# CLINICAL STUDY PROTOCOL

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|---|---|
| **Protocol Title:** | AdvanTIG-205: A Phase 2, Randomized Study of Ociperlimab (BGB-A1217) and Tislelizumab With Chemotherapy in Patients With Previously Untreated Locally Advanced, Unresectable, or Metastatic Non-Small Cell Lung Cancer (NSCLC) |
| **Brief Title** | NA |
| **Protocol Number:** | AdvanTIG-205 |
| **Amendment Number:** | Amendment 4.0 Global |
| **Investigational Medicinal Product(s):** | Ociperlimab (BGB-A1217) and Tislelizumab (BGB-A317) |
| **Regulatory Agency Identification Number(s):** | EudraCT 2021-001075-17<br>NCT05014815 |
| **Sponsor:** | BeiGene, Ltd.<br>c/o BeiGene USA, Inc.<br>1840 Gateway Drive<br>Third Floor<br>San Mateo, California 94404, USA |
| **Approval Date:** | *See electronic signature* |
| **Contact Information:** | BeiGene Medical Officer<br>Phone: 1.877.828.5568<br>Email: clinicaltrials@beigene.com |

Approved Date 1/30/2024

# INVESTIGATOR SIGNATURE PAGE

I have read the protocol, appendices, and accessory materials related to Study AdvanTIG-205 and agree to the following:

- To conduct this study as described by the protocol and any accessory materials.
- To protect the rights, safety, and welfare of the patients under my care.
- To provide oversight to all personnel to whom study activities have been delegated. This includes personnel at my site as well as personnel working in any facility where study activities are my responsibility.
- To control all investigational products provided by the sponsor and maintain records of the disposition of those products.
- To conduct the study in accordance with all applicable laws and regulations, the requirements of the ethics committee of record for my clinical site, and current GCP as outlined by ICH E6(R2).
- To obtain approval for the protocol and all written materials provided to patients before initiating the study at my site.
- To obtain informed consent – and updated consent in the event of new information or amendments – from all patients enrolled at my study site before initiating any study-specific procedures or administering investigational products to those patients.
- To maintain records of each patient participation and all data required by the protocol in an accurate and timely manner.

Acceptance of this protocol constitutes my agreement that no confidential information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd. or one of its affiliates unless and only to the extent required by applicable laws and regulations.

| **Name:** | **Title:** | **Institution:** |
|---|---|---|
| **Signature:** | | **Date:** |

# DOCUMENT HISTORY

| Amendment Version Number | Approval Date | Type of Protocol Amendment |
|---|---|---|
| AdvanTIG-205 Amendment 3.0 | 23 September 2022 | Substantial |
| AdvanTIG-205 Amendment 2.0 | 30 March 2022 | Substantial |
| AdvanTIG-205 Amendment 1.0 | 11 June 2021 | Substantial |
| Original protocol | 06 April 2021 | Not applicable |

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# SYNOPSIS

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|---|
| **Name of Sponsor/Company:** BeiGene, Ltd. |
| **Investigational Products:** Ociperlimab (BGB-A1217) and Tislelizumab (BGB-A317) |
| **Title of Study:** AdvanTIG-205: A Phase 2, Randomized Study of Ociperlimab (BGB-A1217) and Tislelizumab With Chemotherapy in Patients With Previously Untreated Locally Advanced, Unresectable, or Metastatic Non-Small Cell Lung Cancer (NSCLC) |
| **Protocol Identifier:** AdvanTIG-205 |
| **Phase of Development:** 2 |
| **Number of Patients:** Approximately 270 |
| **Study Centers:** Approximately 84 centers globally |
| **Study Objectives:**<br>**Primary:**<br>• To compare progression-free survival (PFS) between Arm A (ociperlimab in combination with tislelizumab and chemotherapy) and Arm B (placebo in combination with tislelizumab and chemotherapy) in the Intent-to-Treat (ITT) Analysis Set, as assessed by investigators per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)<br>**Secondary:**<br>• To evaluate overall response rate (ORR) and duration of response (DOR) in Arm A (ociperlimab in combination with tislelizumab and chemotherapy) versus Arm B (placebo in combination with tislelizumab and chemotherapy), as assessed by investigators per RECIST v1.1<br>• To compare overall survival (OS) in Arm A (ociperlimab in combination with tislelizumab and chemotherapy) and Arm B (placebo in combination with tislelizumab and chemotherapy)<br>• To evaluate the safety and tolerability profile of ociperlimab in combination with tislelizumab and chemotherapy compared to tislelizumab in combination with chemotherapy<br>**Exploratory:**<br>• To evaluate disease control rate (DCR), clinical benefit rate (CBR), and time to response (TTR) in Arm A (ociperlimab in combination with tislelizumab and chemotherapy) versus Arm B (placebo in combination with tislelizumab and chemotherapy), as assessed by investigators per RECIST v1.1<br>• To evaluate the potential association of exploratory biomarkers with response or resistance of ociperlimab and tislelizumab, and patient prognosis<br>• To compare health-related quality of life (HRQoL) between Arm A (ociperlimab in combination with tislelizumab and chemotherapy) and Arm B (placebo in combination with tislelizumab and chemotherapy)<br>• To characterize the pharmacokinetics (PK) of ociperlimab and tislelizumab<br>• To determine host immunogenicity to ociperlimab and tislelizumab |

**Study Endpoints:**

**Primary:**

- PFS (time from the date of randomization to the date of the first objectively documented tumor progression, or death, whichever occurs first) in the ITT Analysis Set of Arm A (ociperlimab in combination with tislelizumab and chemotherapy) versus Arm B (placebo in combination with tislelizumab and chemotherapy), as assessed by investigators per RECIST v1.1

**Secondary:**

- ORR as assessed by investigators (proportion of patients with a documented, confirmed complete response [CR] or partial response [PR] per RECIST v1.1) and DOR as assessed by investigators (time from the first determination of an objective response per RECIST v1.1 until the first documentation of progression or death, whichever occurs first) in Arm A (ociperlimab in combination with tislelizumab and chemotherapy) and Arm B (placebo in combination with tislelizumab and chemotherapy)
- OS (time from the date of randomization to the date of death due to any cause) in the ITT Analysis Set of Arm A (ociperlimab in combination with tislelizumab and chemotherapy) versus Arm B (placebo in combination with tislelizumab and chemotherapy)
- The incidence and severity of adverse events according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI-CTCAE v5.0)

**Exploratory:**

- DCR (proportion of patients with confirmed CR or confirmed PR or stable disease [SD]), CBR (proportion of patients with confirmed CR or confirmed PR or durable SD), and TTR (time from randomization to the first occurrence of a documented objective response) in Arm A (ociperlimab in combination with tislelizumab and chemotherapy) versus Arm B (placebo in combination with tislelizumab and chemotherapy) as assessed by investigators per RECIST v1.1
- Status of exploratory biomarkers, including but not limited to expression of T-cell immunoglobulin and ITIM domain (TIGIT), CD226, CD155, CD112, and programmed cell death ligand-1 (PD-L1), gene expression profiling (GEP), circulating tumor DNA (ctDNA), tumor mutation burden (TMB), gene mutations and microsatellite instability (MSI), tumor-infiltrating immune cells (TILs), and extracellular vesicles (EVs) in archival and/or fresh tumor tissue or blood before and after study treatment or at disease progression/reoccurrence, and the association between these biomarkers and clinical efficacy, disease status, and resistance.
- HRQoL will be assessed using 2 validated patient-reported outcomes (PRO), including European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30) and its lung cancer module (Quality of Life Questionnaire- Lung Cancer 13 [QLQ-LC13]).
- Serum concentrations of ociperlimab and tislelizumab at prespecified timepoints.
- Immunogenic responses to ociperlimab and tislelizumab, evaluated through detection of anti-drug antibodies (ADAs).

**Study Design:**

This is a randomized, investigator- and patient-blinded, sponsor-unblinded, multicenter, Phase 2 study designed to evaluate the efficacy and safety of ociperlimab in combination with tislelizumab and histology-based chemotherapy versus placebo in combination with tislelizumab and histology-based chemotherapy in patients with previously untreated locally advanced, unresectable, or metastatic NSCLC that does not harbor epidermal growth factor receptor (*EGFR*) mutations, anaplastic lymphoma kinase (*ALK*) translocations, *BRAF V600E* mutations, or c-ROS oncogene-1 (*ROS1*) mutations. Patients with non-squamous NSCLC will receive either cisplatin or carboplatin in combination with pemetrexed, with the choice of platinum (cisplatin or carboplatin) selected at the investigator's discretion. Patients with squamous NSCLC will receive carboplatin and either paclitaxel or nab-paclitaxel at the investigator's discretion.

Approximately 270 patients will be enrolled globally (including a minimum of 25% of non-Asian patients).

The PD-L1 expression is tested centrally. Local PD-L1 results may be utilized under certain circumstances for enrollment.

The study will target to enroll patients to ensure that it reflects a representative distribution of PD-L1 expression in NSCLC (approximately 40% PD-L1 TC < 1%) and to ensure that it reflects a representative histology distribution in the NSCLC population without driver mutation (approximately 30% squamous NSCLC).

Eligible participants will be randomized in a 1:1 ratio to receive one of the following treatment regimens:

**Induction phase (4 to 6 cycles, every 3 weeks):**

- Arm A: Ociperlimab 900 mg intravenously (IV) + tislelizumab 200 mg IV + histology-based chemotherapy
- Arm B: Placebo IV + tislelizumab 200 mg IV + histology-based chemotherapy

For patients with squamous NSCLC, the histology-based chemotherapy regimen will be carboplatin area under the concentration-time curve (AUC) 5 or 6 on Day (D) 1 + paclitaxel 175 or 200 mg/m$^2$ (D1) or nab-paclitaxel 100 mg/m$^2$ (D1, D8, D15) administered every 3 weeks.

For patients with non-squamous NSCLC, the histology-based chemotherapy regimen will be cisplatin 75 mg/m$^2$ or carboplatin AUC 5 (D1) + pemetrexed 500 mg/m$^2$ IV (D1) administered every 3 weeks.

**Maintenance phase (every 3 weeks):**

For patients with non-squamous NSCLC:

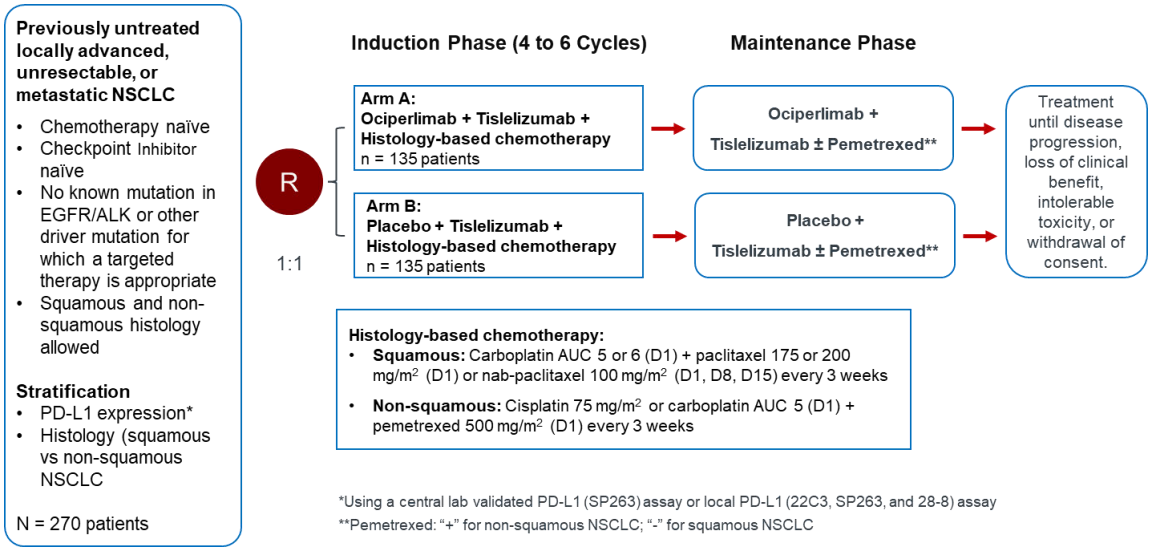
- Arm A: Ociperlimab 900 mg IV + tislelizumab 200 mg IV + pemetrexed 500 mg/m$^2$ once every 3 weeks
- Arm B: Placebo IV + tislelizumab 200 mg IV + pemetrexed 500 mg/m$^2$ once every 3 weeks

For patients with squamous NSCLC:

- Arm A: Ociperlimab 900 mg IV + tislelizumab 200 mg IV once every 3 weeks
- Arm B: Placebo IV + tislelizumab 200 mg IV once every 3 weeks

All study treatments will be administered until intolerable toxicity, withdrawal of informed consent, or the time point at which, in the investigator's opinion, the patient is no longer benefiting from study therapy.

