CLINICAL STUDY PROTOCOL

Protocol Title:	Phase 1/1b Study Investigating Safety, Tolerability, Pharmacokinetics and Preliminary Antitumor Activity of Anti-TIGIT Monoclonal Antibody BGB-A1217 in Combination with Anti-PD-1 Monoclonal Antibody Tislelizumab (BGB-A317) in Patients with Unresectable Locally Advanced or Metastatic Solid Tumors
Protocol Number:	BGB-900-105 (AdvanTIG-105)
Phase:	1/1b
Investigational Products:	Ociperlimab (BGB-A1217) and Tislelizumab (BGB-A317)
Proposed Indication(s):	Advanced Solid Tumors
Sponsor:	BeiGene, Ltd. c/o BeiGene USA, Inc. 1840 Gateway Drive Third Floor San Mateo, California 94404, USA
Sponsor Medical Monitor:	[redacted] Phone: [redacted] Email: [redacted]
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NCT Number	NCT04047862

FINAL PROTOCOL APPROVAL SHEET

Phase 1/1b Study Investigating Safety, Tolerability, Pharmacokinetics and Preliminary Antitumor Activity of Anti-TIGIT Monoclonal Antibody BGB-A1217 in Combination with Anti-PD-1 Monoclonal Antibody Tislelizumab (BGB-A317) in Patients with Unresectable Locally Advanced or Metastatic Solid Tumors

BeiGene, Ltd., Approval:

See electronic signature	*See electronic signature*
Sponsor Medical Monitor	Date

INVESTIGATOR SIGNATURE PAGE

Protocol Title: Phase 1/1b Study Investigating Safety, Tolerability, Pharmacokinetics and Preliminary Antitumor Activity of Anti-TIGIT Monoclonal Antibody BGB-A1217 in Combination with Anti-PD-1 Monoclonal Antibody Tislelizumab (BGB-A317) in Patients with Unresectable Locally Advanced or Metastatic Solid Tumors

Protocol Identifier: BGB-900-105 (AdvanTIG-105)

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 Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd., or one of its affiliates.

Instructions for Investigator: Please SIGN and DATE this signature page. 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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_____

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SYNOPSIS

Name of Sponsor/Company:	BeiGene, Ltd.
Investigational Product(s):	Ociperlimab (also known as BGB-A1217) and Tislelizumab (also known as BGB-A317)
Title of Study:	Phase 1/1b Study Investigating Safety, Tolerability, Pharmacokinetics and Preliminary Antitumor Activity of Anti-TIGIT Monoclonal Antibody BGB-A1217 in Combination with Anti-PD-1 Monoclonal Antibody Tislelizumab (BGB-A317) in Patients with Unresectable Locally Advanced or Metastatic Solid Tumors
Protocol Identifier:	BGB-900-105 (AdvanTIG-105)
Phase of Development:	1/1b
Number of Patients:	Approximately 294 to 564 evaluable patients may be enrolled Phase 1: Approximately 44 to 64 patients Phase 1b: Approximately 250 to 500 evaluable patients in 10 prespecified cohorts (20 to 40 evaluable patients each for Cohorts 1 to 8, 30 to 60 evaluable patients for Cohort 9, and 60 to 120 evaluable patients for Cohort 10 [3 arms, with 20 to 40 evaluable patients per arm])
Study Centers:	Phase 1: Up to 10 centers (Australia and China) Phase 1b: Up to 85 centers globally

Study Objectives:

Phase 1

Primary:

- To assess the safety and tolerability of ociperlimab in combination with tislelizumab in patients with advanced solid tumors
- To determine the maximum tolerated dose (MTD) or maximum administered dose (MAD) of ociperlimab in combination with tislelizumab
- To determine the recommended Phase 2 dose (RP2D) of ociperlimab in combination with tislelizumab

Secondary:

- To assess the preliminary anticancer activity of ociperlimab in combination with tislelizumab
- To characterize the pharmacokinetics (PK) of ociperlimab in combination with tislelizumab
- To assess host immunogenicity to ociperlimab in combination with tislelizumab

Exploratory:

- To assess predictive, prognostic, and/or pharmacodynamic biomarkers including any association with response to ociperlimab treatment, exposure levels, and mechanism(s) of resistance

Phase 1b

Primary:

- To assess overall response rate (ORR) determined by investigator per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) for patients in each dose-expansion cohort

Secondary:

- To evaluate disease control rate (DCR), duration of response (DOR), and progression-free survival (PFS) determined by investigator per RECIST v1.1 for patients in each dose-expansion cohort
- To further characterize the safety and tolerability of ociperlimab in combination with tislelizumab with or without chemotherapy
- To further characterize the PK of ociperlimab in combination with tislelizumab with or without chemotherapy
- To further assess host immunogenicity to ociperlimab in combination with tislelizumab with or without chemotherapy
- To evaluate the association of PD-L1 and TIGIT expression level with clinical efficacy

Exploratory:

- To assess overall survival (OS) for each tumor expansion cohort
- To further assess predictive, prognostic, and/or pharmacodynamic biomarkers, including any association with response to ociperlimab in combination with tislelizumab with or without chemotherapy and/or mechanism(s) of resistance

Study Endpoints:

Phase 1

Primary Endpoints:

- Adverse events (AEs) and serious AEs (SAEs) as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 [NCI-CTCAE v5.0]), timing, seriousness, and relationship to study drugs; physical examinations, electrocardiograms (ECGs), and laboratory assessments as needed; and AEs meeting protocol-defined dose-limiting toxicity (DLT) criteria
- MTD or MAD, as defined as the highest dose at which less than one-third of patients experienced a DLT or the highest dose administered, respectively
- RP2D of ociperlimab monotherapy and/or in combination with tislelizumab, determined by MTD or MAD, as well as long-term tolerability, PK, efficacy, and any other relevant data as available

Secondary Endpoints:

- ORR, DOR, and DCR, as assessed using RECIST v1.1 (as described in Section 10.2)
- Serum concentrations at specified timepoints and PK parameters of ociperlimab and tislelizumab
- Immunogenic responses to ociperlimab and tislelizumab, evaluated through the detection of antidrug antibodies (ADAs)

Exploratory Endpoints:

- Biomarkers from patient-derived tumor tissue(s) and/or blood (or blood derivative) samples obtained before, during, and/or after treatment with ociperlimab and their association with clinical efficacy. Biomarkers may include, but not limited to, expression of TIGIT, CD226, CD155, CD112, and PD-L1 in tumor tissues, tumor mutation burden, microsatellite instability (MSI) status, and gene mutations in tissue and blood, immune cell subpopulations and gene expression profiling on peripheral blood and/or tumor tissues, and concentrations of cytokines and soluble proteins in plasma or serum

Phase 1b

Primary Endpoints:

- ORR, as determined from investigator derived tumor assessments per RECIST v1.1 for each tumor expansion cohort (described in Section 10.2.2)

Secondary Endpoints:

- PFS, DOR, and DCR, as determined from investigator-derived tumor assessments per RECIST v1.1 for each tumor expansion cohort (described in Section 10.2.3)
- AEs and SAEs as characterized by type, frequency, severity (as graded by NCI-CTCAE v 5.0), timing, seriousness, and relationship to study drugs; physical examinations, ECGs, and laboratory assessments as needed for each tumor expansion cohort
- Serum ociperlimab and tislelizumab concentrations at specified timepoints with or without chemotherapy
- Immunogenic responses to ociperlimab and tislelizumab, evaluated through the detection of ADAs with or without chemotherapy
- PD-L1 and TIGIT expression as the predictive biomarker for efficacy (including but not limited to ORR and PFS)

Exploratory Endpoints:

- Overall survival-defined as the date of the first dose of study drug to the date of death due to any cause (as described in Section 10.2.4).
- Biomarkers from patient-derived tumor tissue(s) and/or blood (or blood derivatives) samples obtained before, during and/or after treatment with ociperlimab in combination with tislelizumab with or without chemotherapy and their association with clinical efficacy. Biomarkers may include but not limited to expression of CD226, CD155, and CD112 in tumor tissues, tumor mutation burden, MSI status and gene mutations in tissue and blood, Epstein-Barr virus (EBV) status, immune cell subpopulations and gene expression profiling on peripheral blood and/or tumor tissues, and concentrations of cytokines and soluble proteins in plasma or serum.

Study Design

This is an open-label, multicenter, Phase 1 and Phase 1b study to evaluate the safety and preliminary antitumor activity of ociperlimab in combination with tislelizumab in patients with unresectable locally advanced or metastatic solid tumors.

- Dose Escalation: A modified 3+3 scheme will be used for sequential cohorts of approximately 4 increasing dose levels of ociperlimab, evaluated in combination with 200 mg of tislelizumab, to determine the MTD or MAD, RP2D, safety, PK, and other key endpoints for ociperlimab in combination with tislelizumab.
- The combination RP2D will be determined primarily from the Phase 1 safety, tolerability and PK data analyzed in its entirety, but may also consider any available efficacy and/or exploratory data.
- Dose verification in China: Before Chinese patients join the Phase 1b study, safety and tolerability of ociperlimab (RP2D) will be assessed as a monotherapy, and in combination with tislelizumab (200 mg once every 3 weeks [Q3W]) in Chinese patients. The Safety Monitoring Committee (SMC) will define the RP2D for Chinese patients based on the safety data from ociperlimab, combined with tislelizumab 200 mg, before Chinese patients join the Phase 1b study.
- Dose Expansion: Approximately 190 to 380 evaluable patients in 9 prespecified tumor-type cohorts will receive ociperlimab (900 mg) in combination with tislelizumab (200 mg Q3W) with or without chemotherapy. An interim analysis will be conducted on approximately the first 20 patients in Cohorts 1 to 8 who had ≥1 evaluable postbaseline tumor assessment. Based on the interim analysis for a given cohort, up to 40 evaluable patients with ≥ 1 evaluable postbaseline tumor assessment may be enrolled for Cohorts 1 to 8. An interim analysis will be conducted based on approximately the first 30 patients in Cohort 9 who had ≥ 1 evaluable postbaseline tumor assessment. Up to 60 evaluable patients in total may be enrolled based on interim analysis for Cohort 9.
- Cohort 10: Approximately 60 to 120 evaluable patients with metastatic non-small cell lung cancer (NSCLC) (3 arms, with approximately 20 to 40 patients per arm) will be randomized in an open-label setting to ociperlimab 450 mg, 900 mg, or 1800 mg in combination with tislelizumab 200 mg Q3W.

Patients will receive study drug until they meet a study treatment discontinuation criterion (see Section 7.5).

Study Assessments:

Tables of scheduled study assessments for Phase 1 and Phase 1b are provided in Appendix 1, respectively. Patients will be closely monitored for safety and tolerability throughout the study.

Dose Limiting Toxicity Definition and Assessment

All AEs will be graded according to NCI-CTCAE v5.0. The occurrence of any of the following AEs will be considered a DLT if they occur within 28 days of receiving ociperlimab on Cycle 1 Day 1 and are deemed to be related to ociperlimab and/or tislelizumab.

Definition of DLT

Hematologic:

1. Grade 4 neutropenia lasting > 7 days
2. ≥ Grade 3 febrile neutropenia
3. Grade 3 thrombocytopenia with clinically significant bleeding
4. Grade 4 thrombocytopenia lasting > 7 days
5. ≥ Grade 4 anemia

Non-hematologic:

1. ≥ Grade 4 toxicity
2. Grade 3 toxicity that is clinically significant and does not resolve to baseline or ≤ Grade 1 within 7 days of initiating optimal supportive care

Note: The following AEs will not be considered DLTs:

- Grade 3 endocrinopathy that is adequately controlled by hormonal replacement
- Grade 3 rash
- Grade 3 infusion-related AE that is transient (resolving within 6 hours of onset).
- Grade 3 nausea, vomiting, or diarrhea lasting for ≤ 72 hours with adequate antiemetic and/or other supportive care
- Grade 3 fatigue lasting for ≤ 7 days
- Grade 3 or higher electrolyte abnormality that lasts for ≤ 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions

Patients will be considered not evaluable for DLTs, if they 1) withdraw from the study during the DLT assessment window, 2) did not receive ≥ 80% of each scheduled study drug administration during the DLT assessment window and/or 3) received supportive care during the DLT assessment window that confounds the evaluation of DLTs (not including supportive care described as part of the DLT definition). Patients who are not DLT evaluable must be replaced, if needed.

Clinically important or persistent AEs that are not part of the DLT criteria may also be considered a DLT following review by the sponsor in consultation with the investigators. All AEs should be considered potentially related to the study drug regardless of investigator/sponsor causality assessment, excluding toxicities clearly related to disease progression or intercurrent illness. Additionally, any clinically significant AEs that occur after the DLT assessment window (eg, late immune-mediated AE [imAE]) for a given dose level, may be considered regarding subsequent dose escalation decisions. In such cases where patients have been safely dosed at the next dose level, additional dose escalation criteria (eg, increased minimum number of patients or expanded DLT assessment window) for subsequent dose levels will be considered by the sponsor in consultation with participating investigators. Every DLT will be discussed in SMC to help the determination of RP2D.

Dose Verification in China

Before Chinese patients join the Phase 1b study, ociperlimab (RP2D; determined from the dose-escalation stage) as a monotherapy (Cohort 1A) and in combination with tislelizumab (200 mg Q3W) (Cohort 1B) will be assessed. For each cohort, 6 to 10 Chinese patients will be enrolled to assess the safety and tolerability of the combination RP2D similar to the Phase 1 as outlined in Section 3.2.2. The assessment period will be 21 days, with ociperlimab RP2D administered on Cycle 1 Day 1 alone in Cohort 1A, and in combination with tislelizumab 200 mg administered on Cycle 1 Day 1 in Cohort 1B. De-escalation will be performed if excessive DLTs were observed, and a lower dose will be assessed in Cohort 2A (monotherapy) and Cohort 2B (in combination with tislelizumab) as specified in Section 3.2.2. All available safety data, including AEs and laboratory assessments, will be reviewed by the sponsor's medical monitor and study team members from Pharmacovigilance/Drug Safety, and Biostatistics with input from other members as appropriate. The SMC will recommend the RP2D for Chinese patients based on the safety data of ociperlimab combined with tislelizumab 200 mg before they join the Phase 1b study.

Tumor Assessments

Tumor imaging will be performed ≤ 28 days before the first dose of study drugs. During the study, tumor imaging will be performed approximately every 6 weeks (± 7 days) for the first 54 weeks, then every 12 weeks (± 7 days) thereafter.

Response will be assessed by investigators using RECIST v1.1. If radiographic progressive disease (PD) is suspected by the investigator to reflect pseudoprogression, patients may continue treatment with study drugs as long as the patient meets criteria below and until PD is confirmed by repeated imaging ≥ 4 weeks later (but not exceeding 6 to 8 weeks from the date of initial documentation of PD). At the investigator's discretion, if a patient could continue to benefit from ociperlimab and tislelizumab after PD per RECIST v1.1 criteria, the patient may continue ociperlimab and tislelizumab. The following criteria must be met in order to treat patients with suspected pseudoprogression or who may continue to benefit from study treatment beyond radiologic PD:

- Absence of clinical symptoms and signs of PD (including clinically significantly worsening of laboratory values)
- Stable Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 1 (Appendix 3)
- 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 after PD confirmation and inform patients that this practice is not considered standard in the treatment of cancer.

The decision to continue study drugs beyond initial investigator-assessed progression must be agreed by the medical monitor and documented in the study records. Patients who receive study treatment beyond progression will have tumor assessments performed according to the original schedule until study treatment discontinuation (Section 8.5).

A patient who discontinues study drugs early for reasons other than PD (eg, toxicity) will continue to undergo tumor assessments following the original plan until the patient meets one of the discontinuation criteria (see Section 7.5).

Duration of Patient Participation:

This study will consist of 5 periods:

1. **Screening Period** will be performed ≤ 28 days before first dose of ociperlimab.
2. **Treatment Period** starts with the first study drug administration and ends when the patient is discontinued from study treatment for any reason.
3. **End-of-Treatment/Safety Follow-up Period:** Patients who permanently discontinue study drugs will be asked to return to the clinic for the End-of-Treatment (EOT) which is required to be conducted ± 7 days after EOT decision and the Safety Follow-up Visit which is required to be conducted 30 days (± 7 days) after the last dose of study drugs unless otherwise specified or before the initiation of subsequent anticancer therapy, whichever occurs first. In addition, telephone contacts with patients should be conducted to assess imAEs and concomitant medications (if appropriate, ie, associated with an imAE or is a subsequent anticancer therapy) at 60 and 90 days (± 14 days) after the last dose of study drugs regardless of whether or not patients started a subsequent anticancer therapy. If patients report a suspected imAE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated.
4. **Efficacy Follow-up Period:** Patients who discontinue study drugs for reasons other than PD (eg, toxicity) will continue to undergo tumor assessments following the original tumor assessment schedule until the patient experiences PD, withdraws consent, dies, or starts subsequent anticancer therapy, or for any other reason listed in Section 7.5.2, whichever occurs first.
5. **Survival Follow-up (Phase 1b):** In Phase 1b, patients will be followed for survival and to obtain information on subsequent anticancer therapy information after discontinuation of study

treatment via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (± 14 days) after the Safety Follow-up Visit or as directed by the sponsor until death, withdrawal of consent, loss to follow-up, or end of study.
Study Population: **Phase 1:** Patients with histologically or cytologically confirmed unresectable locally advanced or metastatic solid tumors previously treated with standard systemic therapy or for which treatment is not available or not tolerated, and who have not received prior therapy targeting TIGIT. **Phase 1b:** Patients with histologically or cytologically confirmed tumor types based on the disease cohorts as below: • **Cohort 1:** Patients with metastatic squamous NSCLC • **Cohort 2:** Patients with metastatic non-squamous NSCLC • **Cohort 3:** Patients with metastatic NSCLC (PD-L1 positive, tumor cell expression [TC] ≥ 1%) • **Cohort 4:** Patients with extensive-stage small cell lung cancer (ES-SCLC) • **Cohort 5:** Checkpoint inhibitor (CPI)-experienced NSCLC patients who have received 1 or 2 prior therapies, including an anti-PD-(L)1 in the most recent line of treatment, and progressed after a best response of complete response (CR), partial response (PR), or stable disease (SD) • **Cohort 6:** Patients with metastatic esophageal squamous cell carcinoma (ESCC) • **Cohort 7:** Patients with metastatic esophageal adenocarcinoma (EAC) • **Cohort 8:** Patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) (PD-L1 positive, visually-estimated Combined Positive Score [vCPS] ≥ 1%) • **Cohort 9:** Patients with metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma • **Cohort 10:** Patients with metastatic NSCLC (PD-L1 positive, TC ≥ 1%)
Key Eligibility Criteria: Adult patients (≥ 18 years of age or the legal age of consent, at the time of voluntarily signing of informed consent) with histologically or cytologically confirmed tumor type based on the disease cohorts (metastatic squamous NSCLC; metastatic non-squamous NSCLC; metastatic NSCLC with PD-L1 positive; extensive-stage SCLC; CPI-experienced NSCLC; metastatic ESCC; metastatic EAC; recurrent or metastatic HNSCC with PD-L1 positive; metastatic G/GEJ adenocarcinoma). All patients are also required to demonstrate an ECOG Performance Status score of ≤ 1 and adequate organ function.
Investigational Product, Dose, and Mode of Administration: **Phase 1** **Dose Escalation in Australia:** For dose escalation, a 28-day DLT observation period will be utilized in the first cycle. A flat dose of ociperlimab will be administered intravenously as a single agent on Day 1 of each cycle followed by a 200 mg tislelizumab administered intravenously on Day 8. To be DLT evaluable, patients must receive ociperlimab alone on Day 1 of Cycle 1, followed by tislelizumab alone on Cycle 1 Day 8 (+ 2 days). Refer to Section 5.4.1 and Section 5.4.2 regarding continued treatment of patients who are unable to receive tislelizumab on Cycle 1 Day 8 (+2 days). If no DLT(s) are observed thereafter and through the completion of the initial 28-day cycle, patients will receive ociperlimab and tislelizumab

on Day 29 and every 21 days (ie, Q3W) thereafter, as outlined in Section 5.2.1 and Appendix 1, until patients meet a treatment discontinuation criterion. Except for the dose escalation DLT period, a 21-day treatment cycle is planned for all cycles.

The starting ociperlimab dose level (50 mg) will initially be evaluated in 1 patient (sentinel patient), whereas the second ociperlimab dose level (150 mg) will be evaluated in 3 or more patients. Escalation from the first ociperlimab dose level will proceed if no DLT is observed in the DLT evaluable patient. If a DLT is observed in this sentinel patient, the dose will be further explored following the 3+3 rules. Starting with the 150 mg ociperlimab dose level, escalation of the ociperlimab dose level will proceed if no DLT is observed during the DLT period in a minimum of 3 evaluable patients.

However, if a DLT occurs within the DLT observation period for a given dose level, enrollment for that dose level and dose finding decisions will proceed per the 3+3 design rules as follows:

a. ociperlimab dose escalation will advance if the first cycle DLT rate < 33%;
b. ociperlimab dose escalation will stop if the first cycle DLT rate is ≥ 33%. A minimum of 6 patients will be enrolled to the current dose level of ociperlimab if DLT rate is 33% (eg, 1/3) or the next lower dose level if DLT rate is >33% (eg, 2/3 or 3/3);
c. The MTD dose level is defined as the highest dose level at which < 33% of the patients experience a DLT.

For dose escalation decisions, only DLTs occurring within 28 days of Cycle 1 Day 1 for the corresponding dose level will be evaluated. However, as noted below and in Section 3.2.1.4, additional considerations may be taken into account if clinically significant toxicity(ies) is observed, regardless of when it occurred.

Based upon emerging clinical data, lower, intermediate and/or higher dose levels and/or alternative dosing intervals of ociperlimab may also be evaluated. However, the dosing regimen of tislelizumab will remain fixed for each different ociperlimab dose level evaluated.

The combination RP2D will be determined primarily from the Phase 1 safety, tolerability and PK data analyzed in its entirety, but may also consider any available efficacy and/or exploratory data, from a minimum of 6 patients.

Dose Verification in China:

Before Chinese patients join the Phase 1b study, safety and tolerability of ociperlimab (RP2D) will be assessed as a monotherapy, and in combination with tislelizumab (200 mg Q3W) in Chinese patients. The SMC will define the RP2D for Chinese patients based on the safety data from ociperlimab, combined with tislelizumab 200 mg, before Chinese patients join the Phase 1b study.

Phase 1b

For dose expansion, tislelizumab (200 mg) in combination with ociperlimab (RP2D) with or without chemotherapy will be administered Q3W starting on Cycle 1 Day 1.

For Cohort 10, tislelizumab (200 mg) in combination with ociperlimab 450 mg, 900 mg, or 1800 mg will be administered Q3W starting on Cycle 1 Day 1 in the 3 arms.

Statistical Methods:

Descriptive statistics will be mainly used in describing the safety, tolerability, and the anticancer activities of the ociperlimab as monotherapy and in combination with tislelizumab. The safety and efficacy data will be presented by study phase. Data from Phase 1 will be summarized by dose except that data from dose verification in Chinese patients will be summarized as a separate part by cohort. Data from Phase 1b (dose expansion) will be summarized by tumor type. For Cohort 10, data will be summarized by treatment arm and total. The sample sizes are mainly determined following 3+3 design for dose escalation and two-stage design based on Bayesian predictive probability for dose expansion.

Analysis Sets:

- Safety Analysis Set includes all patients who received ≥ 1 dose of study drugs. This will be the analysis set for the safety analyses.
- Efficacy Evaluable Analysis Set includes all patients who received ≥ 1 dose of study drugs, have evaluable disease at baseline, and ≥ 1 evaluable postbaseline tumor response assessment unless any clinical PD or death occurred before the first postbaseline tumor assessment.
- DLT Evaluable Analysis Set includes patients who received ≥ 80% each of the assigned doses ociperlimab and tislelizumab according to the treatment schedule, remained on study during the DLT observation period, and had sufficient safety evaluation or patients who experienced a DLT within the DLT observation period.
- The PK Analysis Set includes all patients who received ≥ 1 dose of study drug(s) and have ≥ 1 derivable PK parameter.
- The ADA Analysis Set includes all patients who received ≥ 1 dose of study drug(s) and have both baseline ADA and ≥ 1 postbaseline ADA results.

Efficacy Analyses:

Primary and/or secondary efficacy endpoints will be based upon investigators' tumor assessments per RECIST v1.1 and will be summarized as follows to evaluate the preliminary antitumor activity of ociperlimab in combination with tislelizumab with or without chemotherapy:

- ORR is defined as the proportion of patients who had CR or PR.
- DOR is defined as the time from the first determination of an overall response per RECIST v1.1, until the first documentation of progression or death, whichever comes first.
- DCR is defined as the proportion of patients with best overall response (BOR) of CR, PR, or SD.
- PFS is defined as the time from the date of the first dose of study drugs to the date of the first documentation of PD assessed by the investigator using RECIST v1.1 or death, whichever occurs first.
- OS is defined as time from the first dose of study drugs to the date of death due to any cause.

PFS and DOR will be estimated using the Kaplan-Meier method. Waterfall plots of maximum tumor shrinkage per patient will be presented.

Safety Analyses:

Safety will be determined by the spontaneous reporting of AEs and by laboratory values (hematology, clinical chemistry, coagulation, and urinalysis). Vital signs, physical examinations, and ECG findings will also be used in determining the safety profile. The severity of AEs will be graded according to the NCI-CTCAE v5.0. The incidence of DLTs and treatment-emergent adverse events (TEAEs) will be reported as the number (percentage) of patients with TEAEs by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) and changes from baseline, will be determined for laboratory parameters and vital signs.

Pharmacokinetic Analyses:

Noncompartmental analysis will be carried out for ociperlimab and tislelizumab serum concentrations. The PK analyses will include patients with sufficient data to enable estimation of key parameters, and the parameters such as C_{max}, C_{min}, T_{max}, $AUC_{0\text{-}21d}$, CL, and Vss (as appropriate for data collected) may be derived and summarized with descriptive statistics (mean, standard deviation, and coefficient of variation).

Individual and mean serum ociperlimab and tislelizumab concentration versus time data will be tabulated and plotted by dose level except that the data from dose verification in Chinese patients will be tabulated and plotted separately by cohort.

Additional PK analyses may be conducted as appropriate.

Sample Size Consideration:

The study may enroll up to approximately 294 to 564 evaluable patients:

- Phase 1: Approximately 44 to 64 patients
- Phase 1b: Approximately 250 to 500 evaluable patients

For dose escalation in Phase 1, 32 patients should be sufficient to evaluate the safety and tolerability of increasing dose levels of ociperlimab in combination with tislelizumab per the modified 3+3 design rules with extra patients on R2PD for further evaluation. An extra 12 to 32 Chinese patients will receive ociperlimab as monotherapy or in combination with tislelizumab as dose verification. Overall, 44 to 64 patients will be enrolled in Phase 1.

For dose expansion in Phase 1b, 10 cohorts are planned, with approximately 20 to 40 evaluable patients for Cohorts 1 to 8, and 30 to 60 evaluable patients for Cohort 9. For Cohort 10, approximately 60 to 120 evaluable patients (20 to 40 patients for each of the 3 arms) will be enrolled. A two-stage design based on Bayesian predictive probability (Lee and Liu 2008) will be implemented for these cohorts. The predictive probability of achieving a potential target ORR will be calculated in the interim analysis for Cohorts 1 to 8 after approximately 20 evaluable patients have completed ≥ 1 postbaseline tumor assessment, for Cohort 9 after approximately 30 evaluable patients have completed ≥ 1 postbaseline tumor assessment, and for Cohort 10 after approximately 20 evaluable patients in each arm have completed ≥ 1 postbaseline tumor assessment. The interim analysis will be carried out in a timely manner as soon as data becomes available. The enrollment beyond 20 evaluable patients for Cohorts 1 to 8, 30 evaluable patients for Cohort 9, and 20 evaluable patients for each arm of Cohort 10 may be allowed before the assessment is performed. The potential target ORR can be chosen based on historical rate and may be further updated with the study conduct when relative emerging information becomes available. If the predictive probability is less than 0.2 for the first 20 evaluable patients in Cohorts 1 to 8, for the first 30 evaluable patients in Cohort 9, and the first 20 evaluable patients in each arm of Cohort 10, enrollment will stop. If the predictive probability is larger than 0.8, enrollment may stop with high confidence of achieving potential target ORR. If the predictive probability is between 0.2 and 0.8, extra 20 evaluable patients for Cohorts 1 to 8, extra 30 evaluable patients for Cohort 9, and extra 20 evaluable patients for each arm of Cohort 10 may be enrolled to evaluate the anticancer activities.

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
5-FU	5-fluorouracil
ADAs	antidrug antibodies
AE	adverse event
AJCC	American Joint Committee on Cancer
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-muscle/brain
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	maximum observed plasma concentration
CPI	Checkpoint inhibitor
CPS	Combined Positive Score
CR	complete response
CT	computed tomography
DCR	disease control rate
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EAC	esophageal adenocarcinoma
EDC	electronic data capture (system)
EOT	End-of-Treatment (Visit)
ESCC	esophageal squamous cell carcinoma
ES-SCLC	extensive-stage small cell lung cancer
FDG	fluorine-18 [F-18] fluorodeoxyglucose
FFPE	formalin-fixed paraffin embedded
GCP	Good Clinical Practice
GC	Gastric cancer
G/GEJ	Gastric or gastroesophageal junction
GEP	gene expression profiling
GFR	glomerular filtration rate
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBV	hepatitis B virus

Abbreviation	Definition
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HNSCC	head and neck squamous cell carcinoma
ICF	informed consent form
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IgG1	immunoglobulin G1
imAE	immune-mediated adverse event
IRB	Institutional Review Board
IRC	Independent Review Committee
ITIM	immunoreceptor tyrosine-based inhibitory motif
ITT	immunoreceptor tail tyrosine
MAD	maximum administered dose
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MSI	microsatellite instability
MTD	maximum tolerated dose
NOAEL	no-observed-adverse-effect level
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NK	natural killer
NSCLC	non-small cell lung cancer
ORR	overall response rate
PBMC	peripheral blood mononuclear cells
PD	progressive disease
PD-1	programmed cell death protein-1
PD-L1	programmed cell death protein-ligand 1
PET	positron-emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PVR	Poliovirus receptor
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
QT	measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SCLC	small cell lung cancer
SMC	Safety Monitoring Committee
T3	triiodothyronine

Abbreviation	Definition
T4	Thyroxine
TEAE	treatment-emergent adverse event
TIGIT	T-cell immunoreceptor with Ig and ITIM domains
TIM-3	T cell immunoglobulin and mucin-domain containing-3
tislelizumab	BGB-A317
TIL	tumor-infiltrating lymphocyte
t_{max}	time to maximum plasma concentration
TPS	tumor proportion score
TMB	tumor mutation burden
ULN	upper limit of normal
vCPS	visually-estimated Combined Positive Score

1. INTRODUCTION AND RATIONALES

1.1. Introduction

Immune surveillance plays a critical role in preventing progression and metastasis. However, tumors have developed resistance mechanisms to suppress and/or escape the host immune system, thereby enabling tumorigenesis to proceed unchecked (Schreiber et al 2011; Swann and Smyth 2007). One such resistance mechanism involves upregulation of immune checkpoint receptors expressed on immune cells (eg, effector T cells), such as programmed cell death protein-1 (PD-1) and T cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif (ITIM) domain (TIGIT) (Johnston et al 2014; Chauvin et al 2015).

Blocking antibodies targeting PD-1/programmed cell death protein-ligand 1 (PD-L1) have achieved remarkable results in the treatment of many types of tumors, but it is also worth noting that this therapeutic strategy typically achieves a < 30% overall response rate (ORR) as a monotherapy in patients whose tumors exhibit low positive PD-L1 expression and/or are microsatellite stable (Chen and Han 2015; Gong et al 2018; Vanella et al 2017). In addition, dual PD-1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) blockade further improved clinical outcome in melanoma patients (Wolchok et al 2013). It is therefore expected that targeting multiple immune inhibitory pathways in the tumor microenvironment will prove useful for more patients with advanced cancers. For example, the inhibitory activity of TIGIT has been shown to be dependent on expression levels of its costimulatory counterpart CD226 (DNAX accessory molecule-1 or DNAM-1), either through competition for a common ligand or via direct interaction (Yu et al 2009; Johnston et al 2014). Subgroup analysis of patients with the highest TIGIT/CD226 ratio that were treated with anti-PD-1 and/or anti–CTLA-4 agents showed a significantly worse progression free survival of 2 months versus 12 months ($p = 0.039$) (Fourcade et al 2018). The combination of anti-PD-1/anti–PD-L1 with anti-TIGIT therapies has also shown significant synergistic antitumor effects and increased immune activation relative to anti–PD-1 monotherapy in both colon and glioblastoma mouse models (Johnston et al 2014; Hung et al 2018). Based upon this, the following combination of drugs will be evaluated in patients with advanced malignancies.

Ociperlimab (also known as BGB-A1217) is a humanized, immunoglobulin G1-wild type monoclonal antibody against TIGIT.

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

1.2. Ociperlimab as a TIGIT Inhibitor

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 1-120, and the transmembrane domain and cytoplasmic C-terminal tail comprises residues 121-223.

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 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 (Chauvin et al 2015; Joller et al 2014; Lozano et al 2012). A similar phenomenon was also observed for NK cells (Stanietsky et al 2009; Zheng et al 2017).

TIGIT is also expressed on $FoxP3^+$ regulatory T (Treg) cells, especially in tumor tissues (Joller et al 2014; Kurtulus et al 2015). TIGIT-positive Treg cells demonstrated greater suppressive functions when compared to TIGIT-negative 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 outcome upon immune checkpoint blockade (Fourcade et al 2018). Some studies have also shown that TIGIT suppresses immune responses mediated by dendritic cells by binding with PVR, especially in enhancement of IL-10 production and the inhibition of IL-12 production (Yu et al 2009).

As an immune "checkpoint" molecule, TIGIT initiates inhibitory signaling in immune cells when engaged by its ligands, PVR (CD155) and 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; Levin et al 2011; Stanietsky et al 2009; Yu et al 2009). 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: ~100nM) but delivers a positive signal and enhances cytotoxicity of T cells and NK cells (Bottino et al 2003; Stanietsky et al 2009). High affinity binding of TIGIT to PVR could compete off CD226-PVR interaction, therefore reducing T cells or NK cells activation (Stanietsky et al 2009).

The cytoplasmic tail of TIGIT has an inhibitory ITIM and an immunoreceptor tail tyrosine (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. Then the phosphorylations of

TIGIT would lead to binding of Grb2 and β-arrestin 2 and subsequently recruitment of SHIP-1 and SHP-2 to terminate PI3K and NK-κB signaling in the NK cells (Liu et al 2013; Stanietsky et al 2009). Engagement of agonistic TIGIT antibody induced T-cell receptor complex disruption (Stanietsky et al 2009). In addition, interaction between TIGIT and PVR on dendritic cells could lead to phosphorylation of PVR and modulation of ERK activation in dendritic cells (Yu et al 2009).

Up-regulation of TIGIT expression in tumor-infiltrating lymphocytes (TILs) has been reported in many types of cancers, such as lung (Tassi et al 2017), stomach (He et al 2017), breast (Gandara et al 2018; Gil Del Alcazar et al 2017), esophageal (Xie et al 2016), brain (Hung et al 2018), acute myeloid leukemia (Kong et al 2016), and melanoma (Mahnke et al 2016). Interestingly, TIGIT expression appears to be minimally expressed by peripheral effector cells while significantly up-regulated by tumor localized effector cells, which strongly suggests that the tumor microenvironment utilizes TIGIT signaling to further suppress/evade immune-mediated tumor cytotoxicity (Johnston et al 2014). Further, up-regulation of TIGIT signaling plays an important role in immune tolerance to cancer, similar to its function in the presence of chronic viral infections (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 either in 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. In addition, the observed efficacy was associated with an increased activity of effector T cells ($CD8^+$ and $CD4^+$) and also with Treg depletion within the tumor microenvironment. Argast and colleagues activity (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 achieved remarkable results in the treatment of many different tumor types. However, based upon the rate of primary and secondary resistance to PD-1 blockade, it is apparent that additional immuno-regulatory mechanism(s) underlie tumor immune escape. Indeed, research shows that the TIGIT pathway cooperates with PD-1 to maximize the suppression of effector TILs as well as 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. Nonclinical

1.2.1.1. Pharmacology

Ociperlimab binds to the extracellular domain of human TIGIT with high specificity and affinity (equilibrium dissociation constant [K_D] = 0.135 nM), as demonstrated by target-binding assays and SPR 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)". In addition, 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 significantly inhibited tumor growth compared with either therapy alone.

Ociperlimab has constant region of a wild-type human immunoglobulin G1 (IgG1) to enable the Fc-mediated effector functions. Ociperlimab has demonstrated competent binding to 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 the cell-based assays.

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

1.2.1.2. 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 are the most relevant species based on the homology sequence of TIGIT, though 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 (Q2W) 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 be false positives. 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 normal human frozen tissues using an immunohistochemistry (IHC) 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 IHC 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.

1.2.2. Clinical Experience

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

Clinical data has been released for Merck's MK-7684 (Golan et al 2018) and OncoMed's OMP-313M32 (Sharma et al 2018). A total of 68 patients have been treated with MK-7684 alone or MK-7684 in combination with pembrolizumab (an anti–PD-1 antibody) in a Phase 1 study sponsored by Merck, with doses ranging from 2.1 mg to 700 mg. Merck's MK-7684 enrolled patients with metastatic solid tumors that failed standard treatment options, measurable disease, and Eastern Cooperative Oncology Group (ECOG) Performance Status 0-1 for the Phase 1 dose escalation. The preliminary results showed that MK-7684 was well tolerated in the dose escalation phase of the study, with no dose-limiting toxicity (DLT). AEs that occurred in > 15% of patients were fatigue (n = 5, 15%) for MK-7684 monotherapy and pruritus (n = 10, 21%) for MK-7684 and pembrolizumab combination therapy. Further, only 2 treatment-related AEs ≥ Grade 3 were reported (Grade 3 anemia and Grade 3 diarrhea) for monotherapy and 5 treatment-related AEs ≥ Grade 3 were reported for combination with pembrolizumab (5 Grade 3: alanine aminotransferase [ALT] increased, colitis, γGT increased, hypersensitivity, and rash maculopapular). Of the 34 evaluable patients treated with MK-7684 alone, one partial response ([PR] 1/34 [3.0%]) and a 35% disease control rate (DCR) were observed. For combination of MK-7684 and pembrolizumab, 6 PRs (6/34, [18%]) and a 48% DCR were observed. In addition, linear pharmacokinetics (PK) were reported at doses 200 mg and above of MK-7684.

