.1%

10. STUDY COMMITTEES

10.1. Independent Review Committee

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

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

10.2. Independent Data Monitoring Committee

Safety monitoring and efficacy review will be performed by an IDMC. The first safety monitoring and review will occur after approximately 42 patients (≥ 18 patients each for Arm A and C, ≥ 6 patients for Arm B) have been randomized and treated for ≥ 30 days from C1D1 or no later than 6 months after first patient enrolled. The subsequent safety monitoring and review will be conducted as determined by the IDMC, or approximately every 6 months thereafter. The IDMC may recommend study modification including early termination of the study due to safety concerns, or for evidence of compelling efficacy at the pre-planned interim analyses. Enrollment may continue during these IDMC safety reviews. The function and membership of the IDMC will be described in the IDMC charter.

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

Following IDMC review and discussion, the sponsor will make all final decisions regarding any change in study conduct. More details could be found in the IDMC charter.

10.3. Steering Committee

The study conduct will be overseen by a steering committee composed of selected clinicians.

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

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

11.2. Access to Information for Auditing or Inspections

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

12. QUALITY ASSURANCE AND QUALITY CONTROL

12.1. Regulatory Authority Approval

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

12.2. Quality Assurance

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

12.3. Study Site Inspections

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

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

12.4. Drug Accountability

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

At study initiation, the monitor will evaluate the site's standard operating procedure for study drug disposal/destruction to ensure that it complies with the sponsor 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 International Council for Harmonisation E6 guideline for GCP and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will also comply with the requirements of the International Council for Harmonisation 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 IRB/IEC correspondence and approval of the amended ICF/other information and the approved amended ICF/other information must be forwarded to the sponsor promptly.

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

13.2.1. Protocol Amendments

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

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

13.3. Informed Consent

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

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

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

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

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

- names or initials (full or partial);
- full dates of birth;
- contact information (such as phone numbers or home or email addresses);

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

Patient personal and medical information obtained during this study is confidential and may only be disclosed to third parties as permitted by the signed ICF (or a separate authorization for the use and disclosure of personal health information that has been signed by the patient), unless permitted or required by law. In limited circumstances, such as in connection with insurance purposes or patient support services ancillary to certain study sites (eg, for patient travel or reimbursement), the principal investigator and site may provide certain of this personal or medical information to the sponsor or its representatives. Such personal or medical information may not be provided as part of the protocol (eg, as part of the eCRF, or on samples or reports submitted to the central lab).

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

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

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

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

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

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

13.5. Financial Disclosure

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

14. DATA HANDLING AND RECORD KEEPING

14.1. Data Collection and Management Responsibilities

14.1.1. Data Entry in the Electronic Case Report Form

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

14.1.2. Data Collection

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

Data collection in the eCRF should follow the instructions described in the eCRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered in the eCRF. The investigator or designee must sign the completed casebooks to attest to their accuracy, authenticity, and completeness.

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

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

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

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

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

14.2. Data Integrity and In-house Blinding

Due to the open-label design of the study, access to the patient-level clinical data in the EDC system will be assigned to predefined study personnel only. Functions/persons with access to the EDC system shall be prohibited from using the EDC system to generate unnecessary listings/summaries that may introduce unwanted bias, or share such outputs from the EDC system with other functions/persons who do not have access to the EDC. In addition, the central imaging vendor will perform the central imaging review without knowledge of treatment arm assignment. More details of data integrity and in-house blinding will be provided and described in the Data Integrity Protection Plan (DIPP).

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 2) patient clinical source documents.

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

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

Following closure of the study, the investigator must maintain all study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (eg, audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and personnel. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (eg, microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible, are a true and accurate copy of the original, and meet accessibility and retrieval standards, including 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 or local laws or regulations, or the sponsor's standards/procedures; otherwise, the retention period will default to 15 years.

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

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and the sponsor to store these in sealed containers 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 contract research organization managing the biological samples, for the shorter of a period of up to 10 years or as allowed by the IRB/IEC.

14.4. Protocol Deviations

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

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

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 International Council for Harmonisation Guideline for Structure and Content of Clinical Study Reports (ICH E3). An abbreviated report may be prepared in certain cases.

The results of this study will be published or presented at scientific meetings in a timely, objective, and clinically meaningful manner that is consistent with good science, industry and regulatory guidance, and the need to protect the intellectual property of the sponsor, regardless of the outcome of the study. The data generated in this clinical study are the exclusive property of the sponsor and are confidential. For a multicenter study, the first publication or disclosure of study results shall be a complete, joint multicenter publication, or disclosure coordinated by the sponsor. Thereafter, any secondary publications will reference the original publication(s). Authorship will be determined by mutual agreement and all authors must meet the criteria for authorship established by the International Committee of Medical Journal Editors or stricter local criteria (International Committee of Medical Journal Editors 2020).

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

14.6. Study and Study Center Closure

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

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

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

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

Financial compensation to 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, expertise, or other intellectual or industrial property rights that are conceived or reduced to practice by the study center personnel during the course of or as a result of the study are the sole property of the sponsor and are hereby assigned to the sponsor.

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

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

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

These restrictions do not apply to:

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

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

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16. APPENDICES

APPENDIX 1. SCHEDULE OF ASSESSMENTS

Assessment	Pre-screening [a]	Screening [b]	Treatment Cycles				End-of-Treatment Visit [c]	Safety Follow-Up [d]	Tumor assessment/Survival Follow-up [e]
			Cycles 1 to 3 (Arm A and B: every 21 days; Arm C every 14 or 28 [f] days)			≥ Cycle 4 and up to 12 months (Arm A and B: every 21 days; Arm C every 14 or 28 [f] days)			
Days (Window)	**-120 to the initiation of screening**	**-28 to -1**	**1 (+2 or ±3) [g]**	**8 (±3)**	**15 (±3)**	**1 (±3)**	**0 to 7 days**	**30 (±7), 60, 90, and 120 (±14) days after last dose**	**Every 12 weeks (±7 or 14 days)**
Prescreening informed consent [a]	X	-	-	-	-	-	-	-	-
Informed consent [b]	-	X	-	-	-	-	-	-	-
Inclusion/exclusion criteria	-	X	-	-	-	-	-	-	-
Randomization [h]	-	X	-	-	-	-	-	-	-
Demographics/medical history /prior medications or procedures[i]	-	X	-	-	-	-	-	-	-
Concomitant medication /procedures evaluation	-	Continuous from ≤ 28 days before randomization until 30 days after the last dose of study treatment							-
AE evaluation [j]	-	Continuous from informed consent until 30 days after the last dose of study treatment for AEs; 90 days after the last dose of ociperlimab or tislelizumab or durvalumab for imAEs. All SAEs considered related to the study treatment that are brought to the attention of the Investigator should be reported regardless of time since the last dose of treatment.							
Physical examination [k]	-	X	X	-	-	X	X	-	-
Vital signs/height and weight [l]	-	X	X	-	-	X	X	-	-
ECOG PS	-	X	X	-	-	X	X	-	-
Pulmonary function Test [m]	-	X	Clinically indicated; Notes for sites in Japan: SpO2 at each subsequent visits before dosing						
12-lead electrocardiogram	-	X	Only if clinically indicated				X	-	-
Hematology Laboratory [n]	-	X	X	X	X	X	X	-	-

Assessment	Pre-screening [a]	Screening [b]	Treatment Cycles				End-of-Treatment Visit [c]	Safety Follow-Up [d]	Tumor assessment/Survival Follow-up [e]
			Cycles 1 to 3 (Arm A and B: every 21 days; Arm C every 14 or 28 [f] days)			≥ Cycle 4 and up to 12 months (Arm A and B: every 21 days; Arm C every 14 or 28 [f] days)			
Days (Window)	**-120 to the initiation of screening**	**-28 to -1**	**1 (+2 or ±3) [g]**	**8 (±3)**	**15 (±3)**	**1 (±3)**	**0 to 7 days**	**30 (±7), 60, 90, and 120 (±14) days after last dose**	**Every 12 weeks (±7 or 14 days)**
Chemistry laboratory [n]	-	X	X	X	X	X	X	-	-
CK and CK-MB [n]	-	X	X	X	X	X	X	-	-
Coagulation laboratory [n]	-	X	X	-	-	X	X	-	-
Thyroid function (o)[o]	-	X	Cycle 3 or each cycle[o]			Every 2 cycles or each cycle[o]	X	-	-
HBV/HCV/HIV test[p]	-	X	As clinically indicated					-	-
Urinalysis [n]	-	X	As clinically indicated					-	-
β-hCG pregnancy test[q]	-	X	X	-	-	X	X	X	-
Tumor assessment CT/MRI	-	X	Tumor imaging will be performed approximately every 9 weeks (± 7 days) from randomization, for the first 54 weeks, and every 12 weeks (± 7 days) thereafter based on RECIST v1.1. Following the first progression assessed by IRC, patients will be assessed every 12 weeks (± 7 days) for a second progression (using the patient's status at the first progression as reference for assessment of second progression).						
FDG-PET/CT or bone scan; and brain MRI with contrast or head CT scan with contrast[r]	-	X	Only if clinically indicated						
QLQ-C30, QLQ-LC13, EQ-5D-5L[s]	-	-	Cycle 1 and every 6 weeks thereafter				X	-	-
PGI-S[s]	-	-	X	-	-	At Week 25 and Week 43	-	-	-
PRTSE[s]	-	-	Week 7, Week 25, and Week 43				-	-	-

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Assessment	Pre-screening [a]	Screening [b]	Treatment Cycles				End-of-Treatment Visit [c]	Safety Follow-Up [d]	Tumor assessment/Survival Follow-up [e]
			Cycles 1 to 3 (Arm A and B: every 21 days; Arm C every 14 or 28 [f] days)			≥ Cycle 4 and up to 12 months (Arm A and B: every 21 days; Arm C every 14 or 28 [f] days)			
Days (Window)	**-120 to the initiation of screening**	**-28 to -1**	**1 (+2 or ±3) [g]**	**8 (±3)**	**15 (±3)**	**1 (±3)**	**0 to 7 days**	**30 (±7), 60, 90, and 120 (±14) days after last dose**	**Every 12 weeks (±7 or 14 days)**
Pharmacokinetics[t]	-	-	X[t]	-	-	Cycle 5, 9, 17	X	-	-
Anti-ociperlimab and anti-tislelizumab blood samples[u]	-	-	X[u]	-	-	Cycle 5, 9, 17	X	-	-
Archived tumor[v]	X	-	-	-	-	-	-	-	-
Fresh tumor biopsy[v]	X (if needed)	-	-	-	-	-	X (optional)	-	-
Biomarkers: whole blood[w]	-	-	X[w]	-	-	X (optional)	X (optional)	-	-
EGFR/ALK/ROS1/RET testing on tumor tissue (if status not available)[x]	X	-							
Tislelizumab ± Ociperlimab or durvalumab administration	-	-	X	-	-	X	-	-	-
Survival status	-	-	-	-	-	-	-	X	X
Subsequent therapy since IP discontinuation	-	-	-	-	-	-	-	X	X

Abbreviations: ADA, antidrug antibody; AE, adverse event; ALK, anaplastic lymphoma kinase; β-hCG, beta human chorionic gonadotropin; C, Cycle ; cCRT, concurrent chemoradiotherapy; CD, cluster of differentiation; CK, creatine kinase; CK-MB, creatine kinase cardiac muscle isoenzyme; CT, computed tomography; D, day; DLCO, diffusing capacity of the lungs for carbon monoxide; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer-Quality of Life C30 questionnaire; EOT, End of Treatment; EQ-5D-5L, European Quality of Life-5 Dimensions health state classifier to 5 Levels; FDG-PET, fluorodeoxyglucose - positron emission tomography; FEV, forced expiratory volume; FFPE, formalin-fixed paraffin-embedded; GEP, gene expression profiling; 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; IEC, Independent Ethics Committee; IP, investigational product; IRB, Institutional Review Board; IRC, Independent Review Committee; IRT, integrated response technology; LC13, Lung Cancer Module of EORTC QLQ-C30; MRI, magnetic resonance imaging; NCI, National Cancer Institute;

NSCLC, non-small cell lung cancer; PD, progressive disease; PD-L1, programmed cell death protein-ligand 1; PK, pharmacokinetics; PRO, patient-reported outcomes; PGI-S, patient reported global impression of severity; RECIST v1.1, Response Evaluation Criteria in Solid Tumors Version 1.1; SAE, serious adverse event; TIL, tumor-infiltrating lymphocyte; TMB, tumor mutational burden.

[a] All patients will undergo prescreening for central evaluation of PD-L1 status up to 120 days before randomization. PD-L1 status will be determined centrally using either a previously obtained archival tumor tissue or fresh biopsy tissue sample collected prior to the initiation of cCRT. A separate prescreening informed consent must be obtained.

[b] Written informed consent is required before performing any study-specific tests or procedures at Screening Visit. 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.

[c] The date of End-of-Treatment (EOT) is defined as the date investigator determines that study treatment will no longer be used. For Arm A, patients shall have an EOT Visit only if both study drugs were discontinued. Patients shall have an EOT Visit within 7 days after the date investigator determines that study treatment will no longer be used, or before the initiation of a new anticancer treatment, whichever occurs first. However, the EOT Visit may occur later than 7 for specific circumstances, such as prolonged hospitalization. If routine laboratory tests (eg, hematology, serum chemistry, CK and CK-MB, coagulation, etc) are completed within 7 days before the EOT Visit, these tests need not be repeated. Tumor assessment is not specially required at the EOT Visit. Patients who discontinue study treatment before disease progression confirmed by the IRC will need to undergo tumor assessments as outlined in Section 7.6, in some cases the time window of tumor assessment might overlap with EOT and/or Safety Follow-up visit. In the cases the time window of EOT and Safety Follow-up visit overlapped, these two visits can be combined.

[d] The Safety Follow-up Visit could be completed at the site or by telephone. Note for sites in Germany: a 120-Day Safety Follow-up Visit for pregnancy test will be implemented at the site or by telephone.

[e] Patients whose disease has not progressed at the end of the 12-month study treatment period will continue to perform tumor imaging every 12 weeks (± 7 days) until progressive disease per RECIST v1.1. Following the first progression assessed by IRC, patients will be assessed every 12 weeks (± 7 days) for a second progression (using the patient's status at the first progression as reference for assessment of second progression). A patient's second progression status is defined according to local standard clinical practice and may involve any of: objective radiological, symptomatic progression or death. Measurements per RECIST v1.1 will not be collected for assessment of PFS2.Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (± 14 days) after the 90-Day Safety Follow-up Visit until death, loss to follow-up, withdrawal of consent, or end of study by sponsor. All patients will be followed for survival and subsequent anticancer therapy information unless a patient requests to be withdrawn from follow-up. Schedule of Survival Follow-up Visit can be modulated to combine with tumor assessment of PFS or PFS2 for operational convenience while keeping the follow-up visits interval as approximately every 12 weeks

[f] Durvalumab regimen:10 mg/kg Q2W (or 1500 mg Q4W where the dosage has been approved by a local health authority). For the patient whose body weight is < 30 kg, only the regimen of durvalumab 10 mg/kg Q2W is applicable. Refer to local prescribing information of durvaluamb for detailed instructions.

[g] Patients should have Cycle 1 Day 1 (C1D1) dosing initiated within 2 business days of randomization. For C2D1 and C3D1, patients should receive study drugs with ± 3 days.

[h] Patients will be randomized into either Arm A or Arm B or Arm C via IRT.

[i] Includes age or year of birth, sex, and self-reported race/ethnicity; history of treatment for the primary diagnosis, including prior medication, loco-regional treatment(s), and surgical treatment(s). Information on radiographic studies performed before study entry may be collected for review by the investigator. Pre-existing AEs at baseline should be recorded as medical history. Refer to Section 7.2.3 for additional information.

[j] The AEs and laboratory abnormalities will be graded per NCI-CTCAE v5.0. All AEs will also be evaluated for seriousness. After the main informed consent form has been signed, during the screening period, 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. Immune-mediated AEs (serious or nonserious) should be reported until 90 days after the last dose of ociperlimab, tislelizumab, or durvalumab regardless of whether or not the patient starts a new anticancer therapy. All SAEs considered related to the study treatment that are brought to the attention of the Investigator should be reported regardless of time since the last dose of treatment.

[k] At the Screening Visit, a complete examination will be conducted, including evaluations of 1) head, eyes, ears, nose and throat; 2) cardiovascular; 3) dermatological; 4) musculoskeletal; 5) respiratory; 6) gastrointestinal; and 7) neurological systems. At subsequent visits (and as clinically indicated), limited, symptom-directed physical examinations will be performed. For patients enrolled in Japan, bilateral lung auscultation will be performed at screening and subsequent visits.

[l] Vital signs collected on study include body temperature (˚C), pulse rate, and blood pressure (systolic and diastolic). Pulse rate and blood pressure should be collected while the patient is in a seated position after resting for 10 minutes. The patient's vital signs are required to be recorded within 60 minutes before, during, and within 30 minutes after the completion of infusion of study treatment (ociperlimab and tislelizumab in Arm A, tislelizumab in Arm B, and durvalumab in Arm C). For subsequent infusions, vital signs will be collected within 60 minutes before infusion and, if clinically indicated, during and within 30 minutes after the completion of infusion. Weight is required to be measured once on the scheduled assessment day and before study treatment if there is any. Height measurements are only required at screening. Note for sites in Germany: when both ociperlimab and tislelizumab are administered, vital signs are required to be measured at 3 timepoints (within 60 minutes before, during, and within 30 minutes after the completion of infusion) throughout all treatment periods. When tislelizumab alone or durvalumab is administered, the 3 timepoint vital signs are required for the first infusion, and vital signs within 60 minutes before infusion are required at subsequent infusions.

[m] Pulmonary function testing includes assessment of spirometry and oxygenation. The assessment of oxygenation should include at least pulse oximetry (percutaneous arterial oxygen saturation, SpO_2) at rest and with exercise; an assessment of diffusion capacity is optional. Respective test results should 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, absolute FEV1 value < 1L, FEV1 of age and sex adjusted predicted performance levels < 50%, DLCO (if performed) < 40% 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. Notes for sites in Japan: at each subsequent visits before dosing, an assessment of oxygenation is to be performed including at least SpO_2 at rest and with exercise, an assessment of diffusion capacity is optional; a spirometry test may be repeated as clinically indicated.

[n] Local and/or central laboratory assessments on serum chemistry, hematology, CK and CK-MB, coagulation, and urinalysis will be conducted, of which certain elements will be collected as specified in Appendix 2. If hematology and serum chemistry at screening are not performed within 7 days before the planed C1D1, these tests should be repeated and reviewed before randomization. If the coagulation test has been performed and reviewed during screening, it is not mandatory to repeat this test before C1D1 unless the investigator deems necessary. Hematology, serum chemistry (including liver function tests), CK and CK-MB as specified in Appendix 2 should be performed weekly for the first 9 weeks for Arm A and B (equal to 3 cycles) and first 8 weeks for Arm C (equal to 4 cycles for Q2W regimen, 2 cycles for Q4W regimen), at the beginning of each subsequent cycle, and the EOT Visit. After Cycle 1, these laboratory tests are to be performed and reviewed within 48 hours before study drug administration. Urinalysis is to be conducted during the treatment period only if clinically warranted. Refer to Section 7.5.4 and Section 8.3.5 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.