The study schema is as follows:




Abbreviations: ALK, anaplastic lymphoma kinase; AUC, area under the concentration-time curve; D, day; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand-1; R, randomization; WT, wild type

**Study Assessments:**

PFS and tumor response will be assessed by the investigators using RECIST v1.1. Tumor imaging (computed tomography [CT] with or without contrast or magnetic resonance imaging [MRI]) must be performed within 28 days prior to randomization. All study assessments will occur every 9 weeks ± 7 days for the first 52 weeks and every 12 weeks ± 7 days thereafter. Patients who discontinue study treatment early for reasons other than radiologic disease progression (eg, toxicity) will continue to undergo tumor assessments following the original plan until the patient begins a subsequent anticancer treatment, experiences radiologic disease progression or death, withdraws consent, is lost to follow-up, or until the study terminates, whichever occurs first.

Patients will be evaluated for any adverse events (AEs) and serious adverse events (SAEs) (all severity grades, per NCI-CTCAE v5.0). After informed consent has been signed but prior to the administration of the study drug(s), only SAEs should be reported. After initiation of the study drug(s), all AEs and SAEs, regardless of relationship to the study drug(s), will be reported until either 30 days after the last dose of study treatment or chemotherapy, or until the initiation of a new anticancer therapy, whichever occurs first. Immune-related AEs (serious or non-serious) should be reported until 90 days after the last dose of ociperlimab (or placebo) and/or tislelizumab, regardless of whether or not the patient starts a new anticancer therapy. All SAEs considered related to the study drug(s) that are brought to the attention of the investigator should be reported, regardless of time since the last dose of treatment.

**Duration of Patient Participation:**

The duration of the study from first patient randomized to final analysis for PFS is estimated to be approximately 33 months.

**Study Population:**

**Key Inclusion Criteria**

- Age ≥ 18 years on the day of signing the ICF (or the legal age of consent in the jurisdiction in which the study is taking place).
- Histologically or cytologically documented locally advanced or recurrent NSCLC that is not eligible for curative surgery and/or definitive radiotherapy, with or without chemotherapy, or metastatic non-squamous or squamous NSCLC.
- No prior systemic therapy for locally advanced or metastatic squamous or non-squamous NSCLC, including but not limited to chemotherapy or targeted therapy. Patients who have received prior neoadjuvant, adjuvant chemotherapy, or chemoradiotherapy with curative intent for nonmetastatic disease must have experienced a disease-free interval of ≥ 6 months from the last dose of chemotherapy and/or concurrent radiotherapy prior to randomization.
- Archival tumor tissue or fresh biopsy (if archival tissue is not available) for the determination of PD-L1 levels and retrospective analyses of other biomarkers. If local PD-L1 testing will be used for patient randomization purposes, confirmation of tumor sample receipt by the central laboratory is required before patient randomization (preferably from the same block used for local PD L1 testing). Local PD-L1 testing must be performed using an approved assay (limited to 22C3, SP263, and 28-8) at a certified laboratory and according to the manufacturer's instructions.
- At least one measurable lesion by the investigator per RECIST v1.1.
- Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 1.
- Adequate organ function as indicated by the following laboratory values during screening.
- For full inclusion criteria, see Section 4.1.

**Key Exclusion Criteria**

- Known mutations in:
  - *EGFR* gene

    Note: For non-squamous NSCLC, patients with unknown *EGFR* mutation status will be required to have a tissue-based *EGFR* test either locally or at the central laboratory before enrollment, or endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA)–based *EGFR* test locally. Patients found to have *EGFR*-sensitizing mutations will be excluded.
  - *ALK* fusion oncogene.
  - *BRAF V600E*
  - *ROS1*
- Prior treatment with EGFR inhibitors, ALK inhibitors, or targeted therapy for other driver mutations.
- Any prior therapy targeting T-cell costimulation or checkpoint pathways in metastatic NSCLC.
- Any condition that required systemic treatment with either corticosteroids (> 10 mg daily of prednisone or equivalent) or other immunosuppressive medication ≤ 14 days before randomization.

- Infection (including tuberculosis infection, etc.) requiring systemic antibacterial, antifungal, or antiviral therapy within 14 days before randomization.

For full exclusion criteria, see Section 4.2.

**Investigational Product, Dose, and Mode of Administration:**

**Ociperlimab**

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

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

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

Refer to the pharmacy manual for details regarding intravenous administration, accountability, and disposal. Refer to the Ociperlimab (BGB-A1217) Investigator's Brochure for other details regarding ociperlimab.

**Tislelizumab**

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

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

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

Refer to the pharmacy manual for details regarding intravenous administration, accountability, and disposal. Please also refer to the Tislelizumab (BGB-A317) Investigator's Brochure for other details regarding tislelizumab.

**Dose and Mode of Administration:**

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

Ociperlimab 900 mg will be administered on Day 1 of each 21-day cycle (once every 3 weeks) after tislelizumab.

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

The initial infusions (Day 1 of Cycle 1 and Cycle 2) will be delivered over 60 (± 5) minutes; if this is well tolerated, then the subsequent infusions may be administered over 30 (± 5) minutes, which is the shortest time period permissible for infusion. Tislelizumab and ociperlimab/placebo must not be concurrently administered with any other drug (refer to Section 6).

As a routine precaution, after the infusion of ociperlimab and tislelizumab on Day 1 of Cycle 1 and Cycle 2, patients must be monitored for at least 120 minutes afterward in an area with resuscitation equipment and emergency agents. From Cycle 3 onward, a ≥ 60-minute monitoring period is required in an area with resuscitation equipment and emergency agents.

Guidelines for treatment interruption or discontinuation and for the management of immune-mediated adverse events (imAEs) and infusion-related reactions are provided in detail in Appendix 7.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

**Non-Investigational Therapy, Dose, and Mode of Administration:**

Matching placebo for ociperlimab will be administered as an intravenous infusion every 3 weeks.

Chemotherapy regimens (Section 3.3 and Section 5.1.3):

Carboplatin AUC 5 or 6 will be administered as an intravenous infusion once every 3 weeks on Day 1 of each cycle for 4 to 6 cycles.

Cisplatin 75 mg/m$^2$ will be administered as an intravenous infusion once every 3 weeks on Day 1 of each cycle for 4 to 6 cycles.

Paclitaxel 175 or 200 mg/m$^2$ will be administered as an intravenous infusion once every 3 weeks on Day 1 of each cycle for 4 to 6 cycles.

Nab-paclitaxel 100 mg/m$^2$ will be administered as an intravenous infusion once every 3 weeks on Day 1, Day 8, and Day 15 of each cycle for 4 to 6 cycles.

Pemetrexed 500 mg/m$^2$ will be administered as an intravenous infusion once every 3 weeks on Day 1 of each cycle.

**Statistical Methods:**

PFS is the primary endpoint in the ITT Analysis Set of the study. The secondary endpoints of ORR and OS will be tested sequentially once PFS superiority of Arm A over Arm B has been demonstrated.

**Analysis Sets:**

- The ITT Analysis Set includes all randomized patients. Patients will be analyzed according to their randomized treatment arm. This will be the primary analysis set for efficacy and HRQoL analyses.
- The Per-Protocol (PP) Analysis Set includes all randomized patients who received ≥ 1 dose of the assigned study drug and had no critical protocol deviations. Critical protocol deviations will be determined and documented before the database lock for the primary analyses.
- The Safety Analysis Set includes all randomized patients who received ≥ 1 dose of study drug. This will be the analysis set for the safety analyses.
- The PK Analysis Set includes all patients who received ≥ 1 dose of any component of study drug per the protocol and for whom any postdose PK data are available.
- The Immunogenicity Analysis Set includes all patients who received ≥ 1 dose of any component of study drug for whom both baseline ADA and ≥ 1 postbaseline ADA results are available.

**Primary Efficacy Endpoint Analysis:**

The primary analyses will be performed when approximately 194 PFS events have been observed.

PFS in ITT Analysis Set

The null hypothesis ($H_0$) to be tested is:

$H_0$: PFS in Arm A ≤ PFS in Arm B

against the alternative hypothesis ($H_1$):

$H_1$: PFS in Arm A > PFS in Arm B

A stratified log-rank test to compare PFS distribution between ociperlimab + tislelizumab + chemotherapy (Arm A) and placebo + tislelizumab + chemotherapy (Arm B) will be the primary efficacy analysis, stratified by PD-L1 expression (three levels: < 1% TC versus 1% to 49% TC versus ≥ 50% TC) and histology (squamous versus non-squamous NSCLC). It will be performed once the targeted PFS event number is reached. A significance level of 1-sided alpha of 0.025 will be used in the PFS testing.

PFS as assessed by investigators per RECIST v1.1 will be estimated using the Kaplan-Meier method in the ITT Analysis Set. PFS will be censored at the last adequate tumor assessment if 1 of the following occurs by the time of analysis: absence of event, a new anticancer therapy is given, or the event occurred after ≥ 2 missing tumor assessments. For cases with missing baseline tumor assessment, a death occurring ≤ 19 weeks from the randomization date will be considered a PFS event. Clinical or symptomatic progressions without supportive radiologic data will not be considered as PFS events.

The median PFS and 2-sided 95% confidence interval (CI) using the method of Brookmeyer and Crowley will be summarized. The cumulative probability of PFS at every 6 months including PFS rate at 6 and 12 months, if estimable, will be calculated for each treatment arm and presented with 2-sided 95% CIs. Standard error for PFS rates will be calculated based on Greenwood's formula. Kaplan-Meier survival probabilities for each arm will be plotted over time.

The treatment effect will be estimated by fitting a Cox regression model to the PFS times, including treatment arm as a factor and PD-L1 expression (three levels: < 1% TC versus 1% to 49% TC versus ≥ 50% TC) and histology (squamous versus non-squamous NSCLC) as strata. From this model, the hazard ratio (HR) of PFS will be estimated and presented with a 2-sided 95% CI.

Subgroup analysis of PFS will be performed by PD-L1 expression, histology, region, and other key risk factors that are to be described in the statistical analysis plan.

**Secondary Efficacy Endpoint Analyses:**

Best overall response (BOR) is defined as the best response per RECIST v1.1 recorded from randomization until data cut, progressive disease, or start of a new anticancer treatment. The null hypotheses of no difference in ORR per RECIST v1.1 assessed by investigators between ociperlimab + tislelizumab + chemotherapy (Arm A) and placebo + tislelizumab + chemotherapy (Arm B) will be tested in a Cochran-Mantel-Haenszel (CMH) test adjusting for stratification factors (PD-L1 expression [three levels: < 1% TC versus 1% to 49% TC versus ≥ 50% TC] and histology [squamous versus non-squamous NSCLC]) in the ITT Analysis Set. Patients with no postbaseline response assessment (for any reason) will be considered non-responders. The 2-sided 95% CI for the odds ratio in ORR will be calculated, as well as Clopper-Pearson 95% CIs of ORR for each treatment arm.

DOR as assessed by investigators will be derived using the similar censoring rule as for PFS and summarized descriptively in the responders receiving ociperlimab + tislelizumab + chemotherapy (Arm A) versus placebo + tislelizumab + chemotherapy (Arm B).

OS will be compared between ociperlimab + tislelizumab + chemotherapy (Arm A) and placebo + tislelizumab + chemotherapy (Arm B) in a 1-sided, stratified log-rank test using stratification factors of PD-L1 expression (three levels: < 1% TC versus 1% to 49% TC versus ≥ 50% TC) and histology (squamous versus non-squamous NSCLC).