A total of 18 patients have been treated with OMP-313M32 alone in a Phase 1 study sponsored by OncoMed, with doses ranging from 0.3 mg/kg to 20 mg/kg. Oncomed's OMP-313M32 enrolled patients with advanced solid tumors into either a Phase 1a single-agent portion (dose escalation in all comers + expansion in selected tumor types) or a Phase 1b combination [PD-(L)1 refractory] portion with nivolumab (dose escalation). The preliminary results showed that OMP-313M32 was well tolerated in the dose escalation phase of the study, with no DLT. Treatment-related AEs that occurred in > 15% of patients were rash (n = 5; 27.8%), fatigue (n = 3, 16.7%), nausea (n = 3, 16.7%), and pruritus (n = 3, 16.7%) for OMP-313M32 monotherapy. Grade 3 or higher treatment-related AEs included rash (n=3, 16.7%), fatigue (n=1, 5.6%), hypophosphatemia (n=1, 5.6%), and autoimmune hepatitis (n=1, 5.6%). Of the 18 patients treated with OMP-313M32 alone, there were no responses, yet a 38.9% DCR was observed. Based upon the established safety as a monotherapy, OncoMed has initiated the dose expansion with the combination of OMP-313M32 and nivolumab (an anti–PD-1 antibody) in patients with non-small cell lung, head and neck, esophageal, gastric, cervical, triple negative breast, anal, and hepatocellular cancers or microsatellite instability-high (MSI-H) tumors (NCT03119428). In addition, there are several ongoing Phase 2 and Phase 3 studies of anti-TIGIT antibodies evaluating the efficacy and tolerability in the non-small cell lung cancer (NSCLC) (NCT03563716, NCT04294810, NCT04165070 and NCT04262856) and extensive-stage small cell lung cancer (ES-SCLC) (NCT04256421).

The Phase 1 study data of tiragolumab was released in 2020 American Association for Cancer Research (AACR). No objective responses occurred in 23 patients treated with tiragolumab monotherapy in Phase 1a. However, 11% patients had achieved PR in 44 patients treated with tiragolumab combined with atezolizumab in Phase 1b (Bendell et al 2020). A total of 135 patients with previously untreated PD-L1–selected NSCLC have been treated with tiragolumab 600 mg IV Q3W plus atezolizumab 1200 mg IV Q3W (n = 67) or atezolizumab 1200 mg IV Q3W plus placebo IV Q3W (n = 68) in a Phase 2 study (CITYSCAPE) sponsored by Genentech/Roche (Rodriguez-Abreu et al 2020). Patients were randomly assigned to one of these treatment groups and were stratified by tumor proportion score (TPS) (1% to 49% or ≥ 50%), histology (squamous versus non-squamous), and tobacco use (yes or no). Preliminary efficacy results showed a clinically meaningful improvement in ORR and median progression-free survival (mPFS) in patients treated with tiragolumab plus atezolizumab (ORR 31%; mPFS 5.42 months) compared with those treated with atezolizumab plus placebo (ORR 16%; mPFS 3.58 months). This improvement was still observed 6 months later: tiragolumab plus atezolizumab (ORR 37%; mPFS 5.55 months) compared with atezolizumab plus placebo (ORR 21%; mPFS 3.88 months). In addition, analysis at this 6-month follow up timepoint showed a greater improvement in ORR in patients in the PD-L1 TPS ≥ 50% subgroup who received tiragolumab plus atezolizumab (ORR 66%) compared with atezolizumab plus placebo (ORR 24%). Based on observed efficacy and safety results, Genentech/Roche is conducting an ongoing Phase 3 study (SKYSCRAPER 01) in first-line PD-L1 TPS ≥ 50% NSCLC (NCT04294810).

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

1.2.2.1. 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). Seventy-six 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 DLT period without DLTs in the Phase 1 dose-escalation part of the study. Twenty-five 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 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%) experienced ≥ 1 treatment-emergent adverse event (TEAE) and 77 patients (57.9%) experienced ≥ 1 TEAE related to ociperlimab. TEAEs ≥ Grade 3 in severity were experienced by 53 of 133 patients (39.8%), and 8 patients (6.0%) experienced ≥ Grade 3 TEAE related to ociperlimab. Forty-seven patients (35.3%) had serious TEAEs, 7 (5.3%) of these were considered related to ociperlimab. Nine patients (6.8%) experienced TEAEs that led to discontinuation of ociperlimab. Six patients (4.5%) experienced TEAE that led to death, but none of them were assessed as related to ociperlimab. No TEAEs were considered to be DLT.

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

1.2.2.2. Clinical Pharmacology

The first-in-human study AdvanTIG-105 evaluating safety and tolerability of ociperlimab in combination with tislelizumab in advanced solid tumors is still ongoing. Preliminary PK data are available from a total of 51 patients treated with ociperlimab 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. Serum concentrations of ociperlimab decreased in biexponential manner after administration. The mean elimination half-life ranged from 7.1 to 10.5 days. In Cycle 1, ociperlimab exposures (AUC and C_{max}) increased approximately dose proportionally from the 50 mg to the 1800 mg dose. Postdose PK sampling duration may not be sufficient for robust characterization of elimination half-life using noncompartmental analysis (NCA); hence, the reported half-life values should be interpreted with caution.

The TIGIT receptor occupancy data were available as of 23 July 2021 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 AdvanTIG-105. Complete TIGIT receptor occupancy (100%) was observed on CD8+ and CD4+ T cells, and regulatory T cells in peripheral blood at all the tested dose levels.

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

1.2.2.3. Efficacy

The first-in-human Study AdvanTIG-105 evaluating 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 patients were treated with ociperlimab 150 mg, 6 patients were treated with ociperlimab 450 mg, and 16 patients were treated with ociperlimab 900 mg. 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 (SD) was 54 weeks (1 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 Investigator's Brochure (IB).

1.3. Tislelizumab as a PD-1 Inhibitor

1.3.1. Pharmacology

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

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

Tislelizumab is an IgG4-variant antibody to gamma fragment crystallizable region (Fc) receptors (FcγR) such as FcγRI and FcγRIIIA, and it has very low binding affinity to Complement 1q (C1q), a subunit of complement 1. In vitro assays with tislelizumab suggest either low or no antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), or complement-dependent cytotoxicity (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.

1.3.2. Toxicology

The toxicity and safety profile of tislelizumab was characterized in single-dose toxicology studies in mice and cynomolgus monkeys and in a 13-week, repeat-dose toxicology study in cynomolgus monkeys. Tissue cross-reactivity was evaluated in normal frozen tissues from both humans and monkeys. The cytokine release assays were conducted using fresh human whole blood cells. The pivotal toxicology studies were conducted following Good Laboratory Practice (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 repeat-dosing regimens spanned to 3-fold higher than the maximum of the intended human doses. Cynomolgus monkey was the only relevant species based on the target sequence homology and binding activity.

Overall, no apparent toxicity was noted in mice or monkey toxicity studies. No tissue cross-reactivity was found in either human or monkey tissues, nor was any effect on cytokine release observed in the human whole-blood assay. The toxicokinetic profile was well characterized, with dose proportional increases in systemic exposure without apparent accumulation or sex difference. Immunogenicity was observed without apparent immunotoxicity or effect on the systemic exposure. The 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, Study AdvanTIG-105.

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

1.3.3. 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 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. Tislelizumab PK was generally similar between Chinese patients and patients of other ethnic groups and across tumor types. Please refer to the Tislelizumab Investigator's Brochure for more detailed information on the clinical pharmacology of tislelizumab.

1.3.4. Prior Clinical Experience of 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.

1.3.4.1. 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.

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 treatment exposure duration was 4.1 months (range: 0.1 to 41.5) and median study follow-up duration was 11.5 months (range: 0.1 to 58.9).

Overall, there were 2150 patients in the pooled monotherapy studies: 1992 patients treated in 7 solid tumor studies and 158 patients treated in 3 hematologic malignancy studies.

Solid tumor studies included the following: BGB-A317_Study_001 (Phase 1a/1b advanced solid tumors), BGB-A317-102 (Phase 1/2 advanced solid tumors), BGB-A317-204 (Phase 2 locally advanced or metastatic urothelial bladder cancer), BGB-A317-208 (Phase 2 previously-treated unresectable hepatocellular carcinoma), BGB-A317-209 (Previously-treated locally advanced unresectable or metastatic MSI-H or Mismatch Repair Deficient [dMMR] Solid Tumors), BGB-A317-302 (Phase 3 advanced unresectable/metastatic esophageal squamous cell carcinoma), and BGB-A317-303 (Phase 3 non−small cell lung cancer).

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

Of the 1992 patients with solid tumors treated with tislelizumab monotherapy, 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%).

Two hundred sixty-nine 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 each, 1.0%).

1.3.4.1.2. Treatment-Emergent Serious Adverse Events

Of the 1992 patients with solid tumors treated with tislelizumab monotherapy, 706 patients (35.4%) experienced ≥ 1 treatment-emergent 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 each, 1.0%).

Two hundred and nine patients (10.5%) experienced ≥ 1 tislelizumab-related treatment-emergent SAE. The most common treatment-emergent SAEs deemed related to tislelizumab were pneumonitis (31 patients, 1.6%). All other tislelizumab-related treatment-emergent SAEs occurred in less than 1% of patients.

1.3.4.1.3. Immune-Mediated Adverse Events

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

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

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

Of the 1912 patients with solid tumors included in the pooled analysis of imAEs, 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 each, 0.6%). Analysis of the patients with ≥ 1 imAE that was

also ≥ Grade 3 in severity showed that 73 patients (3.8%) experienced such events. 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%).

1.3.4.1.4. Infusion-Related Reactions

Infusion-related reactions, including high-grade hypersensitivity reactions, following the administration of tislelizumab are uncommon. Of the 1992 patients treated with tislelizumab monotherapy, 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 each, 0.2%). There were 5 patients (0.3%) with ≥ Grade 3 infusion-related reactions. The most common ≥ Grade 3 IRRs was infusion-related reaction (2 patients, 0.1%). All other ≥ Grade 3 IRRs occurred in single patients.

1.3.4.1.5. Liver Laboratory Abnormalities

Of the 1743 patients in the solid tumor group (excluding Study BGB-A317-208) of pooled monotherapy studies, 32 patients (1.8%) experienced ALT or AST levels > 3 x upper limit of normal (ULN) with a concurrent total bilirubin level > 2 x ULN. Concurrent elevation of ALP (eg, ALP > 2 x ULN) was observed in 29 of these 32 patients. Of the remaining 3 patients, none met the criteria for a Hy's law case.

The 3 patients in the solid tumor group (excluding Study BGB-A317-208) with liver laboratory abnormalities consistent with potential for Hy's law were evaluated for the clinical cause of the observed changes. One patient (BGB-A317-303-086007-033) met lab criteria for Hy's law marginally based on a single occurrence of AST and bilirubin elevation at an unscheduled visit following Cycle 35. These results were not considered clinically significant by the investigator. The levels returned to the normal range on Day 1 of Cycle 36. Patients BGB-A317-001-45-207 and BGB-A317-102-06-225 were females with advanced metastatic gastric or liver cancer with extensive hepatic involvement and confirmed hepatic disease progression at the time of the observed hepatic laboratory abnormalities. Neither met the criteria for a Hy's law case, which is based on laboratory criteria and a lack of an alternative medical cause for the observed changes.

1.3.4.1.6. Fatal Adverse Events

Out of 1992 patients in the solid tumor group of pooled monotherapy studies, 163 (8.2%) died ≤ 30 days after their last dose of tislelizumab. 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%).

1.3.4.2. Efficacy Assessment of Tislelizumab

As of 20 May 2021, efficacy data 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 which are summarized below.

1.3.4.2.1. Study BGB-A317_Study_001

Study BGB-A317_Study_001 was a Phase 1a/1b, open-label, multiple-dose, dose-escalation, and dose-expansion study to investigate the safety, PK, and antitumor activities of tislelizumab in patients with advanced tumors. Phase 1a consisted of dose-escalation and dose-finding components. Phase 1b investigated efficacy and safety in select tumor types. The efficacy endpoints of the study included ORR, DCR, best overall response (BOR), and clinical benefit rate as assessed by the investigator per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1).

In Phase 1a, patients received intravenous tislelizumab 0.5, 2, 5, or 10 mg/kg Q2W; 2 or 5 mg/kg administered Q2W or Q3W; or 200 mg Q3W. In Phase 1b, patients received intravenous tislelizumab 5 mg/kg Q3W.

Of the 451 patients treated with tislelizumab in the study, BORs of complete response (CR) were reported in 6 patients (1.3%) and of PR in 54 patients (12.0%). The resulting overall clinical response rate (CR + PR) was 13.3%. Additionally, there were 141 patients (31.3%) with a BOR of SD.

The greatest ORRs were seen in cholangiocarcinoma (31.3%), head and neck squamous cell carcinoma (29.4%), colorectal cancer (15.0%), gastric cancer (13.0%), and ovarian cancer (12.2%).

1.3.4.2.2. Study BGB-A317-102

Study BGB-A317-102 is a Phase 1/2 study investigating safety, tolerability, PK, and preliminary antitumor activities of tislelizumab 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 is an indication-expansion study. The efficacy endpoints include ORR, DCR, and clinical benefit rate as assessed by the investigator per RECIST v1.1.

Tumor responses were summarized for all disease cohorts composed of > 15 enrolled patients. These data represent 238 of 300 patients (79.3%) treated with ≥ 1 dose of tislelizumab in the study. Tislelizumab (200 mg Q3W) demonstrated preliminary antitumor activity across multiple tumor types. Of the presented indications, ORR was ≥ 15% in nasopharyngeal carcinoma (43%), MSI-H/dMMR solid tumors (19%), NSCLC (18%), gastric cancer (17%), hepatocellular carcinoma (HCC) (17%), and melanoma (15%). The median duration of response (DOR) was only mature for the nasopharyngeal carcinoma cohort, which had a DOR of 8.3 months (range: 3.9 months to not estimable) with a median follow-up of 4.8 months.

1.3.4.2.3. Study BGB-A317-203

Study BGB-A317-203 is a Phase 2, single-arm, multicenter study of tislelizumab monotherapy in patients with relapsed or refractory classical Hodgkin's lymphoma (cHL) in China. The efficacy endpoints of the study include ORR, CR rate, and time to response assessed by the Independent Review Committee (IRC) per Lugano 2014 Classification.

The Modified Safety Analysis Set consists of all patients treated with tislelizumab who had confirmed cHL. Of the 70 patients in this analysis set, BORs of CR were reported in 47 patients

(67.1%) and of PR in 14 patients (20.0%). The resulting overall clinical response rate was 87.1%. Additionally, there were 2 patients (2.9%) with a BOR of SD.

1.3.4.2.4. Study BGB-A317-204

Study BGB-A317-204 is a Phase 2, single-arm, multicenter study of tislelizumab monotherapy in patients with previously treated, PD-L1+, locally advanced or metastatic urothelial bladder cancer. The efficacy endpoints of the study include ORR and DCR as assessed by the IRC per RECIST v1.1.

The primary analysis set for this study is the Efficacy Evaluable Analysis Set (N = 104), which consists of all patients treated with tislelizumab who had ≥ 1 measurable baseline target lesion as assessed by the IRC per RECIST v1.1. A summary of tumor responses is from a modified efficacy analysis set (N = 101) that excludes all patients who had prior platinum-compound intolerance (n = 3). Of the 101 patients, BORs of CR were reported in 10 patients (9.9%) and of PR in 15 patients (14.9%). The resulting overall clinical response rate was 24.8%. Additionally, there were 14 patients (13.9%) with a BOR of SD.

1.3.4.2.5. Study BGB-A317-207

Study BGB-A317-207 is a Phase 2, open-label study of tislelizumab monotherapy in patients with relapsed or refractory mature T- and NK-cell neoplasms. The efficacy endpoints of the study include ORR, DOR, progression-free survival (PFS), and overall survival (OS).

The study consists of 3 disease cohorts:

- Cohort 1: relapsed/refractory extranodal NK/T-cell lymphoma (nasal or non-nasal type)
- Cohort 2: other relapsed/refractory mature T-cell neoplasms (limited to the following histologies: peripheral T-cell lymphoma [not otherwise specified], angioimmunoblastic T-cell lymphoma, or anaplastic large cell lymphoma)
- Cohort 3: relapsed/refractory cutaneous T-cell lymphoma (limited to mycosis fungoides and Sézary syndrome)

Efficacy data for patients in Cohort 1 (N = 22) and Cohort 2 (N = 44) (data cutoff 11 October 2019) are summarized. Of the 22 patients in Cohort 1, ORR was 31.8%; BORs of CR were reported in 4 patients (18.2%) and of PR in 3 patients (13.6%). Of the 44 patients in Cohort 2, ORR was 20.5%; BORs of CR were reported in 3 patients (6.8%) and of PR in 6 patients (13.6%).

1.3.4.2.6. Study BGB-A317-208

Study BGB-A317-208 is a Phase 2 open-label, multicenter study of tislelizumab monotherapy in patients with previously treated unresectable HCC. The primary endpoint of this study is ORR as assessed by the IRC per RECIST v1.1 in the Safety Analysis Set. The Safety Analysis Set consists of patients who have received any dose of tislelizumab.

Of the 249 patients in the Safety Analysis Set, ORR was 13.3%; BORs of CR were reported in 3 patients (1.2%) and of PR in 30 patients (12.0%).

1.4. Study Rationale

As described earlier, despite the wealth of evidence supporting TIGIT's role in promoting tumor immune tolerance, TIGIT blockade alone (ie, ociperlimab monotherapy) is unlikely to result in an effective antitumor response according to existing anti-TIGIT clinical data (Section 1.2). Therefore, the clinical development of ociperlimab focuses on rational combinations, such as with tislelizumab. Taking this into account, the dose escalation study was designed to minimize a patient's exposure to ociperlimab monotherapy and therefore maximize the patient's potential therapeutic benefit while simultaneously achieving the clinical objective of characterizing the safety and efficacy of ociperlimab in combination with tislelizumab.

The appropriateness of the study design is also based upon the following data, which suggest the combination of ociperlimab + tislelizumab will be safe and tolerable with a manageable safety profile:

1. Based upon the ociperlimab animal toxicology data, which showed no toxicity at the maximal allowed dose (Section 1.2.1.2), and confirmed clinically by 2 other anti-TIGIT therapies (Golan et al 2018; Sharma et al 2018), ociperlimab/TIGIT blockade is expected to be safe and well tolerated;
2. The starting dose of ociperlimab is predicted to have an 82-fold exposure margin based on toxicology data (Section 1.4.1.1);
3. Tislelizumab and/or other anti-PD-1 therapies have shown to be safe and tolerable, both as a monotherapy and in combination with other effector T-cell stimulating immune-oncology agents (Section 1.3 [Wang et al 2017; Esin et al 2017; Boutros et al 2016; Naing et al 2018]);
4. The combination of anti-TIGIT and anti-PD-1 was publicly reported to be well tolerated in patients resulting in commencement of the dose expansion (Merck Inc 2018; Oncomed Pharmaceuticals, Inc 2018);
5. An extensive clinical, laboratory and electrocardiogram (ECG) monitoring plan has been established to closely monitor patient safety so as to identify and address immune-mediated toxicities as early as possible (Appendix 1);
6. A comprehensive and effective algorithm based upon guidelines from the European Society for Medical Oncology or American Society for Clinical Oncology has been established to monitor, diagnose and manage immune-mediated toxicities (Appendix 8);
7. For reasons described in Section 1.2, there is no intention to clinically evaluate, characterize and/or develop ociperlimab for use as a monotherapy.

It is important to emphasize the safety experience gained from prior clinical studies whereby anti-PD-1 has been evaluated in combination with another effector T-cell activating immune-oncology agent. In general, the combinations lead to similar AEs compared to anti-PD-1 alone, although in some cases with greater frequency, severity and/or earlier onset but ultimately shown to be safe, tolerable and if necessary, manageable with standard of care (Section 1.3, [Wang et al 2017, Esin et al 2017, Boutros et al 2016, Naing et al 2018]). However, TIGIT and PD-1 have overlapping immuno-regulatory functions and in the absence of activation, peripheral effector T-cells typically do not express TIGIT, thereby limiting the potential for peripheral immune autoreactivity (Johnston et al 2014). Therefore, there is a

distinct possibility that the combination of ociperlimab and tislelizumab will result in a safety profile (type, frequency, severity, timing, etc.) that is similar to tislelizumab alone. Regardless, an effective diagnostic and treatment algorithm is available to address immune mediated toxicities related to PD-1 blockade alone or the combined blockade of multiple immune-regulatory pathways.

The dosing schema during the DLT assessment window was designed based upon the following rationales: 1) allows for the evaluation of acute toxicities related to ociperlimab alone (eg, immediate and/or non-immediate hypersensitivity reactions, cytokine release syndrome, delayed infusion reactions, etc [Baldo 2013; Picard 2017]) as well as early onset immune mediated toxicities related to the combination of ociperlimab and tislelizumab; 2) based upon the projected half-life and trough levels of ociperlimab, the chosen dosing schema also provides sufficient exposure throughout the DLT assessment period that is estimated to achieve approximately 90% TIGIT receptor occupancy in PBMCs, which is necessary to fully and consistently evaluate the safety of ociperlimab alone or in combination with tislelizumab; 3) based upon the time to event profile of immune mediated toxicities related to checkpoint therapies, it is unlikely that the toxicity profile of ociperlimab monotherapy will differ significantly for a 3-week versus 1-week observation period thereby negating the benefit of evaluating ociperlimab alone for the first Cycle while only serving to delay optimal treatment of cancer patients with advanced disease; 4) all toxicities regardless of when they occur will be taken into consideration regarding dosing decisions; 5) if unexpected toxicity is observed, the protocol does allow for immediate implementation of additional dose escalation criteria (eg, extension of the DLT period) as described in Section 3.2.1.

Another important consideration is that the safety profile of tislelizumab has been characterized in over 2150 patients (Tislelizumab Investigator's Brochure), thereby serving as a safety reference when evaluating and/or characterizing the safety of ociperlimab in combination with tislelizumab. Finally, the sponsor has in place a multi-layered process for ensuring patient safety in part through close collaboration between study investigators and the sponsor study team. The study will also utilize the sponsor's established processes for the continuous collection, review, and aggregate analyses of all safety data.

In summary, the current dose escalation study design allows patients, most of whom have failed multiple prior lines of therapy and/or experiencing rapid disease progression typical for a Phase 1 study, the opportunity to obtain maximal therapeutic benefit without compromising patient safety or clinical objectives.

1.4.1. Rationale for the Choice of Doses

1.4.1.1. Rationale for the Starting Dose of Ociperlimab

A starting dose of 50 mg Q3W is proposed in this first-in-human study for ociperlimab. The selection of this starting dose was based on the tumor growth inhibition (TGI) data from the efficacy of ociperlimab in the GL261 murine glioma tumor model in humanized TIGIT knock-in mice. The maximum drug concentration of ociperlimab after the first dose (C_{max}, the first dose) or $AUC_{1\text{-}168h}$ was correlated with the percent TGI observed in GL261 mouse tumor model. The EC50 (and EC90) parameters were estimated as 3.7 μg/mL (12.9 μg/mL) for C_{max}, the first dose and 14.2 μg/day/mL (70 μg/day/mL) for the $AUC_{1\text{-}168h}$ variables. By achieving the same EC90

for $AUC_{1\text{-}168h}$ or C_{max}, the first dose in humans as those in the transgenic mice, the human starting dose for ociperlimab was estimated to be 50 mg. Ociperlimab non-clinical safety data and clinical experience from competitor anti-TIGIT monoclonal antibodies justifies the proposed dose. The proposed dosing interval of every 3 weeks is supported by PK evaluations and allows for a convenient integration with tislelizumab dosing regimen and other common chemotherapeutic regimens.

The highest non–severely toxic dose or NOAEL from the 3-month repeated dose toxicology study in monkeys was determined to be 100 mg/kg (Ociperlimab Investigator's Brochure, Section 4.1.1.5), with the one-sixth highest non–severely toxic dose calculated as 16.7 mg/kg (body-weight based) or 9.8 mg/kg (exposure-based); this provides a wide safety margin at the proposed starting dose. Based on the steady-state AUC and C_{max} at 100 mg/kg NOAEL dose in the 3-month toxicity study in monkeys (Ociperlimab Investigator's Brochure), the projected safety margins at the proposed starting dose of 50 mg are 82 and 115, respectively, which reflects favorably on the safety profile of ociperlimab.

Furthermore, clinical experience with similar anti-TIGIT monoclonal antibodies, OMP-313M32 (OncoMed Pharmaceuticals) and MK-7684 (Merck), suggest that the anti-TIGIT antibodies can be administered safely either as monotherapy or in combination with anti–PD 1 antibody in patients. The OMP 313M32 doses were escalated up to 20 mg/kg every 2 weeks as monotherapy and MK-7684 doses were escalated up to 700 mg Q3W both as monotherapy and in combination with 200 mg pembrolizumab Q3W without any DLTs (Golan et al 2018; Sharma et al 2018). Ociperlimab is also an IgG1 antibody similar to OMP 313M32 and MK-7684, and these clinical findings may be applicable.

1.4.1.2. Rationale for the Selection of Ociperlimab Doses in Cohort 10

Three dose levels of ociperlimab 450 mg, 900 mg, and 1800 mg in combination with tislelizumab 200 mg in patients with metastatic NSCLC (PD-L1 positive, tumor cell expression [TC] ≥ 1%) have been selected for Cohort 10. The choice of the doses will provide wide exposure range and thus allowing for conducting exposure-response analyses of data from a specific tumor type.

1.4.1.3. Rationale for the Selection of Tislelizumab Dose

The PK, safety, and efficacy data obtained from the first-in-human study BGB-A317_Study_001 (Desai et al 2020) as well as other clinical study data, were analyzed in aggregate to determine the recommended dose for pivotal studies of tislelizumab. The dose of 200 mg intravenously Q3W was selected for further evaluation.

Rates of treatment-related AEs and SAEs observed in patients receiving 2 mg/kg and 5 mg/kg Q2W and Q3W were comparable, suggesting no clear dose-dependence across these regimens. Similarly, confirmed ORRs in patients treated with tislelizumab 2 mg/kg and 5 mg/kg Q2W ranged between 10% and 15%, compared to a range of 15% to 38% for patients treated at 2 mg/kg and 5 mg/kg Q3W.

According to PK data from BGB-A317_Study_001(Desai et al 2020), Phase 1a, the clearance of tislelizumab was found to be independent of body weight, ethnicity, and gender, and the

observed serum exposure of a 200-mg dose fell between serum exposure observed after 2 mg/kg and 5 mg/kg doses (dose range with comparable safety and efficacy rates).

Additionally, no unexpected treatment-related AEs occurred in the 200-mg fixed dose cohort (BGB-A317_Study_001, Phase 1a, Part 3) when compared to body-weight-based cohorts. Of the evaluable patients treated (n = 13), 3 patients (23%) had a BOR of PR, 4 patients (31%) had a BOR of SD, and 6 patients (46%) had a BOR of progressive disease (PD). Therefore, clinical activity with a manageable and tolerable safety profile is expected to be maintained in patients receiving tislelizumab 200 mg Q3W.

Therefore, the recommended dose for pivotal studies for tislelizumab of 200 mg Q3W will be utilized for the combination with ociperlimab; however, alternate doses or dose schedules may be evaluated based on emerging clinical data.

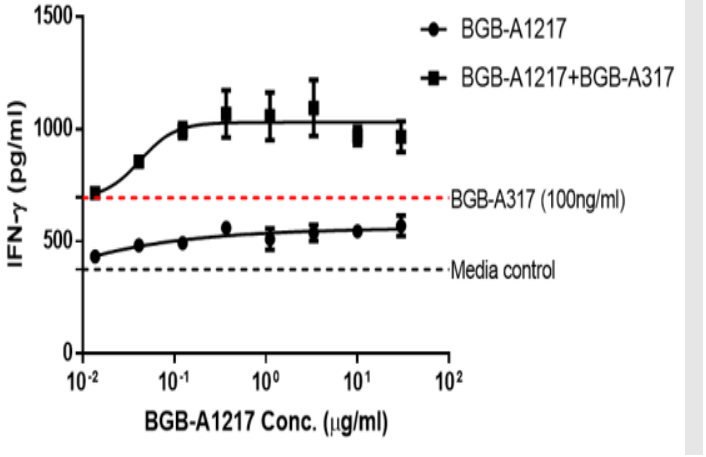
1.4.2. Rationale for Combination of Ociperlimab and Tislelizumab in the Treatment of Advanced Solid Tumors

Blocking antibodies targeting PD-1 have achieved remarkable results in the treatment of many types of tumors. However, it is also worth noting that this therapeutic strategy typically achieves a < 30% ORR as a monotherapy in patients whose tumors exhibit low positive PD-L1 expression and/or are microsatellite stable (Chen and Han 2015).

TIGIT and PD-1 function as immune checkpoint receptors in the overlapping regulation of immune tolerance. As noted above, TIGIT and PD-1 have been shown to be overexpressed on the TILs from patient samples of various solid tumors including, but not limited to NSCLC, head and neck squamous cell carcinoma, gastric carcinoma, ovarian cancer, and triple-negative breast cancer. Subsequently, the activation of TIGIT and PD-1 represent TILs from both patients or animals across solid tumor types with the most exhausted immunophenotype (ie, cytokine expression, proliferation etc.), which can be reversed with combined blockade of TIGIT and PD-1. Interestingly, TIGIT expression on effector T-cells is strongly correlated with PD-1 expression and the expression both of which is upregulated following effector activation (Johnston et al 2014). As such, immune escape via PD-1 will be sustained in patients with PD-L1 positive tumors thereby negating TIGIT blockade alone.

The overlap in expression and function indicates that TIGIT and PD-1 cooperate to promote effector cell exhaustion which may impede an effective antitumor immune response. Indeed, the combined blockade of TIGIT and PD-1 significantly increased IFN-γ production in vitro relative to the increase seen for TIGIT or PD-1 blockade alone, thus demonstrating that the combined blockade of TIGIT and PD-1 can mitigate effector cell exhaustion following activation and chronic antigen stimulation (Figure 1).

Figure 1: Combined Blockade of TIGIT and PD-1 with Ociperlimab and Tislelizumab (BGB-A317) Enhances IFN-γ secretion in Mixed Lymphocyte Reaction



Abbreviations: Conc., concentration; IFN-γ, interferon-gamma.
A conventional mixed lymphocyte reaction assay was performed. In brief, "stimulator PBMCs" from a healthy donor were pre-treated with OKT3 (40 ng/mL, eBioscience) and co-cultured with a mixture of "responder" A549/OS8-PD-L1 and A549/PD-L1 cells in complete RPMI1640 media plus ociperlimab and/or tislelizumab/BGB-A317 (100 ng/mL) in a 96-well flat-bottom plates for 18 hours. The secretion of IFN-γ into the cell culture was performed using an IFN-γ ELISA kit (eBioscience) and analyzed as a readout of T-cell function. All conditions were performed in duplicates and results are shown as mean ± SD.

Further, combined blockade of TIGIT and PD-L1 resulted in a greater antitumor effect in vivo compared to either TIGIT or PD-L1 blockade alone as observed in a CT26 colorectal tumor model (Figure 2 [a, b]). Importantly, mice that achieved a CR on treatment with the combination of anti-TIGIT and anti-PD-L1 were able to mount a protective antitumor response when re-inoculated with CT26 tumor cells but not syngeneic EMT6 breast cancer cells (Figure 2 [c]). The ability to reject a secondary inoculation with CT26 cells suggests an induction of tumor antigen-specific immunity in the mice previously treated with the combination (Johnston et al 2014).

Figure 2: The Combination of Anti-TIGIT and Anti-PD-1 Treatment Is More Effective Than Anti-PD-1 Inhibitors Alone

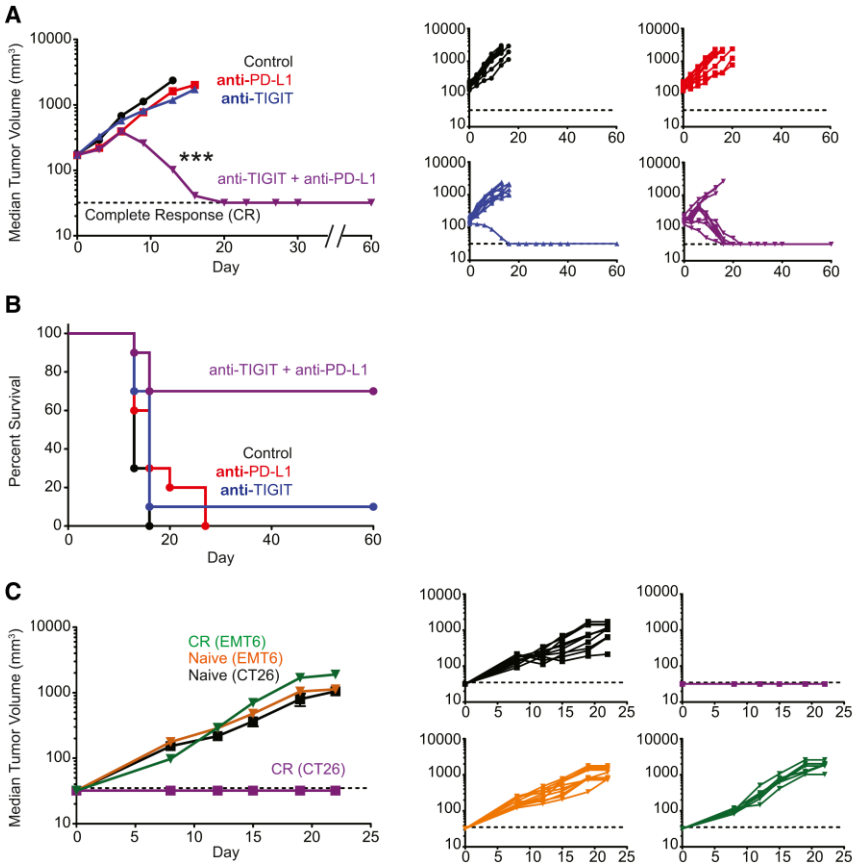


Figure 2A: Groups of BALB/c mice (n = 10) were inoculated subcutaneously in the right thoracic flank with $1x10^5$ CT26 colon carcinoma cells. After 2 weeks tumors reach 150-200mm^3, mice were randomized into treatment groups and treated intraperitoneally with either control (cIg), anti-PD-L1 (10mg/kg), anti-TIGIT (25 mg/kg) or their combination (35 mg/kg) 3 times per week for 3 weeks. Tumor were measured 2 times per week by caliper and volumes calculated by modified ellipsoid formula. Animals whose tumors shrank to 32mm^3 or smaller were considered to be CR, while those whose tumors grew to larger than 2000mm^3 were considered to have progressed and euthanized. The median (left) and individual (right) tumor volumes for treatment groups are shown.
Figure 2B: Survival time for mice in 2A.
Figure 2C: Approximately 60 days after inoculation with CT26 cells, BALB/c treated with the combination of anti-PD-L1 and anti-TIGIT that reached CR, along with naïve control mice, were re-inoculated with CT26 cells in the left thoracic flank or inoculated with EMT6 breast carcinoma cells in their mammary fat pads and followed for tumor growth (n=7-10).

Based upon the overlapping expression profiles and immuno-regulatory functions, the improved in vivo antitumor effects, as well as the potential for TIGIT-mediated adaptive resistance, there is strong scientific rationale to evaluate the antitumor effects derived from the combined blockade of TIGIT and PD-1 in advanced solid tumors.

1.4.3. Rationale for Combination of Ociperlimab, Tislelizumab, and Platinum-based Doublet Chemotherapy in NSCLC (Phase 1b)

Upregulation of TIGIT expression in tumor infiltrating lymphocytes (TILs) has been reported in NSCLC (Tassi et al 2017). 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). Preclinical studies have also indicated that platinum-based chemotherapy elicits tumor CD8 + T-cell infiltration and sensitized tumors to immune checkpoint blockade therapy, which results in a durable control of cancer (Pfirschke et al 2016).

The results from the pivotal Phase 3 study (Lu et al 2020) support tislelizumab in combination with platinum and pemetrexed as a potential new standard for first-line treatment of advanced non-squamous NSCLC. The addition of tislelizumab resulted in significantly improved PFS by IRC (9.7 months versus 7.6 months; p = 0.0044, hazard ratio [HR] = 0.30 [95% CI: 0.462 to 0.902]) as well as higher ORR by IRC and longer DOR by IRC than observed with chemotherapy alone in relevant patients. No new safety signals were identified with the addition of tislelizumab to standard chemotherapy. The safety profile of tislelizumab in combination with platinum and pemetrexed was consistent with the known risks of each study treatment component. Most AEs were mild or moderate in severity and were manageable.

The robust results were also observed in another Phase 3 study (Wang et al 2020) for first-line treatment of advanced squamous NSCLC, irrespective of PD-L1 expression. Both tislelizumab in combination with carboplatin + paclitaxel/nab-paclitaxel demonstrated statistically significant prolonged PFS as compared with paclitaxel + carboplatin treatment arm (HR 0.524 with median 7.6 months [95% CI: 5.95 to 9.79] versus 5.5 months [95% CI: 4.21 to 5.65] and HR 0.478 with median 7.6 month [95% CI: 5.75 to 11.01] versus 5.5 months [95% CI: 4.21 to 5.65]), respectively. The ORR assessed by IRC was higher for tislelizumab in combination with paclitaxel + carboplatin (72.5%) and higher for tislelizumab in combination with nab-paclitaxel + carboplatin (74.8%) than with chemotherapy alone (49.6%). The DOR by IRC was also longer in paclitaxel + carboplatin (8.2 months) with HR 0.461 and nab-paclitaxel + carboplatin (8.6 months) with HR 0.446 than in paclitaxel + carboplatin (4.2 months). These findings further validated the benefit of adding tislelizumab to platinum-based chemotherapy. The safety profile of tislelizumab in combination with carboplatin and paclitaxel or nab-paclitaxel was well-tolerated. And the safety profile exhibited in this study was in line with the known chemotherapy agents, tislelizumab, and underlying NSCLC. Most AEs were reported to be mild or moderate in severity and manageable.