[o] Analysis of free T3 or total T3, free T4 or total T4, and thyroid stimulating hormone will be performed by a central laboratory or the local study site laboratory. Thyroid function tests will be performed at screening, every 2 cycles for Arm A and Arm B (ie, Cycles 3, 5, 7, etc.), every 2 cycles for durvalumab-Q2W (ie, Cycles 3, 5, 7, etc.) and every cycle for durvalumab-Q4W, and at the EOT Visit.

[p] Testing will be performed by a central laboratory and/or the local laboratory at screening (and as clinically indicated) and will include HBV/HCV serology (HBsAg, hepatitis B surface antibody [HBsAb], hepatitis B core antibody [HBcAb], and HCV antibody). In the case of positive HBsAg result or positive HCV antibody result, these tests will be followed by viral load assessment (HBV DNA or HCV RNA) at screening. After screening, HBV/HCV serology (HBsAg, HBsAb, HBcAb, and HCV antibody) and viral load assessment (HBV DNA and HCV RNA) may be performed if clinically indicated; for patients who have detectable HBV DNA or HCV RNA at screening or upon repeated testing, respective viral load testing will be performed every 12 weeks. Note for sites in

Germany and where required by the Health Authority or local guidelines: An HIV serology test (including antigen and/or antibodies) will be conducted at baseline for the patients with unknown HIV status, and patients with positive HIV test will be excluded.

[q] 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 first dose of study treatment. Urine pregnancy tests will be performed at each cycle before dosing, at EOT, and at each Safety Follow-up Visit., Note for sites in Germany: a 120-Day Safety Follow-up Visit for pregnancy test will be implemented at the site or by telephone. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.

[r] If PET/CT is performed at screening, bone scan is not required at screening. PET/ CT or bone scan should be performed for the whole body, or sufficient to rule out distant metastases (eg, from skull base to knees). MRI (or CT scan if MRI is contraindicated or not readily available) with contrast of the head is required at screening. If the patient's disease stage was confirmed as Stage III NSCLC (AJCC 2017) based on PET/CT or bone scan and brain imaging via MRI or CT with contrast performed before cCRT, these tests are not required to repeat at screening.

[s] Patients will be asked to complete three PROs, that include the EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L questionnaires before any clinical activities are performed, or any health-related discussion with the health care providers, during on-study clinic visits at C1D1 and every 6 weeks thereafter for up to 12 months and/or EOT, whichever comes first. Patients also are asked to complete 2 questionnaires that include PGI-S at C1D1, Day1 of Week 25, and Day1 of Week 43 (all arms), and PRTSE at Day 1 of Week 7, Week 25, and Week 43 (all Arms). For patients in Arm C who receive Q4W regimen, if the questionnaires visit falls into the interval of two dosing visits, it could be re-scheduled to combine with the neariest next dosing cycle visit.

[t] Only for patients randomized to Arm A and Arm B: Procedures for collection of ociperlimab and tislelizumab PK and ADA samples are described in the laboratory manual. Predose (within 60 minutes before starting infusion) PK samples are required to be collected at Day 1 of Cycles 1, 2, 5, 9, 17, and at the EOT Visit for both ociperlimab and tislelizumab. Postdose (within 30 minutes after completing infusion) PK samples for both ociperlimab and tislelizumab are required to be collected on Day 1 of Cycles 1 and 5. Should a patient present with any ≥ Grade 3 imAE, an additional blood PK sample may be taken to determine the serum concentration of ociperlimab or tislelizumab. These tests are required when it is allowed by local regulations/IRBs/IECs.

[u] All immunogenicity (ADAs) blood samples (serum) will be collected predose (within 60 minutes before dose) on dosing days Day 1 of Cycles 1, 2, 5, 9, 17, and the EOT Visit for both ociperlimab and tislelizumab in Arm A or tislelizumab in Arm B. 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.

[v] Tissue-based biomarkers (including but not limited to PD-L1, TIGIT, CD226, CD155, CD112, GEP, TMB, MSI, gene mutation profiles, and TILs) will be assessed on baseline and/or at disease progression/reoccurrence. Archival tumor tissues (FFPE block [preferred] or approximately 15 [at least 6] freshly cut unstained FFPE slides) or a tumor biopsy at baseline are required to be collected prior to cCRT during prescreening. For patients with readily accessible tumor lesions and who consent to the biopsies, a fresh biopsy will be collected prior to cCRT. Optional biopsies will also be taken at the EOT Visit after disease progression. (Note: For the sites in mainland China, tissues will be obtained to test the expression of PD-L1, TIGIT, CD226, CD155, CD112, GEP, TMB, MSI, gene mutation profiles, and TILs at baseline, and at disease progression/reoccurrence).

[w] Blood sample must be collected at C1D1 (predose) for blood based biomarker test. Optional blood will be collected at C3D1 (predose), C4D1 (predose) and at the EOT Visit after the disease progression. Collected blood samples will be used to explore association of blood-based biomarkers with response, resistance, and prognosis. Written informed consent is required before optional blood samples collection. (Note: Blood-based biomarkers, including ctDNA, TMB, MSI, gene mutational profiles, and extracellular vesicle (EVs), will be explored in the blood samples which will be collected in the sites in mainland China).

[x] For patients with nonsquamous NSCLC histology with unknown EGFR mutation status, tissue-based test results are mandatory at screening; patients with unknown ALK, ROS1 and RET status may be enrolled. Patients with squamous NSCLC and unknown EGFR, ALK, ROS1, or RET status will not be required to be tested at screening. EGFR mutation status may be assessed locally or at a central laboratory. An additional ≥ 6 slides are required if EGFR mutation status needs to be tested in the central lab.

APPENDIX 2. CLINICAL LABORATORY ASSESSMENTS

Serum Chemistry	**Hematology**	**Coagulation**	**Urinalysis (screening and as clinically indicated)**	**Thyroid Function**
Alkaline phosphatase	Hemoglobin	Prothrombin time [a]	pH	Thyroid stimulating hormone
Alanine aminotransferase	Hematocrit	Partial thromboplastin time or activated partial thromboplastin time	Specific gravity	Free T3 or Total T3
Aspartate aminotransferase	White blood cell count	International normalized ratio	Glucose	Free T4 or total T4
Albumin	Neutrophil count		Protein	
Total bilirubin	Lymphocyte count		Ketones	
Direct bilirubin	Platelet count		Blood	
Blood urea nitrogen or urea			24-hour protein [b]	
Potassium				
Sodium				
Calcium [c]				
Creatinine				
Glucose				
Lactate dehydrogenase				
Total protein				
Magnesium				
Phosphorus				
Chloride				
Creatine kinase/ CK-MB [d]				

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

[a] For sites in France, prothombine rate (%) will be measured. Other coagulation assessment maybe performed per local guidance.

[b] 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.

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

[d] Cardiac enzyme testing is to monitor potential event of immune-related myocarditis. CK/CK-MB can be tested separately or in combination with other serum chemistry assessments. In the event that CK-MB fractionation is not

available, assess troponin I and/or troponin T instead. Investigators should make every effort to perform either CK-MB, troponin I and/or troponin T consistently at screening and at follow up visits.

APPENDIX 3. EASTERN COOPERATIVE ONCOLOGY GROUP 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. 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.

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

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

APPENDIX 5. CONTRACEPTION GUIDELINES AND DEFINITIONS OF "WOMEN OF CHILDBEARING POTENTIAL," "NO CHILDBEARING POTENTIAL"

Contraception Guidelines

The Clinical Trials Facilitation Group's recommendations related to contraception and pregnancy testing in clinical trials include the use of highly effective forms of birth control (Clinical Trials Facilitation Group 2020). These methods include the following:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with the inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with the inhibition of ovulation:
  - oral
  - injectable
  - implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized male partner, provided that the vasectomized partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of surgical success
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of exposure associated with the study treatment).

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

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

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

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

As defined in this protocol, "women of childbearing potential" are female patients who are physiologically capable of becoming pregnant, ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile.

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 a postmenopausal follicle-stimulating hormone concentration (FSH) > 30 mIU/mL and all alternative medial causes for the lack of spontaneous menses for ≥ 12 months have been ruled out, such as polycystic ovarian syndromes, 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 2020).

The followings are approved or permitted in Japan:

- Intrauterine devices (IUD, all types) or intrauterine hormone releasing systems (IUS)
- Orally combined (estrogen- and progestogen-containing) hormonal contraception associated with the inhibition of ovulation

Other contraceptions are also accepted:

- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment)*

  (*: Sexual abstinence may be used as a contraceptive method only if it is in line with the patients' usual and preferred lifestyle.)

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, MA: Little, Brown and Co.; 1964:p 114.

APPENDIX 7. EUROPEAN ORGANISATION FOR RESEARCH AND TREATMENT OF CANCER QUALITY OF LIFE CANCER QUESTIONNAIRE QLQ-C30

EORTC QLQ-C30 (version 3)

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

Please fill in your initials: _ _ _ _

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

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

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

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

Please go on to the next page

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

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

APPENDIX 8. 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 9. THE 5-LEVEL VERSION OF EUROPEAN QUALITY OF LIFE 5-DIMENSIONAL QUESTIONNAIRE

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

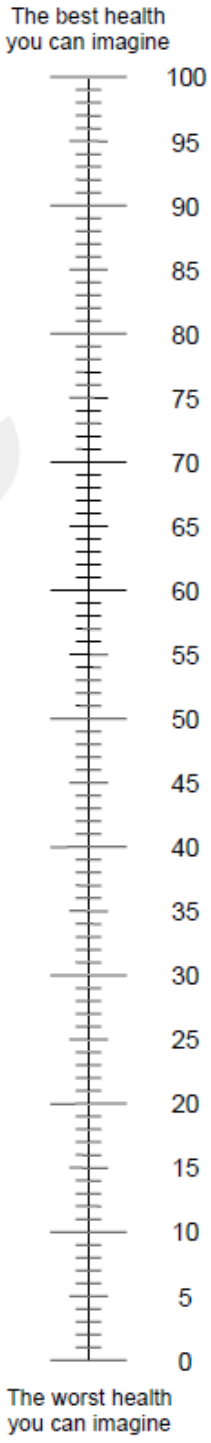
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

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

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

YOUR HEALTH TODAY = ☐



APPENDIX 10. PATIENT GLOBAL IMPRESSION OF SEVERITY (PGI-S)

Please fill in your subject ID: _____

Today's date: _____

During **the past week**, how severe were your lung cancer symptoms (for example, coughing, pain in the chest and pain in the arms and shoulders, numbness and tingling in your fingers, coughing blood, etc.).

Please choose only 1 answer for each question.

- ☐ Not at all
- ☐ Mildly
- ☐ Moderately
- ☐ Very
- ☐ Extremely

Appendix 11. PATIENT REPORTED TREATMENT-RELATD SIDE-EFFECT BURDEN (PRTSE)

Please fill in your subject ID: _____

Today's date: _____

Were you bothered by side effects of your treatment?

☐ Not at all bothered
☐ Mildly bothered
☐ Moderately bothered
☐ Very bothered
☐ Extremely bothered

Appendix 12. Immune-Mediated Adverse Event Evaluation and Management

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

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

- What was the temporal relationship between initiation of study drugs and the AE?
- How did the patient respond to withdrawal of study drugs?
- Did the event recur when study drugs was/were reintroduced?
- Was there a clinical response to corticosteroids?
- Is the event an autoimmune endocrinopathy?
- Is PD or an alternative diagnosis a more likely explanation?

When alternative explanations to autoimmune toxicity have been excluded, the imAE field associated with the AE in the electronic case report form should be checked.

Recommended diagnostic tests in the management of possible immune-mediated adverse events	
Immune-mediated toxicity	**Diagnostic evaluation guideline**
Thyroid disorders	Scheduled and repeat thyroid function tests (TSH and T4).
Hypophysitis	Check visual fields and consider pituitary endocrine axis blood profile. Perform pituitary and whole brain MRI in patients with headache, visual disturbance, unexplained fatigue, asthenia, weight loss, and unexplained constitutional symptoms. Consider consultation with an endocrinologist if an abnormality is detected.
Pneumonitis	All patients presenting with new or worsened pulmonary symptoms or signs, such as an upper respiratory infection, new cough, shortness of breath or hypoxia should be assessed by high-resolution CT. Consider pulmonary function test including DLCO. Radiographic appearance is often nonspecific. Depending on the location of the abnormality, bronchoscopy and bronchoalveolar lavage or lung biopsy may be considered. Consult with a respiratory medicine physician for cases of uncertain cause.
Neurological toxicity	Perform a comprehensive neurological examination and brain MRI for all CNS symptoms; review alcohol history and other medications. Conduct a diabetic screen, and assess blood B12/folate, HIV status, TFTs, and consider autoimmune serology. Consider the need for brain/spine MRI/MRA and nerve conduction study for peripheral neuropathy. Consult with a neurologist if there are abnormal findings.

Recommended diagnostic tests in the management of possible immune-mediated adverse events	
Immune-mediated toxicity	**Diagnostic evaluation guideline**
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 3-4; every 2-3 days if Grade 2, until recovering). Review medications (eg, statins, antibiotics) and alcohol history. Perform liver screen including hepatitis A/B/C serology, hepatitis E PCR and assess anti-ANA/SMA/LKM/SLA/LP/LCI, iron studies. Consider imaging (eg, ultrasound scan for metastases or thromboembolism). Consult with a hepatologist and consider liver biopsy.
Renal toxicity	Review hydration status and medication history. Test and culture urine. Consider renal ultrasound scan, protein assessment (dipstick/24-hour urine collection), or phase-contrast microscopy. Refer to nephrology for further management assistance.
Dermatology	Consider other causes by conducting a physical examination; consider dermatology referral for skin biopsy.
Joint or muscle inflammation	Conduct musculoskeletal history and perform complete musculoskeletal examination. Consider joint X-ray and other imaging as required to exclude metastatic disease. Perform autoimmune serology and refer to rheumatology for further management assistance. For suspected myositis/rhabdomyolysis/myasthenia include: CK, ESR, CRP, troponin I and consider a muscle biopsy.
Myocarditis	Perform ECG, echocardiogram, troponin I, and refer to a cardiologist.

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

Treatment of Immune-mediated Adverse Events

- Immune-mediated AEs can escalate quickly; study treatment interruption, close monitoring, timely diagnostic work-up, and treatment intervention, as appropriate, with patients is required

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

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

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
	3-4 Moderate-severe symptoms	Refer patient to an endocrinologist for assessment and treatment. Initiate pulse IV methylprednisolone 1 mg/kg for patients with headache/visual disturbance due to pituitary inflammation. Convert to oral prednisolone and taper over at least 1 month. Maintain hormone replacement according to endocrinology advice. Maintain hormone replacement according to endocrinology advice.	Hold study treatment for patients with headache/visual disturbance due to pituitary inflammation until resolved/improved to Grade 2 or less. Discontinuation is usually not necessary.
Pneumonitis	**1** Radiographic changes only	Monitor symptoms every 2-3 days. If appearance worsens, treat as Grade 2.	Consider holding study treatment until appearance improves and cause is determined.
	2 Symptomatic: exertional breathlessness	Commence antibiotics if infection suspected. Add oral prednisolone 1 mg/kg/day if symptoms/appearance persist for 48 hours or worsen. Consider *Pneumocystis* infection prophylaxis. Taper corticosteroids over at least 6 weeks. Consider prophylaxis for adverse steroid effects: eg, blood glucose monitoring, vitamin D/calcium supplement.	Hold study treatment (Note for sites in Japan: However, in the case that symptoms are controlled on prednisolone ≤ 10 mg/day, treatment can be continued.) Retreatment is acceptable if symptoms resolve completely or are controlled on prednisolone ≤ 10 mg/day. Discontinue study treatment if symptoms persist with corticosteroid treatment. (Note for sites in Japan: If the event recurs upon reintroduction of study treatment, the patient should discontinue the treatment.)

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
	3-4 Severe or life-threatening symptoms Breathless at rest	Admit to a hospital and initiate treatment with IV methylprednisolone 2-4 mg/kg/day. If there is no improvement, or worsening after 48 hours, add infliximab 5 mg/kg (if no hepatic involvement). Convert to oral prednisolone and taper over at least 2 months. Cover with empiric antibiotics and consider prophylaxis for *Pneumocystis* infection and other adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement.	Discontinue study treatment.
Neurological toxicity	**1** Mild symptoms	–	Continue study treatment.
	2 Moderate symptoms	Treat with oral prednisolone 0.5-1 mg/kg/day. Taper over at least 4 weeks. Obtain neurology consultation.	Hold study treatment; resume when resolved/improved to Grade 0-1.
	3-4 Severe/life-threatening	Initiate treatment with oral prednisolone or IV methylprednisolone 1-2 mg/kg/day, depending on symptoms. Taper corticosteroids over at least 4 weeks. Consider azathioprine, MMF, cyclosporine if no response within 72-96 hours.	Discontinue study treatment.
Colitis/diarrhea	**1** Mild symptoms: < 3 liquid stools per day over baseline and feeling well	Symptomatic management: fluids, loperamide, avoid high fiber/lactose diet. If Grade 1 persists for > 14 days manage as a Grade 2 event.	Continue study treatment.
	2 Moderate symptoms: 4-6 liquid stools per day over baseline, or abdominal pain, or blood in stool, or nausea, or nocturnal episodes	Oral prednisolone 0.5 mg/kg/day (non-enteric coated). Do not wait for any diagnostic tests to start treatment. Taper steroids over 2-4 weeks, consider endoscopy if symptoms are recurring.	Hold study treatment; resume when resolved/improved to baseline grade.
	3 Severe symptoms: > 6 liquid stools per day over baseline, or if episodic within 1 hour of eating	Initiate IV methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Consider prophylaxis for adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement.	Hold study treatment; retreatment may be considered when resolved/improved to baseline grade and after discussion with the study medical monitor.

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
	4 Life-threatening symptoms	If no improvement in 72 hours or symptoms worsen, consider infliximab 5 mg/kg; if no perforation, sepsis, TB, hepatitis, NYHA Grade III/IV CHF or other immunosuppressive treatment: MMF or tacrolimus. Consult gastroenterologist to conduct colonoscopy/sigmoidoscopy.	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: IV methylprednisolone 0.5-1 mg/kg/day; convert to oral prednisolone and taper over at least 4 weeks.	Hold study treatment. Re-treat when AE is resolved or improved to mild rash (Grade 1-2) after discussion with the study medical monitor.
	4 Skin sloughing > 30% BSA with associated symptoms (eg, erythema, purpura, epidermal detachment)	Initiate IV methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Admit to a hospital and seek urgent dermatology consultation.	Discontinue study treatment.
Hepatitis	**1** ALT or AST > ULN to 3 x ULN	Check LFTs within 1 week and before the next dose check LFTs to verify that there has been no worsening. If LFTs are worsening, recheck every 48-72 hours until improvement is seen.	Continue study treatment if LFTs are unchanged or improving. Hold study treatment if LFTs are worsening until improvement is seen.
	2 ALT or AST 3-5 x ULN	Recheck LFTs every 48-72 hours: For persistent ALT/AST elevation: consider oral prednisolone 0.5-1 mg/kg/day for 3 days then taper over 2-4 weeks. For rising ALT/AST: start oral prednisolone 1 mg/kg/day and taper over 2-4 weeks; re-escalate dose if LFTs worsen, depending on clinical judgement.	Hold study treatment; treatment may be resumed when resolved/improved to baseline grade and prednisolone tapered to ≤ 10 mg.