In the absence of confirmation of death, patients will be censored either at the date that the patient was last known to be alive or the date of data cutoff, whichever comes earlier. The median OS and 2-sided 95% CI using the method of Brookmeyer and Crowley will be summarized. The cumulative probability of OS at every 6 months including OS rate at 12 months and 24 months if estimable, will be calculated for each treatment arm and presented with 2-sided 95% CIs. Standard error for survival rates will be

calculated based on Greenwood's formula. Kaplan-Meier survival probabilities for each arm will be plotted over time.

The treatment effect will be estimated by fitting a Cox regression model to the OS times including treatment arm as a factor and PD-L1 expression (three levels: < 1% TC versus 1% to 49% TC versus ≥ 50% TC) and histology (squamous versus non-squamous NSCLC) as strata. From this model, the HR of OS will be estimated and presented with a 2-sided 95% CI.

**Exploratory Efficacy Analyses:**

The proportion and its corresponding Clopper-Pearson 95% CI for each of the response categories (eg, CR, PR, SD, progressive disease [PD], not evaluable [NE], and not assessable [NA]) will be presented for the ociperlimab + tislelizumab + chemotherapy (Arm A) and placebo + tislelizumab + chemotherapy (Arm B). DCR and CBR, as assessed by investigators, will be analyzed similarly to ORR. TTR will be summarized using descriptive statistics, such as mean, median, and standard deviation. Only patients who have achieved an objective response will be included in the analysis of TTR.

HRQoL will be analyzed via postbaseline scores of EORTC QLQ-C30's Global Health Status (GHS)/QoL and functional and symptom scale scores and single item scores and symptoms measured by QLQ-LC13. Observed values and changes from baseline will be summarized using descriptive statistics. Postbaseline scores of GHS and physical function (PF) of the QLQ-C30 and dyspnea, coughing, hemoptysis, pain in chest, peripheral neuropathy, and pain in the arms and shoulders symptoms of the QLQ-LC13 will be further analyzed using a mixed-model analysis at prespecified timepoints and compared between Treatment Arms A and B.

**Safety Analyses:**

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

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

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

**Pharmacokinetic Analysis**

PK samples will be collected in this study as outlined in the Schedule of Assessments in Appendix 1.

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

**Immunogenicity Analysis**

Immunogenicity samples will be collected in this study as outlined in the Schedule of Assessments in Appendix 1.

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.

**Sample Size Considerations:**

The sample size calculation is driven by the primary efficacy analysis of PFS in the comparison between ociperlimab + tislelizumab + chemotherapy (Arm A) and placebo + tislelizumab + chemotherapy (Arm B) in the ITT Analysis Set. The number of PFS events needed is based on the assumption of an exponential distribution with the targeted median PFS improvement. The 1-sided overall Type I error in the study is set at 0.025. The table below summarizes the statistical assumption and power in the sample size calculation. Assuming an approximately 10% dropout rate for PFS, 1:1 randomization, and 14 months enrollment time, approximately 270 patients will be enrolled in order to observe approximately 194 PFS events approximately 33 months after study start.

**Hazard Ratio and Median PFS Assumption, Number of Events, Alpha and Power in the Primary Hypothesis Test**

| Endpoint | HR | Median in Arm A (months) | Median in Arm B (months) | Number of events | 1-Sided Alpha | Power |
|---|---|---|---|---|---|---|
| PFS | 0.65 | 13.7 | 8.9 | 194 | 0.025 | 85% |

Abbreviations: HR, hazard ratio; PFS, progression-free survival.

# LIST OF ABBREVIATIONS AND TERMS

| Abbreviation | Definition |
|---|---|
| ADA | antidrug antibody |
| AE | adverse event |
| ALK | anaplastic lymphoma kinase |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| AUC | area under the concentration-time curve |
| BGB-A1217 | ociperlimab |
| BGB-A317 | tislelizumab |
| CBR | clinical benefit rate |
| CI | confidence interval |
| CR | complete response |
| CT | computed tomography |
| ctDNA | circulating tumor DNA |
| DCR | disease control rate |
| DOR | duration of response |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report form |
| EDC | electronic data capture (system) |
| EGFR | epidermal growth factor receptor |
| EORTC QLQ-C30 | European Organization for Research and Treatment of Cancer Quality of Life Questionnaire- Core 30 |
| EORTC QLQ-LC13 | European Organization for Research and Treatment of Cancer Quality of Life Questionnaire- Lung Cancer 13 |
| EOT | End-of-Treatment |
| EV | extracellular vesicle |
| FDG | fluorodeoxyglucose |
| GEP | gene expression profiling |
| GHS | Global Health Status |
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |

| Abbreviation | Definition |
|---|---|
| HIV | human immunodeficiency virus |
| HRQoL | health-related quality of life |
| ICF | informed consent form |
| ICH | International Council for Harmonisation |
| IEC | Independent Ethics Committee |
| IgG | immunoglobulin G |
| imAE | immune-mediated adverse event |
| IRB | Institutional Review Board |
| IRR | infusion-related reaction |
| IRT | Interactive Response Technology |
| ITT | Intent-to-Treat (Analysis Set) |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | magnetic resonance imaging |
| MSI | microsatellite instability |
| NCI-CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| NSCLC | non-small cell lung cancer |
| ORR | overall response rate |
| OS | overall survival |
| PD | progressive disease |
| PD-1 | programmed cell death protein-1 |
| PD-L1 | programmed cell death ligand-1 |
| PET | positron emission tomography |
| PFS | progression-free survival |
| PK | pharmacokinetic(s) |
| PR | partial response |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| *ROS1* | c-ROS oncogene-1 |
| RP2D | recommended Phase 2 dose |
| SAE | serious adverse event |
| TC | tumor cell |
| TEAE | treatment-emergent adverse event |

| Abbreviation | Definition |
|---|---|
| TIGIT | T-cell immunoglobulin and ITIM domain |
| TIL | tumor-infiltrating immune cell |
| TMB | tumor mutation burden |
| TPS | Tumor Proportion Score |
| TTD | time to deterioration |
| TTR | time to response |
| ULN | upper limit of normal |

# 1. INTRODUCTION

## 1.1. Background Information on Non-small Cell Lung Cancer

Lung cancer is the most common cancer, with approximately 2.21 million new diagnoses and 1.8 million deaths worldwide in 2020, which corresponds to the highest incidence among cancers and the most common cancer-related mortality (WHO Cancer 2021). The disease is more common in men than women, representing 16.8% of all cancers in men and 8.8% of all cancers in women. In China, lung cancer is the leading cause of cancer-related death in both men and women, with an estimated 610,200 deaths and an estimated 733,300 new cases in 2015 (Chen et al 2016). Non-small cell lung cancer (NSCLC) originates from the epithelial cells of the lung and accounts for 80% to 85% of all lung cancers. There are 3 main histological subtypes of NSCLC: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, which constitute 40%, 25%, and 10% of lung cancers, respectively (PDQ Adult Treatment Editorial Board [NSCLC] 2020).

The prognosis for lung cancer patients is relatively poor, and greatly depends on the stage at which the cancer is detected. Lung cancer staging is performed worldwide according to the tumor, lymph node, and metastasis (TNM) Classification of Malignant Tumors, Eighth Edition (Amin et al 2017). If lung cancer is diagnosed in its earliest stages, cure is possible through surgery or chemo-radiation therapy. Unfortunately, lung cancer cases are most often detected at a relatively late stage. Fifty-five percent of patients with newly diagnosed NSCLC have distal metastases (Stage IV). Stage IVA patients (any T, any N, M1) present with contralateral lung involvement, malignant pleural effusion, and malignant pericardial effusion (M1a) or with metastases in a single location outside the chest, for instance, a distal lymph node or organ such as brain, liver, or bone (M1b). Stage IVB patients (any T, any N) present with disease that has spread to multiple locations (either distal lymph nodes or organs, M1c). The 5-year survival rate for patients with Stage IV NSCLC is 5% (Siegel et al 2020). For NSCLC patients with oncogenic drivers (eg, epidermal growth factor receptor [*EGFR*] mutation, anaplastic lymphoma kinase [*ALK*] rearrangements), the prognosis improved a lot due to development of targeted therapies within the last decades, such as erlotinib, gefitinib, osimertinib, or dacomitinib for patients with *EGFR* mutation, crizotinib, ceritinib, alectinib, or brigatinib for patients with *ALK* rearrangements. Nevertheless, the prevalence of oncogenic drivers is low, with the prevalence of *EGFR* mutation ranging from 7% to 64% (Midha et al 2015), and the prevalence of *ALK* rearrangements ranging from 3% to 7% (Horn and Pao 2009; Koivunen et al 2008; Choi et al 2008). However, patients with NSCLC without actionable mutation, still represent a population with unmet medical need.

## 1.2. Current Treatment of Metastatic Non-small Cell Lung Cancer Without Actionable Mutations

### 1.2.1. Chemotherapy

Treatment of metastatic NSCLC patients depends on disease histology, the presence of actionable mutations, age, performance status (PS), comorbidities, and patient's preferences.

Patients without actionable mutations regardless of programmed cell death ligand-1 (PD-L1) status and with PS 0 to 2 may receive 4 to 6 cycles of platinum-based doublets with or without

maintenance. Patients with higher risk of neurotoxicity may receive carboplatin/nab-paclitaxel. Carboplatin based doublets are also considered for patients with PS2 (ESMO 2020).

Patients with squamous NSCLC and PS 0 to 2 may receive platinum-based doublets with either gemcitabine, vinorelbine, or taxanes. Patients with non-squamous NSCLC are given pemetrexed-based combination chemotherapy with carboplatin or cisplatin (ESMO 2020). Before the emergence of immunotherapy, platinum-based chemotherapy reached median progression-free survival (PFS) of less than 6 months, and median overall survival (OS) of less than 12 months (Kelly et al 2001; Sandler et al 2006; Scagliotti et al 2008; Schiller et al 2002).

### 1.2.2. Anti-PD-1/PD-L1 Therapy

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

Single-agent pembrolizumab was approved by the US Food and Drug Administration (FDA) as first-line therapy for patients with metastatic NSCLC whose tumors expressed PD-L1 (Tumor Proportion Score [TPS] ≥ 1%) based on results from the KEYNOTE-024 (Reck et al 2016) and the KEYNOTE-042 (Mok et al 2019) studies. In the KEYNOTE-024 study, pembrolizumab showed a significant improvement in PFS (10.3 months versus 6 months [HR = 0.5; 95% confidence interval [CI]: 0.37, 0.68; $p < 0.001$]) and in the OS rate at 6 months (80.2% versus 72.4% [HR = 0.6; 95% CI: 0.4, 0.9; $p = 0.005$]) compared to platinum-based chemotherapy. In the KEYNOTE-042 study, pembrolizumab showed a significant improvement in the overall survival (16.7 months versus 12.1 months [HR = 0.81; 95% CI: 0.71, 0.93; $p = 0.0036$]) compared to platinum-based chemotherapy.

Single-agent atezolizumab was also approved by the FDA as first-line therapy of patients with metastatic NSCLC whose tumors have high PD-L1 expression (PD-L1 stained ≥ 50% of tumor cells [TC ≥ 50%] or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 10% of the tumor area [IC ≥ 10%]) with no *EGFR* or *ALK* genomic tumor aberrations based on results from the Phase 3 Impower 110 trial. The study showed that atezolizumab monotherapy demonstrated a 7.1-month improvement in OS versus chemotherapy, with a median OS of 20.2 months and 13.1 months, respectively (HR = 0.59; 95% CI: 0.40, 0.89; $p = 0.0106$) in these patients (Herbst et al 2020).

Nivolumab in combination with ipilimumab was approved as first-line treatment for patients with metastatic NSCLC whose tumors express PD-L1 (≥ 1%), with no *EGFR* or *ALK* genomic tumor aberrations based on the finding of the CheckMate-227 study (Hellmann et al 2019).

Pembrolizumab in combination with platinum-based chemotherapy were approved by the FDA as a first-line treatment for patients with metastatic non-squamous and squamous NSCLC with no *EGFR* or *ALK* genomic aberrations based on the results from KEYNOTE-189 and KEYNOTE-407 studies (Gadgeel et al 2020; Paz-Ares et al 2018). In the KEYNOTE-189 study, pembrolizumab plus chemotherapy demonstrated a 3.9-month improvement in PFS versus chemotherapy, with a median PFS of 8.8 months and 4.9 months, respectively (HR = 0.52; 95% CI: 0.43-0.64; $p < 0.0001$), and significant improvement in the OS rate at 12 months (69.2%

versus 49.4% [HR = 0.49; 95% CI: 0.38, 0.64; p < 0.0001]). In the KEYNOTE-407 study, pembrolizumab plus chemotherapy demonstrated a 4.6-month improvement in OS versus chemotherapy, with a median OS of 15.9 months and 11.3 months, respectively (HR = 0.64; 95% CI: 0.49, 0.85; p = 0.0017), and a 1.6- month improvement in PFS versus chemotherapy with a median PFS of 6.4 months and 4.8 months, respectively (HR = 0.56; 95% CI: 0.45, 0.70; p < 0.0001).