The consistent clinical benefit and safety profile of other anti-PD-1/PD-L1 antibodies combined with platinum-doublet chemotherapy is observed in first-line NSCLC setting, shown in Table 1. Keynote-189 study showed pembrolizumab plus pemetrexed-carboplatin or cisplatin has superior OS and PFS over pemetrexed-carboplatin or cisplatin in metastatic non-squamous NSCLC (Gadgeel et al 2020), while Keynote-407 study showed pembrolizumab plus paclitaxel or nab-paclitaxel-carboplatin has superior OS and PFS over paclitaxel or nab-paclitaxel-carboplatin in metastatic squamous NSCLC(Paz-Ares et al 2018). US Food and Drug Administration (FDA) has approved pembrolizumab combined with platinum-doublet chemotherapy in first-line

NSCLC with squamous and non-squamous histology regardless of PD-L1 expression based upon the two studies. Atezolizumab has been approved by the FDA in metastatic non-squamous NSCLC in first-line with the combination with nab-paclitaxel-carboplatin which had superior OS over nab-paclitaxel-carboplatin regardless of PD-L1 expression (West et al 2019).

Table 1: Safety and Efficacy Summary of Pembrolizumab With Chemotherapy in First-line NSCLC

	Pembrolizumab (KN-189)	**Pembrolizumab (KN-407)**	**Atezolizumab (IMpower130)**
Treatment	Pembro+Pem+Carbo/Cis vs Pem+Carbo/Cis	Pembro+Carbo+nab-Pac/Pac vs Carbo+nab-Pac/Pac	Atezo+Nab-Pac+Carbo vs Nab-Pac+Carbo
Patient number	405 vs 202 pts	278 vs 280 pts	451 vs 228 pts
Histology	NSQ	SQ	NSQ
Median PFS, months	ITT: 8.8 vs 4.9, HR = 0.52	ITT: 6.4 vs 4.8, HR = 0.56	ITT: 7.0 vs 5.5, HR = 0.64
Median OS, Months	ITT: NR vs 11.3, HR = 0.49	15.9 vs 11.3, HR = 0.64	ITT: 18.6 vs 13.9, HR = 0.79, p = 0.033
ORR, %	47 vs 18.9	57.9 vs 38.4	49.2 vs 31.9
Median DOR, months	11.2 vs 7.8	7.7 vs 4.8	8.4 vs 6.1
Treatment-related AEs Gr 3-5, %	69.8 vs 68.2	Paclitaxel: 63.9 vs 59.3 Nab-paclitaxel: 78.9 vs 81.4	75 vs 61

Abbreviations: AEs, adverse events; Atezo, atezolizumab; Carbo, carboplatin; Cis, cisplatin; DOR, duration of response; HR, hazard ratio; ITT, intent-to-treat; Nab-Pac, nab-paclitaxel; NSQ, non-squamous non-small cell lung cancer; ORR, overall response rate; OS, overall survival; Pem, pemetrexed; Pembro, pembrolizumab; Pac, paclitaxel; PFS, progression-free survival; pts, patients; SQ, squamous non-small cell lung cancer; vs, versus

The Cancer Genome Atlas (TCGA) dataset showed the upregulation of TIGIT and PVR expression in tumor samples compared with normal samples in both adenocarcinoma lung cancer and squamous cell lung cancer (TCGA). The TCGA RNAseq dataset illustrated NSCLC patients with low expression of PVR have longer survival (p = 0.0082) (GEPIA2). This is consistent with the important role of TIGIT/PVR signaling pathway in the immune tolerance to cancer (Section 1.2). In addition, increased expression of TIGIT and PD-1 in human non-small cell lung cancer suggests potential synergy of combining of anti-TIGIT antibody and anti-PD-1 antibody (Solomon and Garrido-Laguna 2018).

Ociperlimab, tislelizumab, and platinum-based doublet chemotherapy have nonoverlapping anticancer mechanisms, and likely to have synergistic and/or added activity. Both ociperlimab plus tislelizumab and tislelizumab plus chemotherapy are tolerable. Adding ociperlimab to tislelizumab and platinum-based doublet chemotherapy will likely further enhance the overall clinical activity of tislelizumab plus platinum-based doublet chemotherapy and prevent progression/disease related death in stage IV NSCLC in the front line.

1.4.4. Rationale for Combination of Ociperlimab and Tislelizumab in NSCLC With PD-L1 Positive (Tumor Cell Expression ≥ 1%) Population (Phase 1b)

Anti-PD-1 antibody monotherapy has been the new standard of care for patients with a PD-L1 TPS of 1% or greater based on Keynote-042 study (Mok et al 2019). In this study, 1274 patients with a PD-L1 TPS of 1% or greater were allocated to pembrolizumab (n = 637) or chemotherapy (n = 637) and included in the Intention-to-Treat Population. Overall survival was significantly longer in the pembrolizumab group than in the chemotherapy group in PD-L1 ≥ 1% with 16.7 months versus 12.1 months (HR = 0.81, [95% CI: 0.71 to 0.93], p = 0.0018). Treatment-related adverse events of Grade 3 or worse occurred in 18% treated patients in the pembrolizumab group and in 41% in the chemotherapy group and led to death in 2% and 2% patients, respectively.

As described in the section of clinical experience (Section 1.2.2), anti-TIGIT antibody combined with anti-PD-1 showed good tolerability and preliminary efficacy in some solid tumors. The increased expression of TIGIT and PD-1 suggested a synergy in combination of anti-TIGIT antibody and anti-PD-1 antibody in human NSCLC (Section 1.4.3). Ociperlimab plus tislelizumab will more likely enhance the antitumor activity in the front-line NSCLC with PD-L1 positive patients. Study AdvanTIG-105 will evaluate clinical activity of ociperlimab and tislelizumab in PD-L1 positive (TC ≥ 1%) patients with stage IV NSCLC.

1.4.5. Rationale for Combination of Ociperlimab and Tislelizumab and Platinum-based Doublet Chemotherapy in SCLC (Phase 1b)

In a Phase 2 study of locally advanced or metastatic non-squamous NSCLC, squamous NSCLC, and extensive-stage SCLC, tislelizumab was evaluated in combination with first-line platinum-based doublet chemotherapy, respectively. Seventeen patients with extensive-stage SCLC were treated with tislelizumab plus etoposide-cisplatin or carboplatin with ORR of 47.1%. Patients tolerated well with ≥ Grade 3 treatment-related AE of 76.5% and imAE of 23.5%. The Phase 3 study of extensive-stage SCLC exploring tislelizumab in combination with etoposide-cisplatin or carboplatin is ongoing (BGB-A317-312).

In addition, both atezolizumab plus carboplatin-etoposide and durvalumab plus etoposide-carboplatin/cisplatin have been approved as first-line treatment in extensive-stage SCLC with superior clinical efficacy over chemotherapy and good tolerability (shown in Table 2).

Table 2: Safety and Efficacy Summary of Atezolizumab and Durvalumab With Chemotherapy in First-Line Extensive-Stage SCLC

	IMpower 133 (Atezolizumab+EP vs EP)	**Caspian (Durvalumab+EP vs EP)**
ORR, %	60.2 vs 64.4	67.9 vs 57.6
DOR, months	4.2 vs 3.9	5.1 vs 5.1
Median PFS, months	5.2 vs 4.3	5.1 vs 5.4
Median OS, months	12.3 vs 10.3 (p = 0.0154)	13.0 vs 10.3 (p = 0.0047)

Treatment-related Grade 3-4 AEs, %	56.6 vs 56.1	46 vs 52

Abbreviations: AEs, adverse events; DOR, duration of response; EP, etoposide; ORR, overall response rate; PFS, progression-free survival

The published data shows PVR is broadly expressed in SCLC cell lines and tumor tissues. And high PVR expression was associated with poor prognosis, advanced tumor stage and large tumor size. PVR expression may represent an important targeted immune checkpoint in lung cancer. The blockade of TIGIT pathway may represent a potent therapeutic strategy to combine different checkpoint blocking agents for SCLC therapy (Yu et al 2018). In the Phase 1b stage of Study AdvanTIG-105, we will evaluate the clinical activity with the addition of ociperlimab to the combination of tislelizumab plus platinum-based doublet chemotherapy in first-line treatment of extensive-stage SCLC.

1.4.6. Rationale for Combination of Ociperlimab, Tislelizumab, and Chemotherapy in Esophageal Cancer

In a Phase 2 study of locally advanced or metastatic esophageal squamous cell carcinoma (ESCC) and gastric/gastroesophageal junction (G/GEJ) adenocarcinoma, tislelizumab was evaluated in combination with cisplatin and fluorouracil. Fifteen patients with ESCC were treated with tislelizumab plus cisplatin and fluorouracil with confirmed ORR of 46.7% and DCR of 80%. Patients tolerated well with ≥ Grade 3 TEAEs of 86.7% and ≥ Grade 1 imAEs of 80% (Xu et al 2020). The Phase 3 study of first line tislelizumab in combination with chemotherapy for unresectable, locally advanced recurrent or metastatic ESCC is ongoing (BGB-A317-306).

Pembrolizumab plus chemotherapy versus chemotherapy as first-line therapy in patients with advanced esophageal cancer has been evaluated in KEYNOTE-590, a Phase 3 global study (Kato et al 2020). In this study, 749 patients were allocated to pembrolizumab plus chemotherapy (n = 373) or chemotherapy (n = 376) and included in the Intention-to-Treat Analysis Set. Overall survival was significantly longer in the pembrolizumab plus chemotherapy group than that in the chemotherapy group with 12.4 months versus 9.8 months (HR = 0.73 [0.62 to 0.86], p < 0.0001). PFS was superior in the pembrolizumab plus chemotherapy group than in the chemotherapy group with 6.3 months versus 5.8 months (HR = 0.65 [0.55 to 0.76], p < 0.0001). Treatment-related adverse events of Grade 3 or worse occurred in 71.9% treated patients in the pembrolizumab plus chemotherapy group and in 67.6% in the chemotherapy group and led to death in 2.4% and 1.4% patients, respectively. Immune-mediated AE and infusion reactions occurred in 25.7% treated patients in pembrolizumab plus chemotherapy group and in 11.6% treated patients in chemotherapy group (Kato et al 2020).

In the TCGA RNAseq dataset, TIGIT expression was significantly increased in esophageal cancer tissue (including ESCC and esophageal adenocarcinoma [EAC]) compared with normal tissue and highly correlated with PD1 expression (Spearman correlation r = 0.84, p < 0.001). PD-L1 was reported to be expressed on both tumor cells and immune cells in ESCC and EAC tumor tissue, with relatively higher PD-L1 positive prevalence in the former, indicating a relatively inflamed tumor macroenvironment favorable for immunotherapy. About 40-50% PD-L1 positive prevalence by Combined Positive Score (CPS) ≥ 10, TC ≥ 1% or visually-estimated CPS (vCPS) ≥ 10% was reported in ESCC (Keynote-181/590,

ATTRACTION-3, ESCORT, BGB-A317-001/102). A trend of higher TIGIT expression was also found in the PD-L1 vCPS high subgroup and a subgroup of non-responders showed numerically higher TIGIT expression level compared with the responder subgroup in ESCC patients in BGB-A317-102/001 study. These data imply the potential synergistic effect of anti-TIGIT plus anti-PD-1 in esophageal cancer.

1.4.7. Rationale for Combination of Ociperlimab and Tislelizumab in Head and Neck Squamous Cell Carcinoma With PD-L1 Positive (vCPS ≥ 1%) Population

Anti-PD-1 antibody monotherapy has been the new standard of care for recurrent or metastasis HNSCC patients with a PD-L1 CPS of ≥ 1 based on Keynote-048 study (Burtness et al 2019). In this study, 882 patients were allocated to pembrolizumab alone (n = 301), pembrolizumab with chemotherapy (n = 281) or cetuximab with chemotherapy (n = 300) and included in the Intention-to-Treat Population. At the second interim analysis, pembrolizumab alone improved OS versus cetuximab with chemotherapy in the CPS of 20 or more population (median 14.9 months versus 10.7 months, HR = 0.61 [95% CI: 0.45 to 0.83], p = 0.0007) and CPS of 1 or more population (12.3 months versus 10.3 months, HR=0.78 [0.64 to 0.96], p = 0.0086) and was non-inferior in the total population (11.6 months versus 10.7 months, HR = 0.85 [95% CI: 0.71 to 1.03]). At final analysis, ≥ Grade 3 worse all-cause adverse events occurred 55% in the pembrolizumab alone group, and 83% in the cetuximab with chemotherapy group. Adverse events led to death in 8% of the pembrolizumab alone group and in 10% of the cetuximab with chemotherapy group, respectively (Burtness et al 2019).

As described in the section of clinical experience (Section 1.2.2) anti-TIGIT antibody combined with anti-PD-1 showed good tolerability and preliminary efficacy in some solid tumors. The increased expression of TIGIT and PD-1 suggested a synergy in combination of anti-TIGIT antibody and anti-PD-1 antibody in HNSCC. Study AdvanTIG-105 will evaluate clinical activity of ociperlimab and tislelizumab in PD-L1 positive (vCPS ≥ 1%) patients with recurrent or metastatic HNSCC.

1.4.8. Rationale for Combination of Ociperlimab, Tislelizumab, and Chemotherapy in Gastric Cancer

In a Phase 2 study of locally advanced or metastatic ESCC and G/GEJ adenocarcinoma, tislelizumab was evaluated in combination with oxaliplatin and oral capecitabine. Fifteen patients of G/GEJ adenocarcinoma were treated with tislelizumab plus oxaliplatin and capecitabine with confirmed ORR of 46.7% and DCR of 80%. Patients tolerated well with ≥ Grade 3 TEAEs of 66.7% and ≥ Grade 1 imAEs of 73.3% (Xu et al 2020). The Phase 3 study of first-line tislelizumab in combination with chemotherapy for unresectable, locally advanced recurrent or metastatic gastric cancer is ongoing (BGB-A317-305).

Nivolumab plus chemotherapy versus chemotherapy as first-line therapy in patients with advanced G/GEJ cancer/EAC has been evaluated in CheckMate 649, a Phase 3 global study (Moehler et al 2020). In this study, 1581 patients were allocated to nivolumab plus chemotherapy (n=789) or chemotherapy (n=792) and included in the Intention-to-Treat population. Overall survival was significantly longer in patients with tumors expressed PD-L1 CPS ≥ 5 in the nivolumab plus chemotherapy group than in the chemotherapy group (14.4 months versus 11.1 months, HR = 0.71 [95% CI: 0.59 to 0.86], p<0.0001). PFS was superior in patients with tumors expressed PD-L1 CPS ≥ 5 in the nivolumab plus chemotherapy group than in the chemotherapy group (7.7 months versus 6.0 months, HR = 0.68 [95% CI: 0.56 to 0.81], p < 0.0001). Serious treatment-related adverse events occurred in 22% of patients in the nivolumab plus chemotherapy group and in 12% of patients in the chemotherapy group, respectively. Adverse events leading to death occurred in 2% of patients in the nivolumab plus chemotherapy group and in 1% of patients in the chemotherapy group, respectively (Moehler et al 2020).

Additionally, enhanced nivolumab plus chemotherapy versus chemotherapy as first-line therapy in patients with advanced G/GEJ cancer has also been evaluated in ATTRACTION-4 study (Boku et al 2020). It included patients from Japan, Korea and Taiwan. In this study, 724 patients were allocated to nivolumab plus chemotherapy (n = 362) or chemotherapy (n = 362) and included in the Intention-to-Treat Population. PFS was superior in the nivolumab plus chemotherapy group than in the chemotherapy group (10.45 months versus 8.34 months HR = 0.68 [95% CI: 0.51 to 0.9], p = 0.0007). Serious treatment-related AEs occurred in 24.5% of patients in the nivolumab plus chemotherapy group and in 14.2% of patients in the chemotherapy group, respectively. Treatment-related AEs led to discontinuation occurred in 6.1% of patients in the nivolumab plus chemotherapy group and in 4.7% of patients in the chemotherapy group, respectively.

Additionally, TIGIT expression was observed to be highly expressed in gastric tumor tissue compared with normal tissue and highly correlated with PD1 expression in the TCGA RNAseq dataset.

1.4.9. Biomarker Strategy Rationale

Biomarker analyses will be performed to study the following aspects of ociperlimab and tislelizumab treatments: 1) target engagement (in Phase 1 only); 2) treatment effects induced in patients; 3) biomarkers predictive of response or resistance.

Ociperlimab TIGIT and tislelizumab PD-1 receptor occupancy on peripheral blood cells will be used to demonstrate TIGIT or PD-1 target engagement by the antibodies in Phase 1. Blockade of TIGIT and PD-1 checkpoint pathways have shown to enhance the activation of T and NK cells (Johnston et al 2014; Chauvin et al 2015). Treatment effects in patients will be studied with the main focus on T, NK cell activations (may include but not limited to activation/proliferation markers on these cells, activation signatures, cytokines secreted by activated T and NK cells) by comparing these cells in peripheral blood before, during and after treatment.

Higher PD-L1 expression was reported to be associated with better clinical efficacy in 1L NSCLC treated with anti-TIGIT antibody tiragolumab plus Tecentriq in CITYSCAPE study. Superior ORR and PFS were observed in the PD-L1 ≥ 50% subgroup compared with PD-L1 1-49% subgroup (Rodriguez-Abreu et al 2020). TIGIT and PVR were reported to be mainly expressed on immune cells and tumor cell respectively in tumor tissue with varied expression levels across tumor types (Fourcade et al 2018; MacDonald et al 2016). The association of TIGIT and PVR expression with clinical efficacy of anti-TIGIT combinational therapy is still to be explored. Besides, other biomarkers including tumor mutational burden, microsatellite instability, abundance and location of TILs, and immune related gene expression profile are reported to be 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 anti-PD1 or anti-PD-L1 antibody treatment. This advised 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, expression of TIGIT pathway molecules including TIGIT, CD226, CD155, CD112, as well as tumor PD-L1 expression, tumor mutational burden, TILs and gene expression profile will be studied in relationship with clinical response to ociperlimab in combination with tislelizumab treatment to explore predictive biomarkers.

1.5. Benefit-Risk Assessment

The first-in-human Study AdvanTIG-105 evaluating safety, tolerability, and clinical benefit of ociperlimab in combination with tislelizumab in solid tumors is still ongoing. 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; Section 1.4.2). Combined with the clinical efficacy that has been demonstrated for PD-1 blockade/tislelizumab (Section 1.3), the data strongly suggest that ociperlimab has the potential to improve and/or extend the therapeutic benefits of tislelizumab, both in the treatment-naïve as well as disease progression settings.

As discussed earlier (Section 1.2.1.2, Section 1.2.2, Section 1.4.1, Section 1.4.2), 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 an 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 (Appendix 8). It is

important to note that peripheral effector T-cells typically do not express TIGIT, which is in contrast to 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 1.4.1, PD-1 blockade by tislelizumab has been evaluated in more than 1350 patients with a safety and efficacy profile similar to what has been reported for other anti-PD-(L)1 therapies.

As shown 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 1.4.1 and Section 9 for information regarding additional safeguards and considerations related to potential risk.

In addition, available data from clinical trials of other anti-PD-1 antibodies, tislelizumab, nivolumab, and pembrolizumab, have demonstrated favorable benefit/risk ratio. Available data indicates that combining standard treatment of chemotherapy and tislelizumab has a manageable safety profile and very promising antitumor activity when administered as first-line therapy in patients with advanced lung cancer (Section 1.4).

RP2D will be determined after discussion with Safety Monitoring Committee (SMC) before the initiation of dose expansion (Phase 1b). Phase 1b study is designed to include a safety run-in stage during which 6 patients will be treated with tislelizumab 200 mg plus ociperlimab 900 mg and standard chemotherapy regimen in the 6 cohorts (squamous NSCLC Cohort 1, non-squamous NSCLC Cohort 2, extensive-stage SCLC Cohort 4, ESCC Cohort 6, EAC Cohort 7, G/GEJ adenocarcinoma Cohort 9). Safety data will be reviewed by a SMC after the 6 patients in each cohort have completed ≥ 1 cycle of treatment (Section 3.3). If there are no new unexpected safety signals detected, the enrollment will continue up to 20 to 40 evaluable patients for Cohort 1, 2, 4, 6, and 7, 30 to 60 evaluable patients for Cohort 9, and 20 to 40 evaluable patients for each of the 3 arms in Cohort 10.

To assure an ongoing favorable benefit-risk assessment for patients enrolled in Study AdvanTIG-105, significant safety events will be evaluated by the investigator and sponsor; in the event of unacceptable toxicity, such as treatment-related death or unexpected treatment-related Grade 4 toxicity, the study will be stopped with the concurrence of both the SMC and sponsor.

In summary, there is strong scientific rationale that the combined blockade of the TIGIT pathway and PD-1 pathway with or without standard chemotherapy may result in enhanced antitumor activity and benefit bigger patient populations as compared to anti-PD-1 monotherapy without a major increase in the risk of immune-related toxicities.

1.6. Study Conduct

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

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives for Dose Escalation

2.1.1. Primary Objectives

- To assess the safety and tolerability of ociperlimab in combination with tislelizumab in patients with advanced solid tumors
- To determine the MTD or maximum administered dose (MAD) of ociperlimab in combination with tislelizumab
- To determine the RP2D of ociperlimab in combination with tislelizumab

2.1.2. Secondary Objectives

- To assess the preliminary anticancer activity of ociperlimab in combination with tislelizumab
- To characterize the PK of ociperlimab in combination with tislelizumab
- To assess host immunogenicity to ociperlimab in combination with tislelizumab

2.1.3. Exploratory Objectives

- To assess predictive, prognostic, and/or pharmacodynamic biomarkers including any association with response to ociperlimab treatment, exposure levels, and mechanism(s) of resistance

2.2. Study Objectives for Dose Expansion

2.2.1. Primary Objective

- To assess ORR determined by investigator per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) for patients in each dose-expansion cohort

2.2.2. Secondary Objectives

- To evaluate DCR, DOR, and PFS determined by investigator per RECIST v1.1 for patients in each dose-expansion cohort
- To further characterize the safety and tolerability of ociperlimab in combination with tislelizumab with or without chemotherapy
- To further characterize the PK of ociperlimab in combination with tislelizumab with or without chemotherapy
- To further assess host immunogenicity to ociperlimab in combination with tislelizumab with or without chemotherapy
- To evaluate the association of PD-L1 and TIGIT expression with clinical efficacy

2.2.3. Exploratory Objectives

- To assess OS for each tumor expansion cohort
- To further assess predictive, prognostic, and/or pharmacodynamic biomarkers, including any association with response to ociperlimab in combination with tislelizumab with or without chemotherapy and/or mechanism(s) of resistance

2.3. Study Endpoints for Dose Escalation

2.3.1. Primary Endpoints

- AEs and SAEs as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 [NCI-CTCAE v5.0]), timing, seriousness, and relationship to study drugs; physical examinations, ECGs, and laboratory assessments as needed; and AEs meeting protocol-defined DLT criteria
- MTD or MAD, as defined as the highest dose at which less than one-third of patients experienced a DLT or the highest dose administered, respectively
- RP2D of ociperlimab monotherapy and/or in combination with tislelizumab, determined by MTD or MAD, as well as long-term tolerability, PK, efficacy, and any other relevant data as available

2.3.2. Secondary Endpoints

- ORR, DOR, and DCR, as assessed using RECIST v1.1 (as described in Section 10.2)
- Serum concentrations at specified timepoints and PK parameters of ociperlimab and tislelizumab
- Immunogenic responses to ociperlimab and tislelizumab, evaluated through the detection of ADAs

2.3.3. Exploratory Endpoints

- Biomarkers from patient-derived tumor tissue(s) and/or blood (or blood derivative) samples obtained before, during, and/or after treatment with ociperlimab and their association with clinical efficacy. Biomarkers may include, but not limited to, expression of TIGIT, CD226, CD155, CD112 and PD-L1 in tumor tissues, tumor mutation burden, MSI status and gene mutations in tissue and blood, immune cell subpopulations and gene expression profiling (GEP) on peripheral blood and/or tumor tissues, and concentrations of cytokines and soluble proteins in plasma or serum.

2.4. Study Endpoints for Dose Expansion

2.4.1. Primary Endpoint

- ORR, as determined from investigator derived tumor assessments per RECIST v1.1 for each tumor expansion cohort (as described in Section 10.2.2)

2.4.2. Secondary Endpoints

- PFS, DOR, and DCR as determined from investigator derived tumor assessments per RECIST v1.1 for each tumor expansion cohort (as described in Section 10.2.3)
- AEs and SAEs as characterized by type, frequency, severity (as graded by NCI-CTCAE v5.0), timing, seriousness, and relationship to study drugs; physical examinations, ECGs, and laboratory assessments as needed for each tumor expansion cohort
- Serum ociperlimab and tislelizumab concentrations at specified timepoints with or without chemotherapy
- Immunogenic responses to ociperlimab and tislelizumab, evaluated through the detection of ADAs with or without chemotherapy
- PD-L1 and TIGIT expression as the predictive biomarker for efficacy (including but not limited to ORR and PFS)

2.4.3. Exploratory Endpoints

- Overall survival-defined as the date of the first dose of study drug to the date of death due to any cause (as described in Section 10.2.4)
- Biomarkers from patient-derived tumor tissue(s) and/or blood (or blood derivatives) samples obtained before, during and/or after treatment with ociperlimab in combination with tislelizumab with or without chemotherapy and their association with clinical efficacy. Biomarkers may include but are not limited to expression of CD226, CD155, CD112 in tumor tissues, tumor mutation burden, MSI status, and gene mutations in tissue and blood, Epstein-Barr virus (EBV) status, immune cell subpopulations and GEP on peripheral blood and/or tumor tissues, and concentrations of cytokines and soluble proteins in plasma or serum.

3. STUDY DESIGN

3.1. Summary of Study Design

This is an open-label, multicenter, Phase 1 and Phase 1b clinical trial to investigate safety, tolerability, pharmacokinetics and preliminary antitumor activity of anti-TIGIT monoclonal antibody ociperlimab in combination with anti-PD-1 monoclonal antibody tislelizumab (BGB-A317) with or without chemotherapy in patients with unresectable locally advanced or metastatic solid tumors. The study designs for Phase 1 and Phase 1b are presented in Figure 3, Figure 4, and Figure 5, respectively.

Approximately 44 to 64 patients will be enrolled in Phase 1 and 250 to 500 evaluable patients will be enrolled in Phase 1b. Phase 1 will be conducted across up to 10 sites in Australia and China. Phase 1b will be conducted across approximately up to 85 sites globally. For all Phase 1 and Phase 1b study assessments and procedures, see Section 8 and Appendix 1.

Phase 1

Dose Escalation in Australia: A flat dose of ociperlimab will be administered intravenously as a single agent on Day 1 of each cycle. In the first cycle, 200 mg tislelizumab will be administered intravenously on Day 8. Patients will be monitored for DLTs for 28 days following the first administration of ociperlimab. If tolerated, patients will receive ociperlimab and tislelizumab on Day 29 and every 21 days (ie, Q3W) thereafter until they meet a discontinuation criterion (Section 7.5). The doses of ociperlimab to be tested are 50, 150, 450, and 900 mg, while the dose level of tislelizumab will be fixed at 200 mg. However, if warranted, different dose levels and/or dosing schedules of ociperlimab (eg, up to 1600 mg) and tislelizumab may be explored to confirm the optimal dosing regimen of ociperlimab and tislelizumab (Figure 3). Refer to Section 3.2.1 for the details of dose escalation study in Australia.

RP2D will be determined after discussion with SMC before the initiation of dose expansion. Refer to Section 3.2.1.5 for the result of RP2D determination.

Dose Verification in China: Before Chinese patients join the Phase 1b study, safety and tolerability of ociperlimab (RP2D) will be assessed as a monotherapy, and in combination with tislelizumab (200 mg Q3W) in Chinese patients. The SMC will define the RP2D for Chinese patients based on the safety data from ociperlimab, combined with tislelizumab 200 mg, before Chinese patients join the Phase 1b study.

Refer to Section 3.2.2 for the details of dose verification study in China.

Phase 1b

Approximately 250 to 500 evaluable patients (having measurable disease at baseline and postdose) will be enrolled into 10 different disease cohorts, including:

- **Cohort 1** (n = 20 to 40): Patients with metastatic squamous NSCLC will be treated with ociperlimab plus tislelizumab plus paclitaxel/nab-paclitaxel plus carboplatin.
- **Cohort 2** (n = 20 to 40): Patients with metastatic non-squamous NSCLC will be treated with ociperlimab plus tislelizumab plus pemetrexed plus cisplatin/carboplatin.
- **Cohort 3** (n = 20 to 40): Patients with metastatic NSCLC (PD-L1 positive, TC ≥ 1%) will be treated with ociperlimab plus tislelizumab.
- **Cohort 4** (n = 20 to 40): Patients with extensive-stage SCLC will be treated with ociperlimab plus tislelizumab plus etoposide plus cisplatin/carboplatin.
- **Cohort 5** (n = 20 to 40): Checkpoint inhibitor (CPI)-experienced NSCLC patients will be treated with ociperlimab plus tislelizumab.
- **Cohort 6** (n = 20 to 40): Patients with metastatic ESCC will be treated with ociperlimab plus tislelizumab plus cisplatin plus 5-FU/paclitaxel.
- **Cohort 7** (n = 20 to 40): Patients with metastatic EAC will be treated with ociperlimab plus tislelizumab plus cisplatin plus 5-FU/paclitaxel.
- **Cohort 8** (n = 20 to 40): Patients with recurrent or metastatic HNSCC (PD-L1 positive, [vCPS] ≥ 1%) will be treated with ociperlimab plus tislelizumab.
- **Cohort 9** (n = 30 to 60): Patients with unresectable, locally advanced, recurrent or metastatic G/GEJ adenocarcinoma will be treated with ociperlimab plus tislelizumab plus oxaliplatin plus capecitabine or ociperlimab plus tislelizumab plus cisplatin plus 5-FU.
- **Cohort 10** (n = 20 to 40 per arm, 3 dose arms): Patients with metastatic NSCLC (PD-L1 positive, TC ≥ 1%) will be treated with ociperlimab plus tislelizumab.

Depending on the allocated cohort, Phase 1b will include different stages (Figure 5). For Cohorts 1, 2, 4, 6, 7, and 9, patients will receive ociperlimab combined with tislelizumab and chemotherapy. Phase 1b includes a safety run-in stage and a dose-expansion stage. For Cohorts 3, 5, and 8, patients will receive ociperlimab combined with tislelizumab. Phase 1b includes dose-expansion stage. For details of Phase 1b, please refer to Section 3.3.

For Cohorts 1 to 8 and the 3 dose arms in Cohort 10, an interim analysis will be conducted based on approximately the first 20 patients who have had ≥ 1 on-study tumor assessment (Section 10.7). Based upon the interim analysis for a given cohort, up to 40 evaluable patients may be enrolled for that cohort as described in Section 10.7. For Cohort 9, the interim analysis will be conducted based on approximately the first 30 patients who have had ≥ 1 postbaseline tumor assessment. Up to 60 evaluable patients in total may be enrolled based on the interim analysis for Cohort 9.

Patients will receive study drug until they meet a study treatment discontinuation criterion (Section 7.5).

All patients will be closely monitored for AEs throughout the study and for ≥ 30 days after the last dose of study treatment or until initiation of another anticancer therapy, whichever occurs first. AEs will be graded according to the NCI-CTCAE v5.0. Refer to Section 9 for additional and specific information regarding AE monitoring and reporting.

PK analysis will be performed for ociperlimab and tislelizumab with or without chemotherapy. Biomarker analysis will include, but not limited to, TIGIT, CD226, CD155, CD112, and PD-L1 expression in tumors, TIL analysis, tumor mutation burden, MSI status and gene mutations in tissue and blood, EBV status, cytokine analysis in plasma, peripheral blood cell population analysis, and/or GEP in tissue and blood (Section 8.4).

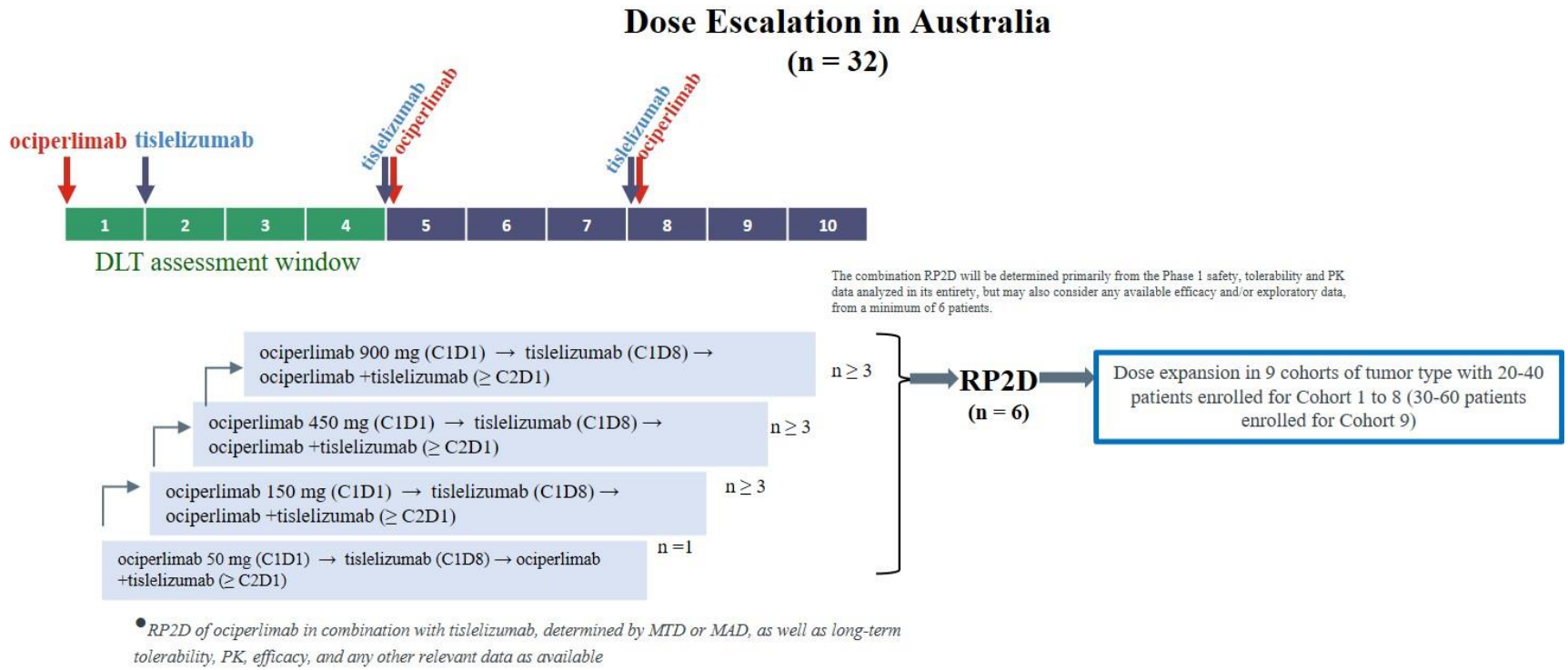
Preliminary anticancer activity will be evaluated by the investigator using RECIST v1.1, (Section 8.5 and/or Appendix 9).

Patients may continue to receive ociperlimab and tislelizumab beyond the initial investigator-assessed PD, as defined by RECIST v1.1, provided that the patient has investigator-assessed clinical benefit and is tolerating study drugs. Refer to Section 7.5 and Section 8.5 for additional considerations regarding treatment continuation and withdrawal. Patients who, at time of progression, have an ongoing AE that leads to treatment discontinuation and has completed the scheduled Safety Follow-up Visit will be followed until the event resolves, the investigator assesses the event as stable, the patient is lost to follow-up, or the patient starts a subsequent anticancer therapy. If a patient discontinues study drugs due to reasons other than PD or death, tumor assessments should continue to be performed following the scheduled assessment plan until the start of subsequent anticancer therapy, PD, death, lost to follow-up, or withdrawal of consent for efficacy follow-up (Section 7.4.2).

Patients who have discontinued study drugs should return to the site for an End-of-Treatment (EOT) Visit within ≤ 7 days as detailed in Section 7.4.1. After the EOT Visit, patients will have scheduled follow-up visits for safety and, if applicable, for efficacy per the Schedule of Assessments (Appendix 1).