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
	3 ALT or AST 5-20 x ULN	ALT/AST < 400 IU/L and normal bilirubin/INR/albumin: Initiate oral prednisolone 1 mg/kg and taper over at least 4 weeks. ALT/AST > 400 IU/L or raised bilirubin/INR/low albumin: Initiate IV (methyl)prednisolone 2 mg/kg/day. When LFTs improve to Grade 2 or lower, convert to oral prednisolone and taper over at least 4 weeks.	Hold study treatment until improved to baseline grade; reintroduce only after discussion with the study medical monitor.
	4 ALT or AST > 20 x ULN	Initiate IV methylprednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 6 weeks.	Discontinue study treatment.
	Worsening LFTs despite steroids: If on oral prednisolone, change to pulsed IV methylprednisolone If on IV, add MMF 500-1000 mg twice a day If worsens on MMF, consider addition of tacrolimus Duration and dose of steroid required will depend on severity of event		
Nephritis	**1** Creatinine 1.5 x baseline or > ULN to 1.5 x ULN	Repeat creatinine weekly. If symptoms worsen, manage as per criteria below.	Continue study treatment.
	2 Creatinine > 1.5 x -3X baseline or > 1.5 x -3X ULN	Ensure hydration and review creatinine in 48-72 hours; if not improving, consider creatinine clearance measurement by 24-hour urine collection. Discuss with nephrologist the need for kidney biopsy. If attributed to study drug, initiate oral prednisolone 0.5-1 mg/kg and taper over at least 2 weeks. Repeat creatinine/U&E every 48-72 hours.	Hold study treatment. If not attributed to drug toxicity, restart treatment. If attributed to study drug and resolved/improved to baseline grade: Restart study drug if tapered to < 10 mg prednisolone.
	3 Creatinine > 3 x baseline or > 3X-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 IV (methyl)prednisolone 1-2 mg/kg. Taper corticosteroids over at least 4 weeks.	Hold study treatment until the cause is investigated. If study drug suspected: Discontinue study treatment.
	4 Creatinine > 6 x ULN	As per Grade 3, patient should be managed in a hospital where renal replacement therapy is available.	Discontinue study treatment.

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
Diabetes/ hyperglycemia	**1** Fasting glucose value ULN to 160 mg/dL; ULN to 8.9 mmol/L	Monitor closely and treat according to local guideline. Check for C-peptide and antibodies against glutamic acid decarboxylase and islet cells are recommended.	Continue study treatment.
	2 Fasting glucose value 160-250 mg/dL; 8.9-13.9 mmol/L	Obtain a repeat blood glucose level at least every week. Manage according to local guideline.	Continue study treatment or hold treatment if hyperglycemia is worsening. Resume treatment when blood glucose is stabilized at baseline or Grade 0-1.
	3 Fasting glucose value 250-500 mg/dL; 13.9-27.8 mmol/L	Admit patient to hospital and refer to a diabetologist for hyperglycemia management. Corticosteroids may exacerbate hyperglycemia and should be avoided.	Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1.
	4 Fasting glucose value > 500 mg/dL; > 27.8 mmol/L	Admit patient to hospital and institute local emergency diabetes management. Refer the patient to a diabetologist for insulin maintenance and monitoring.	
Ocular toxicity	**1** Asymptomatic eye exam/test abnormality	Consider alternative causes and prescribe topical treatment as required.	Continue study treatment.
	2 Anterior uveitis or mild symptoms	Refer patient to an ophthalmologist for assessment and topical corticosteroid treatment. Consider a course of oral steroids.	Continue study treatment or hold treatment if symptoms worsen or if there are symptoms of visual disturbance.
	3 Posterior uveitis/panuveitis or significant symptoms	Refer patient urgently to an ophthalmologist. Initiate oral prednisolone 1-2 mg/kg and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1; reintroduce only after discussion with the study medical monitor.
	4 Blindness (at least 20/200) in the affected eyes	Initiate IV (methyl)prednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks.	Discontinue study treatment.
Pancreatitis	**2** Asymptomatic, blood test abnormalities	Monitor pancreatic enzymes.	Continue study treatment.
	3 Abdominal pain, nausea and vomiting	Admit to hospital for urgent management. Initiate IV (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when amylase/lipase	Hold study treatment; reintroduce only after discussion with the study medical monitor.

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

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
		severe activity restriction or dysphagia. If symptoms do not improve add immunosuppressant therapy. Taper oral steroids over at least 4 weeks.	evidence of myocardial involvement.
Myocarditis	**< 2** Asymptomatic but significantly increased CK-MB or increased troponin OR clinically significant intraventricular conduction delay	Admit to hospital and refer to a cardiologist. Transfer all patients with moderate/severe cardiac symptoms or any increase in cardiac serum markers to the coronary care unit. Initiate oral prednisolone or IV (methyl)prednisolone at 1-2 mg/kg/day. Manage symptoms of cardiac failure according to local guidelines. If no immediate response change to pulsed doses of (methyl)prednisolone 1 g/day and add MMF, infliximab or anti-thymocyte globulin.	Hold study treatment until completely resolved or myocarditis has been ruled out.
	2 Symptoms on mild-moderate exertion		Discontinue study treatment unless cardiac involvement has been excluded and symptoms have completely resolved.
	3 Severe symptoms with mild exertion		
	4 Life-threatening		
Other immune-mediated adverse events	**≤ 2**	Clinical management per local guideline based on adverse event type and severity.	Continue study treatment.
	3		Hold study treatment until improved to Grade 0-1. For recurrent Grade 3: Discontinue study treatment.
	4		Discontinue study treatment.

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

Appendix 13. Response Evaluation Criteria in Solid Tumors (RECIST) Guidelines, Version 1.1

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

DEFINITIONS

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

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

Measurable Disease

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

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

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

Nonmeasurable Disease

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

Bone lesions:

- Bone scan, 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 non-measurable.

Cystic lesions:

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

Lesions with prior local treatment:

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

Target Lesions

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

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

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline

sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target Lesions

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

GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE

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

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

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

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

- Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following CR or surgical resection is an endpoint.
- Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in CR. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and prostate-specific antigen response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.
- Cytology, histology: These techniques can be used to differentiate between partial response (PR) and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease (SD) to differentiate between response (or SD) and progressive disease (PD).

RESPONSE CRITERIA

Evaluation of Target Lesions

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

qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

- Target lesions that become "too small to measure." While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure."
- When this occurs, it is important that a value be recorded on the electronic case report form (eCRF). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.
- Lesions that split or coalesce on treatment: When non-nodal lesions "fragment," the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion."

Evaluation of Non-target Lesions

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

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

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

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

New Lesions

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

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

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

While fluorine-18 [F-18] fluorodeoxyglucose (FDG)-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible "new" disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

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

Evaluation of Best Overall Response

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

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

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
Stable disease	Non-PD or not all evaluated	No	Stable disease
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

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

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

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

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

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

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

CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

Confirmation

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

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

Duration of Overall Response

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

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

Duration of Stable Disease

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

The clinical relevance of the duration of SD varies in different studies and diseases If the proportion of patients achieving SD 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 SD.

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

APPENDIX 14. CHRONIC KIDNEY DISEASE EPIDEMIOLOGY COLLABORATION (CKD-EPI) AND COCKCROFT-GAULT (CG) EQUATION

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 (Scr) is reported in mg/dL. This equation is recommended when EGFR values above 60 mL/min/1.73 m^2 are desired.

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

where:

- Scr is serum creatinine in mg/dL,
- κ is 0.7 for females and 0.9 for males,
- α is -0.329 for females and -0.411 for males,
- min indicates the minimum of Scr /κ or 1, and
- max indicates the maximum of Scr /κ or 1.

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

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

Note, the unit of the value generated by the website above is mL/min/1.73 m^2, this is standardized to a body surface area (BSA) value of 1.73 m^2, will not be appropriate in patients with BSAs different than the standard (1.73 m^2). To individualize GFR for drug dosing, need to convert mL/min/1.73 m^2 to mL/min via multiplying the standardized GFR by the individual's BSA calculated using an appropriate formula and divide by 1.73 (US FDA 2020).
BSA formulas deemed as appropriate (US FDA 2020)

Du Bois formula (Dubios D et al 1916): $BSA = 0.007184 \times W^{0.425} \times H^{0.725}$

Mosteller formula (Mosteller 1987): $BSA = 0.016667 \times W^{0.5} \times H^{0.5}$

The online calculator for BSA can be found here:
https://www.calculator.net/body-surface-area-calculator.html

Cockcroft-Gault Equation

For Serum Creatinine Concentration (SCr) in mg/dL [a]

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

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

For Serum Creatinine Concentration (SCr) in µmol/L [a]

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

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

a Age in years and weight in kilograms.

b Recommend using ideal body weight if the patient's BMI > 30 kg/m^2 in calculation of estimated CrCl.

c Ideal body weight (IBW) formula (Devine 1974):

IBW for males (kg) = 49.9 kg + 0.89 kg/cm × (height − 152.4 cm)

APPENDIX 15. RECOMMENDED DOSAGE MODIFICATIONS FOR ADVERSE REACTIONS OF DURVALUMAB

This table is cited from durvalumab prescribing information approved by US FDA (date, version). Note, in countries/regions other than US, some recommended dosage modifications of durvalumab prescribing information approved by local health authority may differ from that approved by US FDA. In such cases, please refer to the recommendations approved by the local health authority.

Adverse Reaction	Severity[1]	Dosage Modification
Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.1)]*		
Pneumonitis	Grade 2	Withhold[2]
	Grade 3 or 4	Permanently discontinue
Colitis	Grade 2 or 3	Withhold[2]
	Grade 4	Permanently discontinue

Adverse Reaction	Severity[1]	Dosage Modification
Hepatitis with no tumor involvement of the liver	ALT or AST increases to more than 3 and up to 8 times the ULN or total bilirubin increases to more than 1.5 and up to 3 times ULN	Withhold[2]
	ALT or AST increases to more than 8 times ULN or total bilirubin increases to more than 3 times the ULN	Permanently discontinue
Hepatitis with tumor involvement of the liver[3]	AST or ALT is more than 1 and up to 3 times ULN at baseline and increases to more than 5 and up to 10 times ULN or AST or ALT is more than 3 and up to 5 times ULN at baseline and increases to more than 8 and up to 10 times ULN	Withhold[2]
	AST or ALT increases to more than 10 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Endocrinopathies	Grade 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity
Nephritis with Renal Dysfunction	Grade 2 or 3 increased blood creatinine	Withhold[2]
	Grade 4 increased blood creatinine	Permanently discontinue
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold[2]

Adverse Reaction	Severity[1]	Dosage Modification
	Confirmed SJS, TEN, or DRESS	Permanently discontinue
Myocarditis	Grade 2, 3, or 4	Permanently discontinue
Neurological Toxicities	Grade 2	Withhold[2]
	Grade 3 or 4	Permanently discontinue
Other Adverse Reactions		
Infusion-related reactions *[see Warnings and Precautions (5.2)]*	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue

ALT = alanine aminotransferase, AST = aspartate aminotransferase, DRESS = Drug Rash with Eosinophilia and Systemic Symptoms, SJS = Stevens Johnson Syndrome, TEN = toxic epidermal necrolysis, ULN = upper limit normal

[1] Based on National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.
[2] Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone 10 mg per day or less (or equivalent) within 12 weeks of initiating steroids.
[3] If AST and ALT are less than or equal to ULN at baseline in patients with liver involvement, withhold or permanently discontinue IMFINZI based on recommendations for hepatitis with no liver involvement.

Source: durvalumab prescribing information approved by US FDA. Note: in countries/regions other than US, some recommended dosage modifications of durvalumab prescribing information approved by the local health authority may differ from that approved by US FDA. In such cases, please refer to the recommendations approved by the local health authority.

APPENDIX 16. LIST OF PROHIBITED CHINESE HERBAL AND PATENT MEDICINES

The following table provides examples of Chinese herbal and patent medications that may be used to treat cancer or have immune-stimulating properties. **This list is not intended to be all-inclusive.**

Ginsenoside-Rg3 capsule	CIDAN Capsule
Yangzheng Xiaoji Jiaonang	Huaer Keli
Huazheng Huisheng Koufuye	Haishengsu injection
Juzentaihoto	Xiaoaiping Wan/Pian/Jiao Nang/Ke Li
Cinobufacini/Huachansu injection	Xiaoaiping Zhusheye
Cinobufacini/Huachansu Pian/Capsules	Niuhuang Xingxiao pill
Boerning capsule	Polyporus polysaccharide injection
Norcantharidin Pian	Hedyotis Dissusa wild injection
Shendan Sanjie Jiaonang	Zi Long jin pian
Shengqi Fuzheng Zhusheye	Ganfule Jiaonang / GFL tablet
Shen Lian Jiao Nang/Ke Li	Zhongjiefeng tablet
Ma Te Ling injection	Weifuchun pill
Hui Sheng Kou Fu Ye	Ai Di Zhu She Ye
Fufang Banmao Jiaonang	Qizhen Jiaonang
Fufang Hongdoushan Jiaonang	Zedoary turmeric oil injection
Fufang Kushen Zhusheye	Kanglixin Jiaonang
Tian Xian capsule	Jinpu capsule
Qining injection	Jinlong Capsules
Weimaining Jiao Nang	Lentinan
Anerxin/Ginseng polysaccharide injection	Yadanzi/Brucea javanica Youru Zhusheye
Ankangxin Jiaonang	Yadanziyou Ruan jiao nang/Kou Fu Ru Ye
Antike capsule	Shelian Jiaonang
Yanshu injection	Bozhi Glycopeptide Injection
Ping Xiao Pian/Jiao Nang	Delisheng Injection
Kanglixin Jiaonang	Elemene Injection
Kang'ai Zhusheye	Sodium Cantharidinate Injection
Kanglaite Injection	Xianchan tablet
Kanglaite Soft Capsules	Xihuang Wan

APPENDIX 17. PATIENT CARE AND STUDY CONDUCT FOR PATIENTS ENROLLED WITH PA 1.0

1. STUDY DESIGN OF PA 1.0

1.1. Summary of Study Design

This is an open-label, randomized, multicenter study to compare the efficacy and safety of ociperlimab (BGB-A1217) plus tislelizumab plus cCRT followed by ociperlimab plus tislelizumab (Arm A) or tislelizumab plus cCRT followed by tislelizumab (Arm B) versus cCRT followed by durvalumab (Arm C) in previously untreated, unresectable LA NSCLC.

Newly diagnosed Stage III patients with histologically confirmed, locally advanced, and unresectable NSCLC are eligible. Patients are enrolled and randomized in a 1:1:1 ratio to Arm A, Arm B, or Arm C in this study. Randomization will be stratified by age (< 65 years versus ≥ 65 years), PD-L1 expression in TC (≥ 1% versus < 1%), and histology (squamous versus nonsquamous).

During the treatment period, in Arm A, patients will receive 2 cycles of ociperlimab 900 mg Q3W combined with tislelizumab 200 mg Q3W with cCRT (cCRT phase), and receive ociperlimab combined with tislelizumab Q3W for a maximum of 12 months after the completion of cCRT phase. In Arm B, patients will receive 2 cycles of tislelizumab 200 mg Q3W combined with cCRT (cCRT phase), and receive tislelizumab 200 mg Q3W for a maximum of 12 months after the completion of cCRT phase. In Arm C, patients will undergo 2 cycles of cCRT (cCRT phase), and receive durvalumab 10 mg/kg Q2W (or 1500 mg Q4W where the dosage has been approved by a local health authority) for a maximum of 12 months after the completion of cCRT phase. All 3 arms will receive study drugs until a maximum of 12 months after the completion of cCRT phase, PD per RECIST v1.1, unacceptable toxicity, death, or another discontinuation criterion is met, whichever occurs first.

During the cCRT phase, the choice of chemotherapy regimen to be used as part of study treatment will be at the investigator's discretion as specified in Section 2.2.3 of Appendix 17. For the 3 arms, RT should start concurrently with chemotherapy in the beginning of Cycle 1, in the best case, on Cycle 1 Day 1 (C1D1). If local technical or logistical circumstances do not allow the start of RT on C1D1, RT is strongly recommended to start within 3 days after C1D1, but no later than 7 days after C1D1. For Arm A and Arm B, immunotherapy (ociperlimab plus tislelizumab for Arm A, tislelizumab for Arm B) will be given starting from C1D1 during the cCRT phase, and continued until up to 12 months after the completion of cCRT phase, or PD per RECIST v1.1, unacceptable toxicity, death, or another discontinuation criterion is met, whichever occurs first. For Arm C, durvalumab will be commenced within 42 days after the cCRT phase until up to 12 months after the completion of cCRT phase, or PD per RECIST v1.1, unacceptable toxicity, death, or another discontinuation criterion is met, whichever occurs first.

End-of-Treatment (EOT) Visit, Safety Follow-up Visit, and Survival Follow-up Visit will be conducted to monitor the patient's status and collect data beyond study treatment.