Based on results from the IMpower130 trial, atezolizumab in combination with carboplatin/nab-paclitaxel was approved as a first-line treatment of patients with metastatic non-squamous NSCLC who have no *EGFR* or *ALK* genomic tumor aberrations. Both median OS and median PFS in the intent-to-treat wild-type genotype populations (patients without *EGFR* or *ALK* alterations), were significantly improved in the atezolizumab arm versus the chemotherapy arm (OS: 18.6 months versus 13.9 months [HR = 0.80; 95% CI: 0.64, 0.99; p = 0.0384]; PFS: 7.2 months versus 6.5 months [HR = 0.75; 95% CI: 0.63, 0.91; p = 0.0024]) (West et al 2019).

Nivolumab and ipilimumab combination with platinum-doublet chemotherapy was also approved by the FDA as first-line treatment for metastatic or recurrent NSCLC with no *EGFR* or *ALK* genomic tumor aberrations, based on the finding of CheckMate-9LA (Paz-Ares et al 2021).

### 1.2.3. New Immunotherapy-Immunotherapy Combinations for Metastatic NSCLC: Anti-TIGIT and Anti-PD-1/PD-L1

Up-regulation of T-cell immunoglobulin and ITIM domain (TIGIT) expression in tumor-infiltrating lymphocytes (TILs) has been reported in many types of cancers, such as lung cancer (Tassi et al 2017). TIGIT pathway cooperates with PD-1 to maximize the suppression of effector TILs as well as to promote resistance to anti-PD-1 therapy. In vitro and in vivo studies showed that 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).

The preliminary results of several ongoing early phase clinical trials showed that anti-TIGIT antibody in combination with anti-PD-1/PD-L1 antibodies have potential for further improving ORR and PFS compared with single agent anti-PD-1/PD-L1 antibodies, and may become a novel therapeutic approach that could bring clinical benefit for metastatic NSCLC without actionable mutation

CITYSCAPE (Rodriguez-Abreu et al 2020) is a Phase 2 randomized study evaluating the anti-TIGIT antibody tiragolumab in combination with atezolizumab versus atezolizumab and placebo as a first-line therapy for PD-L1-selected NSCLC patients with no *EGFR* or *ALK* genomic aberrations. At the time of the report, the study had enrolled 135 patients, 58 of whom had high PD-L1 expression (TPS ≥ 50%). Results from this study demonstrated improvement in overall response rate (ORR) and median PFS in a subset of PD-L1 high patients treated with tiragolumab and atezolizumab (ORR: 37.3% [95% CI: 25.0, 49.6]; PFS: 5.6 months [95% CI: 4.2, 10.4]) compared with those treated with atezolizumab and placebo (ORR: 20.6% [ 95% CI: 10.2, 30.9]; PFS: 3.9 months [95% CI: 2.7, 4.5]). A slightly higher percentage of treatment-related treatment-emergent adverse events (TEAEs) occurred in patients receiving tiragolumab and atezolizumab compared with patients receiving atezolizumab and placebo (81% versus 72%). The most common TEAEs observed in patients treated with tiragolumab and atezolizumab

were low-grade fatigue, pruritus, and arthralgia; the most common imAEs were low-grade rash, infusion-related reactions, and hypothyroidism. Similarly, Grade 3 events were slightly more frequent in the tiragolumab and atezolizumab arm (19%) versus the atezolizumab and placebo arm (15%). Anemia and dyspnea were the most common Grade 3 events, whereas Grade 4 pancreatitis was the most common imAE.

A Phase 1b study is evaluating the anti-TIGIT antibody vibostolimab in combination with pembrolizumab in therapy naive or previously treated, advanced metastatic NSCLC patients who had never received anti-PD-L1 or anti PD-1 therapy (Niu et al 2020). At the time of the report, the study had enrolled 41 patients in this arm, out of whom 13 were considered PD-L1 positive (TPS ≥ 1%) and 12 had a TPS ≤ 1%. Results from this study showed a better ORR and median PFS in patients with TPS ≥ 1% (N = 13; confirmed ORR: 31.0%, 95% CI: 9.0, 61.03; median PFS: 8.4 months, 95% CI: 3.9, 10.2) compared with patients with TPS ≤ 1% (N = 12; confirmed ORR: 25.0%, 95% CI: 6.0, 57.0; median PFS: 4.1 months, 95% CI: 1.9, NR). Ten percent of patients experienced SAEs deemed related to study drug. Eighty-three percent of patients experienced a treatment-related TEAE of any grade, the majority of which were low grade. The most common treatment-related TEAEs were pruritus (34.0%), hypoalbuminemia (29.0%), pyrexia (20.0%), decreased lymphocyte counts (17.0%), fatigue and rash (12.0% each), and infusion related reactions (10.0%). Decreased lymphocyte counts (7.0%) and rash (2.0) were the most common ≥ Grade 3 events.

## 1.3. Background Information on Ociperlimab, a TIGIT Inhibitor

Refer to the Ociperlimab (BGB-A1217) Investigator's Brochure for additional background on ociperlimab.

### 1.3.1. Nonclinical Summary

#### 1.3.1.1. Pharmacology

Ociperlimab, also known as BGB-A1217, is a humanized immunoglobulin G (IgG) 1 monoclonal antibody against TIGIT under clinical development for the treatment of human malignancies.

Ociperlimab binds to the extracellular domain of human TIGIT with high specificity and affinity (equilibrium dissociation constant [KD] = 0.135 nM), as demonstrated by target binding assays and surface plasmon resonance (SPR) characterization. Ociperlimab has shown antitumor activity in both the GL261 mouse glioma tumor model and the CT26.WT mouse colon cancer model in humanized TIGIT knock-in mice. In the MC-38 mouse colon cancer model in humanized TIGIT knock-in mice, ociperlimab in combination with anti-mouse PD-1 significantly inhibited tumor growth compared with either therapy alone.

Ociperlimab has the constant region of a wild-type human immunoglobulin G1 (IgG1) to enable the Fc-mediated effector functions. Ociperlimab has demonstrated competent binding to C1q and all FcγRs and induces antibody-dependent cellular cytotoxicity against a 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 (BGB-A1217) Investigator's Brochure for detailed information regarding pharmacology studies.

#### 1.3.1.2. Toxicology

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

Ociperlimab demonstrated a comparable binding affinity in TIGIT receptor occupancy assays with CD3+ splenocytes from humanized TIGIT knock-in mice compared to CD3+ human peripheral blood mononuclear cells (with EC50 of 48.8 ng/ml versus 63.2 ng/ml, respectively). In addition, ociperlimab showed a significant inhibition of GL261 tumor growth in humanized TIGIT knock-in mice at a dose of ≥ 0.4 mg/kg via weekly intraperitoneal dosing.

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

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

No specific binding of ociperlimab was noted with normal human tissues. A variety of factors might contribute to the negative results, including negligible target expression in normal tissues (Yang 2016; Human Protein Atlas 2019) and sensitivity of the immunohistochemistry method.

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

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

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

### 1.3.2. Prior Clinical Experience With Ociperlimab

As of 28 July 2023, 10 studies with ociperlimab are ongoing (Ociperlimab (BGB-A1217) Investigator's Brochure). Of the 10 ongoing studies, 6 (AdvanTIG-101, AdvanTIG-105, AdvanTIG 202, AdvanTIG-204, AdvanTIG-206, and AdvanTIG-301) have preliminary data available. For more detailed information on ociperlimab safety and efficacy data refer to the most recent edition of the Ociperlimab (BGB-A1217) Investigator's Brochure.

A pooled analysis of monotherapy and combination therapies was conducted to provide a comprehensive safety assessment. As of the data cutoff date of 28 July 2023, a total of 729 patients received ociperlimab treatment in 6 studies, including Study AdvanTIG 101, Study AdvanTIG-105, Study AdvanTIG-202, Study AdvanTIG-204, Study AdvanTIG-206 and Study AdvanTIG-301.

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

Table 1.

Overall, of the 729 patients in the Safety Analysis Set, 708 (97.1%) experienced ≥ 1 TEAE and 534 patients (73.3%) experienced ≥ 1 TEAE related to ociperlimab. TEAEs ≥ Grade 3 in severity were experienced by 440 of 729 patients (60.4%), and 152 patients (20.9%) experienced ≥ Grade 3 TEAE related to ociperlimab. Serious adverse events were experienced by 343 patients (47.1%), and 103 patients (14.1%) had serious adverse events related to ociperlimab. Adverse events leading to discontinuation of ociperlimab were experienced by 107 patients (14.7%). Adverse events leading to death were experienced by 52 patients (7.1%), and 7 patients (1.0%) experienced ≥ 1 ociperlimab-related adverse event leading to death. A single patient (1.4% of 69 dose-limiting toxicity-evaluable patients) experienced a dose-limiting toxicity.

**Table 1: Overview of Treatment-Emergent Adverse Events (Safety Analysis Set)**

| | Ociper Mono [a] (N = 9) n (%) | Ociper + Tisle [b] (N = 346) n (%) | Ociper + Tisle + Chemo [a] (N = 214) n (%) | Ociper + Tisle + cCRT [a] (N = 63) n (%) | Ociper + Tisle + BAT1706 [a] (N = 62) n (%) | Ociper + Tisle Heme (N = 24) n (%) | Ociper + Ritu (N = 11) n (%) | Total (N = 729) n (%) |
|---|---|---|---|---|---|---|---|---|
| Number of Patients with any TEAE | 9 (100.0) | 326 (94.2) | 214 (100.0) | 63 (100.0) | 62 (100.0) | 24 (100.0) | 10 (90.9) | 708 (97.1) |
| Related to Ociperlimab | 7 (77.8) | 233 (67.3) | 157 (73.4) | 57 (90.5) | 55 (88.7) | 17 (70.8) | 8 (72.7) | 534 (73.3) |
| Grade ≥ 3 | 4 (44.4) | 170 (49.1) | 160 (74.8) | 48 (76.2) | 44 (71.0) | 9 (37.5) | 5 (45.5) | 440 (60.4) |
| Related to Ociperlimab | 1 (11.1) | 55 (15.9) | 46 (21.5) | 13 (20.6) | 27 (43.5) | 5 (20.8) | 5 (45.5) | 152 (20.9) |
| Serious TEAE | 4 (44.4) | 144 (41.6) | 115 (53.7) | 36 (57.1) | 31 (50.0) | 9 (37.5) | 4 (36.4) | 343 (47.1) |
| Related to Ociperlimab | 0 (0.0) | 37 (10.7) | 26 (12.1) | 20 (31.7) | 12 (19.4) | 5 (20.8) | 3 (27.3) | 103 (14.1) |
| Leading to Discontinuation of Ociperlimab | 1 (11.1) | 47 (13.6) | 30 (14.0) | 11 (17.5) | 15 (24.2) | 1 (4.2) | 2 (18.2) | 107 (14.7) |
| Related to Ociperlimab | 0 (0.0) | 16 (4.6) | 11 (5.1) | 10 (15.9) | 7 (11.3) | 0 (0.0) | 2 (18.2) | 46 (6.3) |
| Leading to Death | 2 (22.2) | 22 (6.4) | 17 (7.9) | 2 (3.2) | 6 (9.7) | 2 (8.3) | 1 (9.1) | 52 (7.1) |
| Related to Ociperlimab | 0 (0.0) | 3 (0.9) | 0 (0.0) | 2 (3.2) | 1 (1.6) | 0 (0.0) | 1 (9.1) | 7 (1.0) |