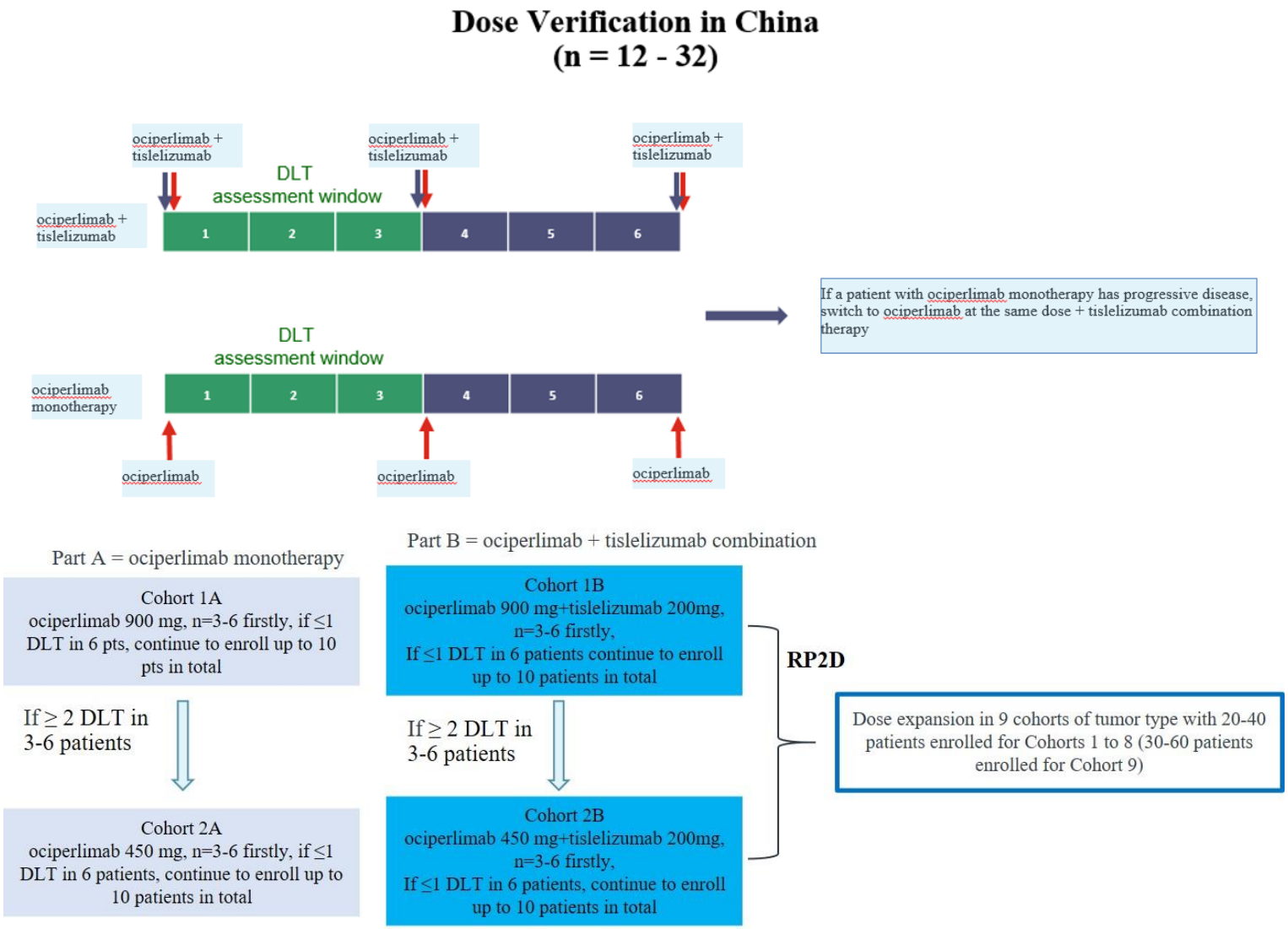
Study procedures and assessments are further detailed in Section 7 and Section 8, respectively, and the Schedule of Assessments can be found in Appendix 1. Specific details regarding Phase 1 and Phase 1b are described in the following sections.

Figure 3: Study Schema for Phase 1 (Dose Escalation in Australia)



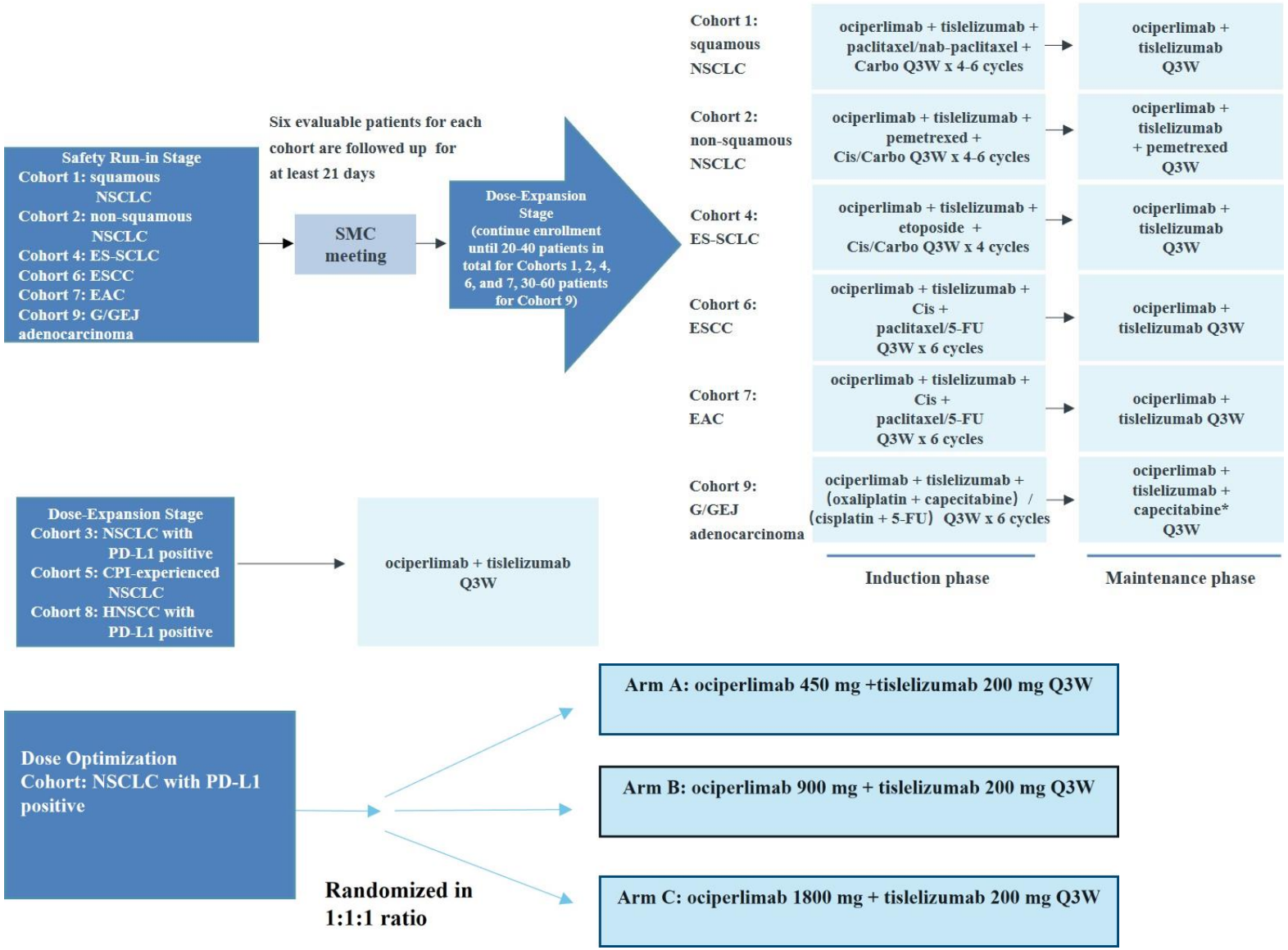
Abbreviations: C, Cycle; D, day; DLT, dose-limiting toxicity; MAD, maxima administered dose; MTD, maximal tolerated dose; PK, pharmacokinetics; RP2D, recommended Phase 2 dose.

Figure 4: Study Schema for Phase 1 (Dose Verification in China)



Abbreviations: DLT, dose-limiting toxicity; mono, monotherapy; pts, patients; RP2D, recommended Phase 2 dose.

Figure 5: Study Schema for Phase 1b



Abbreviations: 5-FU, 5-fluorouracil; Carbo, carboplatin; Cis, cisplatin; EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; G/GEJ, gastric or gastroesophageal junction; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death-1 ligand; Q3W, once every 3 weeks; ES-SCLC, extensive-stage small cell lung cancer; SMC, Safety Monitoring Committee.
Note: For Cohort 9, capecitabine as optional maintenance therapy is for oxaliplatin + capecitabine regimen only.

3.2. Details of Phase 1

3.2.1. Phase 1 (Dose Escalation in Australia)

3.2.1.1. Starting Dose and Dose Escalation Approach

A modified 3+3 scheme will be used for sequential cohorts of approximately 4 increasing dose levels of ociperlimab in combination with tislelizumab in patients with advanced solid tumors (Figure 3) to determine the MTD or MAD, RP2D, safety, PK, and other key endpoints for ociperlimab in combination with tislelizumab.

Except for the dose escalation DLT period, a 21-day treatment cycle is planned for all cycles thereafter.

For dose escalation, a 28-day DLT observation period will be utilized in the first cycle. A flat dose of ociperlimab will be administered intravenously as a single agent on Day 1 followed by a dose of 200 mg tislelizumab administered intravenously on Day 8. To be DLT evaluable, patients must receive ociperlimab alone on Day 1 of Cycle 1, followed by tislelizumab alone on Cycle 1 Day 8 (+ 2 days). Refer to Section 5.4.1 and Section 5.4.2 regarding continued treatment of patients who are unable to receive tislelizumab on Cycle 1 Day 8 (+2 days). If no DLT(s) are observed thereafter and through the completion of the initial 28-day cycle, patients will receive ociperlimab and tislelizumab on Day 29 and every 21 days (ie, Q3W) thereafter, as outlined in Section 5.1.3 and Appendix 1, until patients meet a treatment discontinuation criterion.

Once the criteria outlined below (Section 3.2.1.2, Section 3.2.1.3, and Section 3.2.1.4) have been satisfied for a dose level of ociperlimab, the next dose level will be eligible for patient enrollment.

The starting ociperlimab dose level (50 mg) will initially be evaluated in 1 patient (sentinel patient), whereas the second ociperlimab dose level (150 mg) will be evaluated in 3 or more patients. Escalation from the first ociperlimab dose level will proceed if no DLT is observed in the DLT evaluable patient. If a DLT is observed in this sentinel patient, the dose will be further explored following the 3+3 rules. Starting with the 150 mg ociperlimab dose level, escalation of the BGB A1217 dose level will proceed if no DLT is observed during the DLT period in a minimum of 3 evaluable patients. However, if a DLT occurs within the DLT observation period for a given dose level, enrollment for that dose level and dose finding decisions will proceed per the 3+3 design rules as follows:

a. Ociperlimab dose escalation will advance if the first cycle DLT rate < 33%;
b. Ociperlimab dose escalation will stop if the first cycle DLT rate is ≥ 33%. A minimum of 6 patients will be enrolled to the current dose level of ociperlimab if DLT rate is 33% (eg, 1/3) or the next lower dose level if DLT rate is >33% (eg, 2/3 or 3/3);
c. The MTD dose level is defined as the highest dose level at which < 33% of the patients experience a DLT.

For dose escalation decisions, only DLTs occurring within 28 days of Cycle 1 Day 1 for the corresponding dose level will be evaluated. However, as noted below and in Section 3.2.1.4, additional considerations may be taken into account if clinically significant toxicity(ies) is observed, regardless of when it occurred.

Based upon emerging clinical data, lower, intermediate and/or higher dose levels and/or alternative dosing intervals of ociperlimab may also be evaluated. However, the dosing regimen of tislelizumab will remain fixed for each different ociperlimab dose level evaluated.

The combination RP2D will be determined primarily from the Phase 1 safety, tolerability and PK data analyzed in its entirety, but may also consider any available efficacy and/or exploratory data, from a minimum of 6 patients. Once the combination RP2D is determined, it will then be evaluated in the Phase 1b dose expansion.

3.2.1.2. Rules for Dose Escalation

Dose escalation will occur in accordance with the following modified 3 + 3 dose escalation rules.

For the initial dose escalation cohort (ociperlimab 50 mg Q3W), a single patient will be enrolled.

- If the first evaluable patient enrolled in this cohort does not experience a DLT, dose escalation may proceed.
- If the first evaluable patient enrolled in this cohort experiences a DLT, additional patients (for a minimum of 6 evaluable patients) will be enrolled in that cohort.
  - If less than one-third of evaluable patients in a given cohort experience a DLT (eg, DLTs in fewer than 2 of 6 patients), escalation will proceed to the next higher dose level.

For the remaining dose escalation cohorts, a minimum of 3 patients will be initially enrolled per cohort.

- If none of the first 3 evaluable patients enrolled in a given cohort experience a DLT, dose escalation may proceed.
- If 1 of the first 3 evaluable patients enrolled in a given cohort experiences a DLT, additional patients (for a minimum of 6 evaluable patients) will be enrolled in that cohort.
  - If less than one-third of evaluable patients in a given cohort experiences a DLT (eg, DLTs in fewer than 2 of 6 patients), escalation will proceed to the next higher dose level.

If a DLT is observed in at least one-third or more of patients (eg, 2 or more of up to 6 patients), the MTD will have been exceeded and dose escalation will be stopped.

- Additional patients (for a minimum of 6 evaluable patients) will be assessed for DLTs at the preceding dose level (if a minimum of 6 evaluable patients had not already been assessed at that dose level).
- If the MTD is exceeded at a given dose level, a lower or intermediate dose level may be assessed for toxicity in the same manner as described above.

If the MTD is exceeded at a given dose level, the next highest dose level at which less than one-third of evaluable patients in a given cohort experiences a DLT (eg, DLTs in fewer than 2 of 6 patients) will be declared the MTD.

If less than one-third of evaluable patients (eg, DLTs in fewer than 2 of 6 patients) at the highest dose level experience a DLT, this dose level will be declared the MAD.

All available safety data, including AEs, laboratory assessments, and PK analyses (as available), will be reviewed by the medical monitor and study team members from Pharmacovigilance/Drug Safety, Clinical Pharmacology, and Biostatistics with input from other members as appropriate.

On the basis of a review of real-time safety data and available preliminary PK data and in consultation with the investigators, dose escalation may be halted or modified as deemed appropriate.

3.2.1.3. Assessment of Dose-Limiting Toxicity

For initial dose-finding recommendations, AEs will be assessed per the DLT criteria below (Section 3.2.1.4) during the 28-day DLT assessment window, which starts with the first day of study drug administration.

Patients will be considered evaluable for DLTs if they 1) received ≥ 80% of each scheduled study drug administration during the DLT assessment window and/or 2) experienced a DLT.

Patients will be considered not evaluable for DLTs, if they 1) withdraw from the study, 2) did not receive ≥ 80% of each scheduled study drug administration during the DLT assessment window and/or 3) received supportive care during the DLT assessment window that confounds the evaluation of DLTs (not including supportive care described as part of the DLT definition). Patients who are not DLT-evaluable must be replaced, if needed.

Clinically important or persistent AEs that are not part of the DLT criteria (Section 3.2.1.4) may also be considered a DLT following review by the sponsor in consultation with the investigators. All adverse events should be considered potentially related to the study drug regardless of investigator/sponsor causality assessment, excluding toxicities clearly related to disease progression or intercurrent illness. Additionally, any clinically significant AEs that occur after the DLT assessment window (eg, late imAE) for a given dose level, may be considered regarding subsequent dose escalation decisions. In such cases where patients have been safely dosed at the next dose level, additional dose-escalation criteria (eg, increased minimum number of patients or expanded DLT assessment window) for subsequent dose levels will be considered by the sponsor in consultation with participating investigators. Every DLT will be discussed in SMC to help the determination of RP2D.

Any patient who experiences a DLT may be withdrawn from treatment or may continue to receive either tislelizumab alone or the combination with a lower dose level for ociperlimab following discussion with and approval by the medical monitor.

3.2.1.4. Dose-Limiting Toxicity Definition

All toxicities or AEs will be graded according to the NCI-CTCAE v5.0. A DLT is defined as 1 of the following toxicities occurring during the DLT assessment window (first 28 study days) and considered by the investigator to be related to ociperlimab and/or tislelizumab.

Hematologic:

1. Grade 4 neutropenia lasting > 7 days
2. ≥ Grade 3 febrile neutropenia
3. Grade 3 thrombocytopenia with clinically significant bleeding
4. Grade 4 thrombocytopenia lasting > 7 days
5. ≥ Grade 4 anemia

Non-hematologic:

6. ≥ Grade 4 toxicity
7. Grade 3 toxicity that is clinically significant and does not resolve to baseline or ≤ Grade 1 within 7 days of initiating optimal supportive care

Note: The following AEs will not be considered DLTs:

- Grade 3 endocrinopathy that is adequately controlled by hormonal replacement
- Grade 3 rash
- Grade 3 infusion-related AE that is transient (resolving within 6 hours of onset)
- Grade 3 nausea, vomiting, or diarrhea lasting for ≤ 72 hours with adequate antiemetic and/or other supportive care
- Grade 3 fatigue lasting for ≤ 7 days
- Grade 3 or higher electrolyte abnormality that lasts for ≤ 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions.

Patients will be considered not evaluable for DLTs, if they 1) withdraw from the study during the DLT assessment window, 2) did not receive ≥ 80% of each scheduled study drug administration during the DLT assessment window and/or 3) received supportive care during the DLT assessment window that confounds the evaluation of DLTs (not including supportive care described as part of the DLT definition). Patients who are not DLT-evaluable must be replaced, if needed.

Clinically important or persistent AEs that are not part of the DLT criteria may also be considered a DLT following review by the sponsor in consultation with the investigators. All adverse events should be considered potentially related to the study drug regardless of investigator or sponsor causality assessment, excluding toxicities clearly related to disease progression or intercurrent illness. Additionally, any clinically significant AEs that occur after the DLT assessment window (eg, late imAE) for a given dose level, may be considered regarding subsequent dose escalation decisions. In such cases where patients have been safely dosed at the next dose level, additional dose escalation criteria (eg, increased minimum number of patients or expanded DLT assessment window) for subsequent dose levels will be considered by the sponsor in consultation with participating investigators. Every DLT will be discussed in SMC to help the determination of RP2D.

3.2.1.5. RP2D Determination

The ociperlimab dose of 900 mg 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. Refer to the Ociperlimab Investigator's Brochure for further details.

3.2.2. RP2D Confirmation in Chinese Patients Phase 1 (Dose Verification in China)

Based on the safety results of the dose-escalation trial on ociperlimab conducted in Australia, this study will assess the safety and pharmacokinetic characteristics of flat-dose 900 mg monotherapy and combination with tislelizumab 200 mg Q3W in Chinese patients with advanced malignant solid tumors. Other doses may be further explored based on the safety result and necessity.

Dose verification study in China will occur in cohorts with ociperlimab as monotherapy and cohorts with ociperlimab in combination with tislelizumab (Figure 4). A 21-day treatment cycle will be used for both monotherapy part and combination part. DLT will be assessed among evaluable patients within Cycle 1 (1 to 21 days).

Three to six patients will be enrolled first to assess DLT in Cohort 1A (ociperlimab monotherapy 900 mg Q3W) and Cohort 1B (ociperlimab 900 mg in combined with tislelizumab 200 mg Q3W):

- If none of the 3-6 patients experience a DLT at 900 mg dose level, Cohort 1A will continue to enroll up to 10 patients in total.
- If none of the 3-6 patients experience a DLT at 900 mg dose level combined with tislelizumab, Cohort 1B will continue to enroll up to 10 patients in total.

The following DLT rules apply to both monotherapy and combination part:

- Three additional patients will be enrolled if a DLT is observed in 1 of 3 patients; 2 additional patients will be enrolled if a DLT is observed in 1 of 4 patients; and 1 additional patient will be enrolled if a DLT is observed in 1 of 5 patients.
- If $\leq$ 1 DLT is observed in 6 patients, the cohort will continue to enroll up to 10 patients in total
- If 2 or more patients develop DLT among 3-6 patients in the cohort, the dose level will be considered as exceeding the MTD. All investigators will be informed of such dose level. A lower dose of 450 mg Q3W in both monotherapy (Cohort 2A) and combination part (Cohort 2B) will be evaluated.

DLT will be assessed among evaluable patients within Cycle 1 (1-21 days) (refer to Section 3.2.1.3 for detailed assessment standard). An evaluable patient is defined as the individual who has received $\geq$ 80% of the dose and completed all safety assessments required in Cycle 1, or any patient who has experienced DLT in Cycle 1.

For dose verification decisions, only DLTs occurring within 21 days of Cycle 1 Day 1 for the corresponding dose level will be evaluated. However, as noted below and in Section 3.2.1.4,

additional considerations may be taken into account if clinically significant toxicity(ies) is observed, regardless of when it occurred.

The SMC will define the RP2D for Chinese patients based on the safety data from ociperlimab, combined with tislelizumab 200 mg, before Chinese patients join the Phase 1b study.

Patients in monotherapy part (Cohort 1A/2A) who experience disease progression will be given the option to be treated with ociperlimab at the same dose level combined with tislelizumab.

Any patient who experiences a DLT may be withdrawn from treatment or may continue to receive tislelizumab alone following discussion with and approval by the medical monitor.

3.2.2.1. Dose-Limiting Toxicity Definition

The definition of DLT can be found in Section 3.2.1.4.

3.3. Details of Phase 1b

Depending on the allocated cohort, Phase 1b will include different stages.

For Cohort 1 (squamous NSCLC), Cohort 2 (non-squamous NSCLC), Cohort 4 (extensive-stage SCLC), Cohort 6 (ESCC), Cohort 7 (EAC), and Cohort 9 (G/GEJ adenocarcinoma), patients will receive tislelizumab (200 mg) in combination with ociperlimab (RP2D) and chemotherapy (Section 5). Phase 1b includes a safety run-in stage and a dose-expansion stage. In safety run-in stage, 6 evaluable patients will be enrolled in each cohort and followed up for ≥ 21 days. A SMC will be established by the sponsor and investigators to evaluate the safety and tolerability of the combination therapy when the 6 patients of each cohort have completed the first 21 days treatment. Safety information, including but not limited to all of AEs and laboratory abnormalities, will be reviewed by the SMC. If there is no new unexpected safety signal detected by the SMC, the enrollment will continue until a total of 20 to 40 evaluable patients for Cohorts 1 to 8, 30 to 60 evaluable patients for Cohort 9 and 20 to 40 evaluable patients for each of the 3 arms in Cohort 10 are reached in the dose-expansion stage.

For Cohort 3 and Cohort 10 (NSCLC with PD-L1 positive, TC ≥ 1%), Cohort 5 (CPI-experienced NSCLC), and Cohort 8 (HNSCC with PD-L1 positive, vCPS ≥ 1%), patients will receive tislelizumab (200 mg) in combination with ociperlimab (RP2D or specified doses) (Section 5). Phase 1b includes only dose-expansion stage which will start once the RP2D of ociperlimab is confirmed.

During the maintenance treatment period, prophylactic cranial irradiation is permitted in Cohort 4 (extensive-stage SCLC) as per local standard of care.

For Cohort 10, patients with NSCLC with PD-L1 positive (TC ≥ 1%) will be randomized to receive ociperlimab 450 mg, 900 mg, or 1800 mg in combination with tislelizumab 200 mg in an open-label setting. The randomization will be stratified based on PD-L1 status (TC 1% to 49%, TC ≥ 50%) and histology.

The recommended dose level of tislelizumab (200 mg intravenously Q3W) with ociperlimab will be based upon the available clinical data derived from Phase 1 and any other data as applicable. For all 10 cohorts, ociperlimab and tislelizumab will be continually used Q3W until the patients

would not benefit from therapy under investigator's discretion, intolerable toxicity or withdrawal of consent.

If the frequency of ≥ Grade 3 toxicities or other unacceptable chronic toxicities in the dose-expansion phase suggests that the MTD has been exceeded at that dose level, any remaining accrual of patients at that dose level will be halted. Consideration will then be given to enrolling additional patients into the dose-expansion cohorts and Cohort 10 at a lower dose level.

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

4.1.1. Inclusion Criteria for Phase 1

Each patient must meet all of the following inclusion criteria to be considered eligible for participation in this study:

1. Signed informed consent form (ICF) and able to comply with study requirements.
2. Age ≥ 18 years (or the legal age of consent) at the time the ICF is signed.
3. Histologically or cytologically confirmed unresectable locally advanced or metastatic solid tumors previously treated with standard systemic therapy or for which treatment is not available or not tolerated, and who have not received prior therapy targeting TIGIT.
   - Patients with HCC require Child-Pugh A classification before the first dose of study drugs (Appendix 10)
4. ≥ 1 evaluable lesion per RECIST v1.1.
5. If available, archived, formalin-fixed paraffin-embedded (FFPE) tumor tissue sample (block or approximately 15 freshly cut unstained FFPE slides).
   - If archival tissue is unavailable, optional fresh baseline tumor biopsy is strongly recommended
6. ECOG Performance Status ≤ 1.
7. Adequate organ function as indicated by the following laboratory values during screening:
   a. Absolute neutrophil count ≥ 1.5 x 10^9/L
   b. Platelet count ≥ 100 x 10^9/L
   c. Hemoglobin ≥ 90 g/L, without blood transfusion or growth factor support ≥ 14 days before sample collection
   d. Serum creatinine ≤ 1.5 x ULN or estimated glomerular filtration rate (GFR) ≥ 60 mL/min/1.73 m^2 by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Appendix 7)
   e. Serum total bilirubin ≤ 1.5 x ULN (< 3 x ULN for patients with Gilbert syndrome)
   f. AST and ALT ≤ 3 x ULN
8. Females of childbearing potential must be willing to use a highly effective method of birth control for the duration of the study, and ≥ 120 days after the last dose of study drugs, and have a negative urine or serum pregnancy test ≤ 7 days of the first dose of study drugs (Appendix 5).
9. Nonsterile males must be willing to use highly effective method of birth control for the duration of the study and for ≥ 120 days after the last dose of study drugs (Appendix 5).

4.1.2. Inclusion Criteria for Phase 1b

Each patient must meet all of the following inclusion criteria to be considered eligible for participation in this study:

1. Signed ICF and able to comply with study requirements.
2. Age ≥ 18 years (or the legal age of consent) at the time the ICF is signed.
3. Following determination of RP2D, the combination will be evaluated in histologically or cytologically confirmed tumor types with staging per AJCC 8th edition (Amin et al 2017) in the following disease cohorts:
   a. **Cohort 1:** Have histologically or cytologically confirmed stage IV squamous NSCLC
   b. **Cohort 2:** Have histologically or cytologically confirmed stage IV non-squamous NSCLC
   c. **Cohort 3:** Have histologically or cytologically confirmed stage IV squamous or non-squamous NSCLC with PD-L1 positive (TC ≥ 1%)
      - Patients must have PD-L1 IHC testing with results positive (TC ≥ 1%) performed by a central laboratory during the screening period
      - Patients with tumors of mixed (squamous and non-squamous) or unspecified non-small cell histology are eligible
   d. **Cohort 4:** Have histologically or cytologically confirmed extensive-stage SCLC
   e. **Cohort 5:** Have histologically or cytologically confirmed stage IIIB, IIIC, or IV NSCLC with all of the following:
      - Patients who previously treated with one or two lines of prior standard systemic therapy for locally advanced or metastatic disease (Disease progression within 6 months following completion of local therapy with curative intention including adjuvant chemotherapy after surgical procedure or concurrent chemoradiotherapy with/without consolidation could be considered as treated with 1 line standard systemic therapy)
      - The anti-PD-(L)1 treatment must be the most recent line
      - The best response with anti-PD-(L)1 treatment of the most recent line, should be CR, PR, or SD
   f. **Cohort 6:** Have histologically or cytologically confirmed stage IV ESCC
   g. **Cohort 7:** Have histologically or cytologically confirmed stage IV EAC
   h. **Cohort 8:** Have histologically or cytologically confirmed recurrent or metastatic HNSCC that is considered incurable by local therapies
      - The eligible primary tumor locations are oropharynx, oral cavity, hypopharynx, and larynx.
      - Patients must not have a primary tumor site of nasopharynx (any histology)
      - Patients must have positive PD-L1 IHC testing results (vCPS ≥ 1%) performed by a central laboratory during the screening period

- Known p16 expression for oropharyngeal cancers by local testing. If local p16 testing results are not available, a tumor tissue sample may be submitted for p16 testing at the designated central laboratory. Oral cavity, hypopharynx, and larynx cancer are not required to undergo HPV testing by p16 IHC

i. **Cohort 9:** Have histologically or cytologically confirmed stage IV G/GEJ adenocarcinoma

j. **Cohort 10:** Have histologically- or cytologically-confirmed stage IV squamous or non-squamous NSCLC with PD-L1 positive (TC ≥ 1%)

- Patients must have PD-L1 IHC testing with results positive (TC ≥ 1%) performed by a central laboratory during the screening period
- Patients with unspecified non-small cell histology are not eligible

4. ≥ 1 measurable lesion per RECIST v1.1.
   a. No prior local therapy of selected target lesion(s) OR, if prior local therapy, subsequent progression of each selected target lesion as per RECIST v1.1
5. Archived tumor tissue or fresh biopsy (FFPE block [preferred] or approximately 15 freshly cut unstained FFPE slides, ≥ 8 slides are mandatory) are required to be collected. For Cohorts 3 and 10 (NSCLC with PD-L1 positive, TC ≥ 1%) and Cohort 8 (HNSCC with PD-L1 positive [vCPS ≥ 1%]), prospective PD-L1 IHC testing at the designated central laboratory is mandatory.
6. ECOG Performance Status ≤ 1.
7. Adequate organ function as indicated by the following laboratory values during screening:
   a. Absolute neutrophil count ≥ 1.5 x 10^9/L
   b. Platelet count ≥ 100 x 10^9/L for patients receiving ociperlimab plus tislelizumab plus chemotherapy or ≥ 75 x 10^9/L for patients receiving ociperlimab plus tislelizumab
   c. Hemoglobin ≥ 90 g/L, without blood transfusion or growth factor support ≥ 14 days before sample collection
   d. Serum creatinine ≤ 1.5 x ULN or calculated creatinine clearance (CrCl) ≥ 60 mL/min (Cockcroft-Gault formula) (Appendix 13)
   e. Serum total bilirubin ≤ 1.5 x ULN (< 3 x ULN for patients with Gilbert syndrome)
   f. AST and ALT ≤ 2.5 x ULN or < 5 x ULN if hepatic metastases present.
8. Females of childbearing potential must be willing to use a highly effective method of birth control for the course of the study through 180 days after the last dose of chemotherapeutic agents (14 months after the last dose of cisplatin; 9 months after the last dose for oxaliplatin) or through 120 days after the last dose of study drugs, and have a negative urine or serum pregnancy test ≤ 7 days of the first dose of study drugs (Appendix 5).
9. Nonsterile males must be willing to use highly effective method of birth control for the course of the study through 180 days after the last dose of chemotherapeutic agents (11 months after the last dose of cisplatin; 6 months after the last dose for oxaliplatin) or through 120 days after the last dose of study drugs.

4.2. Exclusion Criteria

4.2.1. Exclusion Criteria for Phase 1

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

1. Active leptomeningeal disease or uncontrolled brain metastasis
   - Patients with equivocal findings or with confirmed brain metastases are eligible if they are asymptomatic and radiologically stable without need for corticosteroids for ≥ 4 weeks before the first dose of study drugs.
2. Active autoimmune diseases or history of autoimmune diseases that may relapse, with the following exceptions:
   - Controlled type 1 diabetes
   - Hypothyroidism (provided it is managed with hormone-replacement therapy only)
   - Controlled celiac disease
   - Skin diseases not requiring systemic treatment (eg, vitiligo, psoriasis, or alopecia)
   - Any other disease that is not expected to recur in the absence of external triggering factors
3. Any active malignancy ≤ 2 years before the first dose of study drugs, except for the specific cancer under investigation and any locally recurring cancer that has been treated with curative intent (eg, resected basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix or breast).
4. Any condition that required systemic treatment with either corticosteroids (> 10 mg daily of prednisone or equivalent) or other immunosuppressive medication ≤ 14 days before the first dose of study drugs, with the following exceptions:
   - Adrenal replacement steroid (dose ≤ 10 mg daily of prednisone or equivalent)
   - Topical, ocular, intra-articular, intranasal, or inhalational corticosteroid with minimal systemic absorption
   - 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)
5. History of interstitial lung disease, noninfectious pneumonitis, or uncontrolled lung diseases, including but not limited to pulmonary fibrosis, acute lung diseases, etc.
6. 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 drugs
7. Severe chronic or active infections (including but not limited to tuberculosis infection) requiring systemic treatment ≤ 14 days before the first dose of study drugs
8. Known history of human immunodeficiency virus (HIV) infection

9. Known history of or active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection except for the following:
   - Patients with untreated chronic HBV or chronic HBV carriers whose HBV deoxyribonucleic acid (DNA) is ≥ 500 IU/mL or patients with positive HCV ribonucleic acid should be excluded. Inactive hepatitis B surface antigen (HBsAg) carriers, treated and stable hepatitis B patients (HBV DNA < 500 IU/mL), and cured hepatitis C patients (as defined by a positive HCV antibody test and negative HCV ribonucleic acid test) may be enrolled.
10. Major surgical procedure, open biopsy, or significant traumatic injury ≤ 4 weeks before the first dose of study drugs or anticipation of need for major surgical procedure during the course of the study
11. Prior immunodeficiency, allogeneic stem cell transplantation, or organ transplantation
12. Any of the following cardiovascular criteria:
    a. Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living, ≤ 28 days before the first dose of study drugs
    b. Symptomatic pulmonary embolism or other clinically significant episode of thromboembolic disease ≤ 28 days before the first dose of study drugs
    c. History of acute myocardial infarction ≤ 6 months before the first dose of study drugs
    d. History of heart failure meeting New York Heart Association Classification III or IV (Appendix 6) ≤ 6 months before the first dose of study drugs
    e. Ventricular arrhythmia ≥ Grade 2 in severity ≤ 6 months before the first dose of study drugs
    f. Cerebrovascular accident ≤ 6 months before the first dose of study drugs
    g. Uncontrolled hypertension: systolic pressure ≥ 160 mmHg or diastolic pressure ≥ 100 mmHg despite anti-hypertension medications ≤ 28 days before the first dose of study drugs
13. History of severe hypersensitivity reactions to other monoclonal antibodies
14. Chemotherapy, immunotherapy (eg, interleukin, interferon, or thymosin), or investigational therapy ≤ 14 days or 5 half-lives (whichever is shorter) before the first dose of study drugs
    - Received any herbal medicine or Chinese patent medicines used to control cancer ≤ 14 days before the first dose of study drugs
15. Toxicities from prior therapy that have not recovered to baseline, ≤ Grade 1, or stabilized, except for AEs not considered a likely safety risk (eg, alopecia, neuropathy, and specific laboratory abnormalities)
16. Live vaccine ≤ 4 weeks before the first dose of study drugs
    - Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed.
17. Medical condition or alcohol or drug abuse or dependence that, in the investigator's opinion, will be unfavorable for the administration of study drugs or will affect the explanation of drug toxicity or AEs or are likely to result in insufficient compliance with study procedures.

18. Concurrent participation in another therapeutic clinical study
19. Any condition that requires treatment with prohibited or restricted concomitant medication or therapy as described in Section 6.

4.2.2. Exclusion Criteria for Phase 1b

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

1. For Cohorts 1, 2, 3, 4, 9, and 10, patients with any prior therapy for metastatic disease, including systemic chemotherapy or local radiotherapy are excluded. If there is prior neoadjuvant/adjuvant chemotherapy, the treatment-free interval from end of neoadjuvant/adjuvant chemotherapy to recurrence should be ≥ 6 months before ICF signing.
2. For Cohorts 6, 7, and 8, patients with any prior systemic therapy for recurrent/metastatic disease are excluded. Patients with prior systemic chemotherapy administered as a part of chemoradiotherapy for locally advanced disease are eligible. If there is prior curatively intended systemic treatment, the treatment-free interval from end of neoadjuvant/adjuvant chemotherapy to recurrence should be ≥ 6 months before ICF signing.
3. Certain types of patients are excluded:
    a. For Cohorts 1, 2, 3, and 5, 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. For Cohort 10, tumors of mixed non-small cell histology are excluded.
    b. For Cohorts 2, 3, 5, and 10, non-squamous NSCLC patients with sensitizing epidermal growth factor receptor (EGFR) mutation, anaplastic lymphoma kinase (ALK) fusion, and c-ros oncogene 1 (ROS1) fusion are excluded. All patients with non-squamous histology must have been tested locally for EGFR, ALK, and ROS1 status. Use of an FDA-approved or local Health Authority approved test is strongly encouraged, or a central laboratory test can be used if a local laboratory test is not available.
    c. For Cohort 9, patients with squamous cell or undifferentiated or other histological type GC or diagnosed with G/GEJ adenocarcinoma with positive HER2 expression. All G/GEJ adenocarcinoma patients must have been tested locally for HER2 status. If local HER2 testing results are not available, a tumor tissue sample may be submitted to the designated central laboratory for HER2 testing.
4. Prior therapy with an anti-PD-1, anti-PD-L1, anti-TIGIT or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways (anti-PD(L)1 exception for Cohort 5).
5. Active leptomeningeal disease or uncontrolled brain metastasis.
    - Patients with equivocal findings or with confirmed brain metastases are eligible if they are asymptomatic and radiologically stable without need for corticosteroids for ≥ 4 weeks before the first dose of study drugs.
6. Palliative radiation treatment within 4 weeks of first dose.

    Note: If palliative radiation treatment is ≥ 4 weeks before first dose but all target lesions were treated with radiotherapy and there was no progression afterwards, the patient is not eligible.
7. For Cohort 6 and 7, patients with any of the following:

- Unintentional weight loss ≥ 5% within 1 month before the first dose
- CTCAE ≥ Grade 2 anorexia within 7 days before the first dose
- Nutritional Risk Index (NRI) < 83.5 (Appendix 12) per investigator's choice.

For Cohort 9, patients with any of the following:

- Unintentional weight loss ≥ 20% within 2 months before randomization
- CTCAE ≥ Grade 2 anorexia within 7 days before randomization.

8. Patients with evidence of fistula (either esophageal/bronchial or esophageal/aorta).
9. Evidence of complete esophageal obstruction not amenable to treatment.
10. Uncontrollable pleural effusion, pericardial effusion, or ascites requiring frequent drainage or medical intervention (clinically significant recurrence requiring an additional intervention within 2 weeks of intervention).
11. Active autoimmune diseases or history of autoimmune diseases that may relapse, with the following exceptions:
    - Controlled type 1 diabetes
    - Hypothyroidism (provided it is managed with hormone-replacement therapy only)
    - Controlled celiac disease
    - Skin diseases not requiring systemic treatment (eg, vitiligo, psoriasis, or alopecia)
    - Any other disease that is not expected to recur in the absence of external triggering factors
12. Any active malignancy ≤ 2 years before the first dose of study drugs, except for the specific cancer under investigation and any locally recurring cancer that has been treated with curative intent (eg, resected basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix or breast).
13. Any condition that required systemic treatment with either corticosteroids (> 10 mg daily of prednisone or equivalent) or other immunosuppressive medication ≤ 14 days before the first dose of study drugs, with the following exceptions:
    - Adrenal replacement steroid (dose ≤ 10 mg daily of prednisone or equivalent)
    - Topical, ocular, intra-articular, intranasal, or inhalational corticosteroid with minimal systemic absorption
    - 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)
14. History of interstitial lung disease, noninfectious pneumonitis, or uncontrolled lung diseases, including but not limited to pulmonary fibrosis, acute lung diseases, etc.