Table 14: Schedule of Assessment for PA 1.0

Assessment	Screening[a]	Treatment Cycles				End-of-Treatment Visit [b]	Safety Follow-up Visit [c]	Tumor Assessment /Survival Follow-up [d]
		Cycles 1 to 2 during cCRT Phase (Cisplatin and Etopside: every 28 days; Chemotherapy other than cisplatin and etopside: every 21 days)			≥ Cycle 3 and up to 12 months (ociperlimab and tislelizumab or tislelizumab: every 21 days; Durvalumab: every 14 or 28[e] days)			
Days (Window)	**-28 to -1**	**1 (+2 or ±3)[f]**	**8 (±3)**	**15 (±3)**	**1 (±3)[g]**	**0 to 7 days**	**30 (±7), 60 and 90 (±14) days after last dose**	**Every 12 weeks (±7 or 14 days)**
STUDY ENTRY AND GENERAL ASSESSMENTS								
Informed consent [a]	X	-	-	-	-	-	-	-
Inclusion/exclusion criteria	X	-	-	-	-	-	-	-
Randomization[h]	X	-	-	-	-	-	-	-
Demographics/medical history/prior medications or procedures[i]	X	-	-	-	-	-	-	-
Concomitant medication/procedures evaluation[i]	Continuous from ≤ 28 days before randomization until 30 days after the last dose of study treatment							-
EGFR/ALK testing on tumor tissue (if status not available)[j]	X	-	-	-	-	-	-	-
Confirmation of mediastinal nodal involvement, if applicable	X		-	-	-	-	-	-

Assessment	Screening[a]	Treatment Cycles				End-of-Treatment Visit [b]	Safety Follow-up Visit [c]	Tumor Assessment /Survival Follow-up [d]
		Cycles 1 to 2 during cCRT Phase (Cisplatin and Etopside: every 28 days; Chemotherapy other than cisplatin and etopside: every 21 days)			≥ Cycle 3 and up to 12 months (ociperlimab and tislelizumab or tislelizumab: every 21 days; Durvalumab: every 14 or 28[e] days)			
Days (Window)	**-28 to -1**	**1 (+2 or ±3)[f]**	**8 (±3)**	**15 (±3)**	**1 (±3)[g]**	**0 to 7 days**	**30 (±7), 60 and 90 (±14) days after last dose**	**Every 12 weeks (±7 or 14 days)**
SAFETY ASSESSMENTS								
AE evaluation[k]	Continuous from informed consent until 30 days after the last dose of study treatment for AEs; 90 days after the last dose of ociperlimab or tislelizumab or durvalumab 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[l]	X	X	X	X	X	X	-	-
Vital signs/height and weight[m]	X	X	X	X	X	X	-	-
ECOG PS	X	X	X	X	X	X	-	-
Body surface area calculation	-	X	X[n]	X[n]	-	-	-	-
Pulmonary function Test[o]	X	Only if clinically indicated						
12-lead electrocardiogram	X	Only if clinically indicated				X	-	-
Hematology laboratory[p]	X	X	X	X	X	X	-	-
Chemistry laboratory[p]	X	X	X	X	X	X	-	-
CK and CK-MB[p]	X	X	X	X	X	X	-	-
Coagulation laboratory[p]	X	X	-	-	X	X	-	-
Thyroid function[q]	X	Every 2 cycles or each cycle[q]				X	-	-

Assessment	Screening[a]	Treatment Cycles				End-of-Treatment Visit [b]	Safety Follow-up Visit [c]	Tumor Assessment /Survival Follow-up [d]
		Cycles 1 to 2 during cCRT Phase (Cisplatin and Etopside: every 28 days; Chemotherapy other than cisplatin and etopside: every 21 days)			≥ Cycle 3 and up to 12 months (ociperlimab and tislelizumab or tislelizumab: every 21 days; Durvalumab: every 14 or 28[e] days)			
Days (Window)	**-28 to -1**	**1 (+2 or ±3)[f]**	**8 (±3)**	**15 (±3)**	**1 (±3)[g]**	**0 to 7 days**	**30 (±7), 60 and 90 (±14) days after last dose**	**Every 12 weeks (±7 or 14 days)**
HBV/HCV test[r]	X	As clinically indicated					-	-
Urinalysis[p]	X	As clinically indicated					-	-
β-hCG pregnancy test[s]	X	X	-	-	X	X	X	-
EFFICACY ASSESSMENTS								
Tumor assessment CT/MRI	X	Tumor imaging will be performed approximately every 9 weeks (± 7 days) from randomization, for the first 54 weeks, and every 12 weeks (± 7 days) thereafter based on RECIST v1.1. The first tumor assessment after randomization (the 9-week tumor assessment) is allowed to be performed within 42 days after cCRT, and should take place before the initiation of immunotherapy after the cCRT phase. Following the first progression assessed by the investigator, patients will be assessed every 12 weeks (± 7 days) for a second progression (using the patient's status at the first progression as reference for assessment of second progression).						
FDG-PET/CT and Brain MRI with contrast or head CT scan with contrast	X	Only if clinically indicated						
QLQ-C30, QLQ-LC13, EQ-5D-5L[t]	-	Cycle 1 and every 6 weeks thereafter				X	-	-
PGI-S[t]	-	X	-	-	At Week 25 and Week 43	-	-	-
PRTSE[t]	-	Week 7, Week 25, and Week 43				-	-	-

Assessment	Screening[a]	Treatment Cycles				End-of-Treatment Visit [b]	Safety Follow-up Visit [c]	Tumor Assessment /Survival Follow-up [d]
		Cycles 1 to 2 during cCRT Phase (Cisplatin and Etopside: every 28 days; Chemotherapy other than cisplatin and etopside: every 21 days)			≥ Cycle 3 and up to 12 months (ociperlimab and tislelizumab or tislelizumab: every 21 days; Durvalumab: every 14 or 28[e] days)			
Days (Window)	**-28 to -1**	**1 (+2 or ±3)[f]**	**8 (±3)**	**15 (±3)**	**1 (±3)[g]**	**0 to 7 days**	**30 (±7), 60 and 90 (±14) days after last dose**	**Every 12 weeks (±7 or 14 days)**
PHARMACOKINETIC ASSESSEMENTS								
Pharmacokinetics[u]	-	X[u]	-	-	Cycle 5, 9, 17	X	-	-
Anti-ociperlimab and anti-tislelizumab blood samples[v]	-	X[v]	-	-	Cycle 5, 9, 17	X	-	-
BIOMARKER ASSESSMENTS								
Archived tumor[w]	X	-	-	-	-	-	-	-
Fresh tumor biopsy[w]	X (if needed)					X (optional) [w]		
Biomarkers: whole blood[x]	-	X (optional)	-	-	X (optional)	X (optional)		
TREATMENT								
Arm A or B: Tislelizumab ± Ociperlimab administration	-	X	-	-	X	-	-	-
Arm C: durvalumab administration	-	-	-	-	X	-	-	-

Assessment	Screening[a]	Treatment Cycles				End-of-Treatment Visit [b]	Safety Follow-up Visit [c]	Tumor Assessment /Survival Follow-up [d]
		Cycles 1 to 2 during cCRT Phase (Cisplatin and Etopside: every 28 days; Chemotherapy other than cisplatin and etopside: every 21 days)			≥ Cycle 3 and up to 12 months (ociperlimab and tislelizumab or tislelizumab: every 21 days; Durvalumab: every 14 or 28[e] days)			
Days (Window)	**-28 to -1**	**1 (+2 or ±3)[f]**	**8 (±3)**	**15 (±3)**	**1 (±3)[g]**	**0 to 7 days**	**30 (±7), 60 and 90 (±14) days after last dose**	**Every 12 weeks (±7 or 14 days)**
Radiotherapy administration[y]	-	60 Gy in 30 fractions (2 Gy per day/5 days per week)			-	-	-	-
Cisplatin Plus Etoposide								
Etoposide administration[z]	-	X (D1-D5)	-	-	-	-	-	-
Cisplatin administration[aa]	-	X	X	-	-	-	-	-
Carboplatin Plus paclitaxel								
Appropriate chemotherapy pre-medications administration[bb]	-	X	X	X	-	-	-	-
Paclitaxel administration[cc]	-	X	X	X	-	-	-	-
Carboplatin administration[dd]	-	X	X	X	-	-	-	-
Cisplatin Plus Pemetrexed								
Appropriate chemotherapy pre-medications administration[ee]	-	X	-	-	-	-	-	-
Pemetrexed administration[ff]	-	X	-	-	-	-	-	-
Cisplatin administration[gg]	-	X	-	-	-	-	-	-

Assessment	Screening[a]	Treatment Cycles				End-of-Treatment Visit [b]	Safety Follow-up Visit [c]	Tumor Assessment /Survival Follow-up [d]
		Cycles 1 to 2 during cCRT Phase (Cisplatin and Etopside: every 28 days; Chemotherapy other than cisplatin and etopside: every 21 days)			≥ Cycle 3 and up to 12 months (ociperlimab and tislelizumab or tislelizumab: every 21 days; Durvalumab: every 14 or 28[e] days)			
Days (Window)	**-28 to -1**	**1 (+2 or ±3)[f]**	**8 (±3)**	**15 (±3)**	**1 (±3)[g]**	**0 to 7 days**	**30 (±7), 60 and 90 (±14) days after last dose**	**Every 12 weeks (±7 or 14 days)**
Carboplatin Plus Pemetrexed								
Appropriate chemotherapy pre-medications administration[hh]	-	X	-	-	-	-	-	-
Pemetrexed administration[ii]	-	X	-	-	-	-	-	-
Carboplatin administration[jj]	-	X	-	-	-	-	-	-
FOLLOW-UP								
Survival status	-	-	-	-	-	-	X	X
Subsequent therapy since IP discontinuation	-	-	-	-	-	-	X	X

Abbreviations: ADA, antidrug antibody; AE, adverse event; ALK, anaplastic lymphoma kinase; β-hCG, beta human chorionic gonadotropin; C, Cycle ; cCRT, concurrent chemoradiotherapy; CD, cluster of differentiation; CK, creatine kinase; CK-MB, creatine kinase cardiac muscle isoenzyme; CR, complete response; CT, computed tomography; D, day; DLCO, diffusing capacity of the lungs for carbon monoxide; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer-Quality of Life C30 questionnaire; EOT, End of Treatment; EQ-5D-5L, European Quality of Life-5 Dimensions health state classifier to 5 Levels; FDG-PET, fluorodeoxyglucose - positron emission tomography; FEV, forced expiratory volume; FFPE, formalin-fixed paraffin-embedded; GEP, gene expression profiling; 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; IRT, integrated response technology; LC13, Lung Cancer Module of EORTC QLQ-C30; MRI, magnetic resonance imaging; NCI, National Cancer Institute; NSCLC, non-small cell lung cancer; PD, progressive disease; PD-L1, programmed cell death protein-ligand 1; PK, pharmacokinetics; PGI-S, patient reported

global impression of severity; PRO-CTCAE, Patient-Reported Outcome Version of Common Terminology Criteria of Adverse Events; PT, prothrombin time; SAE, serious adverse event; TIL, tumor-infiltrating lymphocyte; TMB, tumor mutational burden.

[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] EOT is defined as the date investigator determines that study treatment will no longer be used. For Arm A, patients shall have an EOT visit only if both study drugs were discontinued. Patients shall have an EOT visit within 7 days after the date investigator determines that study treatment will no longer be used, or before the initiation of a new anticancer treatment, whichever occurs first. However, the EOT visit may occur later than 7 days for specific circumstances, such as prolonged hospitalization. If routine laboratory tests (eg, hematology, serum chemistry, CK and CK-MB, coagulation, etc.) are completed within 7 days before the EOT, these tests need not be repeated. Tumor assessment is not specially required at the EOT. Patients who discontinue study treatment before disease progression assessed by the investigator will need to undergo tumor assessments as outlined in Section 4.5 of Appendix 17; in some cases the time window of tumor assessment might overlap with EOT and/or Safety Follow-up visit. In the cases the time window of EOT and Safety Follow-up visit overlapped, these two visits can be combined.

[c] The Safety Follow-up Visit 60-Day and 90-Day Follow-up Visit could be completed at the site or by telephone.

[d] Patients whose disease has not progressed at the end of the 12-month study treatment period will continue to perform tumor imaging every 12 weeks (± 7 days) until progressive disease per RECIST v1.1. Following the first progression assessed by the investigator, patients will be assessed every 12 weeks (± 7 days) for a second progression (using the patient's status at the first progression as reference for assessment of second progression). A patient's second progression status is defined according to local standard clinical practice and may involve any of: objective radiological, symptomatic progression or death. Measurements per RECIST v1.1 will not be collected for assessment of PFS2. 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 for survival and subsequent anticancer therapy information unless a patient requests to be withdrawn from follow-up. Schedule of Survival Follow-up Visit can be modulated to combine with tumor assessment of PFS or PFS2 for operational convenience while keeping the follow-up visits interval as approximately every 12 weeks.

[e] Durvalumab regimen:10 mg/kg Q2W (or 1500 mg Q4W where the dosage has been approved by a local health authority). For the patient whose body weight is < 30 kg, only the regimen of durvalumab 10 mg/kg Q2W is applicable. Refer to local prescribing information of durvaluamb for detailed instructions.

[f] Patients should have Cycle 1 Day 1 (C1D1) dosing initiated within 2 business days of randomization. For C2D1 and C3D1, patients should receive study drugs with ± 3 days.

[g] Cycle 3 Day 1 dosing may be delayed in order to ensure that cCRT is completed before Cycle 3 Day 1 dosing.

[h] Patients will be randomized into either Arm A or Arm B or Arm C via IRT.

[i] Includes age or year of birth, sex, and self-reported race/ethnicity; history of treatment for the primary diagnosis, including prior medication, loco-regional treatment(s), and surgical treatment(s). Information on radiographic studies performed before study entry may be collected for review by the investigator. Pre-existing AEs at baseline should be recorded as medical history. Refer to Section 4.1.3 of Appendix 17 for additional information.

[j] For patients with nonsquamous NSCLC histology with unknown EGFR mutation status, tissue-based test results are mandatory at screening; patients with unknown ALK status may be enrolled. Patients with squamous NSCLC and unknown EGFR mutation or ALK status will not be required to be tested at screening. EGFR mutation status may be assessed locally or at a central laboratory. An additional ≥ 6 slides are required if EGFR mutation status needs to be tested in a central lab.

[k] 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 (including chemoradiotherapy) (s) or

initiation of new anticancer therapy, whichever occurs first. Immune-mediated AEs (serious or nonserious) should be reported until 90 days after the last dose of ociperlimab, tislelizumab, or durvalumab 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.

[l] At the Screening Visit, a complete examination will be conducted, including evaluations of 1) head, eyes, ears, nose, and throat; 2) cardiovascular; 3) dermatological; 4) musculoskeletal; 5) respiratory; 6) gastrointestinal; and 7) neurological systems. For any abnormality at subsequent visits (and as clinically indicated), limited, symptom-directed physical examinations will be performed.

[m] Vital signs collected on study include body temperature (˚C), pulse rate, and blood pressure (systolic and diastolic). Pulse rate and blood pressure should be collected while the patient is in a seated position after resting for 10 minutes. The patient's vital signs are required to be recorded within 60 minutes before, during, and within 30 minutes after the completion of infusion of study treatment (ociperlimab and tislelizumab in Arm A, tislelizumab in Arm B, and durvalumab in Arm C). For subsequent infusions, vital signs will be collected within 60 minutes before infusion and, if clinically indicated, during and within 30 minutes after the completion of infusion. Weight is required to be measured once on the scheduled assessment day and before study treatment if there is any. Height measurements are only required at screening.

[n] Day 8 and Day 15 body surface area calculation only applies for patients who plan to receive chemotherapy on Day 8 and/or Day 15.

[o] Pulmonary function testing includes assessment of spirometry and oxygenation. The assessment of oxygenation should include at least pulse oximetry (percutaneous arterial oxygen saturation, SpO_2) at rest and with exercise; an assessment of diffusion capacity is optional. Respective test results should 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, absolute FEV1 value < 1L, FEV1 of age and sex adjusted predicted performance levels < 50%, DLCO (if performed) < 40% 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.

[p] Local and/or central laboratory assessments on serum chemistry, hematology, CK and CK-MB, coagulation, and urinalysis will be conducted, of which certain elements will be collected as specified in Appendix 2. If hematology and serum chemistry at screening are not performed within 7 days of the planed C1D1, these tests should be repeated and reviewed before randomization. If the coagulation test has been performed and reviewed during screening, it is not mandatory to repeat this test before C1D1 unless investigator deems necessary. Hematology, serum chemistry (including liver function tests), CK and CK-MB as specified in Appendix 2 should be performed weekly during cCRT phase, at the beginning of each subsequent cycle after cCRT, and the EOT Visit. After Cycle 1, these laboratory tests are to be performed and reviewed within 48 hours before study drug administration. Urinalysis is to be conducted during the treatment period only if clinically warranted. Refer to Section 4.4.4 and Section 5.3.5 of Appendix 17 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.

[q] Analysis of free T3 or total T3, free T4 or total T4, and thyroid stimulating hormone will be performed by a central laboratory or the local study site laboratory. Thyroid function tests will be performed at Screening, from C3D1 onwards, every 2 cycles for Arm A and Arm B (ie, Cycles 3, 5, 7, etc.), every 2 cycles for durvalumab-Q2W (ie, Cycles 3, 5, 7, etc.) and every cycle for durvalumab-Q4W, and at the EOT Visit.

[r] Testing will be performed by a central laboratory and/or the local laboratory at screening and will include at screening HBV/HCV serology (HBsAg, HBsAb, HBcAb, and HCV antibody). In the case of positive HBsAg result or positive HCV antibody result, these tests will be followed by viral load assessment (HBV DNA or HCV RNA) at screening. After screening, HBV/HCV serology (HBsAg, HBsAb, HBcAb, and HCV antibody) and viral load assessment (HBV DNA and HCV RNA) may be performed if clinically indicated; for patients who have detectable HBV DNA or HCV RNA at screening or upon repeat testing, respective viral load testing will be performed every 12 weeks.

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

[t] Patients will be asked to complete three PROs, that include the EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L questionnaires before any clinical activities are performed, or any health-related discussion with the health care providers, during on-study clinic visits at C1D1, and every 6 weeks thereafter for up to 12 months and/or EOT, whichever comes first. Patients also are asked to complete 2 questionnaires that include PGI-S at C1D1, Day1 of Week 25, and Day1 of Week 43 (all arms), and PRTSE at Day 1 of Week 7, Week 25, and Week 43 (all Arms). For patients in Arm C who receive Q4W regimen, if the questionnaires visit falls into the interval of two dosing visits, it could be re-scheduled to combine with the nearest next dosing cycle visit.

[u] Only for patients randomized to Arm A and Arm B: Procedures for collection of ociperlimab and tislelizumab PK and ADA samples are described in the Laboratory Manual. Predose (within 60 minutes before starting infusion) PK samples are required to be collected at Day 1 of Cycles 1, 2, 5, 9, 17, and at the EOT Visit for both ociperlimab and tislelizumab. Postdose (within 30 minutes after completing infusion) PK samples for both ociperlimab and tislelizumab are required to be collected on Day 1 of Cycles 1 and 5. Should a patient present with any ≥ Grade 3 imAE, an additional blood PK sample may be taken to determine the serum concentration of ociperlimab or tislelizumab. These tests are required when it is allowed by local regulations/IRBs/IECs.

[v] All immunogenicity (ADAs) blood samples (serum) will be collected predose (within 60 minutes before dose) on dosing days Day 1 of Cycles 1, 2, 5, 9, 17, and the EOT Visit for both ociperlimab and tislelizumab in Arm A or tislelizumab in Arm B. 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.

[w] Tissue-based biomarkers (including but not limited to PD-L1, TIGIT, CD226, CD155, CD112, GEP, TMB, gene mutations, MSI, and TILs) will be assessed on baseline and biopsy tissue at disease progression. Archival tumor tissues (FFPE block [preferred] or approximately 15 [at least 6] freshly cut unstained FFPE slides) with an associated pathology report or a tumor biopsy at baseline are required to be collected. For patients with readily accessible tumor lesions and who consent to the biopsies, a fresh biopsy is highly recommended at baseline. Optional biopsies will also be taken at the time of disease progression. (Note: For the sites in China mainland, tissues will be obtained to test the expression of PD-L1, TIGIT, CD226, CD155, CD112, GEP, TMB, gene mutations, MSI, and TILs at baseline, and at disease progression/reoccurrence).

[x] Optional blood samples will be taken at C1D1 (predose), C3D1 (predose), C4D1 (predose), and at the EOT Visit after the disease progression to explore association of blood-based biomarkers with response, resistance and prognosis. (Note: Blood-based biomarkers, including ctDNA, TMB, MSI, EVs and gene mutational profiles, will be explored in the blood samples which will be collected in the sites in China mainland).

[y] The schedule of radiotherapy and chemotherapy administrations is detailed in the specific section. Once commenced, radiotherapy should be given for 5 consecutive days weekly. Radiotherapy commences on Day 1 of chemotherapy, with a ± 3 days administrative window allowed after C1D1.

1.2. 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. 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 mandatory.