Source: ADSL, ADAE. Data cutoff: 28JUL2023. Data extraction: 28JUL2023.
Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event; cCRT, concurrent chemoradiotherapy; Ociper, ociperlimab; Mono, monotherapy; Tisle, tislelizumab; Chemo, chemotherapy; Heme, hematology; Ritu, rituximab.
A patient with multiple occurrences of an AE is counted only once in the AE category.
All AEs are coded using MedDRA version 26.0 and graded according to NCI-CTCAE version 5.0
Studies include AdvanTIG-105, AdvanTIG-101, AdvanTIG-202, AdvanTIG-204, AdvanTIG-206, and AdvanTIG-301 (Part I).
Ociperlimab monotherapy, ociperlimab + tislelizumab, ociperlimab + tislelizumab + chemotherapy, ociperlimab + tislelizumab + cCRT, ociperlimab + tislelizumab + BAT1706 are treatments in solid tumor studies; ociperlimab + tislelizumab hematology and ociperlimab + rituximab are treatments in hematology study.
[a] The dose level of Ociperlimab is 900 mg.
[b] The dose level of Ociperlimab includes 50 mg, 150 mg, 450 mg, 900 mg and 1800 mg.
The dose level of ociperlimab for hematology study includes 600 mg 900 mg.
/bgb_a1217_bgb_a317/safety/ib_2023/dev/pgm/tlfs/t-aesum.sas 15AUG2023 02:23 t-3-aesum-i.rtf

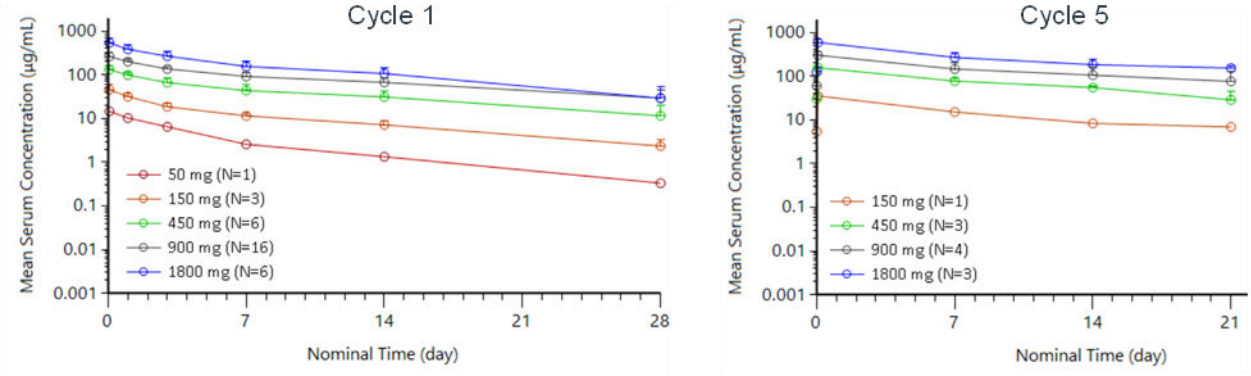
### 1.3.3. Ociperlimab Clinical Pharmacology

Preliminary PK data are available from a total of 52 patients treated with ociperlimab at 50 mg, 150 mg, 450 mg, 900 mg, or 1800 mg dose levels in combination with tislelizumab 200 mg in the dose-escalation and dose-verification portions of Study AdvanTIG-105. The PK data were analyzed using noncompartmental analyses (NCA) using nominal timepoints and nominal dosing information. Ociperlimab exposures increased approximately dose proportionally from the 50 mg to the 1800 mg dose level for maximum observed serum concentration ($C_{max}$) and area under the concentration-time curve (AUC). There was minimal accumulation observed in Cycle 5 following multiple doses. The geometric mean terminal half-life estimate following the first dose ranged from approximately 7 to 11 days. Postdose PK sampling duration may not be sufficient for robust characterization of elimination half-life using noncompartmental analysis and, therefore, reported half-life values should be interpreted with caution. The mean serum concentration-time profiles of ociperlimab are shown in Figure 1.

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

Refer to the Ociperlimab (BGB-A1217) Investigator's Brochure for detailed information on ociperlimab clinical pharmacokinetics and pharmacodynamics.

**Figure 1: Cycles 1 and 5 Mean (+ SD) Serum Concentration-Time Profiles of Ociperlimab in Study AdvanTIG-105**




Abbreviation: SD, standard deviation.
Note: For the 1800 mg dose, only 3 concentrations were available on D28.

## 1.4. Background Information on Tislelizumab

### 1.4.1. Pharmacology

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

Tislelizumab acts by binding to the extracellular domain of human PD-1 with high specificity and affinity (dissociation constant [KD] = 0.15 nM). It competitively blocks binding of both PD-L1 and PD-L2, thus inhibiting PD-1-mediated negative signaling in T cells.

In vitro assays with tislelizumab suggest either low or no antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, or complement-dependent cytotoxicity effects in humans (Labrijn et al 2009; Zhang et al 2018). Tislelizumab was specifically engineered to abrogate these potential mechanisms of T-cell clearance and potential resistance to anti-PD-1 therapy.

Please refer to the Tislelizumab (BGB-A317) Investigator's Brochure for additional details regarding nonclinical studies of tislelizumab.

### 1.4.2. Toxicology

The toxicity and safety profile of tislelizumab was characterized in single-dose toxicology studies in mice and cynomolgus monkeys and in a 13-week, repeat-dose toxicology study in cynomolgus monkeys. 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 showed dose proportional increases in systemic exposure without apparent accumulation or sex difference. Immunogenicity was observed without apparent immunotoxicity or effect on the systemic exposure. The NOAEL of tislelizumab in the 13-week monkey toxicity study was considered to be 30 mg/kg. The safety profile of tislelizumab is considered adequate to support the current study, AdvanTIG-205.

Please refer to the Tislelizumab (BGB-A317) Investigator's Brochure for more detailed information on the toxicology of tislelizumab.

### 1.4.3. Clinical Pharmacology

Tislelizumab exhibited linear PK across the dose range tested in the clinical studies. A population PK (popPK) analysis was conducted using pooled serum concentration data from 2596 patients enrolled in 12 tislelizumab clinical studies. The PK of tislelizumab was best characterized using a 3-compartmental model with a linear clearance mechanism. PK of tislelizumab does not appear to be time varying. The typical estimates of clearance (CL), central volume of distribution ($V_c$), and peripheral volumes 2 and 3 ($V_2$ and $V_3$, respectively), were 0.153 L/day, 3.05 L, 1.27 L, and 2.10 L, respectively, with inter-individual variability in CL (26.3%), $V_c$ (16.7%), $V_2$ (74.7%), and $V_3$ (99.9%). The elimination half-life was estimated to be approximately 23.8 days.

PopPK analyses demonstrated that race, baseline alanine aminotransferase, aspartate aminotransferase, bilirubin, lactate dehydrogenase, estimated glomerular filtration rate, Eastern Cooperative Oncology Group (ECOG) performance status score at baseline did not have statistically significant influences on tislelizumab PK. Baseline body weight, tumor size of solid tumors, albumin, age, sex, immunogenicity, and tumor type were found to be statistically significant covariates on the PK of tislelizumab, however, the exposure changes by these

covariates were approximately 30% or less which is relatively small compared to the overall range estimated for the PK exposures, and hence are not considered clinically relevant.

Please refer to the Tislelizumab (BGB-A317) Investigator's Brochure for more detailed information on the clinical pharmacology of tislelizumab.

### 1.4.4. Prior Clinical Experience With Tislelizumab

Tislelizumab is being developed for the treatment of human malignancies in multiple organs and tissues as monotherapy or in combination with other therapies. The overall safety experience with tislelizumab, as a monotherapy or in combination with other therapeutics, is based on experience in 4588 patients (2569 patients treated with monotherapy and 2019 patients treated with combination therapy) as of the cutoff date 27 October 2023 (Tislelizumab (BGB-A317) Investigator's Brochure). A total of 2569 patients were treated in the monotherapy studies included in the pooled safety analysis. Within the 9 solid tumor monotherapy studies, 2377 patients were treated. Within the 3 hematologic malignancy monotherapy studies, 192 patients were treated.

A pooled analysis of combination studies with tislelizumab and chemotherapy was conducted to provide a comprehensive safety assessment separately from other combination therapy studies. A total of 2019 patients were treated with tislelizumab in combination with chemotherapy in 10 studies as of 27 October 2023.

The patients in the pooled tislelizumab plus chemotherapy combination studies had a median tislelizumab treatment exposure duration of 7.1 months (range: 0 to 58) and a median study follow-up duration of 18.7 months (range: 0 to 58). The median age of patients was 61.0 years, and 80.6% of the patients were male. Most patients were Asian (89.8%). The most common tumor types were NSCLC (723 patients, 35.8%), gastric or gastroesophageal junction adenocarcinoma (25.4%), and esophageal squamous cell carcinoma (20.2%). Over half of patients had no prior systemic anticancer therapy (1340 patients, 66.4%). Refer to the Tislelizumab (BGB-A317) Investigator's Brochure for more detailed information on tislelizumab safety data when given as monotherapy or in combination with chemotherapy.

In addition to the safety data provided in the Tislelizumab (BGB-A317) Investigator's Brochure, other ongoing studies are evaluating the safety profile of tislelizumab when used in combination with chemotherapy in patients with NSCLC.

#### 1.4.4.1. Treatment-Emergent Adverse Events in Chemotherapy Combination Studies

Of the 2019 patients in the pooled tislelizumab plus chemotherapy combination studies, 1984 (98.3%) experienced ≥ 1 TEAE, and 1451 patients (71.9%) experienced ≥ 1 TEAE considered related to tislelizumab treatment. TEAEs ≥ Grade 3 in severity were experienced by 1528 patients (75.7%) and 572 patients (28.3%) experienced a ≥ Grade 3 TEAE considered tislelizumab related. Serious TEAEs were reported in 816 patients (40.4%) and 337 patients (16.7%) experienced a serious tislelizumab-related TEAE. A total of 124 patients (6.1%) experienced ≥ 1 TEAE leading to death.

The most commonly occurring TEAEs were Anaemia (65.0%), Neutrophil count decreased (50.2%), White blood cell count decreased (48.8%), Nausea (42.2%), Decreased appetite (39.2%), and Platelet count decreased (32.6%).

Of the 2019 patients in the pooled tislelizumab plus chemotherapy combination studies, 1451 (71.9%) experienced ≥ 1 TEAE assessed as related to tislelizumab treatment. The most commonly occurring tislelizumab-related TEAEs were Anaemia (16.1%), Alanine aminotransferase increased (15.5%), Aspartate aminotransferase increased (15.0%), Neutrophil count decreased (12.5%), White blood cell count decreased (12.2%), Hypothyroidism (12.0%), and Rash (11.2%).

Of the 2019 patients in the pooled chemotherapy combination studies, 572 (28.3%) experienced ≥ 1 TEAE assessed as related to tislelizumab treatment that was ≥ Grade 3 in severity. The most commonly occurring ≥ Grade 3 tislelizumab-related TEAEs were Neutrophil count decreased (6.1%), White blood cell count decreased (3.3%), Neutropenia (3.1%), Anaemia (2.7%), and Platelet count decreased (2.0%).

#### 1.4.4.2. Treatment-Emergent Serious Adverse Events

Of the 2019 patients in the pooled tislelizumab plus chemotherapy combination studies, 816 (40.4%) experienced ≥ 1 treatment-emergent SAE. The most commonly occurring SAEs were Pneumonia (4.3%), Pneumonitis (2.3%), and Platelet count decreased (2.1%).

Of the 2019 patients treated in the pooled tislelizumab plus chemotherapy combination studies, 337 (16.7%) experienced ≥ 1 tislelizumab-related treatment-emergent SAE. The most commonly occurring SAEs were Pneumonitis (2.1%) and Pneumonia (1.0%). All other SAEs occurred in < 1% of patients.

#### 1.4.4.3. Immune-Mediated Adverse Events

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

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

All imAEs presented here are assessed as related to study drug by the investigator and categorized 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 2019 patients in the pooled tislelizumab plus chemotherapy combination studies, 777 (38.5%) experienced ≥ 1 imAE of any grade. The most commonly occurring imAEs were Rash and Hypothyroidism (13.0% each), Pneumonitis (5.5%), Hyperthyroidism (4.0%), Rash maculo-papular (1.3%), Immune-mediated lung disease (1.2%), and Thyroxine free decreased (1.0%). The categories of imAEs experienced by ≥ 1% of patients were Immune-Mediated Skin Adverse Reaction (16.2%), Immune-Mediated Endocrinopathies (Hypothyroidism) (14.6%), Immune-Mediated Pneumonitis (7.4%), Immune-Mediated Endocrinopathies (Hyperthyroidism) (5.4%), Immune-Mediated Hepatitis (1.4%), Immune-Mediated Endocrinopathies (Diabetes

Mellitus) (1.3%), Immune-Mediated Myocarditis/Pericarditis (1.2%), and Immune-Mediated Colitis (1.0%).