15. 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 drugs.
16. Severe chronic or active infections (including but not limited to tuberculosis infection) requiring systemic treatment ≤ 14 days before the first dose of study drugs.
17. Known history of HIV infection.
18. Known history of or active HBV or HCV infection except for the following:
    - Patients with untreated chronic HBV or chronic HBV carriers whose HBV DNA is ≥ 500 IU/mL or patients with positive HCV ribonucleic acid should be excluded. Inactive HBsAg carriers, treated and stable hepatitis B patients (HBV DNA < 500 IU/mL), and cured hepatitis C patients (as defined by a positive HCV antibody test and negative HCV ribonucleic acid test) may be enrolled.
19. Major surgical procedure, open biopsy, or significant traumatic injury ≤ 4 weeks before the first dose of study drugs or anticipation of need for major surgical procedure during the course of the study.
20. Prior immunodeficiency, allogeneic stem cell transplantation, or organ transplantation.
21. Known dihydropyrimidine dehydrogenase (DPD) deficiency for patients receiving 5-fluorouracil (5-FU) or capecitabine.
22. Any of the following cardiovascular criteria:
    a. Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living, ≤ 28 days before the first dose of study drugs
    b. Symptomatic pulmonary embolism or other clinically significant episode of thromboembolic disease ≤ 28 days before the first dose of study drugs
    c. History of acute myocardial infarction ≤ 6 months before the first dose of study drugs
    d. History of heart failure meeting New York Heart Association Classification III or IV (Appendix 6) ≤ 6 months before the first dose of study drugs
    e. Ventricular arrhythmia ≥ Grade 2 in severity ≤ 6 months before the first dose of study drugs
    f. Cerebrovascular accident ≤ 6 months before the first dose of study drugs
    g. Uncontrolled hypertension: systolic pressure ≥ 160 mmHg or diastolic pressure ≥ 100 mmHg despite anti-hypertension medications ≤ 28 days before the first dose of study drugs
23. History of severe hypersensitivity reactions to other monoclonal antibodies.
24. Chemotherapy, immunotherapy (eg, interleukin, interferon, or thymosin), or investigational therapy ≤ 14 days or 5 half-lives (whichever is shorter) before the first dose of study drugs.
    - Received any herbal medicine or Chinese patent medicines used to control cancer ≤ 14 days before the first dose of study drugs
25. Toxicities from prior therapy that have not recovered to baseline, ≤ Grade 1, or stabilized, except for AEs not considered a likely safety risk (eg, alopecia, neuropathy, and specific laboratory abnormalities).

26. Live vaccine ≤ 4 weeks before the first dose of study drugs.
    - Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed.
    - A non-live COVID-19 vaccine may be administered if recommended per local practice. The vaccine administered cannot be a live or live-attenuated vaccine. For patients to accept COVID-19 vaccine during the course of the study, it is necessary to consult medical monitor.
27. Medical condition or alcohol or drug abuse or dependence that, in the investigator's opinion, will be unfavorable for the administration of study drugs or will affect the explanation of drug toxicity or AEs or are likely to result in insufficient compliance with study procedures.
28. Concurrent participation in another therapeutic clinical study.
29. Any condition that requires treatment with prohibited or restricted concomitant medication or therapy as described in Section 6.
30. Patients not suitable for chemotherapy or immunotherapy, eg, serious imAEs in previous immunotherapy if any, per investigator's discretion for cohorts in Phase 1b.
31. Patients receiving paclitaxel must not have peripheral neuropathy ≥ Grade 2 at baseline.

5. STUDY TREATMENT

5.1. Formulation, Packaging, and Handling

5.1.1. Ociperlimab

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

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

The study drug must be kept at the temperature 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 injection 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.

5.1.3. Chemotherapy Agents

Management (ie, handling, storage, administration, and disposal) of pemetrexed, paclitaxel, nab-paclitaxel, carboplatin, cisplatin, etoposide, 5-FU, oxaliplatin, and capecitabine will be in accordance with relevant local guidelines, prescribing information/summary of product characteristics. The administered dose could be adjusted within ± 5% of the calculated dose at the investigator's discretion. The starting dose of cisplatin can be modified according to local practice with the expectation that the dose remains within the range of 60 to 80 mg/m^2 per cycle. After the starting dose of cisplatin is chosen, all the cycles should follow the same dose level unless necessary modification is needed as specified in Section 5.4.3.

5.2. Dosage, Administration, and Compliance

Treatment with study drugs on Day 1 of Cycle 1 must begin within 3 business days after the patient is enrolled (Section 7.2). Treatment modifications (eg, dose delay/holds) will be based

on specific laboratory and AE criteria, as described in Section 5.4. Guidelines for study treatment modification, delay, or discontinuation as well as management of imAEs or infusion-related reactions are provided in Section 9.7 and Appendix 8.

Accurate records of all study drugs 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.

5.2.1. Ociperlimab and Tislelizumab Combination Dose Escalation

Planned dose level(s) and dosing frequency during dose escalation for ociperlimab and tislelizumab are presented in Table 3.

Table 3: Planned Dose Levels for Ociperlimab and Tislelizumab for Dose Escalation

Study drugs	Dose	Frequency of administration	Route of administration	Duration of treatment
Ociperlimab	50 mg 150 mg 450 mg 900 mg (Lower, intermediate, and/or higher dose levels may be explored.)	Cycle 1 Day 1, Cycle 2 Day 1, then once every 21 days	Intravenous	Refer to Section 7.5.1
Tislelizumab	200 mg	Cycle 1 Day 8, Cycle 2 Day 1, then once every 21 days	Intravenous	Until disease progression, unacceptable toxicity, or voluntary withdrawal of consent per patient decision

Cycle 1 only will be 28 days in length. Thereafter starting with Cycle 2, each cycle will be 21 days in length (ie, Q3W). In the first cycle, ociperlimab will be administered on Day 1, and tislelizumab will be administered on Day 8 (+2 days). Following completion of Cycle 1, patients will then receive tislelizumab on Day 1 of each subsequent 21-day cycle (ie, Q3W) followed by the administration of ociperlimab. Other dosing regimens of ociperlimab may be explored based on safety, PK, and antitumor activities observed in dose levels that are completed. However, the dosing regimen of tislelizumab will remain fixed as shown in Table 3. Ociperlimab and tislelizumab must be administered by intravenous infusion through an intravenous line containing a sterile, non-pyrogenic, low-protein-binding 0.2- or 0.22-micron in-line or add-on filter.

Table 4 outlines the infusion as well as post-infusion monitoring times for ociperlimab and tislelizumab. Monitoring must occur in an area where emergency medical equipment and appropriately trained staff are available. Duration of infusion and post-infusion monitoring can be decreased if ociperlimab and tislelizumab infusion is well tolerated, as outlined in Table 4. Ociperlimab and tislelizumab must not be concurrently infused with any other drug.

Table 4: Administration of Ociperlimab and Tislelizumab and Monitoring Time for Dose Escalation

Cycle	Ociperlimab and Tislelizumab combination
C1D1	Ociperlimab infusion over 60 (± 5) minutes Patient monitoring for ≥ 120 minutes
C1D8	Tislelizumab infusion over 60 (± 5) minutes Patient monitoring for ≥ 120 minutes
C2D1	Tislelizumab infusion over 60 (± 5) minutes followed by Ociperlimab infusion over 60 (± 5) minutes Patient monitoring for ≥ 120 minutes
C3D1	Tislelizumab infusion over 30 (± 5) minutes followed by Ociperlimab infusion over 60 (± 5) minutes Patient monitoring for ≥ 120 minutes
C4D1 onwards	Tislelizumab infusion over 30 (± 5) minutes followed by Ociperlimab infusion over 30 (± 5) minutes Patient monitoring for ≥ 30 minutes

Abbreviations: C, cycle; D, day.
Note: The infusion rate may be decreased, or the infusion may be stopped in the event of an infusion-related reaction. See Section 9.7.1 for details.

5.2.2. Dose Verification in China

Planned dose level(s) and dosing frequency during dose verification in China for ociperlimab and tislelizumab are presented in Table 5:

Table 5: Planned Dose Levels and Dosing Frequency for Ociperlimab as Monotherapy and in Combination With Tislelizumab for Dose Verification

Study drugs	Dose	Frequency of administration	Route of administration	Duration of treatment
Ociperlimab	900 mg 450 mg (if appropriate)	D1 of each cycle, every 21 days	Intravenous	Refer to Section 7.5.1
Tislelizumab	200 mg	D1 of each cycle, every 21 days	Intravenous	Until disease progression, unacceptable toxicity, or voluntary withdrawal of consent per patient decision

Abbreviations: C, cycle; D, day.

A 21-day treatment cycle will be used for ociperlimab alone and in combination with tislelizumab. The administration of ociperlimab will occur in ociperlimab 900 mg monotherapy (Cohort 1A) and ociperlimab 900 mg in combined with tislelizumab (Cohort 1B).

Ociperlimab dose of 450 mg may be explored in both monotherapy and combination cohort (cohort 2A and 2B) if excessive DLT observed in 900 mg dose level. For the combination cohorts (Cohort 1B and 2B), the patients will receive tislelizumab followed by the administration of ociperlimab on Day 1 of each 21-day cycle (ie, Q3W). Ociperlimab and tislelizumab must be administered by intravenous infusion through an intravenous line containing a sterile, non-pyrogenic, low-protein-binding 0.2- or 0.22-micron in-line or add-on filter.

Table 6 outlines the infusion as well as post-infusion monitoring times for ociperlimab as monotherapy and in combination with tislelizumab. Monitoring must occur in an area where emergency medical equipment and appropriately trained staff are available. Duration of infusion and post-infusion monitoring can be decreased if ociperlimab and tislelizumab infusion is well tolerated, as outlined in Table 6. Ociperlimab and tislelizumab must not be concurrently infused with any other drug.

Table 6: Administration of Ociperlimab as Monotherapy or in Combination With Tislelizumab

Cycle	Ociperlimab and Tislelizumab combination	Ociperlimab
C1D1	Tislelizumab infusion over 60 (± 5) minutes Patient monitoring for ≥ 60 minutes followed by ociperlimab infusion over 60 (± 5) minutes Patient monitoring for ≥ 60 minutes	Ociperlimab infusion over 60 (± 5) minutes Patient monitoring for ≥ 60 minutes
C2D1	Tislelizumab infusion over 30 (± 5) minutes Patient monitoring for ≥ 60 minutes followed by ociperlimab infusion over 30 (± 5) minutes Patient monitoring for ≥ 60 minutes	Ociperlimab infusion over 30 (± 5) minutes Patient monitoring for ≥ 60 minutes
C3D1 onwards	Tislelizumab infusion over 30 (± 5) minutes Patient monitoring for ≥30 minutes followed by ociperlimab infusion over 30 (± 5) minutes Patient monitoring for ≥ 30 minutes	Ociperlimab infusion over 30 (± 5) minutes Patient monitoring for ≥ 30 minutes

Abbreviations: C, cycle; D, day.

5.2.3. Ociperlimab and Tislelizumab Combination With or Without Chemotherapy for Phase 1b

The treatment regimen for Phase 1b is listed as follow:

- Cohort 1 (squamous NSCLC): ociperlimab 900 mg (D1) + tislelizumab 200 mg (D1) + carboplatin AUC 5 or 6 (D1) + paclitaxel 200 or 175 mg/m^2 (D1) or nab-paclitaxel 100 mg/m^2 (D1, D8, D15) Q3W for 4 to 6 cycles followed by ociperlimab 900 mg (D1) + tislelizumab 200 mg (D1) Q3W
- Cohort 2 (non-squamous NSCLC): ociperlimab 900 mg (D1) + tislelizumab 200 mg (D1) + cisplatin 75 mg/m^2 (modification within 60 to 80 mg/m^2 is permitted) or carboplatin AUC 5 (D1) + pemetrexed 500 mg/m^2 (D1) IV Q3W for 4 to 6 cycles followed by

ociperlimab 900 mg (D1) + tislelizumab 200 mg (D1) + pemetrexed 500 mg/m^2 (D1) Q3W

- Cohort 3 (NSCLC with PD-L1 positive, TC ≥ 1%): ociperlimab 900 mg (D1) + tislelizumab 200 mg (D1) Q3W
- Cohort 4 (extensive-stage SCLC): ociperlimab 900 mg (D1) + tislelizumab 200 mg (D1) + cisplatin 75 mg/m^2 (modification within 60 to 80 mg/m^2 is permitted) or carboplatin AUC 5 (D1) + etoposide 100 mg/m^2 (D1, D2, D3) Q3W for 4 cycles followed by ociperlimab 900 mg (D1) + tislelizumab 200 mg (D1) Q3W
- Cohort 5 (CPI-experienced NSCLC): ociperlimab 900 mg (D1) + tislelizumab 200 mg (D1) Q3W
- Cohort 6 (ESCC): ociperlimab 900 mg (D1) + tislelizumab 200 mg (D1) + cisplatin 75 mg/m^2 (D1, modification within 60 to 80 mg/m^2 is permitted) + 5-FU 750 to 800 mg/m^2 (D1 to D5) or paclitaxel 200 or 175 mg/m^2 (D1) Q3W for 6 cycles followed by ociperlimab 900 mg (D1) + tislelizumab 200 mg (D1) Q3W
- Cohort 7 (EAC): ociperlimab 900 mg (D1) + tislelizumab 200 mg (D1) + cisplatin 75 mg/m^2 (D1, modification within 60 to 80 mg/m^2 is permitted) + 5-FU 750 to 800 mg/m^2 (D1 to D5) or paclitaxel 200 or 175 mg/m^2 (D1) Q3W for 6 cycles followed by ociperlimab 900 mg (D1) + tislelizumab 200 mg (D1) Q3W
- Cohort 8 (HNSCC with PD-L1 positive, vCPS ≥ 1%): ociperlimab 900 mg (D1) + tislelizumab 200 mg (D1) Q3W
- Cohort 9 (G/GEJ adenocarcinoma): ociperlimab 900 mg (D1) + tislelizumab 200 mg (D1) + [oxaliplatin 130 mg/m^2 (D1) + capecitabine 1000 mg/m^2 twice daily (D1 to D14)] or [cisplatin 75 mg/m^2 (D1, modification within 60 to 80 mg/m^2 is permitted) + 5-FU 750 to 800 mg/m^2 (D1 to D5)] Q3W for 6 cycles followed by ociperlimab 900 mg (D1) + tislelizumab 200 mg (D1) + capecitabine 1000 mg/m^2 twice daily (D1 to D14) Q3W
- Cohort 10 (NSCLC with PD-L1 positive, TC ≥ 1%): ociperlimab 450 mg (D1) or 900 mg (D1) or 1800 mg (D1) + tislelizumab 200 mg (D1) Q3W

For Cohorts 1, 2, 4, 6, 7 and 9, the patients will receive cycles of chemotherapy (4 to 6 cycles for squamous and non-squamous NSCLC; 4 cycles for SCLC; up to 6 cycles for ESCC, EAC, G/GEJ adenocarcinoma) and treatment of ociperlimab plus tislelizumab until disease progression, intolerable toxicity, or withdrawal of consent. For Cohort 9, capecitabine as an optional maintenance therapy is for the oxaliplatin + capecitabine regimen only. For Cohorts 3, 5, 8, and 10, the patients will receive treatment of ociperlimab plus tislelizumab until disease progression, intolerable toxicity, or withdrawal of consent. Dosing schedules of study drugs are provided in Table 7.

For Cohorts 2 and 4, either cisplatin or carboplatin could be selected as initial chemotherapy per investigator's discretion in consideration of individual patient tolerability. For patients who are given cisplatin as an initial treatment and experience any intolerable toxicity assessed as related to cisplatin, the investigator can consider replacing cisplatin with carboplatin as subsequent treatment per investigator's discretion.

For each cycle of drug administration, ociperlimab and tislelizumab will be intravenously infused before chemo drugs. The sequence of chemo drug administration will be conducted in accordance with the relevant local guidance and /or clinical practice.

When the administration is delayed due to management of AEs (eg, infusion-related reaction), the administration of subsequent study drugs might be delayed to the second day of each cycle.

Chemotherapy drug administration should be monitored during infusion. If the site cannot monitor the whole drug administration within 1 day, the administration of chemotherapy drug may be delayed to the second day.

Table 7: Dose, Frequency of Administration, and Route of Administration for Each Study Drug

Study drug	Dose	Frequency of administration	Route of administration
tislelizumab	200 mg	D1 of each cycle	Intravenous
ociperlimab	900 mg (Cohorts 1 to 9) 450 mg (Arm A in Cohort 10) 900 mg (Arm B in Cohort 10) 1800 mg (Arm C in Cohort 10)	D1 of each cycle	Intravenous
paclitaxel	175 or 200 mg/m^2	D1 of each cycle	Intravenous
nab-paclitaxel	100 mg/m^2	D1, D8, and D15 of each cycle	Intravenous
carboplatin	AUC 5 or 6	D1 of each cycle	Intravenous
Cisplatin	75 mg/m^2 (modification within 60 to 80 mg/m^2 is permitted)	D1 of each cycle	Intravenous
Etoposide	100 mg/m^2	D1, D2, and D3 of each cycle	Intravenous
pemetrexed	500 mg/m^2	D1 of each cycle	Intravenous
5-FU	750 or 800 mg/m^2	D1, D2, D3, D4, and D5 of each cycle	Intravenous
Oxaliplatin	130 mg/m^2	D1 of each cycle	Intravenous
capecitabine	1000 mg/m^2	D1 to D14 of each cycle	Oral

Abbreviations: AUC, area under the plasma or serum concentration-time curve; D, Day.

Note: Treatment of paclitaxel or nab-paclitaxel, the choice of paclitaxel 200 or 175 mg/m^2 and carboplatin AUC 5 or 6 will be determined per prescribing information and per local practice according to the treating physician's clinical judgement.

Table 8 outlines the infusion as well as post-infusion monitoring times for ociperlimab, tislelizumab and chemotherapy. Monitoring must occur in an area where emergency medical equipment and appropriately trained staff are available. Duration of infusion and post-infusion monitoring can be decreased if ociperlimab and tislelizumab infusion is well tolerated, as outlined in Table 8.

Table 8: Administration of Ociperlimab, Tislelizumab With or Without Chemotherapy and Monitoring Time for Dose Expansion

Cycle	Ociperlimab and Tislelizumab combination	Ociperlimab, Tislelizumab and chemotherapy combination
C1D1	Tislelizumab infusion over 60 (± 5) minutes Patient monitoring for ≥ 60 minutes followed by Ociperlimab infusion over 60 (± 5) minutes Patient monitoring for ≥ 60 minutes	Tislelizumab infusion over 60 (± 5) minutes Patient monitoring for ≥ 60 minutes followed by Ociperlimab infusion over 60 (± 5) minutes Patient monitoring for ≥ 60 minutes Chemotherapy (refer to labeling and local practice)
C2D1	Tislelizumab infusion over 30 (± 5) minutes Patient monitoring for ≥ 60 minutes followed by Ociperlimab infusion over 30 (± 5) minutes Patient monitoring for ≥ 60 minutes	Tislelizumab infusion over 30 (± 5) minutes Patient monitoring for ≥ 60 minutes followed by Ociperlimab infusion over 30 (± 5) minutes Patient monitoring for ≥ 60 minutes Chemotherapy (refer to labeling and local practice)
C3D1 onwards	Tislelizumab infusion over 30 (± 5) minutes Patient monitoring for ≥ 30 minutes followed by Ociperlimab infusion over 30 (± 5) minutes Patient monitoring for ≥ 30 minutes	Tislelizumab infusion over 30 (± 5) minutes Patient monitoring for ≥ 30 minutes followed by Ociperlimab infusion over 30 (± 5) minutes Patient monitoring for ≥ 30 minutes Chemotherapy (refer to labeling and local practice)

Abbreviations: C, cycle; D, day.
Note: The infusion rate may be decreased, or the infusion may be stopped in the event of an infusion-related reaction. See Section 9.7.1 for details.

5.2.3.1. Tislelizumab Plus Ociperlimab

Patients will receive tislelizumab 200 mg on Day 1 of each subsequent 21-day cycle (ie, Q3W) followed by the administration of ociperlimab RP2D in Cohort 3 (NSCLC with PD-L1 positive, TC ≥ 1%), Cohort 5 (CPI-experienced NSCLC), Cohort 8 (HNSCC with PD-L1 positive, vCPS ≥ 1%). Patients in Arm A, B, and C in Cohort 10 (NSCLC with PD-L1 positive, TC ≥ 1%) will receive tislelizumab 200 mg Q3W followed by the administration of ociperlimab 450 mg, 900 mg, or 180 mg, respectively. Ociperlimab and tislelizumab must be administered by intravenous infusion through an intravenous line containing a sterile, nonpyrogenic, low-protein-binding 0.2- or 0.22 micron in-line or add-on filter. Specific instructions for product preparation and administration are provided in the Pharmacy Manual.

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

The initial infusion (Cycle 1, Day 1) will be delivered over 60 minutes for each drug of ociperlimab and tislelizumab; if this is well tolerated, then the subsequent infusions may be administered over 30 minutes of each drug, which is the shortest period permissible for infusion. Ociperlimab and tislelizumab must not be concurrently administered with any other drug.

Guidelines for dose modification, treatment interruption, or discontinuation and for the management of imAE and infusion-related reactions are provided in detail in Section 9.7 and Appendix 8.

5.2.3.2. Ociperlimab plus Tislelizumab Plus Chemotherapy

Patients will receive tislelizumab 200 mg on Day 1 of each subsequent 21-day cycle (Q3W) followed by the administration of ociperlimab RP2D and chemotherapy in Cohort 1 (squamous NSCLC), Cohort 2 (non-squamous NSCLC), Cohort 4 (extensive-stage SCLC). The administration and compliance of ociperlimab and tislelizumab refers to Section 5.2.3.1. The treatment regimen of each cohort is based on the disease cohort in Section 5.2.3. For the administration and compliance of chemotherapy, please refer to Section 5.2.3.2.1-5.2.3.2.9.

None of the chemotherapy drugs should be concurrently administered with any other drug (ie, intravenous chemotherapy). Each intravenous drug should be administered sequentially (Section 5.2.3). Tislelizumab will be the first drug administered followed by ociperlimab and chemotherapy. All chemotherapy agents' preparation, premedication, administration, infusion time, monitoring, and management of complications are to follow local prescription guideline and regulation.

Pre-infusion pretreatment: (1) Intravenous pretreatment for chemotherapy (eg, antiemetic) should be given in at least 30 minutes later after the completion of ociperlimab infusion (at least 2 hours later after the completion of first time ociperlimab infusion). (2) Oral pretreatment for chemotherapy could be given following local practice, without limitation of intravenous pretreatment.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.4.

5.2.3.2.1. Cisplatin

Cisplatin 75 mg/m^2 will be administered as an intravenous infusion over ≥ 2 hours on Day 1 of every 3 weeks for 6 cycles (4 to 6 cycles for patients with non-squamous NSCLC, 4 cycles for patients with extensive-stage SCLC). Cisplatin dose can be modified according to local practice with the expectation that the dose remains within the range of 60 to 80 mg/m^2 per cycle. All patients should receive adequate hydration (including pretreatment hydration) and diuretics. Additional premedications should be administered as per standard practice.

5.2.3.2.2. Carboplatin

Carboplatin AUC 5 or 6 will be administrated as an intravenous infusion on Day 1 of every 3 weeks for 4 cycles (4 to 6 cycles for patients with squamous and non-squamous NSCLC). Additional premedications should be administered as per standard practice.

The carboplatin dose will be calculated using the Calvert formula as follows:

Carboplatin dose (mg) = target AUC x ([CrCl (mL/min) + 25]

Creatinine clearance (CrCl) calculation is based on the Cockcroft-Gault formula) and should include the most recent serum creatinine and most recent weight.

NOTE: If calculation of the CrCl by the Cockcroft-Gault formula yields a result of > 125 mL/min, then a CrCl should be calculated by an alternative formula per institutional standards or capped at 125 mL/min. The dose of carboplatin may be capped per local standards.

5.2.3.2.3. Pemetrexed

Pemetrexed 500 mg/m^2 will be administered as an intravenous infusion over ≥ 10 minutes on Day 1 of every 3 weeks for 4 to 6 cycles in the induction stage and for continuous cycles in maintenance stage for patients with non-squamous NSCLC. 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.

5.2.3.2.4. Paclitaxel

Paclitaxel 175 or 200 mg/m^2 will be administered as an intravenous fusion over ≥ 3 hours on Day 1 of every 3 weeks for 4 to 6 cycles for patients with squamous NSCLC per local practice. All patients should be pre-medicated with oral or injectable steroids according to the manufacturer's prescribing information and/or standard practice. Additional pre-medications (eg, diphenhydramine, and H2 antagonists) should be administered as per local standard practice.

5.2.3.2.5. Nab-Paclitaxel

Nab-paclitaxel 100 mg/m^2 will be administered as an intravenous infusion over ≥ 30 minutes on Day 1, Day 8, and Day 15 of each cycle for 4 to 6 cycles for patients with squamous NSCLC. In addition, all patients should receive the appropriate pre-medications as per the local approved label. Additional pre-medications should be administered as per standard practice.

5.2.3.2.6. Etoposide

Etoposide 100 mg/m^2 will be administered as intravenous infusion over ≥ 30 minutes on Day 1 to Day 3 of every 3 weeks for 4 cycles for patients with extensive-stage SCLC. Extravasation of infusion should be avoided. Additional pre-medications should be administered as per standard practice.

5.2.3.2.7. 5-fluorouracil

5-FU 750 to 800 mg/m^2 will be administered as continuous intravenous infusion over ≥ 24 hours on Day 1 to Day 5 of every 3 weeks. The actual infusion time of 5-FU should be recorded, and a total infusion time of 120+/- 3 hours is acceptable.

5.2.3.2.8. Oxaliplatin

Oxaliplatin 130 mg/m2 will be administered as intravenous infusion over ≥ 2 hours on Day 1 of every 3 weeks. It may be substituted in place of cisplatin, according to site or investigator preference or standard practice as determined before enrollment (except in China, Taiwan, Japan, and countries where oxaliplatin substitution is not permitted).

5.2.3.2.9. Capecitabine

Capecitabine will be self-administered orally twice daily, from the morning of Day 1 to the evening of Day 14 or from the evening of Day 1 to the morning of Day 15 of each 21-day cycle at the recommended dose of 1000 mg/m2 twice daily. Alternate dose and dosing schedules are allowed according to local and institutional guidelines. An adequate amount of supply of capecitabine will be dispensed to patients on Day 1 of each new cycle (Q3W). Capecitabine should be taken with water, within 30 minutes after a meal. If a dose of capecitabine is missed, the patient should take the next dose as scheduled. A double dose of capecitabine should not be administered to make up for missed individual doses.

5.3. Incorrect Administration or Overdose

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

AEs associated with an incorrect administration or overdose of study drugs will be recorded on the AE eCRF. Any SAEs associated with an incorrect administration or overdose must be reported within 24 hours of awareness via the SAE reporting process as described in Section 9.6.2. Supportive care measures should be administered as appropriate.

5.4. Dose Delay or Modification

Every effort should be made to administer the study drugs according to the planned dose and schedule. In the event of significant toxicities, dosing may be delayed and/or 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.

Guidelines for treatment modification or discontinuation as well as the management of infusion-related reactions are provided in detail in Section 9.7 and Appendix 8.

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

- ≤ Grade 2: Maintain dose level

- Grade 3: Omit dose until resolved to ≤ Grade 1 or baseline except for alopecia or AEs that, in the opinion of the investigator, are not considered a safety risk for patient
- Grade 4: Permanent discontinuation from study. Exceptions may be considered following consultation with the medical monitor.

5.4.1. Dose Interruption or Delay for Ociperlimab and Tislelizumab

In Cycle 1 of Phase 1 dose-escalation study, if tislelizumab is delayed beyond Cycle 1 Day 8 (+ 2 days), tislelizumab will not be administered in Cycle 1 but treatment may resume in subsequent cycles as outlined in Section 5.4.2.

Except for Cycle 1 of the dose-escalation stage of the study, if a dose delay is required, both study drugs are to be delayed (ie, ociperlimab and tislelizumab must both be delayed and if applicable re-started at the same time). 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 worsening of hematologic or biochemical parameters, the frequency of relevant blood tests should be increased as clinically indicated.

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

If treatment-related AEs are persistent without any improvement for more than 12 weeks, permanent discontinuation of the study drug should be considered. If the patient recovers from the treatment-related AE after 12 weeks, re-initiation of study drug 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.

For the cohorts without combination with chemotherapy (Cohorts 3, 5, 8, and 10), if a dose is delayed for ociperlimab and tislelizumab for ≤ 10 days for a planned dosing cycle (eg, Cycle 3 Day 1), ociperlimab and tislelizumab should be administered (on the same day with chemotherapy, if applicable). If the delay is > 10 days, the patient should skip both ociperlimab and tislelizumab. Both ociperlimab and tislelizumab will be administered on Day 1 of the next planned cycle (eg, Cycle 4 Day 1).

For the cohorts with combination of chemotherapy (Cohorts 1, 2, 4, 6, 7, and 9): If chemotherapy and immune therapy are delayed together by an AE, both therapies will be re-initiated together when the AE has resolved and posed no safety risk to the patient. The next cycle will be 21 days after that to keep a 21-day window.

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

Two occurrences of dose delays because of treatment-related AEs will be permitted. In the event of a third occurrence of a dose delay due to toxicity, permanent discontinuation of study drug should be considered after consultation with the medical monitor.

5.4.2. Dose Modifications for Ociperlimab and Tislelizumab

There will be no dose reductions allowed for tislelizumab.

For Phase 1 only, if patients are receiving a dose level of ociperlimab that is determined to be beyond the MTD, the dose level of ociperlimab may be reduced following discussion and agreement with the medical monitor. Further, if a patient cannot be dosed with tislelizumab on Cycle 1 Day 8 (+2 days), the patient will not be considered DLT evaluable and will not be eligible to receive ociperlimab at the currently assigned dose level of ociperlimab. However, starting on Cycle 2 Day 1 and every 21 days thereafter, the patient will be eligible, assuming any AE that resulted in a treatment delay has resolved per Section 5.4, to receive the combination of tislelizumab and a lower dose level of ociperlimab that had previously been shown to be tolerable according to the criteria outlined in Section 3.1 and following discussion with the medical monitor.

5.4.3. Dose Modifications of Chemotherapy

Dose modifications for chemotherapy should be performed per prescribing information and per local practice according to the treating physician's clinical judgment. The starting dose of cisplatin can be modified according to local practice with the expectation that the dose remains within the range of 60 to 80 mg/m^2 per cycle. After the starting dose of cisplatin is chosen, all the cycles should follow the same dose level unless necessary modification is needed as specified below.

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). The dose should not be modified for any body weight change of less than 10%.

Study drug related toxicities must be resolved to baseline or Grade 0 and 1 before administering the next dose, except for alopecia, Grade 2 fatigue, or AEs that, in the opinion of the investigator, are not considered a safety risk. A maximum of 2 dose reductions is permitted for each chemotherapeutic agent. 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 dose-expansion stage (Phase 1b) in this study. If additional reductions are required, that chemotherapeutic agent must be discontinued. Chemotherapy treatment may be delayed up to 21 days, if the reason for the delay is toxicity/adverse event. All subsequent chemotherapy doses must be rescheduled according to the last chemotherapy dose administration date.

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:
  - Carboplatin should not be administered to patients whose creatinine clearance is < 45 mL/min.
  - Nephrotoxicity is common with cisplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside antibiotics.

  - Pemetrexed should not be administered to patients whose creatinine clearance is < 45 mL/min.

- Ototoxicity and sensory neural damage should be assessed before each cycle.
- For toxicities not listed above, dose modifications are permitted per local standards.

Guidance regarding dose modifications for certain toxicities is presented in detail in Appendix 11. These serve as guidelines and do not replace investigator judgment and applicable local label recommendations if more stringent.

5.4.4. Criteria for Discontinuing Chemotherapy Regimens

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

- Any Grade 4 peripheral neuropathy
- Persistent Grade 3 paresthesia
- Grade 3 or 4 drug-related thrombocytopenia associated with clinically significant bleeding
- Any drug-related liver function test abnormality value that meets any of the following criteria requires discontinuation:
  - AST or ALT > 5 to 10 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 (or 1 prior reduction for carboplatin) for the same drug-related AE requires discontinuation of the drug(s).
- Any Grade 3 or 4 drug-related hypersensitivity reaction or infusion reaction requires discontinuation of the drug(s) assessed to be causing the reaction. The drug assessed as not related to the hypersensitivity reaction or infusion reaction may be continued.
- Any Grade 4 AE that the investigator considers related to study drug and inappropriate to be managed by dose reduction(s) requires discontinuation of drug(s). The drug not assessed to be related to the event may be continued.
- If any 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.

6. PRIOR AND CONCOMITANT THERAPY

6.1. Prior Therapy

The exclusion criteria (Section 4.2) specify that patients should not have received prior therapies with chemotherapy, immunotherapy (eg, interleukin, interferon, or thymosin), or investigational therapy ≤ 14 days or 5 half-lives (whichever is shorter) before the first dose of study drugs. Patients should not have received any herbal medicine or Chinese patent medicines used to control cancer ≤ 14 days before the first dose of study drugs.

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.

All concomitant medication will be recorded on the eCRF including all prescription, over-the-counter, herbal supplements, and intravenous medications and fluids. All concomitant medication received within 28 days before the first dose of study treatment and 30 days after the last infusion or dose of study treatment should be recorded. If changes (dose, stop, or start) in concomitant medication occur during the study, documentation of drug dosage, frequency, route, date, and reason for use will be recorded on the eCRF.

All concomitant medications, including all prescription and over-the-counter drugs, supplements, and intravenous medications and fluids, taken by or administered to the patient within 28 days before the first dose of study drug(s) and 30 days after the last dose of study drug(s) will be recorded.

Bisphosphonates and RANKL inhibitors are allowed for bone metastases if initiated before enrollment and at a stable dose. Bisphosphonates are permitted during the study for a non-malignant indication. Use of potentially hepatotoxic drugs in patients with impaired hepatic function is allowed but should be carefully monitored.

6.2.1. Systemic Corticosteroids

Systemic corticosteroids administered for the control of imAEs must be tapered gradually (Appendix 8) and must be administered at non-immunosuppressive doses (≤ 10 mg/day of prednisone or equivalent) before the next tislelizumab dose. The short-term use of steroids as prophylactic treatments (eg, patients with contrast allergies to diagnostic imaging contrast dyes) is permitted.

6.2.2. Hepatitis B Treatment

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

6.2.3. Radiation Therapy

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

- Repeat imaging demonstrates no new sites of bone metastases
- The lesion being considered for palliative radiation is not a target lesion for RECIST v1.1
- The case is discussed with the medical monitor and he/she agrees that the conditions required to receive palliative radiation are met

During the maintenance treatment period, prophylactic cranial irradiation (PCI) is permitted for ES-SCLC patients per local standard of care. Patients who achieve CR or PR after cycle 4 may be offered PCI at the investigator's discretion. Imaging of the brain must occur before PCI. Patients selected to receive PCI may receive up to 25 Gy in 10 fractions (or the biologic equivalent), as tolerated by the patient. If given, PCI must begin within 6 weeks (preferably within 2 to 4 weeks) after the last dose of study medication in Cycle 4. Study medication may continue during PCI; However, if it is necessary to suspend study treatment, dosing must be restarted no later than 2 weeks after completion of PCI. Steroids can be administered, as required, during and after PCI.

Additionally, palliative radiation or other focally ablative therapy for other nontarget sites of the disease is permitted if clinically indicated per the investigator's discretion and after consultation with the medical monitor. Whenever possible, these patients should have a tumor assessment of the lesion(s) before receiving the radiation therapy to rule out progression of disease.

6.3. Prohibited Concomitant Medications/Procedures

The following medications are prohibited:

- Any concurrent anticancer therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents including Chinese [or other Country] herbal medicine and Chinese [or other Country] patent medicines for the treatment of cancer [regardless of cancer type]) ≤ 14 days (or ≤ 5 half-lives, if applicable, whichever is shorter) before the first dose of study drugs and during the study.
- Live vaccines within 28 days before the first dose of study drugs and 60 days following the last dose of study drugs.
- Immunosuppressive agents (except to treat a drug-related AE).
- Systemic corticosteroids > 10 mg daily (prednisone or equivalent), except to treat or control a drug-related AE (per protocol) or for short-term use as prophylactic treatment. For treating AEs that are not related to study treatment, consultation with the medical monitor or designee is required before the administration of systemic corticosteroids > 10 mg daily.
- Alcohol abuse and other addictive drugs throughout the study.
- Herbal remedies with immune-stimulating properties (eg, mistletoe extract) or that are known to potentially interfere with liver or other major organ functions (eg, hypericin) ≤ 14 days (or ≤ 5 half-lives, if applicable, whichever is shorter) before the first dose of

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

- Radiation therapy, except for palliative radiation therapy described in Section 6.1.
- The investigator must adhere to the contraindications and precautions found in the prescribing information for each chemotherapy agent.
- Non-steroidal anti-inflammatory drugs (eg, aspirin, ibuprofen, diclofenac, celecoxib, naproxen, indomethacin, piroxicam, etc) are prohibited ≥ 5 days before and 2 days after pemetrexed therapy.

  If concomitant administration of a non-steroidal anti-inflammatory drug is necessary, patients should be monitored closely for toxicity, especially myelosuppression, renal, and gastrointestinal toxicity.

6.4. 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 have an effect on drug-metabolizing enzymes or transporters.

Refer to drug-drug interaction section in manufacturer's prescribing information for the influence of the respective chemotherapy agents on drug metabolizing enzymes or transporters. For example, the metabolism of paclitaxel is catalyzed by cytochrome P-450(CYP)2C8 and CYP3A4. Caution should be exercised when administering paclitaxel or nab-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 are co-administered with nab-paclitaxel, the toxicities may be exacerbated, and the investigator should closely monitor for them. Please refer to a list of strong CYP2C8 and CYP3A4 inhibitors (Flockhart 2007; FDA Drug Development and Drug Interactions 2023) and the prescribing information of paclitaxel and nab-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 non-steroidal anti-inflammatory drugs to patients whose creatinine clearance is < 80 mL/min.