1.3. Treatment Period

After completing all screening activities, eligible patients will be randomized in a 1:1:1 ratio to 3 arms (Arm A, Arm B, and Arm C). Randomization will be stratified by age (< 65 years versus ≥ 65 years), PD-L1 expression in TC (≥ 1% versus < 1%), and histology (squamous versus nonsquamous).

Patients will receive open-label treatments as follows:

- Arm A: Two cycles of ociperlimab 900 mg Q3W combined with tislelizumab 200 mg Q3W intravenously with cCRT, followed by ociperlimab 900 mg Q3W combined with tislelizumab 200 mg Q3W intravenously up to 12 months after the completion of cCRT phase or PD per RECIST v1.1, unacceptable toxicity, or death, or until another discontinuation criterion is met
- Arm B: Two cycles of tislelizumab 200 mg intravenously Q3W combined with cCRT, followed by tislelizumab 200 mg intravenously Q3W up to 12 months after the completion of cCRT phase
- Arm C: Two cycles of cCRT, followed by durvalumab 10 mg/kg intravenously Q2W (or 1500 mg Q4W where the dosage has been approved by a local health authority) up to 12 months after the completion of cCRT phase or PD per RECIST v1.1, unacceptable toxicity, or death, or until another discontinuation criterion is met

Radiological assessment of tumor-response status will be performed approximately every 9 weeks (± 7 days) from randomization, for the first 54 weeks, and every 12 weeks (± 7 days) thereafter based on RECIST v1.1. The first tumor assessment after randomization (the 9-week tumor assessment) is allowed to be performed within 42 days after the cCRT phase, and should take place before the initiation of immunotherapy (ociperlimab and tislelizumab in Arm A, tislelizumab in Arm B, durvalumab in Arm C) after the cCRT phase. Tumor response will be assessed by the investigator. 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, except for the first 9-week tumor assessment.

Tumor response will be assessed by the investigator.

Administration of study treatment will continue up to 12 months following the completion of cCRT, or until PD as assessed by the investigator per RECIST v1.1, unacceptable toxicity, or death, or until another discontinuation criterion is met.

A patient who discontinues study treatment for reasons other than disease progression (eg, toxicity, completion of the 12-month treatment) will continue to undergo tumor assessments following the original plan until the patient experiences PD per RECIST v1.1 assessed by the investigator, withdraws consent, is lost to follow-up, or death, or until the study terminates, whichever occurs first.

Study treatment beyond initial PD per RECIST 1.1

If at the investigator's discretion a patient could continue to benefit from the immunotherapy (ociperlimab and tislelizumab combination treatment in Arm A, tislelizumab in Arm B, or durvalumab in Arm C) after PD per RECIST v1.1, the patient may continue their assigned treatment. The following criteria must be met in order to treat patients who may continue to benefit from study drugs after PD:

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

The decision to continue study drug(s) beyond initial PD per RECIST v1.1 must be agreed upon with the medical monitor and documented in the study records.

Tumor assessment should continue as planned in patients receiving study drug(s) beyond initial PD per RECIST v1.1 criteria. Tumor assessment in such patients should continue until study treatment discontinuation.

To determine the PK properties of ociperlimab and tislelizumab, and host immunogenic response to ociperlimab and tislelizumab, blood samples will be collected at various timepoints as outlined in Table 14.

Optional blood samples will be collected at C1D1 (predose), C3D1 (predose), C4D1 (predose), and at the EOT Visit after the disease progression (Table 14). All these blood samples will be collected to explore association of blood-based biomarkers with response, resistance and prognosis. (Note: Blood-based biomarkers, including ctDNA, TMB, MSI, EVs and gene mutational profiles, will be explored in the blood samples which will be collected in the sites in China mainland).

Safety will be assessed throughout the study by monitoring AEs/SAEs (toxicity grades assigned per NCI-CTCAE v5.0]) and laboratory results. Vital signs, physical examinations, ECOG Performance Status change, electrocardiogram (ECG) results, and other examinations will also be used for safety assessment. Safety assessments are further detailed in Section 4.4 of Appendix 17 and the Schedule of Assessments (Table 14)

1.4. End of Treatment

The End-of-Treatment (EOT) Visit is planned when the investigator determines that study treatment will no longer be used.

The date of End-of-Treatment (EOT) is defined as the date investigator determines that study treatment will no longer be used. Patients shall have an EOT Visit within 7 days after the date investigator determines that study treatment will no longer be used, or before the initiation of a new anticancer treatment, whichever occurs first. For Arm A, patients shall have an EOT Visit only if both study drugs were discontinued. However, the EOT Visit may occur later than 7 days for specific circumstances, such as prolonged hospitalization.

See Table 14 for assessments to be performed at the EOT.

1.5. Safety Follow-up

The Safety Follow-up Visit is planned when the investigator determines that study treatment will no longer be used.

The date of Safety Follow-up Visit is defined as the date when safety assessments and procedures are performed after the last dose of study treatment for an individual patient.

All patients that discontinue study treatment (both study drugs if in Arm A) will have a Safety Follow-up Visit approximately 30 days (± 7 days) after the last dose of study drug or before the initiation of new anticancer therapy, whichever occurs first. This visit will include the collection of data about AEs and serious adverse events (SAEs) that may have occurred after the patient discontinued the study drug. The investigator or his/her designee will continue to collect information on new anticancer therapy given after the last dose of study drug. In the cases the time window of EOT and Safety Follow-up visit overlapped, these two visits can be combined. See Table 14 for assessments to be performed at the Safety Follow-up Visit.

Additional Safety Follow up visits at 60 and 90 days after the last dose of study drug can be required (in clinic or over the phone, as needed based on assessments required). Patients will be contacted by telephone to assess imAEs and relevant concomitant medication use (ie, those associated with an imAE or any new anticancer therapy). These contacts should be made at 60 days (± 14 days) and 90 days (± 14 days) after the last dose of study treatment regardless of whether the patient starts a new anticancer therapy. If a patient reports a suspected imAE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated.

1.6. Survival Follow-up

Patients will be followed for survival follow-up data after discontinuation of study treatment via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (± 14 days) after the 90-Day Safety Follow-up Visit or as directed by the sponsor until death, loss to follow-up, withdrawal of consent, or end of study by the sponsor.

During the survival follow-up period subsequent anticancer therapy information including medication start date, end date, reason for treatment, and date of progression after receiving the subsequent anticancer therapy will be collected.

1.7. Discontinuation From the Study Treatment or From the Study

1.7.1. Discontinuation From Study Treatment

Patients have the right to withdraw from the study or discontinue study treatment at any time for any reason. In addition, the investigator has the right to discontinue a patient from the study treatment at any time. Patients who discontinue study treatment for reasons other than disease progression should be followed for assessments of antitumor activity (Section 4.5 of Appendix 17), safety (Section 4.4 of Appendix 17), and survival (Section 1.6 of Appendix 17), if possible.

The primary reason for discontinuation from the study treatment should be documented on the appropriate electronic case report form (eCRF).

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

- Radiographic disease progression per RECIST v1.1
- AE
- Use of any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents [including herbal medicine and patent medicines] for the treatment of cancer) (Section 3.3 of Appendix 17).
- Patient noncompliance

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

Patients will discontinue from the study treatment for reasons following:

- Patient's decision to withdraw from study treatment
- Any medical condition that the investigator determines may jeopardize the patient's safety, if he or she were to continue the study treatment
- Pregnancy.

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

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

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

1.8. End of Study

The end of study is defined as the timepoint when the final data point is collected from the last patient in the study. This is when the last patient dies, withdraws consent, completes all study assessments, or is lost to follow-up. Alternatively, the end of study is when the sponsor decides to terminate the study.

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

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients
- Overall patient enrollment is unsatisfactory
- A rollover study becomes available

The sponsor will notify each investigator if a decision is made to terminate the study. Should this be necessary, prematurely discontinued patients should be seen as soon as possible for an EOT 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 IRBs/IECs of the early termination of the study.

At the end of study, patients who are still in the originally assigned treatment within 12 months after the cCRT phase and continue to benefit from the treatment at study termination in the opinion of the investigator, will be offered the option to continue treatment in a company-sponsored clinical trial until treatment duration reach 12 months after the cCRT phase or it is commercially available in the country of the patient's residence.

The sponsor has the right to close a site at any time. The decision will be 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)

2. STUDY TREATMENT

2.1. Formulation, Packaging, and Handling

2.1.1. Ociperlimab

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

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

The study drug must be kept at the temperature 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 Investigator's Brochure for other details regarding ociperlimab.

2.1.2. Tislelizumab

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

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

The study drug must be kept at the temperature 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 Tislelizumab Investigator's Brochure for other details regarding tislelizumab.

2.1.3. Durvalumab

Durvalumab is a monoclonal antibody formulated for intravenous infusion in a single-dose vial, containing a total of 500 mg antibody in 10 mL (or 120 mg antibody in 2.4 mL, 50 mg/mL) clear to opalescent, colorless to slightly yellow solution.

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.

Please refer to the Pharmacy Manual for details regarding administration, accountability, and disposal.

2.1.4. Chemotherapy

Management (ie, handling, storage, administration, and disposal) of cisplatin, carboplatin, etoposide, paclitaxel, pemetrexed 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.

2.2. Dosage, Administration, and Compliance

Planned dosage and dosing frequency for study drugs are presented in Table 15 and Table 16.

For Arm A and Arm B, the first dose of the immunotherapy (ociperlimab and tislelizumab in Arm A, tislelizumab in Arm B) is to be administered within 2 business days of randomization. C1D1 is defined as the day of the administration of the first dose of the immunotherapy. Immunotherapy will be given starting from C1D1 in the cCRT phase and continued for a duration up to 12 months after the cCRT phase.

For Arm A and Arm B, during the cCRT phase, immunotherapy administration should be given followed by chemotherapy. In Arm A, ociperlimab and tislelizumab should be administered on the same day if feasible, in case the logistical circumstances do not allow for all of the intravenous study drug (including ociperlimab, tislelizumab, and platinum-based doublet chemotherapy) administration on the same day, then chemotherapy should start as soon as possible within the following 3 days. If the first doses of ociperlimab and tislelizumab were not administered on the same day for reasons other specified, C1D1 is defined as the day of administration of the first dose of tislelizumab.

For Arm C, C1D1 is defined as the day of administration of the first dose of chemotherapy and/or radiation.

The choice of the chemotherapy regimen will be made at the investigator's discretion, but the platinum and pemetrexed regimen is only available for patients with nonsquamous histology.

For all 3 arms, during the cCRT phase, for all patients, RT commences with chemotherapy in the beginning of Cycle 1, in the best case, on C1D1. If local technical or logistical circumstances do not allow the start of RT on C1D1, RT is strongly recommended to start within 3 days after C1D1, but no later than 7 days after C1D1. On the day of treatment, chemotherapy should generally be delivered before RT. It is recommended that RT should follow within 30 to 60 minutes after the completion of chemotherapy or post-cisplatin hydration when administrative circumstance allows, such as when both chemotherapy and RT are administered at the same center/location. However, in other situations, logistical considerations may result in RT being delivered before the administration of chemotherapy or post-cisplatin hydration, eg, when the RT and chemotherapy are delivered at 2 separate centers/locations. It is allowed if RT and/or chemotherapy do not start on C1D1 for administrative reasons, and the start of administration of RT and/or chemotherapy is still within the 3-day window after C1D1. In this case, the full planned dose of RT and chemotherapy should be administered unless other specified.

For the 3 arms, in the event that RT is delayed to allow recovery from toxicities, the administration of immunotherapy (ociperlimab and tislelizumab in Arm A, tislelizumab in Arm B, and durvalumab in Arm C) after cCRT (starting from Cycle 3 Day 1) will not begin until

completion of the full course of RT. Efforts should be made to administer Cycle 3 Day 1 immunotherapy within 14 days after the cCRT phase; if this cannot be managed, Cycle 3 Day 1 immunotherapy should be given no later than 42 days after the cCRT phase.

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 2.5 of Appendix 17. Guidelines for dose modification or treatment discontinuation and for the management of imAE and infusion-related reactions are provided in detail in Section 5.7 of Appendix 17 and Appendix 12.

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

Table 15: Planned Dose, Frequency of Administration, and Route of Administration for Study Drugs

Study drugs	Dose		Frequency of Administration	Route of Administration	Duration of Treatment
Ociperlimab	900 mg		Day 1 of each cycle (21 days)	Intravenous	Refer to Section 1.3
Tislelizumab	200 mg		Day 1 of each cycle (21 days)	Intravenous	Refer to Section 1.3
Durvalumab	10 mg/kg or 1500 mg [a]		Day 1 of each cycle (14 days) or Day 1 of each cycle (28 days)	Intravenous	Refer to Section 1.3
Cisplatin Plus Etoposide	Etoposide	50 mg/m^2	Day 1 to Day 5 of each cycle	Intravenous	2 cycles (each cycle 28 days)
	Cisplatin	50 mg/m^2	Day 1 and Day 8 of each cycle	Intravenous	2 cycles (each cycle 28 days)
Carboplatin Plus Paclitaxel	Paclitaxel	40-50 mg/m^2	Weekly for 6 weeks	Intravenous	6 weeks
	Carboplatin	AUC 2	Weekly for 6 weeks	Intravenous	6 weeks
Cisplatin Plus Pemetrexed	Pemetrexed	500 mg/m^2	Day 1 of each cycle	Intravenous	2 cycles (each cycle 21 days)
	Cisplatin	75 mg/m^2	Day 1 of each cycle	Intravenous	2 cycles (each cycle 21 days)
Carboplatin Plus Pemetrexed	Pemetrexed	500 mg/m^2	Day 1 of each cycle	Intravenous	2 cycles (each cycle 21 days)
	Carboplatin	AUC 5	Day 1 of each cycle	Intravenous	2 cycles (each cycle 21 days)

Abbreviation: AUC, area under the concentration-time curve; Q4W, every 4 weeks.
[a] 1500 mg Q4W will be used where the dosage has been approved by a local health authority.

Table 16: Administration of Ociperlimab and Tislelizumab and Monitoring Time

Cycle	Ociperlimab and Tislelizumab combination in Arm A	Tislelizumab in Arm B
Cycle 1 Day 1	Tislelizumab infusion for ≥ 60 minutes followed by **Ociperlimab** infusion for ≥ 60 minutes Patient monitoring for ≥ 120 minutes	Tislelizumab infusion for ≥ 60 minutes Patient monitoring for ≥ 60 minutes
Cycle 2 Day 1	Tislelizumab infusion for ≥ 60 minutes followed by **Ociperlimab** infusion for ≥ 60 minutes Patient monitoring for ≥ 120 minutes	Tislelizumab infusion for ≥ 60 minutes Patient monitoring for ≥ 60 minutes
Cycle 3 Day 1 onwards	Tislelizumab infusion for ≥ 30 minutes followed by **Ociperlimab** infusion for ≥ 30 minutes Patient monitoring for ≥ 60 minutes	Tislelizumab infusion for ≥ 30 minutes Patient monitoring for ≥ 30 minutes

2.2.1. Ociperlimab and Tislelizumab

Patients will receive tislelizumab 200 mg on Day 1 of each 21-day cycle (ie, Q3W) followed by the administration of ociperlimab 900 mg for Arm A, or patients will receive tislelizumab 200 mg on Day 1 of each 21-day cycle (ie, Q3W) for Arm B.

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

As specified in Table 16, the initial infusion (C1D1 and C2D1) will be delivered for ≥ 60 minutes for each study drug of the immunotherapy in Arm A and Arm B; if this is well tolerated, then the subsequent infusions from Cycle 3 onward may be administered for ≥ 30 minutes for each study drug of the immunotherapy in Arm A and Arm B, which is the shortest period permissible for infusion.

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 the immunotherapy are administered.

As a routine precaution, after infusion of ociperlimab and tislelizumab in Arm A on Day 1 of Cycle 1 and Cycle 2, patients will be monitored for ≥ 2 hours in an area with resuscitation equipment and emergency agents; similarly, after infusion of tislelizumab in Arm B on C1D1 and C2D1, patients will be monitored for ≥ 1 hour. From Cycle 3 onward, at least a 60-minute

monitoring period is required in an area with resuscitation equipment and emergency agents for Arm A, and for Arm B, the monitoring period is at least 30 minutes.

2.2.2. Durvalumab

Durvalumab 10 mg/kg will be administered by intravenous infusion for ≥ 60 minutes every 2 weeks (or 1500 mg Q4W where the dosage has been approved by a local health authority) up to 12 months after the cCRT phase. For the patient whose body weight is < 30 kg, only the regimen of durvalumab 10 mg/kg Q2W is applicable.

Refer to the pharmacy manual and local prescribing information of durvaluamb for detailed instructions on drug preparation, storage, and administration.

2.2.3. Chemotherapy

2.2.3.1. Cisplatin Plus Etoposide

Cisplatin 50 mg/m^2 will be administered on Days 1 and 8, and etoposide 50 mg/m^2 will be administered from Day 1 to Day 5 every 28 days for 2 cycles by intravenous infusion.

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

For etoposide, extravasation of infusion should be avoided.

Additional pre-medications should be administered as per standard practice.

2.2.3.2. Carboplatin Plus Paclitaxel

Carboplatin AUC 2 weekly (by Calvert Equation and Cockcroft-Gault Equation, Appendix 14, and Table 17) and paclitaxel 40 to 50 mg/m² weekly (as per standard of care and treatment guidelines) will be administrated for 6 weeks by intravenous infusion.

Once the initial dose of carboplatin is calculated it does not need to be recalculated for subsequent cycles unless the patient is experiencing toxicity and requires dose modification to a lower dose of carboplatin (Percy Ivy et al 2020).

For paclitaxel, all patients should be pre-medicated with oral or injectable steroids according to the manufacturer's prescribing information and/or standard practice. Due to their immunomodulatory effects, pre-medication with steroids should be limited when clinically feasible. Additionally, in the event of chemotherapeutic agent-related skin rash, topical steroid use is recommended as front-line treatment when clinically feasible.

Needles or intravenous administration sets containing aluminum parts that may come in contact with carboplatin infusion should not be used for the preparation and administration of the drug. Aluminum can react with carboplatin causing precipitate formation and loss of potency.

Additional pre-medications such as diphenhydramine, and H2 antagonists should be administered as per local standard practice.

2.2.3.3. Cisplatin Plus Pemetrexed

Cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 will be administered on Day 1 every 21 days for 2 cycles by intravenous infusion.

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

For pemetrexed, all patients should receive the appropriate supplementation of vitamin B12 and folic acid according to the manufacturer's prescribing information and/or local standard practice. In addition, all patients should receive the appropriate corticosteroid pre-medications as per the local standard practice. Due to their immunomodulatory effects, pre-medication with steroids should be limited when clinically feasible. Additionally, in the event of chemotherapeutic agent-related skin rash, topical steroid use is recommended as front-line treatment when clinically feasible.

Additional pre-medications should be administered as per standard practice.

2.2.3.4. Carboplatin Plus Pemetrexed

Carboplatin AUC 5 (by Calvert Equation and Cockcroft-Gault Equation, Appendix 14, and Table 17) and pemetrexed 500 mg/m^2 will be administered on Day 1 every 21 days for 2 cycles by intravenous infusion.