Of the 2019 patients in the pooled tislelizumab plus chemotherapy combination studies, 162 (8.0%) experienced ≥ 1 imAE that was ≥ Grade 3 in severity. The most commonly occurring ≥ Grade 3 imAEs were Pneumonitis (31 of 2019 patients, 1.5%) and Rash (1.3%). All other ≥ Grade 3 imAEs occurred in < 1.0% of patients.



#### 1.4.4.4. Infusion-Related Reactions

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

Of the 2019 patients in the pooled tislelizumab plus chemotherapy combination studies, 125 (6.2%) experienced ≥ 1 IRR. The most commonly occurring IRRs of any grade were Rash (1.8%) and Chills and Infusion-related reaction (1.2% each). All other IRRs occurred in < 1.0% of patients.

#### 1.4.4.5. Liver Laboratory Abnormalities

In the pooled tislelizumab plus chemotherapy combination studies, 15 (0.8%) of 1975 patients treated with any dose of Tislelizumab or with any postbaseline assessment experienced alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels > 3 x ULN with a concurrent total bilirubin level ≥ 2 x upper limit of normal (ULN). Concurrent elevation of ALP (ie, ALP ≥ 2 x ULN) was observed in 12 of these 15 patients. The remaining 3 patients did not meet true Hy's law criteria.

#### 1.4.4.6. Fatal Adverse Events

Of the 2019 patients in the pooled tislelizumab plus chemotherapy combination studies, 79 (3.9%) died ≤ 30 days after their last dose of tislelizumab. The causes of death for these patients were AEs (2.4%), disease under study (1.3%), disease progression (0.1%), and "other reason" (1 patient; 0.0%). A total of 1171 patients (58.0%) died > 30 days after their last dose of tislelizumab. The causes of death for these patients were disease under study (37.0%), disease progression (10.3%), "other reason" (8.8%), and AEs (1.9%).

Of the 2019 patients in the pooled tislelizumab plus chemotherapy combination studies, 124 (6.1%) experienced ≥ 1 TEAE leading to death. The most commonly occurring TEAEs leading to death were Death (1.0%), General physical health deterioration (0.4%), Pneumonia and Respiratory failure (0.3% each), and Sepsis, Gastrointestinal haemorrhage, and Depressed level of consciousness (0.2% each). All other events occurred in ≤ 0.1% of patients.

Of the 2019 patients in the pooled tislelizumab plus chemotherapy combination studies, 34 (1.7%) experienced ≥ 1 tislelizumab-related TEAE leading to death. The most commonly occurring tislelizumab-related TEAEs leading to death were Death (6 patients; 0.3%), Gastrointestinal haemorrhage and Pneumonitis (3 patients; 0.1% each), and Respiratory failure and Myocarditis (2 patients; 0.1% each). All other events occurred in single patients.

### 1.4.5. Efficacy Assessment of Tislelizumab

Efficacy data in NSCLC are summarized below from 2 completed Phase 1 monotherapy studies in solid tumors, Study BGB-A317_Study_001(data cutoff of May 2019)and Study BGB-A317-102 (data cutoff of 01 December 2018), 1 Phase 2 combination study in NSCLC, Study BGB-A317-206 (data cutoff of 31 December 2019) and from 4 Phase 3 combination studies in NSCLC, Study BGB-A317-303 (data cutoff of 10 August 2020), Study BGB-A317-304 (data cutoff of 26 October 2020), Study BGB-A317-307 (data cutoff of 30 September 2020) and Study BGB-A317-315 (data cutoff of 20 February 2023). Please refer to Tislelizumab (BGB-A317) Investigator's Brochure for more details.

**BGB-A317_Study_001**

Study BGB-A317_Study_001 is a Phase 1a/1b study consisting of a dose escalation phase (1a) and a dose expansion phase (1b) designed to establish the MTD and schedule, determine the recommended Phase 2 dose (RP2D), and investigate the preliminary efficacy of tislelizumab in previously treated patients with select tumor types, including NSCLC.

The RP2D and schedule for tislelizumab was determined to be 200 mg administered once every 3 weeks. Across all disease cohorts (N = 451), 6 patients (1.3%) experienced a complete response (CR), and 54 patients (12.0%) had a partial response (PR), yielding an ORR of 13.3%. Additionally, 141 patients (31.3%) had a best overall response of stable disease. Disease control rate (DCR) was 44.6% (95% CI: 39.92, 49.29), and clinical benefit rate (CBR) was 25.9% (95% CI: 21.96, 30.25). Of the 49 NSCLC patients enrolled in the study, no patients experienced a CR (0%) and 6 patients (12.2%) had a confirmed PR. Stable disease was observed in 23 patients (46.9%). DCR was 59.2% (95% CI: 44.21, 73.00) and CBR was 30.8% (95% CI: 14.33, 51.79).

**BGB-A317-102**

Study BGB-A317-102 is a nonrandomized, Phase 1/2 study of tislelizumab monotherapy evaluating the activity and safety of tislelizumab at the RP2D and schedule of 200 mg given once every 3 weeks in previously treated Chinese patients with select advanced solid tumors, including NSCLC.

In the NSCLC cohort (N = 56), no patients (0%) experienced a CR and 10 patients (18%) had a confirmed PR. Stable disease was observed in 21 patients (38%). ORR was 18% (95% CI: 8.9, 30.4).

**BGB-A317-206**

Study BGB-A317-206 was a Phase 2, open-label, multi-cohort study to investigate the preliminary antitumor activity, safety, and PK of tislelizumab in combination with chemotherapy as first-line treatment in Chinese subjects with locally advanced or metastatic lung cancer.

Efficacy data from BGB-A317-206 (data cutoff 31 December 2019) were presented at the 2020 meeting of the European Society for Medical Oncology (Wang Z et al 2020). A summary of tumor responses for the evaluable patients (N = 54 patients) is shown in Table 2.

**Table 2: Summary of Tumor Response in Study BGB-A317-206 (Efficacy Analysis Set)**

| Category | Non-squamous NSCLC n = 16 | Squamous NSCLC Cohort A n = 15 | Squamous NSCLC Cohort B n = 6 | SCLC n = 17 | Total N = 54 |
|---|---|---|---|---|---|
| **ORR (CR, PR)** | | | | | |
| n (%) | 7 (43.8) | 12 (80.0) | 4 (66.7) | 13 (76.5) | 36 (66.7) |
| Exact 95% CI | (19.8, 70.1) | (51.9, 95.7) | (22.3, 95.7) | (50.1, 93.2) | (52.5, 78.9) |
| **Best Overall Response – Confirmed, n (%)** | | | | | |
| CR | 0 | 0 | 0 | 0 | 0 |
| PR | 7 (43.8) | 12 (80.0) | 4 (66.7) | 13 (76.5) | 36 (66.7) |
| SD | 8 (50.0) | 2 (13.3) | 1 (16.7) | 2 (11.8) | 13 (24.1) |
| PD | 1 (6.3) | 0 | 0 | 1 (5.9) | 2 (3.7) |
| Missing | 0 | 1 (6.7) | 1 (16.7) | 1 (5.9) | 3 (5.6) |
| **DCR (CR, PR, SD)** | | | | | |
| n (%) | 15 (93.8) | 14 (93.3) | 5 (83.3) | 15 (88.2) | 49 (90.7) |
| Exact 95% CI | (69.8, 99.8) | (68.1, 99.8) | (35.9, 99.6) | (63.6, 98.5) | (79.7, 96.9) |
| **CBR (CR, PR, durable SD ≥ 12 weeks)** | | | | | |
| n (%) | 15 (93.8) | 14 (93.3) | 5 (83.3) | 15 (88.2) | 49 (90.7) |
| Exact 95% CI | (69.8, 99.8) | (68.1, 99.8) | (35.9, 99.6) | (63.6, 98.5) | (79.7, 96.9) |
| **CBR (CR, PR, durable SD ≥ 24 weeks)** | | | | | |
| n (%) | 9 (56.3) | 14 (93.3) | 4 (66.7) | 14 (82.4) | 41 (75.9) |
| Exact 95% CI | (29.9, 80.2) | (68.1, 99.8) | (22.3, 95.7) | (56.6, 96.2) | (62.4, 86.5) |

Data cutoff 31 December 2019.
Abbreviations: CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DCR, disease control rate; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, progressive disease; PR, partial response; SCLC, small cell lung cancer; SD, stable disease.
ORR is based on the confirmed CR or PR according to RECIST v1.1. Durable SD is defined as SD duration ≥ 12 or ≥ 24 weeks. Patients with no post-baseline response assessment or assessments as NE were considered as non-responders. CIs were estimated by the exact method.
The confirmation of best overall response must be at least 4 weeks after the initially observed objective response.

### BGB-A317-303

Study BGB-A317-303 is a randomized, open-label, multicenter Phase 3 study in adult patients with histologically confirmed and locally advanced or metastatic NSCLC (squamous or nonsquamous) who have disease progression during or after receiving a platinum-containing regimen.

A total of 805 patients were randomized in the study (535 patients in the tislelizumab arm versus 270 patients in the docetaxel arm). At the prespecified interim analysis (data cutoff date of 10 August 2020), the co-primary endpoint of OS in the Intent-to-Treat (ITT) Analysis Set was met, which demonstrated a statistically significant and clinically meaningful improvement in OS in the tislelizumab arm compared with the docetaxel arm (median OS 17.2 months [95% CI: 15.3 to 20.0 months] versus 11.9 months [95% CI: 10.2 to 13.9 months]; hazard ratio = 0.64 [95% CI: 0.53 to 0.78]; $p < 0.0001$).

**BGB-A317-304 (RATIONALE 304)**

BGB-A317-304 is an ongoing, open-label, randomized, multicenter Phase 3 study designed to compare the efficacy and safety of tislelizumab combined with platinum (cisplatin or carboplatin) and pemetrexed (Arm A) versus platinum and pemetrexed alone (Arm B) as first-line treatment in 334 patients who have Stage IIIB or IV non-squamous NSCLC.

As of the data cutoff of 23 January 2020, an interim analysis demonstrated that the study met its primary endpoint of PFS. As of the data cutoff of 26 October 2020, the final PFS analysis from additional follow-up data showed that, compared with the chemotherapy-only arm, the risk of disease progression or death as assessed by the Independent Review Committee (IRC) was reduced by 37.26% in patients who received tislelizumab in combination with pemetrexed and platinum (HR = 0.628) (data on file). The IRC-assessed median PFS was 9.8 months (CI: 8.94, 11.70 months) in the tislelizumab combination arm and 7.6 months (CI: 5.55, 8.02 months) in the chemotherapy-only arm. The 12-month PFS event-free rate was approximately double in the tislelizumab combination arm as compared with the chemotherapy arm (39.9% versus 19.5%). PFS improvement was consistent across all prespecified subgroups, including investigator-assessed PFS. ORR per IRC review was greater in Arm A than in Arm B (57.8% versus 36.0%). The median DOR in Arm A and Arm B were 10.6 months and 6.9 months, respectively.

The health-related quality of life (HRQoL) data, based on the patient-reported outcomes, further confirmed the clinical benefits with tislelizumab in combination with chemotherapy in this patient population (Lu et al 2020). Compared with Arm B, patients in Arm A experienced a higher reduction of pain and cough symptoms.

HRQoL was measured using 2 validated patient-reported outcomes (PROs): European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and its lung cancer module (Quality of Life Questionnaire- Lung Cancer 13 [QLQ-LC13]) in ITT. Changes in scores from baseline were used to compare the effects of the treatments between the study arms. Measures of HRQoL showed improvements in Arm A compared to Arm B. The Global Health Status (GHS)/QoL of the QLQ-C30 was observed with LS mean changes of 5.7 (95% CI [1.0, 10.5], P=0.018) at 18 weeks. Furthermore, patients in Arm A experienced larger reductions in lung cancer symptoms from baseline than patients in Arm B, with mean change (SD) in coughing (-13.4 [29.10] versus -5.5 [22.92]), chest pain (-5.7 [22.78] versus -3.2 [20.16]), dyspnea (-1.5 [16.42] versus, 2.0 [11.32]), and pain in arm or shoulder (-7.3 [23.46] versus -3.2 [19.38]).