The major route of elimination of carboplatin is renal excretion. The renal effects of nephrotoxic compounds may be potentiated by carboplatin.

While pharmacokinetic data are not available to assess the effect of 5-FU administration on warfarin pharmacokinetics, the elevation of coagulation times that occurs with the 5-FU prodrug

capecitabine is accompanied by an increase in warfarin concentrations. Thus, the interaction may be due to inhibition of cytochrome P450 2C9 by 5-FU or its metabolites.

Formal drug-drug interaction studies with phenytoin have not been conducted, but the mechanism of interaction is presumed to be inhibition of the CYP2C9 isoenzyme by capecitabine and/or its metabolites. Other than warfarin, no formal drug-drug interaction studies between capecitabine and other CYP2C9 substrates have been conducted. Care should be exercised when capecitabine is co-administered with CYP2C9 substrates.

7. STUDY PERIODS, VISITS, OR PROCEDURES

7.1. Screening Period

Screening evaluations will be performed ≤ 28 days before the first dose of ociperlimab for Phase 1 and ≤ 28 days before the first dose of tislelizumab for Phase 1b. A patient who agrees to participate in this study will sign the ICF before undergoing any screening assessment. Refer to Section 8.1 for instructions regarding screening assessments.

7.1.1. Informed Consent and Screening Log

Voluntary, written informed consent for participation in the study must be obtained before performing any study-specific procedures. Results of standard-of-care tests or examinations performed before informed consent has been obtained and ≤ 28 days before the first dose of study drug(s) may be used for screening assessments rather than repeating such tests unless otherwise indicated. ICFs for enrolled patients and for patients who are screened but not enrolled will be maintained at the study site.

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.

For RP2D confirmation in Chinese patients and Phase 1b, after obtaining informed consent, study site personnel will access the Interactive Response Technology (IRT) system to assign a unique number to a potential study patient.

7.2. Enrollment

All screening results and relevant medical history must be available before eligibility can be determined. Prior to enrollment, the investigator is responsible for assessing and confirming that each patient meets all inclusion eligibility criteria for this study and that none of the exclusion criteria apply. All results from the screening procedures and relevant medical history must be available and reviewed by the investigator before eligibility can be determined. No eligibility waivers will be granted.

Sponsor verification of patient eligibility will be managed by way of source data verification in accordance with International Council for Harmonisation E6 guideline.

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

For Cohort 10, the site personnel will access the IRT system to randomize the patient and assign study drugs by permuted block stratified randomization.

7.3. Treatment Period

Patients enrolled will be treated as described in Section 5.2.

Patients may continue to receive study drugs beyond the initial investigator-assessed PD, as defined by RECIST v1.1 provided that the patient has investigator-assessed clinical benefit and is tolerating study drugs. Refer to Section 7.5 and Section 8.5 for additional considerations regarding treatment continuation and withdrawal.

7.4. Follow-up Periods

7.4.1. End-of-Treatment/+30-day Safety Follow-up Visit

Patients who discontinue study treatment for any reason will be asked to return to the clinic for the EOT Visit, which is required to be conducted within 7 days when the EOT decision is made unless otherwise specified or before the initiation of a new anticancer treatment, whichever occurs first. An on-site Safety Follow-up Visit at 30 days (± 7 days) after the last dose of study drugs (including both chemotherapy and immunotherapy, whichever is late) is required. If the time window of this Safety Follow-up Visit and EOT Visit is overlapped, the tests conducted at the EOT Visit can be used for Safety Follow-up Visit and need not be repeated. In addition, 2 safety follow-up by telephone with patients should be conducted to assess imAEs and concomitant medications (if appropriate, such as being associated with an imAE or is a new anticancer therapy) at 60 days (± 14 days) and 90 days (± 14 days) after the last dose of study drugs regardless of whether patients started a new subsequent anticancer therapy. If patients report a suspected imAE at a Safety Follow-up Visit, the investigator should arrange an unscheduled visit if further assessment is indicated.

All AEs, including SAEs, will be collected as described in Section 9.6.

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

7.4.2. Efficacy Follow-up Period

Patients who discontinue study drugs for reasons other than PD (eg, toxicity) will continue to undergo tumor assessments following the original tumor assessment schedule until the patient experiences PD, withdraws consent, dies, or starts subsequent anticancer therapy, or for any other reason listed in Section 7.5.2, whichever occurs first.

If patients refuse to return for these visits or are unable to do so, every effort should be made to contact the patients by telephone to determine their disease status.

7.4.3. Survival Follow-up (Phase 1b)

Patients will be followed for survival and to obtain information on subsequent anticancer therapy information after discontinuation of study treatment via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (± 14 days) after the 30-day Safety Follow-up Visit or as directed by the sponsor until death, withdrawal of consent, loss to follow-up, or end of study.

7.4.4. Lost to Follow-up

If attempts to contact the patient by telephone are unsuccessful, additional attempts should be made to obtain protocol-required follow-up information via all possible alternative methods. It may be possible to obtain the information from other contacts, such as referring physicians or relatives. Each attempt, date, and method of contact should be documented in the patient's source documents. If a patient cannot be contacted despite all attempts, the patient will be considered lost to follow-up, and death information should be obtained through a public record search if local agencies permit.

7.5. Discontinuation From Study Treatment or From the Study

7.5.1. Patient Discontinuation From Study Treatment

Patients have the right to discontinue study treatment at any time for any reason. In addition, the investigator has the right to discontinue a patient from study treatment at any time. Patients who discontinue study treatment for reasons other than PD should be followed for assessments of preliminary anticancer activity (Section 8.5), safety (Section 8.2), and survival (Section 7.4.3), if possible.

Benefits of continuation of study treatment beyond 2 years after start of treatment should be evaluated and discussed with medical monitor (Herbst et al 2020; Kottschade 2019).

The primary reason for discontinuation from study treatment should be documented on the appropriate eCRF. Patients will discontinue study treatment for reasons including, but not limited to, the following:

- Progressive disease
- Adverse events
- Patient decision
- Pregnancy
- Any medical condition that the investigator or sponsor determines may jeopardize the patient's safety if he or she were to continue the study treatment
- Use of any concurrent anticancer therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents including Chinese [or other Country] herbal medicine and Chinese [or other Country] patent medicines for the treatment of cancer [regardless of cancer type])
- Patient noncompliance

Patients who continue treatment after disease progression will discontinue study treatment after 2nd disease progression and/or no response to the continuing treatment after the first PD based on the investigator's assessment following consultation with the medical monitor or designee.

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

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

- Patient withdrawal of consent
- Death
- Lost to follow-up
- Completion of all study assessments

7.6. 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 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 reflected by unacceptable toxicity, such as treatment-related death or unexpected treatment-related Grade 4 toxicity, which is observed with the concurrence of both the SMC and sponsor.
- Overall patient enrollment is unsatisfactory

The sponsor will notify each investigator if a decision is made to terminate the study. Should this be necessary, prematurely discontinued patients must be seen for an EOT/Safety Follow-up Visit as described in Section 7.4.1.

The investigators may be informed of additional procedures to be followed to ensure that adequate consideration is given to the protection of the patients' interests. The investigator will be responsible for informing IRBs/IECs of the early termination of the study.

The sponsor has the right to close a cohort at any time. The related investigators will be notified of the decision in advance. In the cohort that is going to be closed, any patient who, in the opinion of the investigator, continues to benefit from tislelizumab/ociperlimab, will be offered the option to continue the study drug(s) in a company-sponsored clinical trial (if available in the patient's country) or patient supply treatment program until the study drug is commercially available in the country of the patient's residence.

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

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

8. STUDY ASSESSMENTS

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.

Where applicable, 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.

8.1. Screening Assessments

Screening evaluations will be performed ≤ 28 days before the first dose of study drugs (refer to Appendix 1 for details). Patients who agree to participate 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 the first dose of study drugs may be used for the purposes of screening rather than repeating the standard-of-care tests unless otherwise indicated.

Procedures conducted only during the Screening Visit are described in this section. For the description of other assessments that are conducted during screening as well as throughout the study, refer to Safety Assessments (Section 8.2), Tumor and Response Evaluations (Section 8.5), PK and ADA Assessments (Section 8.3) and Biomarkers (Section 8.4) sections.

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

8.1.1. Pulmonary Function Tests

Patients who are suspected of having or known to have serious/severe respiratory conditions, or exhibit significant respiratory symptoms unrelated to the underlying cancer, or with a history of thoracic radiotherapy will undergo pulmonary function testing that may include but is not limited to spirometry and assessment of diffusion capacity done during the screening period to assist the determination of suitability on the study. For test results indicative of significantly impaired pulmonary function, eg, resting pulse oximetry < 90% on room air and further desaturation upon exercise, forced expiratory volume in one second < 60% or carbon monoxide diffusing capacity (if performed) < 60% of age- and sex-adjusted predicted performance levels, the medical monitor needs to be consulted to confirm eligibility. Patients with low pulmonary function will not be advised for enrollment.

8.2. Safety Assessments

8.2.1. Vital Signs

Vital signs will include measurements of body temperature (˚C), pulse rate, and blood pressure (systolic and diastolic). Vital signs will be measured while the patient is in a seated position after resting for 10 minutes. When ociperlimab and tislelizumab are administered, vital signs are required to be measured at 3 timepoints (≤ 60 minutes before the infusion, during the infusion, and ≤ 30 minutes after end of infusion) during all visits.

8.2.2. Physical Examinations

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

At subsequent visits (and as clinically indicated), limited, symptom-directed physical examinations will be performed. New or worsened clinically significant abnormalities are to be recorded as AEs on the eCRF. Refer to Section 9.3 regarding AE definitions and reporting and follow-up requirements.

8.2.3. Eastern Cooperative Oncology Group Performance Status

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

8.2.4. 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.

An investigator may obtain safety laboratory results from the local laboratory as clinically indicated (eg, on the day of a patient's visit before results are available from the central laboratory for dose modifications or AE/SAE monitoring). Results from the central laboratory will serve as the official study laboratory result, where available. If required by local regulations, clinical laboratory evaluations performed by a local (instead of a central) laboratory are acceptable. For abnormal lab results which are Grade 3 or above AEs, a confirmatory test is necessary. Final assessment will base on the updated result.

If clinical chemistry, hematology, and coagulation at screening are not performed ≤ 7 days before study drug administration on Day 1 of Cycle 1, these tests should be repeated and reviewed before study drug administration. After Day 1 of Cycle 1, results are to be reviewed within 72 hours before study drug administration.

For central laboratory assessments, details regarding sample collection and shipment will be provided in a separate laboratory manual.

The following tests will also be conducted in this study at timepoints shown in Appendix 1.

- 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 ≤ 7 days

before the first dose of study drugs. Furthermore, a negative pregnancy test (by urine or blood) must be completed and recorded before administration of study drugs at each cycle. Pregnancy tests will also be performed at the EOT Visit and each Safety Follow-up Visit, until 120 days after last dose of ociperlimab and/or tislelizumab or 180 days after the last dose of chemotherapy (whichever comes later). A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.

- Thyroid function testing (ie, thyroid stimulating hormone, free triiodothyronine [T3], and free thyroxine [T4]). Total T3 can be tested as an alternative to free T3 and total T4 can be tested as an alternative to free T4.
- Hepatitis serology and viral load (refer to Section 8.2.7)

8.2.4.1. Cardiac Enzyme Monitoring

Although immune-mediated myocarditis is a rare complication of immune checkpoint inhibitors, serum creatine kinase and creatine kinase-muscle/brain 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 8 for guidelines for management of suspected immune-mediated myocarditis, respectively). Serum troponins may be substituted per local guidelines if used consistently throughout the study.

8.2.5. Electrocardiograms

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

All ECGs are to be obtained before other assessments scheduled at that same time (eg, vital sign measurements, blood draws, etc). 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.

At each timepoint (Appendix 1), 3 consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine the mean QTcF interval.

8.2.6. 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 9.6.

8.2.7. Hepatitis B and C Testing

Testing will be performed by a central laboratory and/or the local laboratory at screening (and as clinically indicated) and will include HBV/HCV serology (HBsAg, hepatitis B surface antibody [HBsAb], hepatitis B core antibody [HBcAb], and HCV antibody) and viral load assessment (HBV DNA and HCV ribonucleic acid). For patients with negative HBsAg or negative HCV antibody, HBV DNA or HCV RNA is optional based on clinical practice.

Testing at screening is mandatory for patients with HCC in Phase 1. In addition, HCC patients who have detectable HBV DNA or HCV ribonucleic acid at screening will perform the respective viral load test every 4 cycles. In patients without HCC, samples for hepatitis serology and viral load will be collected at screening and may be tested if patients have hepatic AEs (≥ Grade 3) during the study and as clinically indicated.

8.3. Pharmacokinetic Assessment and Antidrug Antibody Testing

Ociperlimab and tislelizumab may elicit an immune response. Patients with signs of any potential immune response will be closely monitored. Validated screening and confirmatory assays will be employed to detect ADAs at multiple timepoints throughout the study. In addition, blood samples will be collected for characterization of ociperlimab and tislelizumab PK. Serum samples will be assayed for ociperlimab and tislelizumab concentrations using validated immunoassays.

Blood sampling for PK and ADA sample collection for ociperlimab and tislelizumab will be collected at the timepoints specified in the Schedule of Assessments (Appendix 1).

PK and ADA assays of ociperlimab and tislelizumab with or without chemotherapy (depending on the allocated cohort) will be managed through a central laboratory. Refer to the laboratory manual for instructions regarding sample collection, handling, labeling, storage, and shipping of laboratory samples.

Timepoints of PK and ADA sample collection for ociperlimab and tislelizumab are provided in Schedule of Assessments for Phase 1 and Phase 1b (Appendix 1C, Appendix 1D, and Appendix 1E).

8.4. Biomarkers

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

Archival or fresh tumor samples will be collected for biomarker analysis. Tissue based biomarkers include but not limited to protein expression of PD-L1, TIGIT, CD226, CD155 and CD112, tumor mutation burden (TMB), MSI and gene mutations, EBV status, immune cell subpopulations, and GEP before, during, and/or after treatment. (Note: For sites in mainland China, tissues will be obtained to test the expression of PD-L1, TIGIT, CD226, CD155, CD112, TMB, MSI, gene mutations, EBV status, immune cell subpopulations, and GEP before, during, and/or after treatment).

- In Phase 1, if available, archived, FFPE tumor tissue sample (block or approximately 15 freshly cut unstained FFPE slides). If archival tissue is unavailable, optional fresh baseline tumor biopsy is strongly recommended.
- In Phase 1b, patients are required to permit the collection of tumor tissue samples or to allow a biopsy to be performed (archival tumor tissues [FFPE blocks or approximately 15 freshly cut unstained slides] or fresh biopsy, ≥ 8 slides are mandatory) for biomarker analysis. If archival tumor tissues are not available, fresh biopsy samples are required. PD-L1 and

TIGIT expression will be required testing for secondary endpoint analysis. For Cohorts 3 and 10 (NSCLC with PD-L1 positive [TC ≥ 1%]) and Cohort 8 (HNSCC with PD-L1 positive [vCPS ≥ 1%]), PD-L1 expression will be prospectively tested using the investigational VENTANA PD-L1 (SP263) Assay at a central laboratory. For Cohort 5 (CPI-experienced NSCLC), fresh tumor biopsy samples or archival tissue samples obtained after prior checkpoint inhibitor treatment are highly recommended. All patients with non-squamous NSCLC and G/GEJ adenocarcinoma must have been tested locally for EGFR/ALK/ROS1 and HER2, respectively. In case a local laboratory test is not available, central laboratory tests can be used and additional slides for these tests should be sent as required.

For Phase 1/1b, optional samples from biopsies performed at first response (PR/CR), Cycle 3 Day 1 or Cycle 2 Day 1, and at EOT Visit after confirmed disease progression are recommended for evaluation of pharmacodynamic effects and resistance mechanism. If feasible, post-treatment biopsy should be taken from the same tumor lesion as the baseline biopsy/archival tissue.

A written informed consent is required for obtaining the optional fresh tumor biopsy samples. 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.

Blood samples will be collected at specified times as described in the Schedule of Assessments (Appendix 1) to be used for blood-based biomarker evaluation. Candidate biomarkers will include but not limited to ociperlimab TIGIT and tislelizumab PD-1 receptor occupancy on peripheral blood cells as target engagement biomarker, peripheral immune cell quantity and phenotype change, GEP, baseline concentration, and dynamic change of cytokine and soluble proteins before, during, and after drug treatment as blood-based pharmacodynamic biomarker to monitor drug effects on patients. Blood-based circulating tumor DNA (ctDNA) status, TMB, gene mutation, MSI status, and Fc gamma receptor polymorphism will be tested as potential predicative biomarkers (Note: For sites in mainland China, blood-based biomarkers, including receptor occupancy, peripheral immune phenotype, GEP, cytokine/soluble proteins, ctDNA, TMB, MSI, Fc gamma receptor polymorphism, and gene mutation profiles, will be explored in blood samples collected before, during and after treatment).

8.5. Tumor and Response Evaluations

Tumor imaging will be performed ≤ 28 days before the first dose of study drugs. Results of standard-of-care tests or examinations performed before informed consent has been obtained and ≤ 28 days before the first dose of study drugs may be used for the purposes of screening rather than repeating the standard-of-care tests. During the study, tumor imaging will be performed approximately every 6 weeks (± 7 days), from Day 1 of Cycle 1, for the first 54 weeks, then every 12 weeks (± 7 days) thereafter (eg, Week 6, Week 12, …, Week 48, Week 54, Week 66, Week 78, Week 90, etc.), 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 response will be assessed before the next administration of investigational product (eg, the first tumor assessment is performed before Cycle 3 Day 1 and no disease progression should be confirmed).

Screening assessments and each subsequent assessment must include computed tomography (CT) scans (with oral/intravenous contrast, unless contraindicated) or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis. An MRI (or CT scan if MRI is contraindicated or not readily available) of the head is required at screening; bone scan or positron-emission tomography (PET) is required if clinically indicated. Other known or suspected sites of disease must be included in the imaging assessments (neck, brain, etc).

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

- Imaging of the brain (preferably MRI or CT) at baseline is required for all screened patients. Screening evaluations will be performed ≤ 28 days before the first dose of study drug(s).
- If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the study, a noncontrast CT of the chest plus a contrast-enhanced MRI (if possible) of abdomen and pelvis should be performed.
- If a CT scan for tumor assessment is performed on a PET/CT scanner, the CT acquisition must be consistent with the standards of a diagnostic CT scan.
- Bone scans (Technetium-99m [TC-99m]) or PET should be performed at screening if clinically indicated. If bone metastases are present at screening and cannot be seen on CT or MRI scans, TC-99m or PET bone scans should be repeated when a CR is suspected in a target lesion or when progression in bone is suspected.
- CT scans of the neck or extremities should be performed at screening, only if clinically indicated, and followed throughout the study, if there is evidence of metastatic disease in these regions at screening.
- At the investigator's discretion, other methods of assessment of target lesions and non-target lesions per RECIST v1.1 may be used.

Response will be assessed by the Investigator using RECIST v1.1 (see Appendix 9). The same evaluator should perform all assessments, if possible, to ensure internal consistency across visits.

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

For immune therapies such as ociperlimab and tislelizumab, pseudoprogression may occur due to immune-cell infiltration and other mechanisms leading to apparent increase of existing tumor masses or appearance of new tumor lesions. Thus, if radiographic PD is suspected by the investigator to reflect pseudoprogression, patients may continue treatment with ociperlimab and tislelizumab until PD is confirmed by repeated imaging ≥ 4 weeks later (but not exceeding 6 to 8 weeks from the date of initial documentation of PD). If at the investigator's discretion a patient could continue to benefit from ociperlimab and tislelizumab after PD per RECIST v1.1 criteria, the patient may continue ociperlimab and tislelizumab. The following criteria must be

met in order to treat patients with suspected pseudoprogression or who may continue to benefit from study treatment beyond radiologic 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 after PD confirmation and inform patients that this practice is not considered standard in the treatment of cancer.

The decision to continue study drugs beyond initial investigator-assessed progression must be agreed to with the medical monitor and documented in the study records.

For patients who continue treatment after disease progression, baseline of tumor assessment will be the results of disease progression instead of the baseline at screening. If the tumor assessment shows disease progression again, treatment will discontinue.

Tumor assessment should continue as planned in patients receiving study drug(s) beyond initial investigator-assessed progression. Tumor assessment in such patients should continue until study treatment discontinuation. A patient who discontinues study drugs early for reasons other than PD (eg, toxicity) will continue to undergo tumor assessments following the original plan until the patient begins a subsequent anticancer therapy, experiences PD, withdraws consent, is lost to follow-up, dies, or until the study terminates, whichever occurs first.

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

8.6. Visit Windows

All visits must occur within ± 3 days from the scheduled date, unless otherwise noted (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 of each cycle should be performed before any study treatment is given unless otherwise noted. Laboratory results must be reviewed before dosing.

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

8.7. 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; physical examination of liver, spleen, and lymph nodes; disease-related constitutional symptoms; and

hematology and clinical chemistry laboratory assessments. The date and reason for the unscheduled visit must be recorded in the source documentation.

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

9. 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.

9.1. Risks Associated With Study Drugs

9.1.1. Risks Associated With Ociperlimab and Tislelizumab

Ociperlimab and tislelizumab are investigational agents that are currently in clinical development. The first-in-human Study AdvanTIG-105 evaluating safety, tolerability, and clinical benefit of ociperlimab in combination with tislelizumab in solid tumors is still ongoing.

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 9.7.3. Ociperlimab-mediated TIGIT inhibition may increase the risk of immune mediated AEs. However, no apparent immunotoxicity, or toxicity in general, have been observed in animal models treated with ociperlimab. Furthermore, in the absence of activation, peripheral effector T-cells do not typically express TIGIT, thereby minimizing any potential negative additive affect as it relates to peripheral immune tolerance.

Although most imAEs observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Suggested workup procedures for suspected imAEs are provided in Appendix 8.

9.1.2. Risks Associated With Chemotherapeutic Agents

Please refer to the Table 9 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 9: Summary of the Common and Specific Reported Toxicities of the Chemotherapeutic Agents

Agents	Common toxicity	Specific toxicity
Cisplatin	Myelosuppression with leukopenia, thrombocytopenia and anemia; infectious complications; nausea/vomiting and other gastrointestinal tract 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;
Nab-paclitaxel		Peripheral neuropathy
Etoposide		Hypersensitivity reactions; ocular; respiratory; skin; neurologic
5-FU		Neutropenia; neurotoxicity
Oxaliplatin		Hypersensitivity reactions; neuropathy; pulmonary fibrosis; Hepatotoxicity
Capecitabine		Cardiotoxicity; renal failure; phototoxicity

9.2. General Plan to Manage Safety Concerns

9.2.1. Eligibility Criteria

Eligibility criteria were selected to guard the safety of patients in this study. Results from the nonclinical toxicology studies and clinical data with ociperlimab and tislelizumab, as well as the nonclinical/clinical data from other PD-L1/PD-1 inhibitors, were considered. Specifically, patients 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 viral vaccine ≤ 28 days before the first dose of study drugs are excluded from the study. Patients with contraindications for platinum containing doublet chemotherapy are also excluded from the study (Section 4.2) for the full list of exclusion criteria).

9.2.2. Abnormal Liver Function Tests

The finding of an elevated ALT or AST (> 3 x baseline value) in combination with either an elevated total bilirubin (> 2 x ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an AE the occurrence of either of the following:

- Treatment-emergent ALT or AST > 3 x baseline value in combination with total bilirubin > 2 x ULN (of which 35% is direct bilirubin)
- Treatment-emergent ALT or AST > 3 x baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the AE eCRF and reported to the sponsor immediately (ie, no more than 24 hours after learning of the event) via SAE reporting process as described in Section 9.6.2.1.

9.2.3. 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 (Table 10), physical examinations, laboratory measurements (hematology, clinical chemistry, etc), and other assessments including those listed in Appendix 1. In addition, patients will be closely monitored for the development of any signs or symptoms of autoimmune conditions or infection.

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

Serum samples will be drawn for determination of ADAs to ociperlimab and tislelizumab in patients for both the dose-escalation and dose-expansion phases of the study. 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 9.7.

9.3. Adverse Events

9.3.1. Definitions and Reporting

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

Examples of AEs include:

- Worsening of a chronic or intermittent pre-existing condition, including an increase in severity, frequency, duration, and/or has an association with a significantly worse outcome
- New conditions detected or diagnosed after study drugs 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 drugs or a concurrent medication (overdose per se should not be reported as an AE or SAE)

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

9.3.2. Assessment of Severity

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

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

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

Note: The terms “severe” and “serious” are not synonymous. Severity is a measure of intensity (for example, grade of a specific AE, mild [Grade 1], moderate [Grade 2], severe [Grade 3], or life-threatening [Grade 4]); whereas seriousness is classified by the criteria based on the regulatory definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the sponsor to applicable regulatory authorities as described in Section 9.6.2.

9.3.3. Assessment of Causality

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

relationship of the AE or SAE to the study drugs should be considered and investigated. The investigator should consult the Ociperlimab Investigator's Brochure, Tislelizumab Investigator's Brochure, and chemotherapy 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 drugs (ie, there are facts, evidence, or arguments to suggest possible causation). A number of factors should be considered in making this assessment including:

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

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

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

9.3.4. Following Adverse Events

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

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

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

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

New or updated information should be reported to the sponsor according to the SAE instructions provided by the sponsor within the time frames outlined in Section 9.6.2.

9.3.5. Laboratory Test Abnormalities

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

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

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

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

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

9.4. 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

9.5. 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 Ociperlimab Investigator's Brochure, Tislelizumab Investigator's Brochure, and chemotherapy prescribing information.

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

9.6.1. Adverse Event Reporting Period

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

After initiation of study drugs, all AEs and SAEs, regardless of relationship to study drugs, will be reported until either 30 days after last dose of study drugs or initiation of subsequent anticancer therapy, whichever occurs first. Immune-mediated AEs (serious or nonserious) should be reported until 90 days after the last dose of study drugs, regardless of whether or not the patient starts a subsequent anticancer therapy. All SAEs considered related to the study

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

AEs and SAEs should be recorded according to the details in Table 10. For the follow-up period for AEs, see Section 9.3.4. For the definition of TEAEs, see Section 10.3.2.

Table 10: Guidance for Duration of Recording New or Worsening Adverse Events in All Cohorts

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 9.6.4)	
All nonserious AEs, except those due to PD	First dose of study drug	Up to 30 days after last dose, initiation of new anticancer therapy, death, withdrawal of consent, or loss to follow-up, whichever occurs first
Immune-related AEs (serious or nonserious)	First dose of study drug	Up to 90 days after last dose (regardless of initiation of new anticancer therapy), death, withdrawal of consent, or loss to follow-up, whichever occurs first

Abbreviations: AE, adverse event; PD, progressive disease; SAE, serious adverse event.
[a] All SAEs considered related to the study drug(s) that are brought to the attention of the investigator should be reported regardless of time since the last dose of treatment.

9.6.2. Reporting Serious Adverse Events

9.6.2.1. 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 11.

Table 11: Time Frames and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

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

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

9.6.2.2. 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 9.6.2.1. 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 9.3.3.

The sponsor will provide contact information for SAE receipt.

9.6.2.3. 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 9.6.2.1. 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 9.5) will be submitted to all applicable regulatory authorities and investigators for ociperlimab and tislelizumab studies.

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

9.6.3. 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?

9.6.4. Progressive Disease

PD, which is expected in this study population and measured as an efficacy endpoint, should not be reported as an AE term. Instead, the symptoms, signs, or clinical sequelae that result from PD should be reported as the AE term(s).

For instance, a patient presents with pleural effusion resulting from PD of metastasis to lungs. The event term should be reported as "pleural effusion" instead of PD. If a patient experienced fatal multiorgan failure because of PD, the term "multiorgan failure" should be reported as the SAE, with death as outcome, instead of reporting "fatal PD" or "death because of PD." All SAEs and deaths, regardless of relatedness to PD, should be recorded and reported.

9.6.5. 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").

9.6.6. Recording Pregnancies

If a female patient or the partner of a male patient becomes pregnant while the patient is receiving study drugs, or within 120 days after the last dose of ociperlimab and/or tislelizumab, or within 180 days after the last dose of chemotherapy, 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 drugs should be recorded and reported as an SAE.

9.6.7. 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:

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

- Paclitaxel prescribing information
- Nab-paclitaxel prescribing information
- Pemetrexed prescribing information
- Etoposide prescribing information
- Cisplatin prescribing information
- Carboplatin prescribing information
- 5-fluorouracil prescribing information
- Oxaliplatin prescribing information
- Capecitabine prescribing information

9.6.8. 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 9.7.3) should be classified as imAEs and identified as such on the eCRF AE page until Day 90 after treatment discontinuation. Not all ociperlimab and tislelizumab studies include a section in the eCRF AE page where imAEs are clearly identified. Therefore, all studies will rely on the company list of Potential imAEs to identify all cases in each study to be further assessed as imAEs by the sponsor, in addition to those imAEs reported by the investigator via the AE CRF page.

Investigators should consult the guidance on diagnostic evaluation and management of imAEs, which are commonly seen with immune checkpoint inhibitors, in Appendix 8.

An extensive list of potential imAEs appears in Section 9.7.3, Table 13. 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 8.

9.6.9. 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. Individual signs and symptoms of an infusion reaction should be recorded each as a separate AE in the eCRF and identified as an infusion-related reaction. Refer to the eCRF completion guidelines for details.

9.7. Management of Adverse Events of Special Interest

As a routine precaution, following completion of study drugs administration, patients must be monitored for a period afterward in a setting where emergency medical equipment and staff who are trained to respond to medical emergencies are available.

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

9.7.1. 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 12.

Table 12: 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. Subsequent infusions should be given after premedication and at the reduced infusion rate.
Grade 2 - moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, 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. Subsequent infusions should be given after premedication and at the reduced infusion rate.
Grade 3 – severe Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae.	Immediately stop the infusion. Proper medical management should be instituted as described in the text following this table. The patient should be withdrawn from study drug 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 study drug treatment. Hospitalization is recommended.

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

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

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

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

NCI-CTCAE Grade 3 or 4 infusion 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.

9.7.2. 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.

9.7.3. Immune-Mediated Adverse Events

The imAEs 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 13. All conditions similar to those listed should be evaluated in patients receiving ociperlimab or tislelizumab to determine whether they are immune-mediated.

Recommendation for diagnostic evaluation and management of imAEs is based on European Society for Medical Oncology and American Society of Clinical Oncology guidelines (Haanen et al 2017; Brahmer et al 2018) and common immune-mediated toxicities are detailed in Appendix 8. For any AEs not included in Appendix 8, 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 13: Immune-Mediated Adverse Events

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

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

Recommendations for managing imAEs are detailed in Appendix 8.

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

9.7.4. Management of Immune-Mediated AEs in Patients With Pre-Existing Renal Dysfunction

Patients with mild renal dysfunction (estimated GFR ≥ 60 mL/min/1.73 m^2 by CKD-EPI equation) may be enrolled into the study. Therefore, the following algorithm is proposed for the use of steroid treatment in the management of imAEs:

- If the serum creatinine (ie, estimated GFR) is normal at baseline, please see Section 9.7.3 and refer to Appendix 8 for diagnosis and management of patients with imAE related abnormal renal laboratory values.

- If the serum creatinine is Grade 1 at baseline and the increase in serum creatinine meets criteria for serum creatinine increase ≥ Grade 2 after starting treatment with study drugs, refer to Appendix 8 for diagnosis and management of patients with abnormal renal laboratory values. Check the estimated GFR using Appendix 7 and the estimated GFR calculator link. In the setting of a Grade 2 serum creatinine increase only, study treatment can continue unless the serum creatinine increases by ≥ 50% from the baseline value OR the estimated GFR falls below 20 mL/min/1.73 m^2.
- If the serum creatinine is Grade 2 at baseline and the increase in serum creatinine meets criteria for serum creatinine increase ≥ Grade 3 after starting treatment with study drugs, refer to Appendix 8 for diagnosis and management of patients with abnormal renal laboratory values. In the setting of a Grade 3 serum creatinine increase only, study treatment will be held until serum creatinine improves to baseline and treatment may resume only after discussion with the medical monitor.

10. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

This study is designed to establish the safety and tolerability of ociperlimab and tislelizumab to assess preliminary anticancer activities in dose-expansion cohorts.

In general, data from dose escalation will be summarized by dose level except that data from dose verification in Chinese patients will be summarized separately; while data from dose expansion will be summarized by tumor type for Cohorts 1 to 9, unless otherwise specified. For Cohort 10, data will be summarized by treatment arm and total. Details of the statistical analyses will be included in a separate statistical analysis plan.

10.1. Statistical Analysis

Efficacy and safety analyses will be performed by Phase 1 and Phases 1b. In Phase 1, data will be summarized by dose level but data from dose verification in Chinese patients will be summarized separately. In Phase 1b, data will be summarized by tumor type for Cohorts 1 to 9. For Cohort 10, data will be summarized by treatment arm and total.

Descriptive statistics will be mainly used in describing the safety, tolerability, and the anticancer activities of the ociperlimab as monotherapy and in combination with tislelizumab. Confidence intervals will be constructed to describe the precision of the point estimates of interest.

10.1.1. Analysis Sets

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

The Efficacy Evaluable Analysis Set includes all patients who received ≥ 1 dose of study drugs, have evaluable disease at baseline, and ≥ 1 evaluable postbaseline tumor response assessment unless any clinical PD or death occurred before the first postbaseline tumor assessment.

The DLT Evaluable Analysis Set includes patients who received at least 80% each of the assigned doses ociperlimab and tislelizumab according to the treatment schedule, remained on study during the DLT observation period, and had sufficient safety evaluation or patients who experienced a DLT within the DLT observation period.

The PK Analysis Set includes all patients who received ≥ 1 dose of study drug(s) and have ≥ 1 derivable PK parameter.

The ADA Analysis Set includes all patients who received ≥ 1 dose of study drug(s) and have both baseline ADA and ≥ 1 postbaseline ADA results.

10.1.2. Patient Disposition

The number of patients treated, discontinued from study drugs and/or the study will be counted. The primary reason for study drugs and/or study discontinuation will be summarized according to the categories in the eCRF.

Major protocol deviations will be listed.

10.1.3. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized using the Safety Analysis Set and descriptive statistics. Continuous variables include year of birth (or age), weight, and time since initial cancer diagnosis. Categorical variables include gender, ECOG Performance Status, race, number of prior systemic therapies received. Other disease-specific parameters might be summarized in the relevant cohort for dose expansion.

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

10.1.4. Prior and Concomitant Medications

Prior medications will be defined as medications that stopped before the day of first dose of study drugs. Concomitant medications will be defined as medications that 1) were started before the first dose of study drugs and were continuing at the time of the first dose of study drugs, or 2) were started on or after the date of the first dose of study drugs up to 30 days after the patient's last dose (as of the Safety Follow-up Visit). Concomitant medications will be coded using the World Health Organization Drug Dictionary drug codes. Concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class. A listing of prior and concomitant medications will be provided.

10.2. Efficacy Analyses

Primary and/or secondary efficacy endpoints will be based upon investigators' tumor assessments per RECIST v1.1 and will be summarized as follows to evaluate the preliminary anticancer activities of ociperlimab as monotherapy and in combination with tislelizumab:

- ORR is defined as the proportion of patients who had CR or PR.
- DOR is defined as the time from the first determination of an overall response per RECIST v1.1 until the first documentation of progression or death, whichever comes first.
- DCR is defined as the proportion of patients with BOR, as defined in Appendix 9, of a CR, PR, or SD. This will be summarized similarly as ORR.

- PFS is defined as the time from the date of the first dose of study drugs to the date of the first documentation of PD assessed by the investigator using RECIST v1.1 or death, whichever occurs first.
- OS is defined as time from the first dose of study drugs to the date of death due to any cause.

10.2.1. Secondary Efficacy Analysis in Phase 1

The primary objective in dose escalation is to assess patients' safety and PK profile. As a secondary analysis, efficacy endpoints such as ORR and DCR will be summarized by dose, along with their 95% confidence interval based on the Efficacy Evaluable Analysis Set; dose verification in Chinese patients will not be included. For dose verification part, efficacy endpoints will be summarized by cohort.

10.2.2. Primary Efficacy Analysis in Phase 1b

ORR assessed by the investigator and its 95% confidence interval will be summarized for the dose-expansion cohorts based on the Efficacy Evaluable Analysis Set. ORR will be summarized by tumor type in dose-expansion cohorts.

10.2.3. Secondary Efficacy Analysis in Phase 1b

PFS, DOR, and DCR will be summarized for the dose expansion cohorts.

PFS and DOR will be estimated using the Kaplan-Meier method. The median PFS and the cumulative probability of PFS at every 3 months will be calculated and presented with 2-sided 95% CIs. PFS censoring rule will follow United States Food and Drug Administration Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (US FDA 2018).

DOR will be analyzed similarly as PFS. DCR will be analyzed similarly to ORR based on the Efficacy Evaluable Analysis Set. Waterfall plots of maximum tumor shrinkage per patient will be presented.

Association between clinical efficacy and predictive biomarkers (such as PD-L1 and TIGIT expression) will be investigated. Clinically meaningful cutoffs will be used to dichotomize the biomarker evaluable patients to subgroups. Summary statistics of ORR and PFS for PD-L1 and TIGIT expression subgroups will be presented.

10.2.4. Exploratory Efficacy Analysis

OS will be analyzed similarly as describe for PFS (Section 10.2.3) in treated patients.

The correlation of response and exploratory tumor-based and/or blood-based biomarkers may be evaluated.

10.3. Safety Analyses

Safety will be determined by the spontaneous reporting of AEs and by laboratory values (hematology, clinical chemistry, coagulation, and urinalysis). Vital signs, physical examinations, and ECG findings will also be used in determining the safety profile. The severity of AEs will

be graded according to NCI-CTCAE v5.0. The incidence of DLT events and TEAEs will be reported as the number (percentage) of patients with TEAEs by MedDRA system organ class and preferred term. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, and maximum for continuous variables; n [%] for categorical variables) and changes from baseline, will be determined for laboratory parameters and vital signs.