Once the initial dose of carboplatin is calculated it does not need to be recalculated for subsequent cycles unless the patient is experiencing toxicity and requires dose modification to a lower dose of carboplatin (Percy Ivy et al 2020). For patients who have ≥ 10% weight change from baseline or who experience CTCAE ≥ grade 2 renal toxicity (serum creatinine > 1.5 x ULN) recommend recalculating of the carboplatin dose for subsequent cycles. In patients who require carboplatin dose modification, if the creatinine at the time of dose modification is lower than the baseline creatinine that was used, recommend using the prior (higher) creatinine value to base dose modification on (Roisin O and Paul S 2012). Please refer to local prescribing information and local practice if any conflict with the recommendation above.

For pemetrexed, all patients should receive the appropriate supplementation of vitamin B12 and folic acid according to the manufacturer's prescribing information and/or local standard practice. In addition, all patients should receive the appropriate corticosteroid pre-medications as per the local standard practice. Due to their immunomodulatory effects, pre-medication with steroids should be limited when clinically feasible. Additionally, in the event of chemotherapeutic agent-related skin rash, topical steroid use is recommended as front-line treatment when clinically feasible.

Needles or intravenous administration sets containing aluminum parts that may come in contact with carboplatin infusion should not be used for the preparation and administration of the drug. Aluminum can react with carboplatin causing precipitate formation and loss of potency.

Additional pre-medications should be administered as per standard practice.

Table 17: Carboplatin Dose Calculation

Calvert Formula For Carboplatin Dose Calculation (Calvert AH et al 1989)	Carboplatin Dose (mg) = Target area under the curve (AUC mg/mL/min) x (GFR* + 25) *GFR estimated by calculated creatinine clearance (CrCl) using Cockcroft-Gault Equation as Appendix 14.
Other Consideration for carboplatin dose calculation Note, the recommendations below are cited from NCCN Chemotherapy Templates (NCCN 2020), please refer to local guidance if any conflict.	
Maximum Dose Calculation	The FDA has recommended that physicians consider capping the dose of carboplatin for desired exposure (AUC) to avoid potential toxicity due to overdosing. The maximum dose is based on a GFR estimate that is capped at 125 mL/min for patients with normal renal function. For a target AUC = 5, the maximum dose is 5 x 150 = 750 mg For a target AUC = 2, the maximum dose is 2 x 150 = 300 mg
Overweight or obese patients (BMI ≥ 25 kg/m^2)	Consider using an adjusted body weight: Adjusted body weight (kg) = ideal body weight (IBW) + 0.4 x (total body weight [TBW] – IBW) Equation of ideal body weight (Devine 1974): Male: IBW [kg] = 49.9 kg + 0.89 kg/cm × (height − 152.4 cm) Female: IBW [kg] = 45.4 kg + 0.89 kg/cm × (height − 152.4 cm)
Patients with abnormally low serum creatinine (Cr)	Including but not limited to elderly patients: consider using a minimum Cr of 0.7 mg/dL to avoid overestimation of GFR.

2.2.4. Radiation Therapy

The required administration sequence of immunotherapy, chemotherapy, and radiotherapy is specified in Section 2.2 of Appendix 17. Before the patient is dosed with any study treatment, the sequence of administration should be pre-planned per protocol, taking the administrative situation into consideration.

Before inclusion of any patient on 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 radiotherapy dose at 60 Gy for a patient. A patient will be excluded if the patient's radiation treatment plans are likely to encompass a volume of whole lung receiving ≥ 20 Gy in total (V20) of more than 35% of lung volume.

All patients will receive radiotherapy using either a standardized 3-dimensional conformal radiotherapy technique, or intensity modulated radiotherapy (IMRT) on a linear accelerator delivering a beam energy of ≥ 6 MV. The total dose of radiotherapy will be 60 Gy, administered in 30 once-daily fractions of 2 Gy and 5 fractions per week for 6 weeks.

Weekly clinical assessments are required during the cCRT phase. While 60 Gy in 30 fractions 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. Definitive RT will be considered as receiving a minimum of 56 Gy to the planning target volume (PTV).

Every effort should be made to continue the radiotherapy during the concurrent phase in a not delayed manner. Should a patient develop severe esophagitis necessitating dose delay of chemotherapy, the radiotherapy may continue, provided that the investigator believes that supportive care will enable the patient to complete this part of the therapy without excess risk.

Further details on the radiotherapy process are available in the radiotherapy manual.

2.2.4.1. Radiation Dose Specifications

Patients will receive treatment 5 days per week, in once-daily fractions, 2 Gy per fraction, to a target dose of 60 Gy in 30 fractions. 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. No field reductions will be permitted and the entire PTV must be treated daily.

All radiation doses will be calculated with inhomogeneity corrections that take into account the density differences within the irradiated volume (that is, air in the lung and bone). All radiation doses will be calculated using a model-based, or more complex, algorithm (AAA, superposition/convolution, Monte Carlo, or Grid-based Boltzmann solver); no measurement-based, correction-based, or pencil beam algorithms are allowed on this trial. For a complete list of acceptable algorithms, see irochouston.mdanderson.org. If the algorithm allows a choice of reporting dose to medium or dose to water, dose to medium should be used.

2.2.4.2. Variations of Dose Prescription

The variations in dose prescription are described here, and summarized in Table 18 below (Senan et al 2016, NCCN 2021).

No deviation: ≥ 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 ≤ 65%.

Minor deviation: 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 > 65% but ≤ 80%.

Major deviation: Doses in this region are not acceptable. Less than 95% of the PTV is covered by 93% of the prescribed dose, or a contiguous volume of > 1 cm^3 within the PTV receives > 115% of the prescribed dose, or a contiguous volume of > 1 cm^3 outside the PTV receives > 115% of the prescribed dose, or V5 > 80%.

Table 18: Summary of Dose Prescription Variations

	Per Protocol	Variation Acceptable	Variation Unacceptable
PTV volume coverage	≥ 99% of PTV receives at least 93% of prescribed dose	≥ 95% but < 99% of PTV receives at least 93% of prescribed dose	< 95% of PTV receives 93% of prescribed dose
Excessive dose within PTV	No contiguous volume > 1 cm^3 within the PTV receives > 110% of prescribed dose	> 1 cm^3 contiguous volume within PTV receives > 110% but ≤ 115% of prescribed dose	> 1 cm^3 contiguous volume within PTV receives > 115% of prescribed dose
Excessive dose outside PTV	No contiguous volume > 1 cm^3 outside PTV receives > 110% of prescribed dose	> 1 cm^3 contiguous volume outside PTV receives > 110% but ≤ 115% of prescribed dose	> 1 cm^3 contiguous volume outside PTV receives > 115% of prescribed dose
Spinal Cord	$D_{0.03cc}$ ≤ 46 Gy	46 Gy < $D_{0.03cc}$ ≤ 48 Gy	$D_{0.03cc}$ > 48 Gy
Excessive Lung V5/V20 /mean dose	V5 ≤ 65% V20 ≤ 35% Mean dose ≤ 20 Gy	V5 > 65% but ≤ 80%	V5 > 80% V20 > 35% Mean dose > 20Gy
Heart	V50 ≤ 25% Mean dose ≤ 20 Gy	25% < V50 ≤ 33% 20 Gy < Mean dose ≤25Gy	V50 > 33% Mean dose > 25 Gy
Esophagus	Mean dose ≤ 34 Gy	34 Gy < Mean dose ≤ 40 Gy	Mean dose > 40 Gy
Brachial Plexus	$D_{0.03cc}$ ≤ 64 Gy	64 Gy < $D_{0.03cc}$ ≤ 66 Gy	$D_{0.03cc}$ > 66 Gy

Abbreviations: PTV, planning target volume; V =volume.

2.2.4.3. Simulation, Immobilization, and Treatment Imaging

Each patient will be positioned in an institutional-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. A 4-dimensional computed tomography (4DCT) is recommended to be performed during simulation to assess tumor motion. The whole thorax (cricoid to L2) should be covered using < 5 mm 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), Clinical Tumor Volume (CTV), Internal Target Volume (ITV), and Planned Target Volume (PTV) will be defined on all appropriate slices (see definitions in Section 2.2.4.4 of Appendix 17). Intravenous contrast 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 noncontrast 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, at least weekly 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. 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 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.

2.2.4.4. 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

The use of IMRT is preferred over 3DCRT, 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. Regardless of technique, it is recommended to maintain the total lung V5 level at 65% or less.

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. To follow anatomical boundary and clinical discretion when appropriate, the CTV margin may be irregular and not exactly be GTV plus a 0.5 cm margin. 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. When a 4DCT scan is performed, a patient-specific internal target volume (ITV) may be directly derived from planning and appropriate margins added in order to derive a CTV and PTV, respectively. These determinations must be documented but are left to the discretion of the treatment radiation oncologist. This PTV will be used to define the treated volume.

ITV: The ITV is defined as the CTV plus an internal margin to account for target/organ motion. The final PTV is defined to be the ITV plus a setup margin to account for patient positioning uncertainty and machine tolerance.

2.2.4.5. Radiation Treatment Documentation

Regardless of treatment technique, dose volume histograms will be generated for PTV, both lungs, lungs minus PTV, spinal cord, esophagus, heart, and (if near the treatment field) the brachial plexus. The following dose values should be recorded:

- Prescription point dose
- Minimum, maximum ($D_{0.03cc}$), and mean dose in PTV
- Maximum dose ($D_{0.03cc}$) to spinal cord
- V20 and V5 to the lung

2.2.4.6. Organs at Risk

Contouring of normal tissues and organs for radiotherapy planning will be in accordance with published guidelines (Kong et al 2011). See the RT manual for more information. Normal tissue constraints shall be prioritized in the following order for treatment planning:

1 = spinal cord, 2 = lungs, 3 = heart, 4 = esophagus, and 5 = brachial plexus

Spinal cord: The spinal canal will be contoured and taken to represent the spinal cord. The maximum cord dose will be limited to 46 Gy, but patients who receive up to 48 Gy in order to ensure adequate tumor dose will be considered to have as a minor deviation. Patients who receive more than 48 Gy to the cord will be counted as a major deviation.

Lungs: The dose-volume constraint to the lungs is the second highest priority and must be met, except if it conflicts with spinal cord dose constraints. The volume of both lungs (total lung volume minus PTV) that receive more than 20 Gy (V20) should not exceed 35%. Mean lung dose should not exceed 20 Gy. V5 should not exceed 65%.

Heart: The heart will be contoured on all slices; detailed guidance for contouring is per Feng et al 2011. The cranial border will include the infundibulum of the right ventricle and the apex of both atria, and it will exclude the great vessels as much as possible. The caudal border is defined

as the lowest part of the left ventricle that is distinguishable from the liver. The recommended dose limits are 50 Gy < 25%; mean dose ≤ 20 Gy of the heart.

Esophagus: Esophagitis is an expected side effect of concurrent therapy and has a relationship to higher doses of radiation encompassing the entire esophageal circumference. The outer wall of the esophagus will be contoured completely throughout the length of esophagus that is encompassed by a dose of radiation ≥ 46 Gy. Mean esophageal dose should be limited to ≤ 34 Gy, a dose up to ≤ 40 Gy will be considered a variation acceptable.

Brachial Plexus: For tumors in close proximity to the brachial plexus, the plexus should be contoured to ensure that the maximal point dose to this structure is kept under 64 Gy.

Radiation toxicities will be assessed according to NCI-CTCAE v5.0 criteria and reported per Section 5.3. Note that radiation toxicities can arise more than 90 days after the completion of RT.

2.2.4.7. Quality Assurance and Compliance with Protocol-defined Radiation Prescription (Quality Control)

A formal radiotherapy quality assurance (QA) program will be a mandatory component of this study. Eligible radiotherapy facilities will complete a facility questionnaire in order to ensure that they are equipped to deliver radiation to the required quality. Prior to the randomization of the first subject, sites will need to have undergone a "benchmarking" process where a 3-dimensional CT scan of an anonymized clinical case with stage III NSCLC will be electronically transmitted to participating sites by the QA program, and the local radiation oncologists from the sites will be required to contour target volumes and organs-at-risk volumes, in accordance with the quality assurance criteria specified for thoracic radiation therapy as defined in the approved RT QA program. This process will serve to ensure protocol-compliant contouring and radiotherapy planning. The radiotherapy plans will be reviewed by physicists and a radiation oncologist at the QA program, who will provide appropriate feedback to sites participating in this benchmarking. See the radiotherapy manual for additional information.

Credentialing:

Table 19: Credentialing Procedure

Steps	Procedures/ Requirements	Information Link
Step 1	Facility & Motion Management Questionnaire	The MD Anderson Dosimetry Lab electronic facility questionnaire (FQ), should be completed or updated with the most recent information about your institution. To access your site's FQ, email mdadl@mdanderson.org to receive your FQ link. Submit electronically a completed Motion Management Questionnaire located http://rpc.mdanderson.org/mdadl/home.htm
Step 2*	Independent Output Verification	All sites delivering radiation therapy for patients enrolled in this study must have independent output verification.
Step 3*	Benchmark	Sites need to download the DICOM CT benchmark case from the BeiGene website located http://rpc.mdanderson.org/mdadl/home.htm. There is also a document which includes the clinical details of the benchmark case.

		This benchmark must be contoured and planned according to the AdvanTIG-301 protocol (see section 5.2.4 of the protocol)

See the RT Manual for further credentialing information.

Pre-treatment Subject Dosimetry Review:

A pre-treatment subject dosimetry review of a treatment plan will be conducted for at least 1 case per center. The first patient's treatment plan shall be submitted, at a minimum, 5 days prior to start of radiotherapy. Feedback on the treatment plan will be received by the center before radiotherapy commences. The objective of the review is to gain additional assurance that subjects treated at the site will conform to the protocol radiation requirements. Additional QA dosimetry reviews may be done subsequently in a sample of cases during the course of the study. Subjects may have their radiation field altered based on information obtained from these QA reviews. This should be sufficient to ensure adherence to the radiation prescription defined in the protocol.

Post-treatment Subject Dosimetry Review:

All subjects treated by radiation in the study will submit their data to the RT QA team to perform a retrospective radiation dosimetry review. This review will evaluate, for each case, adherence to the protocol radiation prescription. This will be a confirmation of the treatment delivered, and an overall assessment of compliance with protocol stipulations regarding radiation treatment. In case there is any deviation from the protocol, this information will be conveyed to the institution.

2.2.5. Supportive Care

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

All patients are strongly suggested to accept nutrition support if there is any indication including (but not limited to): medium-severe dysphagia; weight loss > 5% in 1 month; BMI < 18.5 kg/m^2; scored patient-generated subjective global assessment ≥ 4 score; and food intake is < 60% required for > 3 days.

2.3. Incorrect Administration or Overdose

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

AEs associated with an incorrect administration or overdose of study drugs will be recorded on the AE eCRF. Any SAEs associated with an incorrect administration or overdose must be reported within 24 hours of awareness via the SAE reporting process as described in Section 5.6.2 of Appendix 17. Supportive care measures should be administered as appropriate.

2.4. Investigational Medicinal Product Accountability

The investigational medicinal products required for completion of this study (ociperlimab, tislelizumab, and durvalumab) will be provided by the sponsor. The investigational site will acknowledge receipt of investigational medicinal products. Any damaged shipments will be replaced.

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

2.5. Dose Delay or Modification

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

Every effort should be made to administer the study drugs according to the planned dose and schedule. In the event of significant toxicities, dosing may be delayed and/or reduced based on the guidelines provided below. Reasons for dose modifications or delays, the supportive measures taken, and the outcome will be documented in the patient's chart and recorded in the eCRF. Skipped doses due to reasons others than AE (eg, COVID-19 lockdown, warfare, etc) should be added at the back end to ensure the total duration of treatment after cCRT in each arm is 12 months or corresponding cycles, ie, a maximum of 17 cycles in Arm A and B, 26 cycles for Q2W regimen, and 13 cycles for Q4W regimen in Arm C.

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.

2.5.1. Dose Interruption or Delay for Ociperlimab and Tislelizumab

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

If treatment is delayed due to TEAEs, treatment may resume only after the AEs have returned to baseline or ≤ Grade 1 severity except for alopecia or 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.

In Arm A and B, if a dose is delayed for the immunotherapy (ociperlimab and tislelizumab in Arm A, tislelizumab in Arm B) for ≤ 10 days for a planned dosing cycle (eg, Cycle 4 Day 1), the immunotherapy should be administered. If the delay is > 10 days, the patient should skip administration of the immunotherapy. The immunotherapy will be administered on Day 1 of the next planned cycle (eg, Cycle 5 Day 1). This 10-day dose delay time window does not apply to Cycle 3 Day 1.

If immune-mediated AEs are persistent without any improvement for more than 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, re-initiation 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.

Management guidelines for imAEs and infusion-related reactions in patients treated with the immunotherapy are presented in Section 5.7 of Appendix 17, and Appendix 12, respectively.

The tumor assessment schedule will not be altered even if the administration of the study drug is delayed, except for the first 9-week tumor assessment.

2.5.2. Dose Reductions for Ociperlimab and Tislelizumab

There will be no dose reductions allowed for ociperlimab or tislelizumab in Arm A and Arm B.

2.5.3. Dose Interruption, Delay or Modification for Durvalumab

There will be no dose reductions allowed for durvalumab. Please refer to prescribing information Table 2 Recommended Dosage Modifications (Appendix 15) approved by US FDA for specific information. Note, in countries/regions other than US, some recommended dosage modifications of durvalumab prescribing information approved by the local health authority may differ from that approved by US FDA. In such cases, please refer to the recommendations approved by the local health authority (Appendix 15).

2.5.4. Dose Delay or Modification for Radiotherapy

Investigators will be advised to suspend the use of chemotherapy given with radiation if they believe that continuing chemotherapy administration will compromise delivery of full-dose radiation in a not delayed manner.

Ideally, radiation therapy should be completed within 42 days. Treatment completion within 49 days will be considered an acceptable deviation.

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. The reasons for delays should be carefully reported in cases where the RT treatment takes longer than 49 days.
- During the cCRT phase, esophagitis is managed according to Table 23 in regard to RT. During this cCRT period, in case of Grade 3 esophagitis related to chemotherapies or ociperlimab or tislelizumab, chemotherapies and/or ociperlimab in combination with

tislelizumab in Arm A, chemotherapies and/or tislelizumab in Arm B, chemotherapies in Arm C should be held if the investigator believes that continued use will jeopardize the delivery of full-dose RT, and radiation is to be continued. Resume the treatment with chemotherapies and/or ociperlimab in combination with tislelizumab in Arm A, or chemotherapies and/or tislelizumab in Arm B, or chemotherapies in Arm C is permitted if there is resolution of the esophagitis to ≤ Grade 2.

- If Grade 4 esophagitis related to RT, chemotherapies, ociperlimab, or tislelizumab occurs; RT, chemotherapies, and/or ociperlimab in combination with tislelizumab in Arm A, or RT, chemotherapies and/or tislelizumab in Arm B, or chemotherapies in Arm C 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 in combination with tislelizumab in Arm A; or RT, chemotherapies and tislelizumab in Arm B; or RT and chemotherapies in Arm C. Resume the treatment with RT, chemotherapies and ociperlimab in combination with tislelizumab in Arm A; or RT, chemotherapies and tislelizumab in Arm B; or RT and chemotherapies in Arm C 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 5.3 of Appendix 17. 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 radiotherapy 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.