**BGB-A317-307 (RATIONALE 307)**

BGB-A317-307 is an ongoing, open-label, randomized, multicenter Phase 3 study designed to compare the efficacy and safety of tislelizumab combined with carboplatin and either paclitaxel

(Arm A) or nab-paclitaxel (Arm B), versus paclitaxel plus carboplatin alone (Arm C) as first-line treatment in 360 patients with untreated Stage IIIB or IV squamous NSCLC.

As of the data cutoff of 06 December 2019, an interim analysis demonstrated that the study met its primary endpoint of PFS (Wang J et al 2021). Additional follow-up data for the final PFS analysis as of the data cutoff of 30 September 2020 are presented below.

The updated final analysis of PFS with a median follow-up of 18.5 months showed consistent results. PFS in Arm A was 7.7 months (CI: 6.74, 10.41 months), which was longer than PFS in Arm C with 5.5 months (CI: 4.21, 5.72 months) with one-sided stratified log-rank test p-value < 0.0001 (data on file). The stratified HR was 0.475 (CI: 0.344, 0.654), indicating a 52.5% reduction in the risk of experiencing a PFS event. PFS assessed by the IRC in Arm B was 9.7 months (CI: 7.39, 11.01 months) and significantly longer than PFS in Arm C with 5.5 months (CI: 4.21, 5.72 months), with a one-sided stratified log-rank test p-value < 0.0001. The HR was 0.451 (CI: 0.324, 0.628), indicating a 54.9% reduction in the risk of experiencing a PFS event.

The ORR assessed by the IRC of the latest analysis was 74.2% (CI: 65.4%, 81.7%) in Arm A versus 49.6% (CI: 40.4%, 58.8%) in Arm C; and 73.9% (CI: 65.1%, 81.6%) in Arm B versus 49.6% (CI: 40.4%, 58.8%) in Arm C.

The median OS at the time of the latest analysis with a median follow-up of 18.5 months was 22.8 months in Arm A, not estimable in Arm B, and 20.2 months in Arm C. The stratified HR for OS were 0.674 (CI: 0.449, 1.010) for Arm A versus Arm C, and 0.752 (CI: 0.504 versus 1.121) for Arm B versus Arm C; these differences correspond to one-sided stratified log-rank test p-values of 0.0271 and 0.08, respectively.

HRQoL results showed that GHS/QoL scores improved for Arm A (mean change of 2.8, SD = 23.2) and Arm B (mean change of 3.9, SD = 18.00) but declined in Arm C (mean change of -1.3, SD = 19.4) by Cycle 5 (Wang J et al 2020). Arm A (mean change of -20.1, SD = 29.2) and Arm B (mean change of -12.7, SD = 33.8) experienced a larger reduction in coughing at Cycle 5 compared to Arm C (mean change of -7.3, SD = 23.2). Similarly, Arm A (mean change of -1.9, SD = 18.1) and Arm B (mean change of -1.8, SD = 19.9) experienced a reduction in dyspnea while Arm C (mean change of 2.4, SD = 15.2) experienced more symptoms. All three arms experienced a reduction in hemoptysis at Cycle 5 with larger reductions observed for Arm A (mean change of -9.4, SD = 19.8) and Arm B (mean change of -9.4, SD = 26.8) compared to Arm C (mean change of -2.3, SD = 19.4). No clinical differences were observed between the three arms in pain events, with all three reporting a reduction in pain symptoms.

On 13 January 2021, tislelizumab received approval from the China National Medical Products Administration (NMPA) for use in combination with two chemotherapy regimens as a first-line treatment for patients with untreated Stage IIIB or IV squamous NSCLC. This tislelizumab combination demonstrated a clinically meaningful benefit as assessed by PFS and response rates.

**BGB-A317-315**

Study BGB-A317-315 is a randomized, double-blind, placebo-controlled, global, Phase 3 study to compare the efficacy and safety of neoadjuvant treatment with tislelizumab plus platinum-based doublet chemotherapy followed by adjuvant tislelizumab versus neoadjuvant

treatment with placebo plus platinum-based doublet chemotherapy followed by placebo in patients with resectable Stage II or IIIA NSCLC.

Efficacy data of major pathological response rate and pathological complete response rate from Study BGB-A317-315 (data cutoff 20 February 2023) were presented at the 2023 European Society for Medical Oncology World Congress (Yue et al 2023).

The major pathological response rate in the ITT Analysis Set was significantly improved in patients treated with tislelizumab plus chemotherapy before surgery (56.2%) versus those treated with placebo plus chemotherapy before surgery (15.0%) (difference: 41.1%; 95% CI: 33.2% to 49.1%, $p < 0.0001$). Additionally, the pathological complete response rate in the ITT Analysis Set was significantly improved in patients treated with tislelizumab plus chemotherapy before surgery (40.7%) versus those treated with placebo plus chemotherapy before surgery (5.7%) (difference: 35.0%; 95% CI: 27.0% to 42.1%, $p < 0.0001$).

## 1.5. Study Rationales

### 1.5.1. Rationale for Ociperlimab and Tislelizumab in the Treatment of NSCLC

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

As discussed in Section 1.2, anti-PD-1/PD-L1 antibodies have been shown to be clinically efficacious in both squamous and non-squamous NSCLC; furthermore, results from other anti-TIGIT + PD-L1 or PD-1 combination studies in NSCLC showed significant enhancement of antitumor activity compared with PD-1/PD-L1 monotherapy, suggesting that anti-TIGIT antibodies have the potential to significantly improve and/or extend the therapeutic benefit of anti-PD-1 therapy in this population , especially in patients expressing higher levels of PD-L1 (Chauvin et al 2015). Studies confirming the activity of these combinations in these patients are currently underway (SKYSCRAPER-01 and AdvanTIG-302).

Unfortunately, many NSCLC patients' tumors do not express high levels of PD-L1, and patients will most likely receive chemotherapy or chemotherapy combined with anti-PD-1/PD-L1 therapy. It is unclear if combining anti-TIGIT with these regimens in patients with low or negative PD-L1 expression will be successful. Subset analysis of the CITYSCAPE trial suggests that the PD-L1 high group (TPS ≥ 50%) was the primary driver of the enhanced activity for the combination but it is not known if the PD-L1 low (or PD-L1-negative) patients would have had greater benefit from the TIGIT + PD-L1 combination if chemotherapy had also been used. As these patients do show some activity with PD-1 monotherapy, it is quite possible that adding both chemotherapy and anti-TIGIT may be superior to PD-1 + TIGIT combinations in this group.

### 1.5.2. Rationale for the Selection of the Ociperlimab Dose in Combination With Tislelizumab

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

Complete TIGIT receptor occupancy was observed in circulating T cells in peripheral blood at all the tested doses of ociperlimab in Study AdvanTIG-105. However, the correlation between TIGIT receptor occupancy in the periphery and in tumor tissues is unknown. In a previous Phase 1 study of tiragolumab, another anti-TIGIT antibody, complete peripheral receptor occupancy was reached at the 30 mg dose level, but the clinical dose of 600 mg was determined as the RP2D, which was 20 times the 30 mg dose (Bendell et al 2020). Similarly, although complete peripheral receptor occupancy was observed at the 50 mg dose level of ociperlimab, the RP2D of 900 mg is approximately 20 times the dose of 50 mg. As of 12 May 2021, a total of 3 patients were assessed to have a confirmed partial response, 1 patient each in the 450 mg, 900 mg, and 1800 mg cohorts. Ociperlimab exposure in all 3 patients with a partial response is consistent with that expected at the 900 mg dose level. The confirmed disease control rates observed in the 450 mg, 900 mg, and 1800 mg cohorts were 60% (3/5), 64.3% (9/14), and 60% (3/5) of patients, respectively.

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

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

### 1.5.3. Rationale for the Selection of the Tislelizumab Dose

The tislelizumab dose of 200 mg once every 3 weeks was selected based on the totality of clinical safety, efficacy, and pharmacokinetic data from Study BGB-A317-001.

- Incidence rates of various treatment-related AEs and serious AEs in patients receiving 2 mg/kg and 5 mg/kg once every 2 weeks or once every 3 weeks were comparable, suggesting a lack of dose or regimen dependance (Wu et al 2019a; Wu et al 2019b).
- The ORRs observed in patients treated with tislelizumab 2 mg/kg once every 2 weeks (10%) or once every 3 weeks (38%) were generally comparable with tislelizumab 5 mg/kg once every 2 weeks (15%) or once every 3 weeks (15%), suggesting a lack of dose or regimen dependence.
- Tislelizumab exhibited linear PK across the dose range of 0.5 mg/kg to 10 mg/kg and no PK differences were observed between 2 dose regimens (once every 2 weeks or once every 3 weeks). Additionally, population PK analysis indicated tislelizumab clearance is

not dependent on body weight, which supports administration of tislelizumab without regard to body weight.

- Incidence of ADAs to tislelizumab did not appear to be related to safety events and efficacy.
- Exposure-response analysis for safety events and efficacy (ORR) across a wide range of tumor types showed flat relationships, with tislelizumab exposure supporting selection of a flat dose within the exposure range of 2 mg/kg and 5 mg/kg.

A flat dose of 200 mg, which is equivalent to 2.86 mg/kg for a 70 kg patient, was chosen based on the comparable safety and efficacy data at the 2 mg/kg and 5 mg/kg dose levels, and the lack of relationship between tislelizumab clearance and body weight. The regimen of tislelizumab 200 mg once every 3 weeks produces tislelizumab concentrations that overlap with those observed with the 2 mg/kg and 5 mg/kg dose levels. The once-every-3-weeks regimen was selected based on the similarity in efficacy and safety data observed between the once-every-2-weeks and once-every-3-weeks regimens. A flat dose offers additional advantages such as convenience in preparation and administration of dose and avoids potential dosing errors. The efficacy and safety of the regimen of tislelizumab 200 mg once every 3 weeks has been assessed subsequently in multiple pivotal Phase 2 and 3 clinical studies.



### 1.5.4. Rationale for Tislelizumab Plus Chemotherapy as the Comparator

While in many countries, pembrolizumab is considered standard of care as first-line therapy for patients with metastatic NSCLC, tislelizumab has shown comparable activity when combined with chemotherapy in this population (see Section 1.4.5 for a discussion of the BGB-A317-304 and BGB-A317-307 studies) and is expected to perform similarly in this study. As the goal of the study is to assess the activity of ociperlimab when combined with tislelizumab and chemotherapy, using tislelizumab with chemotherapy as a comparator should provide an accurate assessment of how the ociperlimab combination performs versus a PD-1 inhibitor alone (either tislelizumab or pembrolizumab) with chemotherapy and also demonstrate the contribution of ociperlimab to the combination.

### 1.5.5. Rationale for Biomarker Strategy

Biomarker analyses in tumor tissues will include but not be limited to the expression of TIGIT, CD226, CD155, CD112, PD-L1, gene expression profiling (GEP), tumor mutation burden (TMB), gene mutations, microsatellite instability (MSI), and TILs to explore potential predictive and prognostic biomarkers and mechanisms of resistance. For sites in mainland China, tissue samples will be limited to the expression of TIGIT, CD226, CD155, CD112, PD-L1, GEP, TMB, gene mutations, MSI, and TILs at baseline and at disease progression/reoccurrence.

In addition, blood-based biomarkers will include but not be limited to circulating tumor DNA (ctDNA), TMB, MSI, gene mutations, and extracellular vesicles (EVs). For sites in mainland China, blood-based biomarkers will be limited to ctDNA, TMB, MSI, gene mutations, and EVs.