Safety data will be summarized using the Safety Analysis Set and by study stage with dose verification in China as a separate stage.

10.3.1. Extent of Exposure

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

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

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

10.3.2. Adverse Events

The AE verbatim descriptions (investigator's description from the eCRF) will be coded using MedDRA. AEs will be coded to MedDRA (Version 20.0 or higher) lower level term, preferred term, and primary system organ class.

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

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by system organ class and preferred term. A patient will be counted only once by the highest severity grade per NCI-CTCAE v5.0 within a system organ class and preferred term, even if the patient experienced ≥ 1 TEAE within a specific system organ class and preferred term. The number (percentage) of patients with TEAEs will also be summarized by relationship to the study drugs.

TEAEs 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, imAE, treatment-related TEAEs, and TEAEs that led to treatment discontinuation or dose modification will be summarized.

10.3.3. 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 visit with the 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.

10.3.4. 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 for all visits. Vital signs will be listed by patient and visit.

10.3.5. Ophthalmologic Examination

Ophthalmologic examination results will be listed for patients who receive the assessments in dose escalation.

10.4. Pharmacokinetic Analyses

Non-compartmental analysis will be carried out for ociperlimab and tislelizumab serum concentrations. The PK analyses will include patients with sufficient data to enable estimation of key parameters, and the parameters such as, C_{max}, C_{min}, T_{max}, $AUC_{0\text{-}21d}$, CL, and Vss (as appropriate for data collected) may be derived and summarized with descriptive statistics (mean, standard deviation, and coefficient of variation).

Individual and mean serum ociperlimab and tislelizumab concentration versus time data will be tabulated and plotted by dose level except that data from dose verification in Chinese patients will be tabulated and plotted separately.

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 Clinical Study Report.

10.5. 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.

10.6. Other Exploratory Analyses

Summary statistics will be provided for pharmacodynamic biomarkers including but not limited to immune cell subtypes in the blood and/or tumor tissue. An exploratory analysis on a potential correlation of these pharmacodynamic biomarkers with the dose, safety, and preliminary anticancer activity will be performed as appropriate.

Exploratory predictive biomarker analyses will be performed in an effort to understand the association of these markers with study drugs response, such as efficacy.

10.7. Sample Size Consideration

The study plans to enroll approximately 294 to 564 evaluable patients:

- Phase 1: Approximately 44 to 64 patients
- Phase 1b: Approximately 250 to 500 evaluable patients in 10 prespecified cohorts (20 to 40 evaluable patients each for Cohorts 1 to 8, 30 to 60 evaluable patients for Cohort 9, and 20 to 40 evaluable patients for each of the 3 arms in Cohort 10)

For dose escalation in Phase 1, 32 patients should be sufficient to evaluate the safety and tolerability of increasing dose levels of ociperlimab in combination with tislelizumab per the modified 3+3 design rules with extra patients on R2PD for further evaluation. An extra 12 to 32 Chinese patients will receive ociperlimab as monotherapy and in combination with tislelizumab as dose verification. Overall, 44 to 64 patients will be enrolled in Phase 1.

For dose expansion in Phase 1b, 10 prespecified cohorts are planned, with approximate 20 to 40 evaluable patients for Cohorts 1 to 8, 30 to 60 evaluable patients for Cohort 9. For Cohort 10, approximately 60 to 120 evaluable patients (20 to 40 patients for each of the 3 arms) will be enrolled. A two-stage design based on Bayesian predictive probability (Lee and Liu 2008) will be implemented for Cohorts 1 to 10. The predictive probability of achieving a potential target ORR will be calculated in the interim analysis for Cohorts 1 to 8 after approximately 20 evaluable patients have completed ≥ 1 postbaseline tumor assessment, for Cohort 9 after approximately 30 evaluable patients have completed at least 1 postbaseline tumor assessment, and for each arm in Cohort 10 after approximately 20 evaluable patients have completed ≥ 1 postbaseline tumor assessment. The interim analysis will be carried out timely when data become available, while the enrollment beyond 20 evaluable patients for Cohorts 1 to 8, 30 evaluable patients for Cohort 9 and 20 evaluable patients for each arm in Cohort 10 may be allowed before the tumor assessment is performed. The potential target ORR can be chosen based on historical rate. The target ORR may be further updated with the study conduct when relative emerging information becomes available. If the predictive probability is less than 0.2 for the first 20 evaluable patients in Cohorts 1 to 8, for the first 30 evaluable patients for Cohort 9, for the first 20 evaluable patients in each arm of Cohort 10, enrollment will stop; if the predictive probability is larger than 0.8, enrollment may stop with high confidence of achieving a potential target ORR; if the predictive probability is between 0.2 and 0.8, extra 20 evaluable patients for

Cohorts 1 to 8, extra 30 evaluable patients for Cohort 9, and extra 20 evaluable patients for each arm of Cohort 10 may be enrolled to evaluate the anticancer activities.

10.8. Interim Analyses

For Cohorts 1 to 8 in Phase 1b, after approximately 20 evaluable patients have completed at least 1 postbaseline tumor assessment, the built-in interim analysis of calculating Bayesian predictive probability will be performed. For Cohort 9, the built-in interim analysis of calculating Bayesian predictive probability will be performed after approximately 30 evaluable patients have completed at least 1 postbaseline tumor assessment. For each arm of Cohort 10, the built-in interim analysis of calculating Bayesian predictive probability will be performed after approximately 20 evaluable patients have completed ≥ 1 postbaseline tumor assessment.

11. STUDY COMMITTEES

11.1. Safety Monitoring Committee

An SMC will be established and include both the sponsor and investigators. The SMC will review all available safety, efficacy, PK, and exploratory data and make recommendations on dose escalation, dose modification, and dose selection for Phase 1 and Phase 1b.

Phase 1 (Dose verification in China): For the Chinese patients who receive ociperlimab as a monotherapy or in combination with tislelizumab in dose verification study, the SMC will review all the safety data (including AEs and laboratory assessments) and make RP2D recommendation before initiation of Phase 1b in China.

Phase 1b (Safety run-in): In each dose-expansion cohort treated with ociperlimab plus tislelizumab plus chemotherapy, the SMC will review all available safety data (including AEs and laboratory assessments) after the first 6 patients have completed at least 1 cycle (21 days) in safety run-in stage and make recommendations if cohorts could be fully open to enrollment.

The SMC may also be called upon by the sponsor on an ad hoc basis where applicable to the conduct of the study. For more details on the SMC, please refer to the SMC charter.

12. 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.

12.1. 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.

12.2. 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.

13. QUALITY ASSURANCE AND QUALITY CONTROL

13.1. 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.

13.2. 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.

13.3. 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.

13.4. 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.

14. ETHICS/PROTECTION OF HUMAN PATIENTS

14.1. 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).

14.2. 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.

14.2.1. 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.

14.3. 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.

14.4. Patient and Data Confidentiality

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

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

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

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

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

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

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

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

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

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

The investigator agrees that all information received from the sponsor, including but not limited to Ociperlimab Investigator's Brochure, Tislelizumab 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.

14.5. 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).

15. DATA HANDLING AND RECORD KEEPING

15.1. Data Collection and Management Responsibilities

15.1.1. 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.

15.1.2. Data Collection

Data required by the protocol will be entered into an 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 the sponsor and should not be made available in any form to third parties without written permission from the sponsor, except for authorized representatives of the sponsor or appropriate regulatory authorities.

15.1.3. Data Management/Coding

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

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

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

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

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

15.2. Study Records Retention

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least 1 of the following 2 categories: 1) investigator's study file, and/or 2) patient clinical source documents.

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

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

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

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

15.3. 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. Any major deviations that might impact patient safety and/or data integrity must be promptly reported by the investigator to the sponsor and to the IRB/IEC, in accordance with established IRB/IEC policies and procedures.

15.4. 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 1995). Note that an abbreviated report may be prepared in certain cases.

The results of this study will be published or presented at scientific meetings in a timely, objective, and clinically meaningful manner that is consistent with good science, industry and regulatory guidance, and the need to protect the intellectual property of the sponsor, regardless of the outcome of the study. The data generated in this clinical study are the exclusive property of the sponsor and are confidential. 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 (International Committee of Medical Journal Editors 2018) or stricter local criteria.

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 details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this study will be presented in the investigator's clinical study agreement. Each investigator agrees that, in accordance with the terms of 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.

15.5. Study and Study Center Closure

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

- Return of all study data to the sponsor
- Resolution and closure of all data queries
- Accountability, reconciliation, and arrangements for unused study 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.

15.6. Information Disclosure and Inventions

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

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

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

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

These restrictions do not apply to:

- Information that becomes publicly available through no fault of the investigator or study center personnel
- Information that is necessary to disclose in confidence to an 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 15.4.

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

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17. APPENDICES

APPENDIX 1. SCHEDULE OF ASSESSMENTS

APPENDIX 1A. PHASE 1 (DOSE ESCALATION IN AUSTRALIA AND DOSE VERIFICATION IN CHINA) SCHEDULE OF ASSESSMENTS

Phase 1 assessment	**Screen-ing** [a]	**Treatment Cycles**									**Safety Follow-up Visit** [b] **Safety follow-up by telephone** [c]			**Efficacy follow-up** [d]
		Cycle 1 (28 days for dose escalation in Australia; 21 days for dose verification in China)				**Cycle 2 (21 days)**			**≥ Cycle 3 (21 days)**	**EOT Visit** [b]				
Visit day	**- 28 to - 1**	**1**	**8**	**15**	**21**	**1**	**8**	**15**	**1**	**EOT decision**	**+ 30 days (Visit)**	**+60 days (Phone call)**	**+90 days (Phone call)**	
Visit window				**± 2**	**± 2**	**± 1**	**± 2**	**± 2**	**± 3**	**± 7**	**± 7**	**± 14**	**± 14**	
Informed consent	x													
Inclusion/ exclusion criteria	x													
Demographics/ medical history/ prior medications [e]	x													
Vital signs/ height and weight [f]	x	x [f]	x	x	x	x [f]	x	x	x [f]	x	x			
Physical examination [g]	x	x				x			x	x	x			

Phase 1 assessment	**Screen-ing** [a]	**Treatment Cycles**									**Safety Follow-up Visit** [b] **Safety follow-up by telephone** [c]			**Efficacy follow-up** [d]
		Cycle 1 (28 days for dose escalation in Australia; 21 days for dose verification in China)				**Cycle 2 (21 days)**			**≥ Cycle 3 (21 days)**	**EOT Visit** [b]				
Visit day	**- 28 to - 1**	**1**	**8**	**15**	**21**	**1**	**8**	**15**	**1**	**EOT decision**	**+ 30 days (Visit)**	**+60 days (Phone call)**	**+90 days (Phone call)**	
Visit window				**± 2**	**± 2**	**± 1**	**± 2**	**± 2**	**± 3**	**± 7**	**± 7**	**± 14**	**± 14**	
ECOG Performance Status	x	x				x			x	x	x			
Triplicate 12-lead ECG [h]	x	Predose and 6 hours after study drugs infusion on Day 1 of Cycles 1 and 5								x	x			
Adverse events [i]	x	x	x	x [i]	x [i]	x	x [i]	x [i]	x	x	x	x	x	
Concomitant medications	x	x	x	x [j]	x [j]	x	x [j]	x [j]	x	x	x	x	x	
Hematology [k]	x [k]	x [k]	x [k]			x [k]			x [k]	x	x			
Serum chemistry [k]	x [k]	x [k]	x [k]			x [k]			x [k]	x	x			
Coagulation parameters [k]	x [k]	As clinically indicated								x	x			
Urinalysis [k]	x [k]	As clinically indicated												
CK and CK-MB [l]	x	x		x	x	x		x	x [l]	x	x			
Pregnancy test [m]	x [m]	x [m]				x [m]			x [m]	x	x			

Phase 1 assessment	**Screen-ing** [a]	**Treatment Cycles**									**Safety Follow-up Visit** [b] **Safety follow-up by telephone** [c]			**Efficacy follow-up** [d]
		Cycle 1 (28 days for dose escalation in Australia; 21 days for dose verification in China)				**Cycle 2 (21 days)**			**≥ Cycle 3 (21 days)**	**EOT Visit** [b]				
Visit day	**- 28 to - 1**	**1**	**8**	**15**	**21**	**1**	**8**	**15**	**1**	**EOT decision**	**+ 30 days (Visit)**	**+60 days (Phone call)**	**+90 days (Phone call)**	
Visit window				**± 2**	**± 2**	**± 1**	**± 2**	**± 2**	**± 3**	**± 7**	**± 7**	**± 14**	**± 14**	
Thyroid function (every 3 cycles) [n]	x [n]								x [n]	x	x			
HBV/HCV tests [o]	x	Every 4 cycles starting at Cycle 5 in HCC patients with detectable HBV DNA at screening or as clinically indicated in all patients								x	x			
Pulmonary function tests [p]	x [p]	As clinically indicated												
PK and ADA [x]		Refer to Pharmacokinetic and Immunogenicity Table, Appendix 1C												
Blood biomarkers [q]		Refer to Biomarker Table, Appendix 1F												
PD receptor occupancy [r]		Refer to Biomarker Table, Appendix 1F												
Tumor assessment [s]	x	For the first 54 weeks, every 6 weeks. Every 12 weeks thereafter												x
Archival or fresh tumor tissue [t]	x	Refer to Biomarker Table, Appendix 1F												

Phase 1 assessment	**Screen-ing** [a]	**Treatment Cycles**									**Safety Follow-up Visit** [b] **Safety follow-up by telephone** [c]			**Efficacy follow-up** [d]
		Cycle 1 (28 days for dose escalation in Australia; 21 days for dose verification in China)				**Cycle 2 (21 days)**			**≥ Cycle 3 (21 days)**	**EOT Visit** [b]				
Visit day	**- 28 to - 1**	**1**	**8**	**15**	**21**	**1**	**8**	**15**	**1**	**EOT decision**	**+ 30 days (Visit)**	**+60 days (Phone call)**	**+90 days (Phone call)**	
Visit window				**± 2**	**± 2**	**± 1**	**± 2**	**± 2**	**± 3**	**± 7**	**± 7**	**± 14**	**± 14**	
Ociperlimab administration [u]		x				x			x					
Tislelizumab administration (dose escalation in Australia) [v]			x			x			x					
Tislelizumab administration (dose verification in China) [w]		x				x			x					

Abbreviations: ADA, antidrug antibody; AE, adverse event; CK, creatine kinase; CK-MB, creatine kinase-muscle/brain; CT, computed tomography; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, End-of-Treatment (Visit), HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ICF, informed consent form; imAE, immune-mediated AE; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; PD, progressive disease; PK, pharmacokinetic; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; T3, triiodothyronine; T4, thyroxine.

Note: Timepoints containing numbers represent timepoints with special considerations for that respective assessment.

a. Written informed consent is required before performing any study-specific procedure. Results of standard-of-care tests or examinations performed before informed consent has been obtained and ≤ 28 days before the first dose of study drugs may be used for screening assessments rather than repeating such tests unless otherwise indicated. The ICF signature alone does not define the start of the Screening Period, but the first study-related assessment date is to be used for the date of the Screening Visit.

b. The EOT Visit is conducted when the investigator determines that study treatment(s) will no longer be used. Patients who discontinue treatment for any reason will be asked to return to the clinic for the EOT Visit within 7 days when the EOT decision is made unless otherwise specified or before the initiation of a new anticancer treatment, whichever occurs first. If routine laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the EOT Visit, these tests need not be repeated. Tumor assessment is not required at the EOT/Safety Follow-up Visit if < 6 weeks has passed since the last assessment.

c. Patients who permanently discontinue ociperlimab/tislelizumab will be asked to return to the clinic for the on-site Safety Follow-up Visit, which is required to be conducted 30 days (± 7 days) after the last dose of ociperlimab/tislelizumab or before the initiation of subsequent anticancer therapy, whichever occurs first. If the time windows of this Safety Follow-up Visit and EOT Visit are overlapped, the safety follow-up can be exempted and the tests required at Safety Follow-up Visit will be conducted at the EOT Visit. In addition, 2 additional Safety Follow-up Visits (by telephone contact) 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 ociperlimab/tislelizumab, regardless of whether patients started a new subsequent anticancer therapy. If patients report a suspected imAE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated.

d. Efficacy follow-up: Patients who discontinue study treatment early for reasons other than disease progression (eg, toxicity) will continue to undergo tumor assessments following the original tumor assessment plan (ie, 6 weeks [± 7 days]) during Year 1 and every 12 weeks (± 7 days) starting Year 2) until the patient experiences disease progression, withdraws consent, dies, or until the study terminates, whichever occurs first.

e. Includes year of birth (or age), gender, self-reported race, 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.

f. Height assessment is required only at screening. Vital signs will include measurements of temperature (˚C), pulse rate, and blood pressure (systolic and diastolic) while the patient is in a seated position after resting for 10 minutes. When ociperlimab and tislelizumab are administered, vital signs are required to be measured at 3 timepoints (≤ 60 minutes before the infusion, during the infusion, and ≤ 30 minutes after end of infusion) during all visits.

g. Refer to Section 8.2.2 for details regarding physical examination assessment requirements for screening and subsequent timepoints. In addition, investigators should solicit patients regarding changes in vision, visual disturbance, or ocular inflammation at each scheduled study visit during study treatment. For any change in vision, referral to an appropriate specialist will be made for further management guidance.

h. The triplicate ECG recordings will be performed at the timepoints specified in the table and when clinically indicated. All ECGs are to be obtained before other assessments scheduled at that same time (eg, vital sign measurements, blood draws, etc). 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.

i. The AEs and laboratory abnormalities will be graded per NCI-CTCAE v5.0. All AEs will also be evaluated for seriousness. After the ICF has been signed, but before the administration of study drugs, only SAEs should be reported to the sponsor. After initiation of study drugs, all AEs and SAEs, regardless of relationship to study drugs, will be reported until either 30 days after last dose of study drugs or initiation of subsequent anticancer therapy, whichever occurs first. Immune-mediated AEs (serious or nonserious) should be reported until 90 days after the last dose of ociperlimab and/or tislelizumab, regardless of whether or not the patient starts a subsequent anticancer therapy. If the investigator learns of any study drug-related SAE, including a death, at any time after a patient has been discharged from the study, he/she should notify the sponsor using the SAE reporting procedure.

j. Review of AEs and concomitant medications may be conducted by telephone on Cycle 1 Days 15 and 21 and Cycle 2 Days 8 and 15 if patient is unable to make it to the clinic.

k. Laboratory assessments of clinical chemistry, hematology, coagulation, and urinalysis will be conducted as outlined in Appendix 2. If clinical chemistry, hematology, and coagulation at screening are not performed ≤ 7 days before study drugs administration on Day 1 of Cycle 1, these tests should be repeated and reviewed before study drug administration. After Day 1 of Cycle 1, results are to be reviewed within 72 hours before study drug administration. Hematology and clinical chemistry (data collected as specified in Appendix 2) will be performed on Day 1 and Day 8 of the first cycle, then on Day 1 on

each subsequent cycle as indicated in Appendix 1A). Urinalysis and/or coagulation test will be conducted during the treatment period only if clinically warranted. Refer to Section 9.3.5 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.

l. CK and CK-MB levels will be evaluated at the timepoints specified within the table and when clinically indicated. Except for Day 1 of Cycle 1, results are to be reviewed within 72 hours before study drug administration where applicable. If the site's laboratory does not perform CK-MB testing, serum troponins (troponin I and/or T) measurements should be performed instead; if only 1 of the troponins is assessed per local standards that same test should be evaluated throughout. If significant abnormalities are detected, the affected patients should be evaluated for possible myocarditis/myositis per institutional guidelines, including additional serum CK/CK-MB, serum troponin levels, ECG, etc.

m. 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 ≤ 7 days before the first dose of study drugs. A negative pregnancy test (by urine or blood) must be completed and recorded ≤ 72 hours before the administration of study drugs at each cycle. Pregnancy tests will also be performed at the EOT Visit and each Safety Follow-up Visit, until 120 days after the last dose of ociperlimab and/or tislelizumab or 180 days after the last dose of chemotherapy, whichever comes later. During the Safety Follow-up period, the pregnancy results (local results are acceptable) will be collected by the investigator or designee via phone call. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.

n. Analysis of free T3, free T4, and thyroid stimulating hormone will be performed by a central laboratory and/or the local study site laboratory. Thyroid function tests will be performed at screening and every 3 cycles after then (eg, Cycles 4, 7, 10, etc) and at EOT/Safety Follow-up Visit. Total T3 can be tested as alternative for free T3 and total T4 can be tested as an alternative to free T4.

o. Testing will be performed by a central laboratory and/or the local laboratory at screening and will include HBV/HCV serology (HBsAg, HBsAb, HBcAb, and HCV antibody), and viral load assessment (HBV DNA and HCV ribonucleic acid). For patients with negative HBsAg or negative HCV antibody, HBV DNA or HCV RNA is optional based on clinical practice. Samples for hepatitis serology and viral load will be collected at screening and may be tested if patients have hepatic AEs (≥ Grade 3) during the study and as clinically indicated.

p. Patients who are suspected of having or known to have serious/severe respiratory conditions or exhibit significant respiratory symptoms unrelated to the underlying cancer, or with a history of thoracic radiotherapy will undergo pulmonary function testing that may include, but is not limited to, spirometry and assessment of diffusion capacity done during the screening period to assist the determination of suitability on the study. For test results indicative of significantly impaired pulmonary function, eg, resting pulse oximetry < 90% on room air and further desaturation upon exercise, forced expiratory volume in one second (FEV1) < 60% or carbon monoxide diffusing capacity (DLCO) (if performed) < 60% of age- and sex-adjusted predicted performance levels, the medical monitor needs to be consulted to confirm eligibility. Patients with low pulmonary function will not be advised for enrollment.

q. Blood biomarker: Refer to Appendix 1F.

r. Receptor occupancy assay: Refer to Appendix 1F.

s. Tumor imaging will be performed ≤ 28 days before the first dose of study drugs. Results of standard-of-care tests or examinations performed before informed consent has been obtained and ≤ 28 days before the first dose of study drugs may be used for the purposes of screening rather than repeating the standard-of-care tests. During the study, tumor imaging will be performed approximately every 6 weeks (± 7 days) for the first 54 weeks, then every 12 weeks (± 7 days) after 54 weeks (eg, Week 6, Week 12, …, Week 48, Week 54, Week 66, Week 78, Week 90, etc.), based on RECIST v1.1. Tumor assessments must include CT scans (with oral/intravenous contrast, unless contraindicated) or MRI of the brain, chest, abdomen, and pelvis. All measurable and evaluable lesions should be assessed and documented at the Screening Visit and reassessed at each subsequent tumor evaluation. The same radiographic procedure used to assess disease sites at screening must be used throughout the study (eg, the same contrast protocol for CT scans). See Section 8.5 for more information.

t. Archival or fresh tumor tissue: Refer to Appendix 1F.

u. Ociperlimab will be given intravenously on Cycle 1 Day 1, Cycle 2 Day 1 and once every 3 weeks thereafter (Section 5.2.1). NOTE: Ociperlimab must always be prepared and administered separately from any other systemic medication including tislelizumab. When ociperlimab infusion takes place on the same day with tislelizumab, ociperlimab infusion must always occur after infusion of tislelizumab has been completed.

v. For dose escalation in Australia, tislelizumab will be given intravenously on Cycle 1 Day 8, Cycle 2 Day 1, and once every 3 weeks thereafter for the remainder of treatment (Section 5.2.1). NOTE: Tislelizumab must always be prepared and administered separately from any other systemic medication including ociperlimab. When tislelizumab infusion takes place on the same day with ociperlimab, ociperlimab infusion must always occur after infusion of tislelizumab has completed.

w. For dose verification in China, tislelizumab will be given intravenously on Cycle 1 Day 1, Cycle 2 Day 1, and once every 3 weeks thereafter for the remainder of treatment in Cohort 1B and Cohort 2B (Section 5.2.2). NOTE: Tislelizumab must always be prepared and administered separately from any other systemic medication including ociperlimab. Ociperlimab infusion must always occur after infusion of tislelizumab has completed.

x. PK and ADA: refer to Appendix 1C.

APPENDIX 1B. PHASE 1B SCHEDULE OF ASSESSMENTS

Phase 1b assessment	**Screening** [a]	**Treatment Cycles**				**EOT Visit** [b]	**Safety Follow-up Visit** [b] **Safety follow-up by telephone** [c]			**Efficacy follow-up** [d]	**Survival follow-up** [w]
		Cycles 1 to 6 (Every 21 days)			**≥ Cycle 7 (Every 21 days)**						
Visit day	**- 28 to - 1**	**1**	**8** [v]	**15** [v]	**1**	**EOT decision**	**+ 30 days (Visit)**	**+ 60 days (Phone call)**	**+ 90 days (Phone call)**		**Every 3 months**
Visit window		**± 3** [y]	**± 1**	**± 2**	**± 3**	**± 7**	**± 7**	**± 14**	**± 14**		**± 14**
Informed consent	x										
Inclusion/exclusion criteria	x										
Demographics/medical history/prior medications [e]	x										
Height, weight, and vital signs [f]	x	x [f]			x [f]	x	x				
Physical examination [g]	x	x			x	x	x				
ECOG Performance Status	x	x			x	x	x				
Triplicate 12-lead ECG [h]	x	As clinically indicated				x	x				
Adverse events [i]	x	x	x [v]	x [v]	x	x	x	x	x		
Concomitant medications	x	x	x [v]	x [v]	x	x	x	x	x		
Hematology [j]	x [j]	x	x [v]	x [v]	x [j]	x	x				

Phase 1b assessment	**Screening** [a]	**Treatment Cycles**				**EOT Visit** [b]	**Safety Follow-up Visit** [b] **Safety follow-up by telephone** [c]			**Efficacy follow-up** [d]	**Survival follow-up** [w]
		Cycles 1 to 6 (Every 21 days)			**≥ Cycle 7 (Every 21 days)**						
Visit day	**- 28 to - 1**	**1**	**8** [v]	**15** [v]	**1**	**EOT decision**	**+ 30 days (Visit)**	**+ 60 days (Phone call)**	**+ 90 days (Phone call)**		**Every 3 months**
Visit window		**± 3** [y]	**± 1**	**± 2**	**± 3**	**± 7**	**± 7**	**± 14**	**± 14**		**± 14**
Serum chemistry [j]	x [j]	x	x [v]	x [v]	x [j]	x	x				
Coagulation parameters [j]	x [j]	As clinically indicated [j]				x	x				
Urinalysis [j]	x	As clinically indicated [j]									
CK and CK-MB [k]	x	x			x	x	x				
Pregnancy test [l]	x [l]	x [l]			x [l]	x	x				
Thyroid function (every 3 cycles) [m]	x [m]	x [m]			x [m]	x	x [m]				
HBV/HCV tests [n]	x [n]	As clinically indicated									
Pulmonary function tests [o]	x [o]	As clinically indicated									
PK and ADA [x]		Refer to Pharmacokinetic and Immunogenicity Table, Appendix 1D and Appendix 1E									
Blood biomarkers [p]		Refer to Biomarker Table, Appendix 1G									
Tumor assessment [q]	x	For the first 54 weeks, every 6 weeks. Every 12 weeks thereafter								x	
Archival or fresh tumor tissue [r]	x	Refer to Biomarker Table, Appendix 1G									

Phase 1b assessment	**Screening** [a]	**Treatment Cycles**				**EOT Visit** [b]	**Safety Follow-up Visit** [b] **Safety follow-up by telephone** [c]			**Efficacy follow-up** [d]	**Survival follow-up** [w]
		Cycles 1 to 6 (Every 21 days)			**≥ Cycle 7 (Every 21 days)**						
Visit day	**- 28 to - 1**	**1**	**8** [v]	**15** [v]	**1**	**EOT decision**	**+ 30 days (Visit)**	**+ 60 days (Phone call)**	**+ 90 days (Phone call)**		**Every 3 months**
Visit window		**± 3** [y]	**± 1**	**± 2**	**± 3**	**± 7**	**± 7**	**± 14**	**± 14**		**± 14**
Ociperlimab administration [s]		x			x						
Tislelizumab administration [t]		x			x						
Chemotherapy [u]		x									
Survival Status											x

Abbreviations: ADA, antidrug antibody; AE, adverse event; CK, creatine kinase; CK-MB, creatine kinase-muscle/brain; CT, computed tomography; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, End-of-Treatment (Visit), HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; imAE, immune-mediated AE; MRI, magnetic resonance imaging; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; PD, progressive disease; PK, pharmacokinetic; Q3W, once every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; T3, triiodothyronine; T4, thyroxine.

Note: Timepoints containing numbers represent timepoints with special considerations for that respective assessment.

a. Written informed consent is required before performing any study-specific procedure. Results of standard-of-care tests or examinations performed before informed consent has been obtained and ≤ 28 days before the first dose of study drugs may be used for screening assessments rather than repeating such tests unless otherwise indicated. The ICF signature alone does not define the start of the Screening Period, but the first study-related assessment date is to be used for the date of the Screening Visit.

b. The EOT Visit is conducted when the investigator determines that study treatment(s) will no longer be used. Patients who discontinue treatment for any reason will be asked to return to the clinic for the EOT Visit within 7 days when the EOT decision is made unless otherwise specified or before the initiation of a new anticancer treatment, whichever occurs first. If routine laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the EOT Visit, these tests need not be repeated. Tumor assessment is not required at the EOT/Safety Follow-up Visit if < 6 weeks has passed since the last assessment.

c. Patients who permanently discontinue ociperlimab/tislelizumab will be asked to return to the clinic for the on-site Safety Follow-up Visit, which is required to be conducted 30 days (± 7 days) after the last dose of ociperlimab/tislelizumab or before the initiation of subsequent anticancer therapy, whichever occurs first. If the time windows of this Safety Follow-up Visit and EOT Visit are overlapped, the safety follow-up can be exempted and the tests required at Safety Follow-up Visit will be conducted at the EOT Visit. In addition, 2 additional Safety Follow-up Visits (by telephone contact) 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 ociperlimab/tislelizumab, regardless of whether patients started a new subsequent anticancer therapy. If patients report a suspected imAE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated.

d. Efficacy follow-up period: Patients who discontinue study drugs for reasons other than PD (eg, toxicity) will continue to undergo tumor assessments following the tumor assessment plan until the patient experiences PD, starts subsequent anticancer therapy, or for any other reason listed in Section 7.5.2, whichever occurs first.

e. Includes year of birth (or age), gender, self-reported race, 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.

f. Height assessment is required only at screening. Vital signs will include measurements of temperature (˚C), pulse rate, and blood pressure (systolic and diastolic) while the patient is in a seated position after resting for 10 minutes. When both ociperlimab and tislelizumab are administered, vital signs are required to be measured at 3 timepoints (≤ 60 minutes before the infusion, during the infusion, and ≤ 30 minutes after end of infusion) during all visits.

g. Refer to Section 8.2.2 for details regarding physical examination assessment requirements for screening and subsequent timepoints. In addition, investigators should solicit patients regarding changes in vision, visual disturbance, or ocular inflammation at each scheduled study visit during study treatment. For any change in vision, referral to an appropriate specialist will be made for further management guidance.

h. The triplicate ECG recordings will be performed at the timepoints specified in the table and when clinically indicated. All ECGs are to be obtained before other assessments scheduled at that same time (eg, vital sign measurements, blood draws, etc). 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.

i. The AEs and laboratory abnormalities will be graded per NCI-CTCAE v5.0. All AEs will also be evaluated for seriousness. After the ICF has been signed, but before the administration of study drugs, only SAEs should be reported to the sponsor. After initiation of study drugs, all AEs and SAEs, regardless of relationship to study drugs, will be reported until either 30 days after last dose of study drugs or initiation of subsequent anticancer therapy, whichever occurs first. Immune-mediated AEs (serious or nonserious) should be reported until 90 days after the last dose of ociperlimab and/or tislelizumab, regardless of whether or not the patient starts a subsequent anticancer therapy. If the investigator learns of any study drug-related SAE, including a death, at any time after a patient has been discharged from the study, he/she should notify the sponsor using the SAE reporting procedure.

j. Local laboratory assessments of clinical chemistry, hematology, coagulation, and urinalysis will be conducted as outlined in Appendix 2. If clinical chemistry, hematology, and coagulation at screening are not performed ≤ 7 days before study drug administration on Day 1 of Cycle 1, these tests should be repeated and reviewed before study drug administration. Hematology and clinical chemistry (data collected as specified in Appendix 2) will be performed within 3 days before Day 1 of each cycle (except for nab-paclitaxel administration, hematology and clinical chemistry will be performed weekly on Day 8 and Day 15 of each cycle for 4 to 6 cycles, see footnote v). The required weekly hematology and serum chemistry tests may take place at an alternative hospital/clinic near the patient's home at the investigator's discretion. The investigator's permission and choice of hospital/clinic should be documented in the patient chart and the medical monitor needs to be notified. Those tests should be taken in one approved hospital/clinic. The test results from this hospital/clinic are acceptable. Urinalysis and/or coagulation test will be conducted during the treatment period only if clinically warranted. Refer to Section 9.3.5 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.

k. CK and CK-MB levels will be evaluated within 3 days before the timepoints specified within the table and when clinically indicated. If the site's laboratory does not perform CK-MB testing, serum troponins (troponin I and/or T) measurements should be performed instead of CK-MB, while CK test should be completed together; if only 1 of the troponins is assessed per local standards that same test should be evaluated throughout. If significant

abnormalities are detected, the affected patients should be evaluated for possible myocarditis/myositis per institutional guidelines, including additional serum CK/CK-MB, serum troponin levels, ECG, etc.

l. 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 ≤ 7 days before the first dose of study drugs. A negative pregnancy test (by urine or blood) must be completed and recorded ≤ 72 hours before the administration of study drugs at each cycle. Pregnancy tests will also be performed at the EOT Visit and each Safety Follow-up Visit, until 120 days after the last dose of ociperlimab and/or tislelizumab or 180 days after the last dose of chemotherapy, whichever comes later. During the Safety Follow-up period, the pregnancy results (local results are acceptable) will be collected by the investigator or designee via phone call. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.

m. Analysis of free T3, free T4, and thyroid stimulating hormone will be performed by a central laboratory and/or the local study site laboratory. Thyroid function tests will be performed at screening and every 3 cycles after then (eg, Cycles 4, 7, 10, etc) and at EOT/Safety Follow-up Visit. Total T3 can be tested as alternative for free T3 and total T4 can be tested as an alternative to free T4. For patients who skip a dose, extra thyroid function tests will be performed based on the investigator's assessment.

n. Testing will be performed by local laboratory at screening and will include HBV/HCV serology (HBsAg, HBsAb, HBcAb, and HCV antibodies), and viral load assessment (HBV DNA and HCV ribonucleic acid). For patients with negative HBsAg or negative HCV antibody, HBV DNA or HCV RNA is optional based on clinical practice. Samples for hepatitis serology and viral load will be collected at screening and may be tested if patients have hepatic AEs (≥ Grade 3) during the study and as clinically indicated.

o. Patients who are suspected of having or known to have serious/severe respiratory conditions or exhibit significant respiratory symptoms unrelated to the underlying cancer, or with a history of thoracic radiotherapy will undergo pulmonary function testing that may include, but is not limited to, spirometry and assessment of diffusion capacity done during the screening period to assist the determination of suitability on the study. For test results indicative of significantly impaired pulmonary function, eg, resting pulse oximetry < 90% on room air and further desaturation upon exercise, forced expiratory volume in one second (FEV1) < 60% or carbon monoxide diffusing capacity (DLCO) (if performed) < 60% of age- and sex-adjusted predicted performance levels, the medical monitor needs to be consulted to confirm eligibility. Patients with low pulmonary function will not be advised for enrollment.

p. Blood biomarkers: Refer to Appendix 1G.

q. Tumor imaging will be performed ≤ 28 days before the first dose of study drugs. Results of standard-of-care tests or examinations performed before informed consent has been obtained and ≤ 28 days before the first dose of study drugs may be used for the purposes of screening rather than repeating the standard-of-care tests. During the study, tumor imaging will be performed approximately every 6 weeks (± 7 days) for the first 54 weeks, then every 12 weeks (± 7 days) after 54 weeks (eg, Week 6, Week 12, …, Week 48, Week 54, Week 66, Week 78, Week 90, etc.), based on RECIST v1.1. Tumor assessments must include CT scans (with oral/intravenous contrast, unless contraindicated) or MRI, with preference for CT, of the chest, abdomen, and pelvis. An MRI (or CT scan if MRI is contraindicated or not readily available) of the head is required at screening; bone scan or PET is required if clinically indicated. 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). See Section 8.5 for more information.

r. Archival or fresh tumor tissue: Refer to Appendix 1G.

s. Ociperlimab will be given intravenously on Day 1 of each 21-day cycle (Q3W) (Section 5.1.3). Note: Ociperlimab must always be prepared and administered separately from any other systemic medication including tislelizumab. When ociperlimab infusion takes place on the same day with tislelizumab, ociperlimab infusion must always occur after infusion of tislelizumab has completed.

t. Tislelizumab will be given intravenously on Day 1 of each 21-day cycle (Q3W) (Section 5.2). Note: Tislelizumab must not be concurrently infused with any other drug.

u. According to pathological diagnosis of primary disease, chemotherapy will be given 6 cycles (pemetrexed plus platinum will be given for 4 to 6 cycles for patients with non-squamous NSCLC, paclitaxel/nab-paclitaxel plus platinum will be given for 4 to 6 cycles for patients with squamous NSCLC, and

etoposide plus platinum will be given for 4 cycles for ES-SCLC). For patients with non-squamous NSCLC and whose disease has not progressed after 4 to 6 cycles of doublet chemotherapy, maintenance treatment of pemetrexed is permitted. For patients with G/GEJ adenocarcinoma and whose disease has not progressed after 6 cycles of oxaliplatin and capecitabine, optional maintenance treatment of capecitabine is permitted. All chemotherapy agents will be given on Day 1 of each cycle, every 3 weeks (nab-paclitaxel will be administered on D1, D8, and D15 of each cycle for 4 to 6 cycles for patients with squamous NSCLC, etoposide 100 mg/m^2 will be administered on Day 1 to Day 3 for 4 cycles for patient with ES-SCLC, 5-fluorouracil 750 to 800 mg/m^2 will be administered on D1 to D5 of each cycle for 6 cycles for patients with ESCC and EAC, capecitabine 1000 mg/m^2 twice a day will be administered on D1 to D14 of each cycle for up to 6 cycles for patients with G/GEJ adenocarcinoma). Refer to Section 5.2 for drug administration in details.

v. A. Procedures during on-site visits for on Day 8 and Day 15 only apply to patients in Cohort 1 with squamous NSCLC receiving nab-paclitaxel at the investigator's discretion for 4 to 6 cycles: hematology and serum chemistry will be performed on D8 and D15 of each cycle.
B. Phone calls by site are recommended on Day 8 and Day 15 for patients in other cohorts than cohort 1 with squamous NSCLC receiving nab-paclitaxel. It is recommended to collect data of AEs and concomitant medications by phone calls. The patient should be asked if any new symptoms have been observed or existing symptoms may have worsened, and if there has been any change to medications. The investigators need to remind patients to return to the clinical study site for further assessment if new AEs arise or worsen.
C. For patients who receive chemotherapy combination therapy (Cohorts 1, 2, 4, 6, 7, and 9), extra hematology and serum chemistry by site or other local hospitals is recommended to be conducted no later than Day 5 of each cycle.

w. Patients will be followed for survival and to obtain information on subsequent anticancer therapy information after discontinuation of study treatment via telephone calls, patient medical records, and/or clinic visits every 3 months (± 14 days) after the 30-day Safety Follow-up Visit or as directed by the sponsor until death, withdrawal of consent, loss to follow-up, or end of study.

x. PK and ADA: refer to Appendix 1D and Appendix 1E.

y. For Cycle 2 Day 1 and the following cycles, a 3-day window is allowed.