Table 23 summarizes the dose modifications of the chemotherapy regimens in cases of Grade 3 or 4 esophagitis.

Table 20 lists esophagitis grading and clinical states according to NCI-CTCAE v5.0.

Table 20: 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.

Acute esophageal toxicity should be managed with diet and medications, alone or in various combinations (Table 21 and Table 22), or comparable regimen, and intervention should be initiated at the first signs or symptoms of esophageal toxicity.

Table 21: 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.

Table 22: 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 4h 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, every day.

2.5.5. Dose Modifications for Chemotherapy Treatment

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 Table 23. 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 Table 23. Suggest to complete all chemotherapy before the last dose of radiotherapy.

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 are not required to modify for any body weight change of < 10%. Calculating the chemotherapy doses by actual body weight is acceptable.

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 reduced 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, ≤ Grade 2 fatigue or neuropathy. A maximum of 2 dose reductions for each chemotherapeutic agent are permitted except for carboplatin plus paclitaxel regimen. 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.

If chemotherapy-related toxicities warrant a dosing delay, chemotherapy administration may restart as soon as it is feasible.

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

SELECTED PRECAUTIONS:

- 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 estimated GFR by CKD-EPI equation or calculated creatinine clearance by Cockcroft-Gault Equation (Appendix 14) is < 60 mL/min or < 45 mL/min, respectively.
- Pemetrexed should not be administered to patients whose estimated GFR by CKD-EPI equation or calculated creatinine clearance is by Cockcroft-Gault Equation (Appendix 14) < 45 mL/min.
- Patients will be allowed to switch from cisplatin to carboplatin in pemetrexed-included regimen if patients become ineligible for cisplatin due to toxicity related to cisplatin if they have completed at least one 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 pre-existing hearing deficit.

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

Table 23: Dose Modification of Chemotherapy

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 that of the preceding administration. Recommended dose modifications for hematologic toxicity are provided in the following table.

Chemotherapy Dose Modification[a] for Hematological Toxicity

(Apply to cisplatin plus etoposide, cisplatin plus pemetrexed, and carboplatin plus pemetrexed regimens)

Adverse event		Treatment
Febrile neutropenia; documented infection		1) The first episode of febrile neutropenia or documented infection will result in antibiotic treatment and reduction by 25% of both drugs doses. 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 (0.5-0.99 x 10^9/L)	Chemotherapy delay until ≤ Grade 1 (≥ 1.5 x 10^9/L); restart with the full dose
	Grade 4 (< 0.5 x 10^9/L)	Chemotherapy delay until recovered to ≤ Grade 1; dose reduction of all further doses by 25%
Thrombocytopenia	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; dose reduction of all further doses by 25%

	Grade 4	Chemotherapy delay until recovered to normal; dose reduction of all further doses by 50%
	Grade 3 associated with clinically significant bleeding	Chemotherapy delay until recovered to normal; dose reduction of all further doses by 50%
Recurrence of Grade 3 or 4 after 2 dose reductions (with either neutropenia or thrombocytopenia)		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.

(Apply to carboplatin plus paclitaxel regimen)

Doses that are missed during the weekly schedule concurrent with radiation will not be made up but will be documented.

Adverse Event		Treatment
Febrile neutropenia; documented infection		Chemotherapy delay until recovered to ≤ Grade 1(ANC ≥ 1.5 x $10^{\wedge 9}$/L)
Neutropenia	Grade 3 or 4	Chemotherapy delay until recovered to ≤ Grade 1(ANC ≥ 1.5 x $10^{\wedge 9}$/L)
Thrombocytopenia	≥ Grade 2 to 4	Chemotherapy delay until recovered to ≤ Grade 1 (platelets < LLN -75000/mm^3)
	≥ Grade 3 associated with clinically significant bleeding	Discontinue chemotherapy

Recommended Dose Modifications for Nonhematologic Toxicities

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

In general, for nonhematologic toxicities greater than or equal to Grade 3, 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 Non-Hematological Toxicities

Toxicity	Grade	Treatment
Renal toxicity	≥ Grade 1	Delay chemotherapy until recovered to Grade 0 or baseline, change cisplatin to carboplatin, if possible; dose reduction by 25% for other drug; if it recurs, discontinue chemotherapy
Ototoxicity	Grade 2	Dose reduction of all further doses of cisplatin by 25%
	Grade 3-4	Delay chemotherapy until recovered to ≤ Grade 2, change cisplatin to carboplatin
Sensory neuropathy [b, c]	Grade 2	Dose reduction for all further doses of cisplatin by 25%
		For carboplatin plus paclitaxel regimen, delay paclitaxel until ≤ Grade 1 while continue carboplatin
	Grade 3	Discontinue cisplatin, change cisplatin to carboplatin; Dose reduction by 25% for etoposide
		For carboplatin plus paclitaxel regimen, discontinue paclitaxel while continuing carboplatin
	Grade 4	Discontinue cisplatin, carboplatin, paclitaxel, and etoposide
Hepatic toxicity (transaminase elevation)	Grade 3 or 4	Dose reduction by 25% for cisplatin and etoposide
Diarrhea	Grade 4	Discontinue chemotherapy
Oral mucositis or stomatitis	≥ Grade 3	Dose reduction for further doses of etoposide by 25%
		Dose reduction for further doses of pemetrexed by 50%
		For carboplatin plus paclitaxel regimen, discontinue chemotherapy for Grade 4
Esophagitis [d, e]	≥ Grade 3	For carboplatin plus paclitaxel regimen, hold chemotherapy until ≤ Grade 2
		For cisplatin plus etoposide regimen, 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], dose reduction of all further dose by 25%

[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 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 in the course of their treatment than anticipated, 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 for carboplatin plus paclitaxel; chemotherapy can be resumed at 75% 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 for carboplatin plus paclitaxel; chemotherapy can be resumed at 75% of previous dose for both drugs.
[f] Skin reactions, paronychia, alopecia, fatigue, and nausea/vomiting which may have resolved to Grade 2 or baseline.

2.5.6. 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 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 toxicity does not resolve within 21 days, that component will be discontinued.

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

3. PRIOR AND CONCOMITANT THERAPY

3.1. Prior Therapy

The exclusion criteria specify that patients should not have received prior therapies targeting PD-1, PD-L1, PD-L2, TIGIT, T-cell costimulation or checkpoint pathways; any prior therapy for lung cancer, including but not limited to chemotherapy, radiotherapy, targeted therapy, biologic therapy, or immunotherapy; any prior radiotherapy to the thorax, including radiotherapy to the esophagus, mediastinum, or for breast cancer; or immunotherapy (eg, interleukin, interferon, or thymosin) or investigational therapy ≤ 14 days or 5 half-lives (whichever is longer) before the first dose of study treatment.

3.2. Permitted Concomitant Medications/Procedures

Unless noted otherwise, 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, hematopoietic growth factors, red blood cell/platelet transfusions) and in a patient's interest are allowed. Opiates and other medication required for pain management of patients are allowed.

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

Bisphosphonates are permitted during the study for a nonmalignant indication. Use of potentially hepatotoxic drugs in patients with impaired hepatic function is allowed but should be carefully monitored.

Vaccines for COVID-19 are allowed except for any live vaccine (ie, live SARS-CoV-2 virus) that may be developed. Attenuated (vector) COVID-19 vaccines are inactivated vaccines and as such, are permitted. It is recommended to avoid COVID-19 vaccination within 72 hours before or after study drug administration during the first 2 treatment cycles and within 24 hours before or after study drug administration thereafter (ie, from Cycle 3 onwards). Vaccinations are considered a concomitant medication and hence should be entered on the eCRF. The specific COVID-19 vaccine should be recorded instead of generic language, eg, mRNA-1273 vaccine (Moderna), BioNTech vaccine (Pfizer), etc.

3.2.1. Systemic Corticosteroids

Systemic corticosteroids administered for the control of imAEs must be tapered gradually (see Appendix 12) and must be administered at non-immunosuppressive doses (≤ 10 mg/day of prednisone [in Japan, prednisolone] or equivalent) before the next immunotherapy (ociperlimab and tislelizumab in Arm A, tislelizumab in Arm B, or durvalumab in Arm C) administration. The short-term use of steroids as prophylactic treatments (eg, patients with contrast allergies to diagnostic imaging contrast dyes) is permitted.

3.2.2. Hepatitis B Treatment

Patients with active hepatitis B, defined as HBV DNA ≥ 500 IU/mL at screening, must initiate antiviral treatment 2 weeks before the first dose of study treatment. The patients would not be eligible unless HBV DNA decreases to < 500 IU/mL. If the patients are treated and eligible,

antiviral treatment must continue until 6 months after the last dose of study drug(s). Patients should continue effective antiviral treatment during the study to decrease potential viral re-activation risk. Tenofovir and entecavir are recommended in the American Association for the Study of Liver Disease (AASLD) guideline because they lack resistance with long-term use (Terrault et al 2016). The investigator may use other antiviral agents, if appropriate, following local guidelines. However, interferon-based therapy for hepatitis B is not permitted on study.

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

3.2.3. Hepatitis C Treatment

Patients with detectable HCV RNA who are receiving treatment at screening must meet the criterion of negative HCV RNA to be eligible. If the patients are treated and eligible, they will remain on continuous, effective antiviral therapy during the study. Investigators can consider treatment with antivirals following the international 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 enrollment and continue treatment during the study and for 6 months after study treatment discontinuation.

3.3. Prohibited Concomitant Medications/Procedures

The following medications are prohibited during the study:

- Any concurrent anticancer therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents including herbal medicine and patent medicines for the treatment of cancer [Appendix 16]).
- Live vaccines within 28 days before the first dose of study drugs and 60 days following the last dose of study drugs.
- Herbal remedies with immune-stimulating properties or that are known to potentially interfere with liver or other major organ functions.
- Patients must notify the investigator of all herbal remedies and supplements used during the study.

3.4. Restricted Concomitant Medications/Procedures

The following medications are restricted during the study:

- Immunosuppressive agents (except to treat a drug-related AE).
- Systemic corticosteroids > 10 mg daily (prednisone [in Japan, prednisolone] or equivalent), except to treat or control a drug-related AE (per protocol) or for short-term use as prophylactic treatment.
- Patients should not abuse alcohol or other drugs during the study.

- Avoid nonsteroidal anti-inflammatory drugs (NSAIDs) (aspirin, ibuprofen etc.) at least 5 days before and 2 days after pemetrexed chemotherapy treatment period.

3.5. Potential Interactions Between the Study Drugs and Concomitant Medications

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

Caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit or induce either CYP2C8 or CYP3A4 (eg, inhibitors ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir, or inducers rifampicin, carbamazepine, phenytoin, efavirenz, and nevirapine). When strong CYP2C8 and CYP3A4 inhibitors (Flockhart 2007; US FDA Development and Drug Interactions) are co-administered with paclitaxel, the toxicities may be exacerbated, and the investigator should closely monitor for them. Please refer to the prescribing information of paclitaxel for more information.

Renal function decreases would result in an increase in systemic exposure of pemetrexed. Pemetrexed should not be administered to patients whose creatinine clearance is < 45 mL/min. Caution should be exercised when administering pemetrexed concurrently with nephrotoxic drugs or drugs that are tubularly secreted. Please refer to the prescribing information of pemetrexed for more information.

4. STUDY ASSESSMENT AND PROCEDURES

A table of scheduled study assessments for PA 1.0 is provided in Table 14. 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.

4.1. Screening Period

Screening evaluations will be performed ≤ 28 days before randomization. A patient who agrees to participate in this study will sign the ICF before undergoing any screening assessment. The screening period begins on the first day that a screening assessment is conducted. Screening evaluations may be repeated as needed within the screening period. The investigator is to assess patient eligibility according to the latest screening assessment results.

Results of standard-of-care tests or examinations performed before informed consent has been obtained and ≤ 28 days before randomization may be used for the purposes of screening rather than repeating the standard-of-care tests unless otherwise indicated.

Procedures conducted only during the Screening Visit are described in this section. 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 *Section* 4.1.5 of Appendix 17 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 4.4 of Appendix 17), Tumor and Response Evaluations (Section 4.5 of Appendix 17), PK and ADA Assessments (Section 4.6 of Appendix 17) and Biomarkers (Section 4.7 of Appendix 17) sections.

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

4.1.1. Informed Consent and Screening Log

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

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before 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.

4.1.2. Patient Numbering

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

4.1.3. 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 history; reproductive status (ie, of childbearing potential or no childbearing potential); history of alcohol consumption and tobacco (ie, former or current or never).; Prior or concomitant medications include 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 radiotherapy, 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.

4.1.4. Females of Childbearing Potential and Contraception

Childbearing potential is defined as being physiologically capable of becoming pregnant, ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile. Refer to Appendix 5 for contraception guidelines and definitions of "women of childbearing potential" and "no childbearing potential."

4.1.5. Pulmonary Function Tests

All patients should take a pulmonary function test (refer to Table 14 for details) at screening to assist in the determination of eligibility for the study.

Pulmonary function testing includes assessment of spirometry and oxygenation. The assessment of oxygenation should include at least pulse oximetry (percutaneous arterial oxygen saturation, SpO_2) at rest and with exercise; an assessment of diffusion capacity is optional. Respective test results should be submitted to the sponsor.

The medical monitor needs to be consulted to confirm eligibility if test results indicate significantly impaired pulmonary function, eg, resting pulse oximetry < 90% on room air and further desaturation upon exercise, absolute forced expiratory volume (FEV1) value < 1L, FEV1 of age and sex adjusted predicted performance levels < 50%, diffusing capacity of the lungs for carbon monoxide (DLCO) (if performed) < 40% of age and sex adjusted predicted performance levels (Pellegrino et al 2005).

Test may be repeated as clinically indicated while on study.

4.1.6. COVID-19 Test

A COVID-19 test may be conducted according to local practice.

4.2. Enrollment

4.2.1. Confirmation of Eligibility

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

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

4.2.2. Randomization

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

4.3. Study Drug Dispensation

All study drugs will be dispensed and administered as described in Section 2.2 of Appendix 17.

4.4. Safety Assessment

4.4.1. Vital Signs

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

The patient's vital signs are required to be recorded within 60 minutes before, during, and within 30 minutes after completion of infusion of study treatment (ociperlimab and tislelizumab in Arm A, tislelizumab in Arm B, and durvalumab in Arm C). For subsequent infusions, vital signs will be collected within 60 minutes before infusion and, if clinically indicated, during and within 30 minutes after the completion of infusion.

Weight is required to be measured once on the scheduled assessment day and before study treatment if there is any. Height measurements are only required at screening.

4.4.2. Physical Examinations

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

Patients should be solicited at every visit for any vision changes (eg, blurred/distorted vision, blind spots, change in color vision, photophobia, tenderness/pain and, eyelid swelling) and should be referred to an ophthalmologist if further evaluation is needed.

At subsequent visits (and as clinically indicated), limited, symptom-directed physical examinations will be performed. New or worsened clinically significant abnormalities will be recorded as AEs on the eCRF. Refer to Section 5.3 of Appendix 17 regarding AE definitions and reporting and follow-up requirements.

4.4.3. Eastern Cooperative Oncology Group Performance Status

ECOG Performance Status (Table 14) will be assessed during the study.

4.4.4. Laboratory Safety Tests

Local and/or central laboratory assessments of clinical chemistry, hematology, coagulation, and urinalysis will be conducted as outlined in Appendix 2 per the timepoints shown in Table 14.

If hematology and serum chemistry at screening are not performed within 7 days before the planed C1D1, these tests should be repeated and reviewed before randomization. If a coagulation test was performed and reviewed during screening, it is not mandated to repeat before C1D1 unless investigator deems necessary. Hematology, serum chemistry (including liver function tests), creatine kinase (CK) and creatine kinase cardiac muscle isoenzyme (CK-MB) as specified in Appendix 2 should be performed weekly during cCRT, at the beginning of each subsequent cycle after cCRT, and the EOT Visit (Table 14). After Cycle 1, these laboratory tests are to be performed and reviewed within 48 hours before study treatment administration. Urinalysis is to be conducted during the treatment period only if clinically warranted.

Local laboratory assessments will include the following:

- Hematology (CBC, including hemoglobin, hematocrit, white blood cell [WBC] count [neutrophils and lymphocyte], and platelet count)
- Serum chemistry (glucose, blood urea nitrogen [BUN] or urea, creatinine, sodium, potassium, magnesium, chloride, calcium, phosphorus, direct bilirubin, total bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase (LDH), total protein, albumin)
- Coagulation test (international normalized ratio, prothrombin time, and activated partial thromboplastin time)
- Urine or serum pregnancy test (for women of childbearing potential, including premenopausal women who have had a tubal ligation)
- Urinalysis (complete [including, but not limited to specific gravity, pH, glucose, protein, ketones] and/or microscopic at screening and if clinically indicated)
- Thyroid function testing (thyroid stimulating hormone [TSH], free T3 or total T3, free T4 or total T4).

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

4.4.4.1. Cardiac Enzyme Monitoring

Although immune-mediated myocarditis is a rare complication of immune checkpoint inhibitors, serum creatine kinase (CK) and creatine kinase cardiac muscle isoenzyme (CK-MB) are monitored in all tislelizumab studies to protect study patients and to quantify the risk of muscle inflammation (see Table 14 for the blood collection schedule and Appendix 12 for guidelines for management of suspected immune-mediated myocarditis, respectively). Serum troponins may be substituted per local guideline if used consistently through the study.

Serum CK and CK-MB testing will be implemented for all patients at screening, at scheduled visits during the treatment periods, and at the EOT. In the event that CK-MB fractionation is not

available, serum troponins (troponin I and/or T) measurements will be performed instead per local guidelines if used consistently throughout the study.

4.4.5. Electrocardiograms

The ECG recordings will be obtained during screening, and as clinically indicated during the treatment period, at the EOT Visit (Table 14).

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

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

4.4.6. 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 5.6 of Appendix 17.

4.4.7. Hepatitis B and C Testing

Testing will be performed by a central laboratory and/or the local laboratory at screening (and as clinically indicated) and will include HBV/HCV serology (HBsAg, hepatitis B surface antibody [HBsAb], hepatitis B core antibody [HBcAb], and HCV antibody). In the case of positive HBsAg result or positive HCV antibody result, these tests will be followed by viral load assessment (HBV DNA or HCV RNA) at screening.

For patients who have detectable HBV DNA or HCV RNA at screening or upon repeat testing, the respective viral load test will be performed every 12 weeks. A detailed schedule is provided in Table 14.

4.5. Tumor and Response Evaluations

Tumor imaging will be performed ≤ 28 days before randomization. Results of standard-of-care tests or examinations performed before obtaining informed consent and ≤ 28 days before randomization may be used for the purposes of screening rather than repeating the standard-of-care tests. During the study, tumor imaging will be performed approximately every 9 weeks (± 7 days) from randomization for the first 54 weeks, and every 12 weeks (± 7 days) thereafter, based on RECIST v1.1. The first tumor assessment after randomization (the 9-week tumor assessment) is allowed to be performed within 42 days after cCRT and should take place before the initiation of immunotherapy after the cCRT phase. If a tumor assessment is missed or conducted outside of the specified assessment window, all subsequent scans should be conducted according to the planned schedule.

Tumor assessments must 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, except for the first 9-week tumor assessment.