APPENDIX 1C. PHASE 1 PHARMACOKINETIC AND IMMUNOGENICITY SAMPLING SCHEDULE FOR OCIPERLIMAB AND TISLELIZUMAB

For Dose Escalation in Australia

Study Week	Study Visit	Time	PK	ADA
1	Cycle 1, Day 1	Predose (-60 min to predose) [a]	Ociperlimab PK	Ociperlimab ADA
		30 (±10) min after end of infusion [b]	Ociperlimab PK	
	Cycle 1, Day 2	24 (± 6) hr after end of infusion on Day 1	Ociperlimab PK	
	Cycle 1, Day 4	72 (± 12) hr after end of infusion on Day 1	Ociperlimab PK	
2	Cycle 1, Day 8 (± 1 day)	Predose (-60 min to predose) [a]	Ociperlimab PK & tislelizumab PK	Tislelizumab ADA
		30 (±10) min after end of tislelizumab infusion	Tislelizumab PK	
3	Cycle 1, Day 15 (± 1 day)	At visit	Ociperlimab PK	
5	Cycle 2, Day 1	Predose (-60 min to predose) [a]	Ociperlimab PK & tislelizumab PK	Ociperlimab ADA & tislelizumab ADA
		30 (±10) min after end of infusion [b]	Ociperlimab PK	
14	Cycle 5, Day 1	Predose (-60 min to predose) [a]	Ociperlimab PK & tislelizumab PK	Ociperlimab ADA & tislelizumab ADA
		30 (±10) min after end of infusion [b]	Ociperlimab PK & tislelizumab PK	
15	Cycle 5, Day 8 (± 1 day)	At visit	Ociperlimab PK	
16	Cycle 5, Day 15 (± 1 day)	At visit	Ociperlimab PK	
17	Cycle 6, Day 1	Predose (-60 min to predose) [a]	Ociperlimab PK & tislelizumab PK	Ociperlimab ADA & tislelizumab ADA
		30 (±10) min after end of infusion [b]	Ociperlimab PK	
26	Cycle 9, Day 1	Predose (-60 min to predose) [a]	Ociperlimab PK & tislelizumab PK	Ociperlimab ADA & tislelizumab ADA

Study Week	Study Visit	Time	PK	ADA
38	Cycle 13, Day 1	Predose (-60 min to predose) [a]	Ociperlimab PK & tislelizumab PK	Ociperlimab ADA & tislelizumab ADA
50	Cycle 17, Day 1	Predose (-60 min to predose) [a]	Ociperlimab PK & tislelizumab PK	Ociperlimab ADA & tislelizumab ADA
74	Cycle 25, Day 1	Predose (-60 min to predose) [a]	Ociperlimab PK & tislelizumab PK	Ociperlimab ADA & tislelizumab ADA
30-day Safety Follow-up Visit		30 (± 7) days after last dose	Ociperlimab PK & tislelizumab PK	Ociperlimab ADA & tislelizumab ADA

Abbreviations: ADA, antidrug antibody; PK, pharmacokinetic; min, minute; hr, hour

Note: Sample collection must be from the arm opposite the one that was used for the study drug infusion. If drug was administered via a central venous catheter, sample collection for PK and ADA should be from a different site.

a. Predose (- 60 min to predose): ≤ 60 minutes before the infusion of the first immunotherapy product

b. 30 (± 10) min after end of infusion: 30 (± 10) min after of end of the last immunotherapy product

For Dose Verification in China (Tislelizumab PK and ADA Samples Not Required for Monotherapy Cohorts) [a]

Study week	Study visit	Time	PK	ADA
1	Cycle 1, Day 1	Predose (-60 min to predose) [b]	Ociperlimab PK & tislelizumab PK	Ociperlimab ADA & tislelizumab ADA
		30 (±10) min after end of infusion [c]	Ociperlimab PK & tislelizumab PK	
	Cycle 1, Day 2	24 (±6) hr after end of infusion [c] on Day 1	Ociperlimab PK	
	Cycle 1, Day 4	72 (±12) hr after end of infusion [c] on Day 1	Ociperlimab PK	
2	Cycle 1, Day 8 (± 1 day)	At visit	Ociperlimab PK	
3	Cycle 1, Day 15 (± 1 day)	At visit	Ociperlimab PK	
4	Cycle 2, Day 1	Predose (-60 min to predose) [b]	Ociperlimab PK & tislelizumab PK	Ociperlimab ADA & tislelizumab ADA
		30 (±10) min after end of infusion [c]	Ociperlimab PK	
13	Cycle 5, Day 1	Predose (-60 min to predose) [b]	Ociperlimab PK & tislelizumab PK	Ociperlimab ADA & tislelizumab ADA
		30 (±10) min after end of infusion [c]	Ociperlimab PK & tislelizumab PK	
14	Cycle 5, Day 8 (± 1 day)	At visit	Ociperlimab PK	
15	Cycle 5, Day 15 (± 1 day)	At visit	Ociperlimab PK	
16	Cycle 6, Day 1	Predose (-60 min to predose) [b]	Ociperlimab PK & tislelizumab PK	Ociperlimab ADA & tislelizumab ADA
		30 (±10) min after end of infusion [c]	Ociperlimab PK	
25	Cycle 9, Day 1	Predose (-60 min to predose) [b]	Ociperlimab PK & tislelizumab PK	Ociperlimab ADA & tislelizumab ADA
37	Cycle 13, Day 1	Predose (-60 min to predose) [b]	Ociperlimab PK & tislelizumab PK	Ociperlimab ADA & tislelizumab ADA

Study week	Study visit	Time	PK	ADA
49	Cycle 17, Day 1	Predose (-60 min to predose) [b]	Ociperlimab PK & tislelizumab PK	Ociperlimab ADA & tislelizumab ADA
73	Cycle 25, Day 1	Predose (-60 min to predose) [b]	Ociperlimab PK & tislelizumab PK	Ociperlimab ADA & tislelizumab ADA
30-day Safety Follow-up Visit		30 (± 7) days after last dose	Ociperlimab PK & tislelizumab PK	Ociperlimab ADA & tislelizumab ADA

Abbreviations: ADA, antidrug antibody; PK, pharmacokinetic; min, minute; hr, hour

Note: Sample collection must be from opposite arm to that used for study drug infusion. If the drug was administered via a central venous catheter, sample collection for PK and ADA should be from a different site.

a. Tislelizumab PK and ADA samples will be collected only for combination therapy cohort or cohorts.

b. Predose (- 60 min to predose): ≤ 60 minutes before the infusion of the first immunotherapy product

c. 30 (± 10) min after end of infusion: 30 (± 10) min after of end of the last immunotherapy product

APPENDIX 1D. PHASE 1B PHARMACOKINETIC AND IMMUNOGENICITY SAMPLING FOR OCIPERLIMAB AND TISLELIZUMAB WITH OR WITHOUT CHEMOTHERAPY FOR COHORTS 1 TO 9

Study Week	Study Visit	Time	PK	ADA
1	Cycle 1, Day 1	Predose (- 60 min to predose) [a]	Tislelizumab PK and ociperlimab PK	Tislelizumab ADA and ociperlimab ADA
		30 (± 10) min after end of infusion [b]	Tislelizumab PK and ociperlimab PK	
4	Cycle 2, Day 1	Predose (- 60 min to predose) [a]	Tislelizumab PK and ociperlimab PK	Tislelizumab ADA and ociperlimab ADA
13	Cycle 5, Day 1	Predose (- 60 min to predose) [a]	Tislelizumab PK and ociperlimab PK	Tislelizumab ADA and ociperlimab ADA
		30 (± 10) min after end of infusion [b]	Tislelizumab PK and ociperlimab PK	
16	Cycle 6, Day 1	Predose (- 60 min to predose) [a]	Tislelizumab PK and ociperlimab PK	Tislelizumab ADA and ociperlimab ADA
25	Cycle 9, Day 1	Predose (- 60 min to predose) [a]	Tislelizumab PK and ociperlimab PK	Tislelizumab ADA and ociperlimab ADA
37	Cycle 13, Day 1	Predose (- 60 min to predose) [a]	Tislelizumab PK and ociperlimab PK	Tislelizumab ADA and ociperlimab ADA
49	Cycle 17, Day 1	Predose (- 60 min to predose) [a]	Tislelizumab PK and ociperlimab PK	Tislelizumab ADA and ociperlimab ADA
73	Cycle 25, Day 1	Predose (- 60 min to predose) [a]	Tislelizumab PK and ociperlimab PK	Tislelizumab ADA and ociperlimab ADA
30-day Safety Follow-up Visit		30 (± 7) days after last dose	Tislelizumab PK and ociperlimab PK	Tislelizumab ADA and ociperlimab ADA

Abbreviations: ADA, antidrug antibody; min, minutes; PK, pharmacokinetic

Note: Sample collection must be from opposite arm to that used for study drug infusion. If drug was administered via a central venous catheter, sample collection for PK & ADA should be from a different site.

a. Predose (- 60 min to predose): ≤ 60 minutes before the infusion of the first immunotherapy product

b. 30 (± 10) min after end of infusion: 30 (± 10) min after of end of the last immunotherapy product

APPENDIX 1E. PHASE 1B COHORT 10 PHARMACOKINETIC AND IMMUNOGENICITY SAMPLING FOR OCIPERLIMAB AND TISLELIZUMAB

Study Week	Study Visit	Time	PK	ADA
1	Cycle 1, Day 1	Predose (- 60 min to predose) [a]	Tislelizumab PK and ociperlimab PK	Tislelizumab ADA and ociperlimab ADA
		30 (± 10) min after end of infusion [b]	Tislelizumab PK and ociperlimab PK	NA
2	Cycle 1, Day 8 (± 1 day)	At visit	Ociperlimab PK	NA
3	Cycle 1, Day 15 (± 1 day)	At visit	Ociperlimab PK	NA
4	Cycle 2, Day 1	Predose (- 60 min to predose) [a]	Tislelizumab PK and ociperlimab PK	Tislelizumab ADA and ociperlimab ADA
13	Cycle 5, Day 1	Predose (- 60 min to predose) [a]	Tislelizumab PK and ociperlimab PK	Tislelizumab ADA and ociperlimab ADA
		30 (± 10) min after end of infusion [b]	Tislelizumab PK and ociperlimab PK	
16	Cycle 6, Day 1	Predose (- 60 min to predose) [a]	Tislelizumab PK and ociperlimab PK	Tislelizumab ADA and ociperlimab ADA
25	Cycle 9, Day 1	Predose (- 60 min to predose) [a]	Tislelizumab PK and ociperlimab PK	Tislelizumab ADA and ociperlimab ADA
37	Cycle 13, Day 1	Predose (- 60 min to predose) [a]	Tislelizumab PK and ociperlimab PK	Tislelizumab ADA and ociperlimab ADA
49	Cycle 17, Day 1	Predose (- 60 min to predose) [a]	Tislelizumab PK and ociperlimab PK	Tislelizumab ADA and ociperlimab ADA
73	Cycle 25, Day 1	Predose (- 60 min to predose) [a]	Tislelizumab PK and ociperlimab PK	Tislelizumab ADA and ociperlimab ADA
30-day Safety Follow-up Visit		30 (± 7) days after last dose	Tislelizumab PK and ociperlimab PK	Tislelizumab ADA and ociperlimab ADA

Abbreviations: ADA, antidrug antibody; min, minutes; NA, not applicable; PK, pharmacokinetic

Note: Sample collection must be from the arm opposite to that used for study drug infusion. If the study drug was administered via a central venous catheter, sample collection for PK and ADA should be from a different site.

a. Predose (- 60 min to predose): ≤ 60 minutes before the infusion of the first immunotherapy product

b. 30 (± 10) min after end of infusion: 30 (± 10) min after of end of the last immunotherapy product

APPENDIX 1F. PHASE 1 BLOOD AND TISSUE BIOMARKER ANALYSIS

For Dose Escalation in Australia

Biomarker assessment	Screening	Treatment Period								
		Cycle 1 [a]				Cycle 2	Cycle 3	Cycle 5	Patients with first PR or CR	EOT Visit after confirmed disease progression
Visit day (days)	**- 28 to - 1**	**1**	**2**	**8**	**15**	**1**	**1**	**1**		**0 to 7**
Ociperlimab/TIGIT receptor occupancy		X	X (24 hours ± 2 hours after end of infusion)	X	X	X		X		
Tislelizumab/PD-1 receptor occupancy		X				X		X		
Blood-based PD biomarker	X	X		X	X	X	X			
Cytokine or soluble proteins in blood		X	X (24 hours ± 2 hours after end of ociperlimab infusion)	X	X	X	X		X (first treatment after confirmation)	X [c]
ctDNA	X								X (first treatment after confirmation)	X [c]
Archival or fresh tumor tissue [b]	X						X (optional)			X (optional)

Abbreviations: C, Cycle; CR, complete response; ctDNA, circulating tumor DNA; D, Day; EOT, End-of-Treatment; FFPE, formalin fixed paraffin embedded; PD, pharmacodynamic; PD-1, programmed cell death protein-1; PR, partial response; TIGIT, T-cell immunoreceptor with Ig and ITIM domains

a. At C1D8, C1D1, C2D1, C3D1 and C5D1, the blood samples should be collected before tislelizumab infusion. Refer to the laboratory manual for additional detailed information.

b. Archival or fresh tumor tissue: archival tumor tissues (FFPE blocks or approximately 15 unstained slides) or fresh biopsy are highly recommended for biomarker analysis. If feasible, post-treatment biopsies should be taken from the same tumor lesion as the baseline biopsy/archival tumor tissues. Written patient informed consent is required for optional fresh tumor biopsies.

c. Blood samples should be collected at EOT Visit after confirmed disease progression.

For Dose Verification in China

Biomarker assessment	Screening	Treatment period								
		Cycle 1[a]				Cycle 2	Cycle 3	Cycle 5	Patients with first PR or CR	EOT Visit after confirmed disease progression
Visit day (days)	**-28 to -1**	**1**	**2**	**8**	**15**	**1**	**1**	**1**		**0 to 7**
Ociperlimab/TIGIT receptor occupancy		X	X (24 hours ± 2 hours after end of ociperlimab infusion)	X	X	X		X		
Tislelizumab/PD-1 receptor occupancy [b]		X				X		X		
RNA-seq (blood)		X		X	X	X	X		X	X [e]
Cytokine/soluble proteins (blood)		X	X (24 hours ± 2 hours after end of ociperlimab infusion)	X	X	X	X		X	X [e]
ctDNA (blood)	X								X	X [e]
Archival or fresh tumor tissue [c]	X								X (optional)	X (optional)
Immunophenotyping (blood)		X		X	X	X				

Abbreviations: CR, complete response; ctDNA, circulating tumor DNA; EOT, End-of-Treatment; FFPE, formalin fixed paraffin embedded; PD, pharmacodynamic; PD-1, programmed cell death protein-1; PR, partial response; RNA-seq, RNA sequencing; TIGIT, T-cell immunoreceptor with Ig and ITIM domains

a. Per current protocol, patient may or may not receive tislelizumab on Cycle 1 Day 8 (C1D8) during first cycle. If the patients receive tislelizumab on C1D8, then the blood samples should be collected before tislelizumab infusion. Blood samples at C1D1, C2D1, C3D1 and C5D1 should be collected before dosing. Refer to the laboratory manual for additional detailed information.

b. Tislelizumab/PD-1 receptor occupancy assay: For the cohorts receiving ociperlimab as monotherapy (Cohort 1A/2A), tislelizumab/PD-1 receptor occupancy assay will not be tested.

c. Archival or fresh tumor tissue: archival tumor tissues (FFPE blocks or approximately 15 unstained slides) or fresh biopsy are highly recommended for biomarker analysis. If feasible, post-treatment biopsies should be taken from the same tumor lesion as the baseline biopsy/archival tumor tissues. Written patient informed consent is required for optional fresh tumor biopsies.

d. If the ctDNA sample collection is missed during screening period, it's acceptable to collect the sample before dosing on Cycle 1 Day 1.

e. Blood samples should be collected at EOT Visit after confirmed disease progression.

APPENDIX 1G. PHASE 1B BLOOD AND TISSUE BIOMARKER ANALYSIS

Biomarker assessment	Cohort	Screening	Treatment Period							
			Cycle 1[e]			Cycle 2 [e]	Cycle 3 [e]	Cycle 5 [e]	Patients with first PR or CR	EOT Visit after confirmed disease progression
Visit Day (Days)		**-28 to -1**	**1**	**8**	**15**	**1**	**1**	**1**		**0 to 7**
Ociperlimab/TIGIT receptor occupancy [a]	Cohort 10 only		X	X	X	X		X		
Immunophenotyping (blood) [a]	Cohorts 3 and 5 only [c]		X	X	X	X		X		
RNA-seq (blood) [a]	Cohorts 3 and 5 only [c]		X	X	X	X				
Cytokine/soluble proteins (blood) [a]	Cohorts 3, 5, and 10 only [c]		X	X	X	X				
ctDNA-based gene mutation profile and Fc gamma receptor polymorphism (blood) [a,b]	All cohorts		X				X			X
Archival or fresh tumor tissue [d]	All cohorts	X				X (optional)			X (optional)	X (optional)

Abbreviations: CPI, checkpoint inhibitor; CR, complete response; ctDNA, circulating tumor DNA; EOT, End-of-Treatment; FFPE, formalin fixed paraffin embedded; HGRAC, Human Genetic Resource Administration of China; hr, hours; MSI, microsatellite instability; NSCLC, non-small cell lung cancer; PD, pharmacodynamic; PD-L1, programmed cell death protein-ligand 1; PR, partial response; RNA-seq, RNA sequencing; TMB, tumor mutation burden.

a. Blood-based immunophenotyping will include peripheral immune cell quantification, and phenotype change. Blood samples will be collected at designated timepoints for prespecified cohorts. Please refer to the laboratory manual for additional detailed information.

b. Blood samples will be taken at predose on Day 1 of Cycle 1, predose on Day 1 of Cycle 3, and at EOT Visit after confirmed disease progression to evaluate ctDNA-based gene mutation profiles (including TMB and MSI) and Fc gamma receptor polymorphism. Please refer to the laboratory manual for additional detailed information.

c. Cohort 3, PD-L1 positive NSCLC cohorts; Cohort 5, CPI-experienced NSCLC cohort.

d. All patients are required to provide archival or fresh tumor tissues (FFPE blocks [preferred] or approximately 15 freshly cut unstained slides [≥ 8 slides are mandatory]) for biomarker analysis. Prospective PD-L1 testing at central laboratory is mandatory for patients in Cohorts 3, 8, and 10. Retrospective collection of exploratory screening archival tissues for China patients is acceptable after HGRAC approval to exploratory analysis. If feasible, post-treatment biopsies should be taken from the same tumor lesion as the baseline biopsy/archival tumor tissues. Written patient informed consent is required for optional post-treatment fresh tumor biopsies. Please refer to Section 8.4 for detailed tissue sample collection requirements.

[e.] On Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1, and Cycle 5 Day 1, blood samples should be collected before dosing.

APPENDIX 2. CLINICAL LABORATORY ASSESSMENTS

Clinical chemistry	**Hematology**	**Coagulation**	**Urinalysis (screening and as clinically indicated)**
Alkaline phosphatase	Red blood cell count	Prothrombin time	pH
Alanine aminotransferase	Hematocrit	Partial thromboplastin time or activated partial thromboplastin time	Specific gravity
Aspartate aminotransferase	Hemoglobin	International normalized ratio	Glucose
Albumin	Monocyte count		Protein
Total bilirubin	Basophil count		Ketones
Blood urea nitrogen or urea	Eosinophil count		Blood
Potassium	Platelet counts		24-hour protein[a]
Sodium	White blood cell count [c]		
Calcium	Neutrophil count		
Creatinine	Lymphocyte count		
Fast glucose			
Lactate dehydrogenase			
Total protein			
Lipase			
Amylase			
Testosterone[b]			
Creatine kinase			

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

[b.] Testosterone assay is only for patients with metastatic castration-resistant prostate cancer. However, the testosterone levels do not need to be checked if the patient has undergone surgical castration for > 4 months before the first dose of study drug. Patients receiving chemical castration should have their testosterone levels checked at baseline and confirmed to be at the castrate levels (< 0.5 ng/mL or 1.735 nM).

[c.] White blood cell count measurements could be adjusted based on local practice with approval of medical monitor

APPENDIX 3. ECOG PERFORMANCE STATUS

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

As published by (Oken et al 1982). Eastern Cooperative Oncology Group, Robert Comis MD, Group Chair.

APPENDIX 4. PRE-EXISTING IMMUNE DEFICIENCIES OR AUTOIMMUNE DISEASES

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

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

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

APPENDIX 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. 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 patient 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," and "Nonsterile males"

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

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

- Surgically sterile (ie, through bilateral salpingectomy, bilateral oophorectomy, or hysterectomy)
- Postmenopausal, defined as:
  - ≥ 55 years of age with no spontaneous menses for ≥ 12 months OR
  - < 55 years of age with no spontaneous menses for ≥ 12 months AND with a postmenopausal follicle-stimulating hormone concentration > 30 IU/mL

"Nonsterile males" are defined as male patients who are physiologically capable of impregnating females.

Adapted from: Clinical Trials Facilitation Group (CTFG) 2014.

APPENDIX 6. NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity (eg, no shortness of breath when walking, climbing stairs, etc).
II	Mild symptoms (eg, mild shortness of breath and/or angina). Slight limitations during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, (eg, walking short distances [20-100 meters]). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound.

Adapted from Dolgin et al 1994.
Original source: Criteria Committee, New York Heart Association, Inc. 1964.

APPENDIX 7. CHRONIC KIDNEY DISEASE EPIDEMIOLOGY COLLABORATION (CKD-EPI) EQUATION

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

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

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

where:

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

κ is 0.7 for females and 0.9 for males,

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

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

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

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

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

APPENDIX 8. IMMUNE-MEDIATED ADVERSE EVENT EVALUATION AND MANAGEMENT

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

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

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

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

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

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

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; CK, creatine kinase; CNS, central nervous system; CRP, C-reactive protein; CT, computed tomography; *D*LCO, diffusing capacity for carbon monoxide; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; FBC, full blood count; INR, international normalized ratio; LCI, liver cytosolic antigen; LFT, liver function test; LKM, liver kidney microsomal antibody; LP, liver pancreas antigen; MRA, magnetic resonance angiogram; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PD, progressive disease; 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.

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
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.
	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. Retreatment is acceptable if symptoms resolve completely or are controlled on prednisolone ≤ 10 mg/day. Discontinue study treatment if symptoms persist with corticosteroid treatment.
	3-4 Severe or life-threatening symptoms Breathless at rest	Admit to a hospital and initiate treatment with IV methylprednisolone 2-4 mg/kg/day. If there is no improvement, or worsening after 48 hours, add infliximab 5 mg/kg (if no hepatic involvement). Convert to oral prednisolone and taper over at least 2 months. Cover with empiric antibiotics and consider prophylaxis for *Pneumocystis* infection and other adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement.	Discontinue study treatment.
Neurological toxicity	**1** Mild symptoms	–	Continue study treatment.

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
	2 Moderate symptoms	Treat with oral prednisolone 0.5-1 mg/kg/day. Taper over at least 4 weeks. Obtain neurology consultation.	Hold study treatment; resume when resolved/improved to Grade 0-1.
	3-4 Severe/life-threatening	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 to 6 liquid stools per day over baseline, or abdominal pain, or blood in stool, or nausea, or nocturnal episodes	Oral prednisolone 0.5 mg/kg/day (non-enteric coated). Do not wait for any diagnostic tests to start treatment. Taper steroids over 2-4 weeks, consider endoscopy if symptoms are recurring.	Hold study treatment; resume when resolved/improved to baseline grade.
	3 Severe symptoms: > 6 liquid stools per day over baseline, or if episodic within 1 hour of eating	Initiate IV methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Consider prophylaxis for adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement. If no improvement in 72 hours or symptoms worsen, consider infliximab 5 mg/kg if no perforation, sepsis, TB, hepatitis, NYHA Grade III/IV CHF or other immunosuppressive treatment: MMF or tacrolimus. Consult gastroenterologist to conduct colonoscopy/sigmoidoscopy.	Hold study treatment; retreatment may be considered when resolved/improved to baseline grade and after discussion with the study medical monitor.
	4 Life-threatening symptoms		Discontinue study treatment.

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
Skin reactions	**1** Skin rash, with or without symptoms, < 10% BSA	Avoid skin irritants and sun exposure; topical emollients recommended.	Continue study treatment.
	2 Rash covers 10%-30% of BSA	Avoid skin irritants and sun exposure; topical emollients recommended. Topical steroids (moderate strength cream once a day or potent cream twice a day) ± oral or topical antihistamines for itch. Consider a short course of oral steroids. Follow-up at least every 5 days is recommended; if there is no improvement of symptoms, further treatment should be considered to prevent progression of rash	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. Judgement of grade 3 or above rash should base on on-site visit or photo instead of phone call monitoring alone.	Hold study treatment. Re-treat when AE is resolved or improved to mild rash (Grade 1-2) after discussion with the study medical monitor.
	4 Skin sloughing > 30% BSA with associated symptoms (eg, erythema, purpura, epidermal detachment)	Initiate IV methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Admit to a hospital and seek urgent dermatology consultation.	Discontinue study treatment.
Hepatitis	**1** ALT or AST > ULN to 3X ULN	Check LFTs within 1 week and before the next dose check LFTs to verify that there has been no worsening. If LFTs are worsening, recheck every 48-72 hours until improvement is seen.	Continue study treatment if LFTs are unchanged or improving. Hold study treatment if LFTs are worsening until improvement is seen.

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
	2 ALT or AST 3-5X ULN	Recheck LFTs every 48-72 hours: For persistent ALT/AST elevation: consider oral prednisolone 0.5-1 mg/kg/day for 3 days then taper over 2-4 weeks. For rising ALT/AST: start oral prednisolone 1 mg/kg/day and taper over 2-4 weeks; re-escalate dose if LFTs worsen, depending on clinical judgement.	Hold study treatment; treatment may be resumed when resolved/improved to baseline grade and prednisolone tapered to ≤ 10 mg.
	3 ALT or AST 5-20X 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 > 20X 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 1.5X baseline or > ULN to 1.5X ULN	Repeat creatinine weekly. If symptoms worsen, manage as per criteria below.	Continue study treatment.
	2 Creatinine > 1.5X-3X baseline or > 1.5X-3X ULN	Ensure hydration and review creatinine in 48-72 hours; if not improving, consider creatinine clearance measurement by 24-hour urine collection. Discuss with nephrologist the need for kidney biopsy. If attributed to study drug, initiate oral prednisolone 0.5-1 mg/kg and taper over at least 2 weeks. Repeat creatinine/U&E every 48-72 hours.	Hold study treatment. If not attributed to drug toxicity, restart treatment. If attributed to study drug and resolved/improved to baseline grade: Restart study drug if tapered to < 10 mg prednisolone.
	3 Creatinine > 3X baseline or > 3X-6X ULN	Hospitalize patient for monitoring and fluid balance; repeat creatinine every 24 hours; refer to a nephrologist and discuss need for biopsy. If worsening, initiate IV (methyl)prednisolone 1-2 mg/kg. Taper corticosteroids over at least 4 weeks.	Hold study treatment until the cause is investigated. If study drug suspected: Discontinue study treatment.

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
	4 Creatinine > 6X ULN	As per Grade 3, patient should be managed in a hospital where renal replacement therapy is available.	Discontinue study treatment.
Diabetes/ hyperglycemia	**1** Fasting glucose value ULN to 160 mg/dL; ULN to 8.9 mmol/L	Monitor closely and treat according to local guideline. Check for C-peptide and antibodies against glutamic acid decarboxylase and islet cells are recommended.	Continue study treatment.
	2 Fasting glucose value 160-250 mg/dL; 8.9-13.9 mmol/L	Obtain a repeat blood glucose level at least every week. Manage according to local guideline.	Continue study treatment or hold treatment if hyperglycemia is worsening. Resume treatment when blood glucose is stabilized at baseline or Grade 0-1.
	3 Fasting glucose value 250-500 mg/dL; 13.9-27.8 mmol/L	Admit patient to hospital and refer to a diabetologist for hyperglycemia management. Corticosteroids may exacerbate hyperglycemia and should be avoided.	Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1.
	4 Fasting glucose value > 500 mg/dL; > 27.8 mmol/L	Admit patient to hospital and institute local emergency diabetes management. Refer the patient to a diabetologist for insulin maintenance and monitoring.	
Ocular toxicity	**1** Asymptomatic eye 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	Hold study treatment; reintroduce only after discussion with the study medical monitor.

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
		amylase/lipase 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 severe activity restriction or dysphagia. If symptoms do not improve add	Hold study treatment until improved to Grade 0-1. Discontinue if any evidence of myocardial involvement.

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
		immunosuppressant therapy. Taper oral steroids over at least 4 weeks.	
Myocarditis	**< 2** Asymptomatic but significantly increased CK-MB or increased troponin OR clinically significant intraventricular conduction delay	Admit to hospital and refer to a cardiologist. Transfer all patients with moderate/severe cardiac symptoms or any increase in cardiac serum markers to the coronary care unit. Initiate oral prednisolone or IV (methyl)prednisolone at 1-2 mg/kg/day. Manage symptoms of cardiac failure according to local guidelines. If no immediate response change to pulsed doses of (methyl)prednisolone 1 g/day and add MMF, infliximab or anti-thymocyte globulin.	Hold study treatment until completely resolved or myocarditis has been ruled out.
	2 Symptoms on mild-moderate exertion		Discontinue study treatment unless cardiac involvement has been excluded and symptoms have completely resolved.
	3 Severe symptoms with mild exertion		
	4 Life-threatening		

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

APPENDIX 9. THE RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) GUIDELINES, VERSION 1.1

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

DEFINITIONS

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

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

Measurable Disease

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

- 10 mm by 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.

Non-measurable Disease

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

Bone lesions:

- Bone scan, 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).
- SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
- Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report 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 drug treatment until the end of treatment considering any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's 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

Target lesions	Non-target lesions	New lesions	Overall response
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

SD 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 DOR and SD as well as the PFS are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should consider many parameters including disease types and stages, treatment periodicity, and standard practice. However, these limitations of the precision of the measured endpoint should be considered if comparisons between trials are to be made.

APPENDIX 10. CHILD-PUGH CLASSIFICATION SCORING SYSTEM

The information presented here has been obtained from the Washington University Medical Center, with sources as follows: Lucey et al 1997; Pugh et al 1973; Trey et al 1996.

Child-Pugh classification is either Grade A (mild: score 5 to 6 points), B (moderate: from 7 to 9 points), or C (severe: from 10 to 15 points) and is determined by both clinical and biochemical parameters (as shown below).

Clinical/biochemical parameter	**Score (anomaly severity)**		
	1	**2**	**3**
Hepatic encephalopathy (NCI-CTCAE grade) [a]	0[b]	1[c] or 2 [d]	3[e] or 4 [f]
Ascites (presence and severity)	None	Mild	Moderate
Total bilirubin (mg/dL)	< 2.0	2.0 to 3.0	> 3.0
Serum albumin (g/dL)	> 3.5	2.8 to 3.5	< 2.8
Prolonged prothrombin time (seconds) or INR[g]	< 4 or < 1.7	4 to 6 or 1.7 to 2.3	> 6 or > 2.3

Abbreviations: INR, international normalized ratio; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events.

[a] Trey et al 1996

[b] Grade 0: Consciousness, personality, neurological examination, and electrocardiogram are all normal.

[c] Grade 1: Restlessness, sleep disorders, irritability/anxiety, hand tremor, writing disorders, 5 CPS waves.

[d] Grade 2: Lethargy, time barrier, discomfort, asterixis, ataxia, three-phase slow wave.

[e] Grade 3: Drowsiness, coma, orientation disorder, over-reflection, stiff/slow wave.

[f] Grade 4: Cannot wake up from coma, no independent personality/behavior, irrational, slow 2-3 CPS Delta activity.

[g] Lucey et al 1997

APPENDIX 11. 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

Adverse Event		Treatment
Febrile neutropenia; documented infection		The first episode of febrile neutropenia or documented infection will result in antibiotic treatment and reduction by 20% of both drugs doses If there is a second episode despite dose reduction, the patient must receive prophylactic antibiotics during the subsequent cycles If there is a third episode, the chemotherapy will be discontinued
Neutropenia	Grade 3 ($0.5\text{-}0.99 \times 10^9$/L)	chemotherapy delay until ≤ Grade 1 (≥ 1.5×10^9/L); restart with the full dose
	Grade 4 (< 0.5×10^9/L)	chemotherapy delay until recovered to ≤ Grade 1; dose reduction of all further doses by 20%
thrombocytopenia	Grade 1	chemotherapy delay until recovered to normal; restart with the full dose
	≥ Grade 2	chemotherapy delay until recovered to normal; dose reduction of all further doses by 20%

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

Recommended Dose Modifications for Non-hematologic 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.

Chemotherapy Dose Modifications for Non-Hematological Toxicity

Toxicity	Grade	Treatment
Hyper-creatinemia	≥ Grade 1	Delay chemotherapy until recovered to Grade 0 or baseline, change cisplatin to carboplatin, if possible; dose reduction by 20% for other drug; if recur, stop chemotherapy
Ototoxicity	Grade 2	Dose reduction of all further doses of cisplatin by 20%
	Grade 3-4	Delay chemotherapy until recovered to ≤ Grade 2, change cisplatin to carboplatin
Sensory neuropathy	Grade 2	Dose reduction for all further doses of cisplatin and/or paclitaxel by 20%
	Grade 3	Stop cisplatin, change cisplatin to carboplatin; stop paclitaxel
	Grade 4	Stop cisplatin/carboplatin, and/or paclitaxel
Other organ toxicity	Grade 2	Delay chemotherapy until ≤ Grade 1 or baseline [a]
	Grade 3-4	Delay chemotherapy until recovered to ≤ Grade 1 or baseline [a], dose reduction of all further dose by 20%

[a.] Skin reactions, paronychia, alopecia, fatigue, nausea/vomiting which may have resolved to Grade 2 or baseline.

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

Recommended Dose Modifications for Nab-paclitaxel

The dose adjustment of nab-paclitaxel refers to approved product labels for dose modifications regarding this regimen. Do not administer nab-paclitaxel on Day 1 of a cycle until absolute neutrophil count (ANC) is at least 1500 cells/mm^3 and platelet count is at least 100,000 cells/mm^3.

- In patients who develop severe neutropenia or thrombocytopenia withhold treatment until counts recover to an absolute neutrophil count of at least 1500 cells/mm^3 and platelet count of at least 100,000 cells/mm^3 on Day 1 or to an absolute neutrophil count of at least 1500 cells/mm^3 and platelet count of at least 50,000 cells/mm^3 on Days 8 or 15 of the cycle. If nab-paclitaxel cannot be administered on Day 15 of the cycle, the next dose of nab-paclitaxel should be administered with carboplatin on Day 1 of the following cycle provided ANC and platelets counts have recovered to permissible levels.
- Withhold nab-paclitaxel for Grade 3-4 peripheral neuropathy. Resumes nab-paclitaxel and carboplatin at reduced doses when peripheral neuropathy improves to Grade 1 or completely resolves.

APPENDIX 12. NUTRITIONAL RISK INDEX

Recent weight loss history of the patient may not always be known and the body weight loss does not take the albumin level into consideration, so the Nutritional Risk Index (NRI) is referenced as an alternative per investigator's choice to assess the patient's nutritional status for the purpose of eligibility. The formula is provided below (Shirasu et al 2018):

NRI = (1.489 × serum albumin) + (41.7 × present body weight / ideal body weight)

The Ideal Body Weight (IBW) formula is based on the Peterson formula (Peterson et al 2016):

IBW (kg) = 2.2 x Target BMI + [3.5 x Target BMI x (Height (m) - 1.5 m)]. For the purpose of this study, we will use a Target BMI of 22, so the formula becomes:

IBW (kg) = 48.4 + [77 x (Height (m) - 1.5 m)]

Or you can use below online calculator to calculate the IBW, and please choose the calculation results of the Peterson formula:

https://www.gigacalculator.com/calculators/ideal-weight-calculator.php

APPENDIX 13. COCKCROFT-GAULT FORMULA AND CALVERT FORMULA

COCKCROFT-GAULT FORMULA:

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

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

Cl_{cr} 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]

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

Cl_{cr} 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 is obese (>30% over ideal body weight) in calculation of estimated CL_{Cr}. Calculating by actual body weight is acceptable.

CALVERT FORMULA:

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

*GFR calculation formula is same as ClCr formula as shown above.

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Signature Page

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