Screening assessments must include:

- FDG-PET/CT performed for the whole body, or sufficient to rule out distant metastases (eg, from skull base to knees).
- If the CT scan portion is with contrast and is of sufficiently high quality, a separate CT scan at screening for the chest, abdomen, and pelvis can be skipped.
- MRI (or CT scan if MRI is contraindicated or not readily available) with contrast of the head is required at screening.
- While centers are encouraged to obtain tissue confirmation of lymph node metastases in N2 or N3 disease, the tumor board/multidisciplinary team in individual cases may dispense with this procedure (AJCC Cancer Staging Manual 2017).

If the CT scan portion of FDG-PET/CT is not qualified enough as specified above, screening assessment must include CT scans (with oral/intravenous contrast, unless contraindicated) of the chest, abdomen, and pelvis; each subsequent assessment should include at least CT scans (with oral/intravenous contrast, unless contraindicated) of the chest and abdomen. If contraindication exists, other modalities can be allowed after consultation with the medical monitor (eg, MRI, CT without contrast).

All measurable and evaluable lesions should be assessed and documented at the Screening Visit and reassessed at each subsequent tumor evaluation. The same radiographic procedure used to assess disease sites at screening must be used throughout the study (eg, the same contrast protocol for CT scans).

- If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the study, a noncontrast CT of the chest plus a contrast-enhanced MRI (if possible) of abdomen and pelvis should be performed.
- If a CT scan for tumor assessment is performed on a PET/CT scanner, the CT acquisition must be consistent with the standards of a diagnostic CT scan.
- MRI (or CT scan if MRI is contraindicated or not readily available) of the head or bone scan is performed if clinically indicated at the discretion of investigator before the discontinuation of tumor assessment.
- At the investigator's discretion, other methods of assessment of target lesion and non-target lesions per RECIST v1.1 may be used.

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

Administration of study treatment will continue until 12 months following the completion of cCRT; PD as assessed by the investigator per RECIST v1.1, unacceptable toxicity, death; or another discontinuation criterion is met.

A patient who discontinues study treatment for reasons other than disease progression (eg, toxicity, completion of the 12-month treatment) will continue to undergo tumor assessments following the original plan until the patient experiences PD per RECIST v1.1, withdraws consent, is lost to follow-up, death, or until the study terminates, whichever occurs first.

Study treatment beyond initial PD per RECIST 1.1

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

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

The decision to continue study drugs beyond initial PD per RECIST v1.1 must be agreed upon with the medical monitor and documented in the study records.

Tumor assessment should continue as planned in patients receiving study drug(s) beyond initial PD per RECIST v1.1. Tumor assessment in such patients should continue until study treatment discontinuation.

Second Progression

Following the first progression assessed by the investigator, patients will be assessed every 12 weeks (± 7 days) for a second progression (using the patient's status at the first progression as reference for assessment of second progression). A patient's second progression status is defined according to local standard clinical practice and may involve any of: objective radiological, symptomatic progression or death. Measurements per RECIST v1.1 will not be collected for assessment of PFS2. The date of PFS2 assessment and investigator's opinion of progression status (progressed or non-progressed) at each assessment will be recorded in the eCRF.

4.6. Pharmacokinetic and Antidrug Antibody Testing

Checkpoint inhibitors may elicit an immune response. Patients with signs of any potential immune response will be closely monitored. Validated screening and confirmatory assays will be employed to detect ADA at multiple timepoints throughout the study. In addition, blood samples will be collected for characterization of ociperlimab and tislelizumab PK at the timepoints specified in the Schedule of Assessments (Table 14).

PK and ADA assays of ociperlimab and tislelizumab will be managed through a central laboratory. Serum samples will be assayed for ociperlimab and tislelizumab concentrations using validated immunoassays.

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

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

4.7. Biomarker

Shipping, storage, and handling of blood samples as well as archival tumor and/or fresh tumor tissues for the assessment of biomarkers will be handled by a central laboratory. Refer to the laboratory manual for details of sample handling and the Schedule of Assessments (Table 14) for timepoints.

Tissue-based biomarkers, including but not limited to the expression of TIGIT, CD226, CD155, CD112, and PD-L1, GEP, TMB, gene mutations and microsatellite instability (MSI), and TILs at baseline, and at disease progression/reoccurrence will be tested. (Note: For the sites in China mainland, tissues will be obtained to test the expression of TIGIT, CD226, CD155, CD112, and PD-L1, GEP, TMB, gene mutations and MSI, and TILs at baseline, and at disease progression/reoccurrence).

Patients are required to provide tumor tissues (archival tumor tissues [FFPE blocks or approximately 15 [≥ 6] freshly cut unstained FFPE slides] or fresh biopsies). If archival tumor tissues are not available, a fresh tumor biopsy is required at baseline. Acceptable fresh biopsy samples include core needle biopsies for deep tumor tissue or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.

If clinically feasible, it is highly recommended to obtain a tumor biopsy at the time of disease progression to explore the immune- or tumor-related biomarkers and biological changes that might drive disease progression or acquired resistance to ociperlimab and tislelizumab or durvalumab. Blood sample must be collected at C1D1 (predose) for biomarker test. Optional blood samples will be collected at C3D1 (predose), at C4D1 (predose), and at the EOT Visit after the disease progression (Table 14). All these blood samples will be collected to explore the association of blood-based biomarkers with response, resistance and prognosis. (Note: Blood-based biomarkers, including TMB, MSI, ctDNA, EVs and gene mutational profiles, will be explored in the blood samples which will be collected in the sites in China mainland).

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

4.8. Health-Related Quality of Life

Patients will be asked to complete 5 PROs, that include the EORTC QLQ-C30 (Appendix 7), EORTC QLQ-LC13 (Appendix 8), EQ-5D-5L questionnaires (Appendix 9), PGI-S (Appendix 10), and PRTSE (Appendix 11) before any clinical activities are performed during on-study clinic visits according to the schedule in Table 14. The questionnaires will be provided in the patient's preferred language.

4.9. Visit Windows

All visits must occur within ± 3 days from the scheduled date, unless otherwise noted (see Table 14). All assessments will be performed on the day of the specified visit unless an acceptable time window is specified. Assessments scheduled on the day of study treatment administration (Day 1) of each cycle should be performed before any study treatment is given unless otherwise noted. Laboratory results must be reviewed before dosing.

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other events, the visit should be scheduled for the nearest feasible date (the visit window is provided in Table 14), with subsequent visits conducted according to the planned schedule every 3 weeks (Arm A and Arm B) or every 2 or 4 weeks (Arm C) from C3D1. For visit schedule of Cycle 1 and Cycle 2, refer to Table 14.

4.10. Unscheduled Visits

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

If an unscheduled visit is necessary to assess toxicity or for suspected PD, 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.

5. 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.

5.1. Risks Associated With Study Treatment

5.1.1. 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 5.7.3 of Appendix 17. Ociperlimab-mediated TIGIT inhibition may increase the risk of imAEs. However, no apparent immunotoxicity, or toxicity in general, has been observed in animal models treated with ociperlimab. Furthermore, in the absence of activation, peripheral effector T cells do not typically express TIGIT, thereby minimizing any potential negative additive 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 workup procedures for suspected imAEs are provided in Appendix 12.

5.1.2. Risks Associated With Durvalumab

Durvalumab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that binds to PD-L1 and blocks the interaction of PD-L1 with PD-1 and CD80. The PD-L1/PD-1 pathway is involved in peripheral tolerance; therefore, such therapy may increase the risk of imAEs similar to PD-L1/PD-1 class drugs, specifically the induction or enhancement of autoimmune conditions. The risks are immune-mediated pneumonitis, hepatitis, colitis, endocrinopathies, nephritis, dermatologic reactions; and other immune-mediated adverse reactions (incidence of less than 1%) such as aseptic meningitis, hemolytic anemia, immune thrombocytopenic purpura, myocarditis, myositis, and ocular inflammatory toxicity, including uveitis and keratitis. Besides immune-related side effects, and infusion-related reactions are common. Overall infection is also very common.

Refer to the durvalumab prescribing information for details.

5.1.3. Risks Associated With Concurrent Chemotherapy

Please refer to Table 24 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 24: The summary of the commonly and specific reported toxicity of the chemotherapeutic agents

Agents	Common toxicity	Specific toxicity
Cisplatin	Leukopenia, thrombocytopenia and anemia; infectious complications; nausea/vomiting and other GI toxicity; hepatic impairment; fatigue; anorexia; constipation	Nephrotoxicity; ototoxicity; peripheral neuropathies
Carboplatin		Ototoxicity and peripheral neuropathies
Pemetrexed		Nephrotoxicity; skin rash
Paclitaxel		Hypersensitivity reaction; neuropathies; myalgia; arthralgia; cardiovascular
Etoposide		Hypersensitivity reactions; ocular; respiratory; skin; neurologic

5.1.4. Risks Associated With Radiotherapy

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

5.2. General Plan to Manage Safety Concerns

5.2.1. 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 25), physical examinations, laboratory measurements (hematology, clinical chemistry, etc), and other assessments including those listed in Table 14. In addition, patients will be closely monitored for the development of any signs or symptoms of autoimmune conditions or infection.

At the start of each cycle, study treatment(s) will be provided only after clinical laboratory results have been reviewed. Administration of study treatment will be performed in a setting where emergency medical equipment and staff who are trained to respond to medical emergencies are available (for additional information, see Section 2.2 of Appendix 17).

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

Investigators are instructed to report all AEs (includes 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 5.7 of Appendix 17.

5.3. Adverse Events

5.3.1. Definitions and Reporting

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

Examples of AEs include:

- Worsening of a chronic or intermittent pre-existing condition, including an increase in severity, frequency, duration, and/or has an association with a significantly worse outcome
- New conditions detected or diagnosed after study treatment administration even though the condition might 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 treatment 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.

5.3.2. Assessment of Severity

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

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

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care, activities of daily living
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

Note: The terms “severe” and “serious” are not synonymous. Severity is a measure of intensity (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 5.6.2 of Appendix 17.

5.3.3. Assessment of Causality

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

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always assesses causality for every SAE before transmission of the SAE report to the sponsor because the causality assessment is 1 of the criteria used when determining regulatory reporting requirements. The investigator may change his/her opinion of causality considering follow-up information, amending the SAE report accordingly.

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

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

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

- There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out
- There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
- There is some evidence to suggest a causal relationship (eg, the AE occurred within a reasonable time after administration of the study treatment[s]). However, the influence of other factors may have contributed to the AE (eg, the patient's clinical condition or other concomitant AEs).

5.3.4. Follow-up of Adverse Events

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

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

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

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

New or updated information should be reported to the sponsor according to the SAE instructions provided by the sponsor within the time frames outlined in Section 5.6.2 of Appendix 17.

5.3.5. Laboratory Test Abnormalities

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

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

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

5.4. Definition of a Serious Adverse Event

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

- Results in death
- Is life-threatening

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

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

5.5. Suspected Unexpected Serious Adverse Reaction

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

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

5.6.1. Adverse Event Reporting Period

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

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 (including chemoradiotherapy) or initiation of new anticancer therapy, whichever occurs first. Immune-mediated AEs (serious or nonserious) should be reported until 90 days after the last dose of ociperlimab, tislelizumab, or durvalumab, regardless of whether the patient starts a new anticancer therapy. All SAEs considered related to the study treatment(s) that are brought to the attention of the investigator should be reported regardless of time since the last dose of treatment.

AEs and SAEs should be recorded according to the details in Table 25. For the follow-up period for AEs, see Section 5.3.4 of Appendix 17. For the definition of treatment-emergent adverse events (TEAEs), see Section 9.3.2.

Table 25: Guidance for Duration of Recording New or Worsening Adverse Events in 3 Arms

Event Type	Record new or worsening events that occur during this period	
	Begin	**End**
SAEs[a]	Signing of informed consent	Up to 30 days after last dose, initiation of new anticancer therapy, death, withdrawal of consent, or loss to follow-up, whichever occurs first
Nonserious AEs due to PD	Do not record (see Section 5.6.4 of Appendix 17)	
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-mediated 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, progressive disease; SAE, serious adverse event.
[a] All SAEs considered related to the study treatment(s) that are brought to the attention of the investigator should be reported regardless of time since the last dose of treatment.

5.6.2. Reporting Serious Adverse Events

5.6.2.1. 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 26.

Table 26: Time Frames and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

	Time frame for sending initial report	Documentation method	Time frame for sending follow-up report	Documentation method	Reporting method
All SAEs	Within 24 hours after first knowledge of the AE	SAE report	As expeditiously as possible	SAE report	Email or fax SAE form or pregnancy form

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

5.6.2.2. 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 5.6.2.1 of Appendix 17. The SAE report will always be completed as thoroughly as possible, including all available details of the event, and forwarded to the sponsor or designee within the designated time frames.

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

The investigator must always provide an assessment of causality for each SAE as described in Section 5.3.3 of Appendix 17.

The sponsor will provide contact information for SAE receipt.

5.6.2.3. Regulatory Reporting Requirements for Serious Adverse Events

The investigator will promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 5.6.2.1 of Appendix 17. The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a drug under clinical investigation.

The investigator, or 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 5.5 of Appendix 17) will be submitted to all applicable regulatory authorities and investigators for ociperlimab, tislelizumab, and durvalumab 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.

5.6.3. 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?

5.6.4. Disease Progression

PD, which is expected in this study population and measured as an efficacy endpoint, should not be recorded as an AE term. Similarly, nonserious AEs that are clearly consistent with the pattern of progression of the underlying disease and are considered unequivocally due to 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 5.6.2 of Appendix 17).

5.6.5. Deaths

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

5.6.6. Pregnancies

If a female patient or the partner of a male patient becomes pregnant while receiving study treatment or within 120 days after the last dose of ociperlimab and tislelizumab in Arm A or tislelizumab in Arm B, or within 3 months after the last dose of durvalumab, or within 180 days after the last dose of chemotherapy or radiotherapy (14 months or 11 months after the last dose of cisplatin for female or male patients, respectively), a pregnancy report form must be completed and expeditiously submitted to the sponsor to facilitate outcome followup. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

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

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

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

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

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

- Tislelizumab Investigator's Brochure
- Ociperlimab Investigator's Brochure
- Durvalumab prescribing information
- Cisplatin prescribing information
- Carboplatin prescribing information
- Pemetrexed prescribing information
- Paclitaxel prescribing information
- Etoposide prescribing information

5.6.8. Assessing and Recording Immune-Mediated Adverse Events

Since treatment with anti-PD-1 or immune checkpoint inhibitors can cause autoimmune disorders, AEs considered by the investigator to be immune-mediated (see Section 5.7.3 of Appendix 17) should be classified as imAEs and identified as such on the eCRF AE page until Day 90 after treatment discontinuation.

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

An extensive list of potential imAEs appears in Table 28. All conditions like those listed should be evaluated to determine whether they are imAEs based on a similar diagnostic process to those reactions that are presented in more detail in Appendix 12.

5.6.9. Recording Infusion-Related Reactions

The symptoms of infusion-related reactions may include but are not limited to fever, chills/rigor, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness, or hypertension. Severe reactions may include acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, or cardiogenic shock. Each individual sign and symptom of an infusion reaction should be recorded each as a separate AE in eCRF and identified as an infusion-related reaction. Refer to the eCRF completion guidelines for details.

5.7. Management of Adverse Events of Special Interest

As a routine precaution, after infusion of ociperlimab and tislelizumab in Arm A on Day 1 of Cycle 1 and Cycle 2, patients must be monitored for at least 2 hours afterwards in an area with resuscitation equipment and emergency agents; similarly, after infusion of tislelizumab in Arm B on C1D1 and C2D1, patients will be monitored for ≥ 1 hour. From Cycle 3 onward, at least a 60-minute monitoring period is required in an area with resuscitation equipment and emergency agents for Arm A, and for Arm B, the monitoring period is at least 30 minutes.

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

5.7.1. Infusion-Related Reactions

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

Treatment modification for symptoms of infusion-related reactions due to study drugs is provided in Table 27.

Table 27: Treatment Modification for Symptoms of Infusion-Related Reactions Due to Study Drugs

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.
Grade 2 - moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, intravenous fluids); prophylactic medications indicated for ≤ 24 hours.	Stop infusion. Infusion may be resumed at 50% of previous rate once infusion-related reactions has resolved or decreased to Grade 1 in severity. Any worsening is closely monitored. Proper medical management should be instituted as described in the text following this table.
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 in the text following this table. The patient should be withdrawn from the study treatment.
Grade 4 – life-threatening Life-threatening consequences; urgent intervention indicated.	Immediately stop the infusion. Proper medical management should be instituted as described in the text following this table. The patient should be withdrawn from the study treatment. Hospitalization is recommended.

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

In Arm A and Arm B, 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. If the patient has a second infusion-related reaction (≥ Grade 2) on the slower infusion rate, the infusion should be discontinued, and the patient should be withdrawn from ociperlimab and tislelizumab treatment.

NCI-CTCAE Grade 1 or 2 infusion reaction: Proper medical management should be instituted, as indicated per the type of reaction. This includes but is not limited to an acetaminophen and/or antihistamine (eg, diphenhydramine or equivalent), antipyretic (eg, paracetamol or equivalent), and, if considered indicated, oral or intravenous glucocorticoids, epinephrine, bronchodilators, and oxygen. In the next cycle, the patient should receive oral pre-medication with an antihistamine (eg, diphenhydramine or equivalent) and an antipyretic

(eg, paracetamol or equivalent), and the patient should be closely monitored for clinical signs and symptoms of an infusion reaction.

NCI-CTCAE Grade 3 or 4 infusion 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 antihistamine, antipyretic, glucocorticoids, epinephrine, bronchodilators, and oxygen.

5.7.2. Severe Hypersensitivity Reactions and Flu-Like Symptoms

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

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

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

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

5.7.3. Immune-Mediated Adverse Events

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

A list of potential imAEs is shown below in Table 28. All conditions similar to those listed should be evaluated in patients receiving ociperlimab and tislelizumab in Arm A, tislelizumab in Arm B to determine whether they are immune-mediated.

Recommendation for diagnostic evaluation and management of imAEs is based on ESMO and American Society of Clinical Oncology guidelines (Haanen et al 2017; Brahmer et al 2018) and

common immune-mediated toxicities are detailed in Appendix 12. For any AEs not included in Appendix 12, refer to the American Society of Clinical Oncology Clinical Practice Guideline (Brahmer et al 2018) for further guidance on diagnostic evaluation and management of immune-mediated toxicities.

Table 28: 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
Musculoskeletal	arthritis; arthralgia; myalgia; myasthenic syndrome/myasthenia gravis; myositis
Blood	anemia; leukopenia; thrombocytopenia
Renal	interstitial nephritis; glomerulonephritis; acute renal failure
Cardiac	pericarditis; myocarditis; heart failure
Neurologic	encephalitis; meningitis; meningoradiculitis; meningoencephalitis; Guillain-Barre syndrome; neuropathy

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

Recommendations for managing imAEs are detailed in Appendix 12.

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

5.7.4. Adverse Events of Special Interest of Durvalumab

Infusion-related reaction, infection, and imAEs are of special interest with durvalumab. Please refer to durvalumab prescribing information which has been approved by local health authority. Appendix 15 provides Table 2 Recommended Dosage Modifications in the durvalumab prescribing information approved by the US FDA for reference.