PD-L1 is expressed in tumor and TILs in advanced NSCLC, and its expression level has been shown to be correlated with clinical efficacy of anti-PD-1 treatment in multiple studies (Topalian et al 2012; Herbst et al 2014; Borghaei et al 2015; Fehrenbacher et al 2016; Herbst et al 2016; Rosenberg et al 2016). PD-L1 IHC 22C3 pharmDx was approved as a companion diagnostic (CDx) to identify patients with NSCLC for treatment with KEYTRUDA (pembrolizumab). In addition, higher PD-L1 expression on tumor cells has also shown to be correlated with enhanced ORR and PFS in anti-PD(L)-1 plus chemotherapy studies (KEYNOTE-189, KEYNOTE-407, IMpower131), suggesting the possible predictive value of PD-L1 in therapies combining anti-PD-1 and chemotherapy in NSCLC.

However, the role of PD-L1 in predicting response to immune combination therapies in patients with NSCLC is still poorly understood. In the CITYSCAPE study, NSCLC patients with higher PD-L1 derived impressive benefit from atezolizumab (anti-PD-L1) plus tiragolumab (anti-TIGIT) compared to atezolizumab alone (PFS of HR 0.29 with 95% CI 0.15-0.53), suggesting PD-L1 could be a predictive biomarker for PD-1 and TIGIT pathway co-targeting treatment in NSCLC (Rodriguez-Abreu et al 2020). In this study, PD-L1 expression in tumor cells (three levels: < 1% versus 1% to 49% versus ≥ 50%) was designed as one of the stratification factors to explore its association with clinical efficacy.

In addition to PD-L1, clinical data from various studies suggested TMB, MSI, abundance and location of TILs, and immune-related GEP are a few factors associated with response to immunotherapies including anti-PD-1 antibodies in different cancers (Vilain et al 2017; Goodman et al 2017; Gandara et al 2018; Jiang et al 2018). Therefore, ctDNA, TMB, MSI, gene mutations, TILs, EVs, and GEP will be studied in relationship with clinical response to ociperlimab in combination with tislelizumab treatment to explore potential predictive or prognosis biomarkers.

Mechanisms of resistance to immunotherapies are also not well understood and need more exploration. Identification of tumor and immune-related features associated with disease progression or acquired resistance to ociperlimab and tislelizumab may increase the understanding of disease pathobiology and provide biological evidence for the combination strategy. In this regard, high TIGIT/CD226 ratio on Treg cells was shown to correlated with poor clinical outcomes in melanoma patients treated with anti-PD 1 or anti-PD-L1 antibodies (Fourcade et al 2018). In addition, a higher frequency of TIGIT+ T cells among PD-1+CD8+ T cells was associated with hyperprogressive disease during PD-1/PD-L1 blockade and inferior survival rate in patients with NSCLC (Kim et al 2019). These results suggest that signaling through the TIGIT pathway in tumor tissues might contribute to resistance to immune checkpoint inhibitors targeting PD-1 or PD-L1. Here, the expression levels of TIGIT pathway molecules including TIGIT, CD226, CD155, and CD112 will also be studied to explore its correlation with the clinical efficacy of ociperlimab plus tislelizumab combined treatment.

## 1.6. Benefit-Risk Assessment

AdvanTIG-205 will evaluate the safety and efficacy of the anti-TIGIT antibody ociperlimab in combination with tislelizumab and chemotherapy in patients with previously untreated locally advanced, unresectable, or metastatic NSCLC that does not harbor *EGFR* mutations, *ALK* translocations, *BRAF V600E* mutations, or c-ROS oncogene-1 (*ROS1*) mutations. There is extensive evidence supporting TIGIT's role in regulating immune response. In addition, the

interaction between the TIGIT and PD-1 pathways has been shown to promote tumor immune escape. The clinical efficacy demonstrated for tislelizumab (Section 1.4.5) and preliminary results from an anti-TIGIT/ anti-PD-L1 competitor combination, suggests that ociperlimab has the potential to improve and/or extend the therapeutic benefits of tislelizumab in the treatment naive setting, especially in patients whose tumors express higher levels of PD-L1. By testing the combination with chemotherapy, there is a good chance that enhanced activity of the combination may be seen in a broader group of patients, including those whose tumors express low or no PD-L1.

As discussed earlier (Section 1.5.1), based on the mechanism(s) of action, and the nonclinical and preliminary clinical data, the combined blockade of TIGIT and PD-1 by ociperlimab and tislelizumab, respectively, is expected to result in immune-mediated toxicities similar to what has been observed with tislelizumab alone or tislelizumab with chemotherapy.

Preliminary safety results from the CITYSCAPE trial (N = 135 patients) support this hypothesis and show that patients treated with the anti-TIGIT/PD-L1 combination experienced less than 10% increase in overall and Grade 3 or 4 TEAEs compared to patients treated with anti-PD-1 and placebo.

The risk of observing augmented safety signals as has been shown for other anti-PD-1-based immune-oncology combinations still remains; therefore, a monitoring plan derived from the European Society for Medical Oncology and American Society for Clinical Oncology has been established to monitor, diagnose, and manage imAEs (Appendix 7). 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 the 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), which should help control toxicity.

Blockade of the PD-1 pathway has demonstrated strong antitumor efficacy either alone or in combination with standard of care chemotherapy in multiple cancer indications. As of 20 May 2020, PD-1 blockade by tislelizumab has been evaluated in more than 1917 patients with a safety and efficacy profile similar to what has been reported for other anti-PD-1/PD-L1 therapies, such as nivolumab and pembrolizumab.

Safety data will be continuously monitored by the sponsor's study team in consultation with investigator(s) as needed. Refer to Section 7.4 and Section 8 for information regarding additional safeguards and considerations related to potential risk.

In summary, there is a strong scientific rationale that the combined blockade of the TIGIT pathway and PD-1 pathway may result in enhanced antitumor activity without a major increase in the risk of immune-mediated toxicities to benefit a larger patient population than single agent anti-PD-1 therapy.

# 2. STUDY OBJECTIVES AND ENDPOINTS

## 2.1. Study Objectives

### 2.1.1. Primary Objective

- To compare progression-free survival (PFS) in Arm A (ociperlimab in combination with tislelizumab and chemotherapy) and Arm B (placebo in combination with tislelizumab and chemotherapy) in the ITT Analysis Set, as assessed by investigators per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)

### 2.1.2. Secondary Objectives

- To evaluate overall response rate (ORR) and duration of response (DOR) in Arm A (ociperlimab in combination with tislelizumab and chemotherapy) versus Arm B (placebo in combination with tislelizumab and chemotherapy), as assessed by investigators per RECIST v1.1
- To compare overall survival (OS) between Arm A (ociperlimab in combination with tislelizumab and chemotherapy) and Arm B (placebo in combination with tislelizumab and chemotherapy)
- To evaluate the safety and tolerability profile of ociperlimab in combination with tislelizumab and chemotherapy compared to tislelizumab in combination with chemotherapy

### 2.1.3. Exploratory Objectives

- To evaluate disease control rate (DCR), clinical benefit rate (CBR), and time to response (TTR) in Arm A (ociperlimab in combination with tislelizumab and chemotherapy) versus Arm B (placebo in combination with tislelizumab and chemotherapy), as assessed by investigators per RECIST v1.1
- To evaluate the potential association of exploratory biomarkers with response or resistance of ociperlimab and tislelizumab, and patient prognosis
- To compare health-related quality-of-life (HRQoL) between Arm A (ociperlimab in combination with tislelizumab and chemotherapy) and Arm B (placebo in combination with tislelizumab and chemotherapy)
- To characterize the pharmacokinetics (PK) of ociperlimab and tislelizumab
- To determine host immunogenicity to ociperlimab and tislelizumab

## 2.2. Study Endpoints

### 2.2.1. Primary Endpoint

- PFS (time from the date of randomization to the date of the first objectively documented tumor progression, or death, whichever occurs first) in the ITT Analysis Set of Arm A (ociperlimab in combination with tislelizumab and chemotherapy)

versus Arm B (placebo in combination with tislelizumab and chemotherapy), as assessed by investigators per RECIST v1.1

### 2.2.2. Secondary Endpoints

- ORR as assessed by investigators (proportion of patients with a documented, confirmed complete response [CR] or partial response [PR] per RECIST v1.1) and DOR as assessed by investigators (time from the first determination of an objective response per RECIST v1.1 until the first documentation of progression or death, whichever occurs first) in Arm A (ociperlimab in combination with tislelizumab and chemotherapy) and Arm B (placebo in combination with tislelizumab and chemotherapy)
- OS (time from the date of randomization to the date of death due to any cause) in the ITT Analysis Set of Arm A (ociperlimab in combination with tislelizumab and chemotherapy) versus Arm B (placebo in combination with tislelizumab plus chemotherapy)
- The incidence and severity of adverse events according to National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v5.0)

### 2.2.3. Exploratory Endpoints

- DCR (proportion of patients with confirmed CR or confirmed PR or stable disease [SD]), CBR (proportion of patients with confirmed CR or confirmed PR or durable SD) and TTR (time from randomization to the first occurrence of a documented objective response) in Arm A (ociperlimab in combination with tislelizumab and chemotherapy) versus Arm B (placebo in combination with tislelizumab and chemotherapy) as assessed by investigators per RECIST v1.1
- Status of exploratory biomarkers, including but not limited to expression of T-cell immunoglobulin and ITIM domain (TIGIT), CD226, CD155, CD112, PD-L1, GEP, ctDNA, TMB, gene mutations, MSI, TILs, and EVs in archival and/or fresh tumor tissue and blood before and after study treatment or at disease progression/reoccurrence, and the association between these biomarkers and clinical efficacy, disease status, and resistance.
- HRQoL will be assessed using 2 validated patient-reported outcomes (PROs), including European Organization for Research and Treatment of Cancer Quality of Life Questionnaire- Core 30 (EORTC-QLQ-C30) and its lung cancer module (Quality of Life Questionnaire-Lung Cancer 13 [QLQ-LC13]).
- Serum concentrations of ociperlimab and tislelizumab at specified timepoints
- Immunogenic responses to ociperlimab and tislelizumab, evaluated through detection of anti-drug antibodies (ADAs)

# 3. STUDY DESIGN

## 3.1. Summary of Study Design

This is a randomized, investigator- and patient-blinded, sponsor-unblinded, multicenter, Phase 2 study designed to evaluate the efficacy and safety of ociperlimab in combination with tislelizumab and histology-based chemotherapy versus tislelizumab in combination with placebo and histology-based chemotherapy in patients with previously untreated locally advanced, unresectable, or metastatic NSCLC whose tumors do not harbor *EGFR*-sensitizing mutations, *ALK* translocations, *BRAF V600E* mutations, *ROS1* mutations, or other genetic mutations for which a targeted therapy is appropriate and accessible.

Patients will be required to sign an informed consent form (ICF) to undergo collection of tissue samples (archival tissue or fresh biopsy) for central evaluation of status and to undergo screening procedures. If the assessments of PD-L1 in the local laboratory meet all requirements (refer to Section 4.1), the local PD-L1 results may be used for randomization.

Approximately 270 patients will be enrolled (including a minimum of 25% of non-Asian patients).

The study will target to enroll patients to ensure that it reflects a representative distribution of PD-L1 expression in NSCLC (approximately 40% PD-L1 TC < 1%) and to ensure that it reflects a representative histology distribution in the NSCLC population without driver mutation (approximately 30% squamous NSCLC).

Eligible participants will be randomized in a 1:1 ratio to receive ociperlimab + tislelizumab + chemotherapy (Arm A) or placebo + tislelizumab + chemotherapy (Arm B). Randomization will be stratified by PD-L1 expression (three levels: < 1% TC versus 1% to 49% TC versus ≥ 50% TC), and histology (squamous versus non-squamous).

During the induction phase (4 to 6 cycles), study treatments will be given as follows:

- Arm A: Ociperlimab 900 mg IV + tislelizumab 200 mg IV + histology-based chemotherapy once every 3 weeks
- Arm B: Placebo IV + tislelizumab 200 mg IV + histology-based chemotherapy once every 3 weeks
- All patients in Arms A and B will receive histology-based chemotherapy:
  - For patients with squamous NSCLC: carboplatin AUC 5 or 6 (D1) + paclitaxel 175 or 200 mg/m$^2$ (D1) or nab-paclitaxel 100 mg/m$^2$ (D1, D8, D15) administered every 3 weeks
  - For patients with non-squamous NSCLC: cisplatin 75 mg/m$^2$ or carboplatin AUC 5 (D1) + pemetrexed 500 mg/m$^2$ (D1) IV administered every 3 weeks

During the maintenance phase, study treatments will be given as follows:

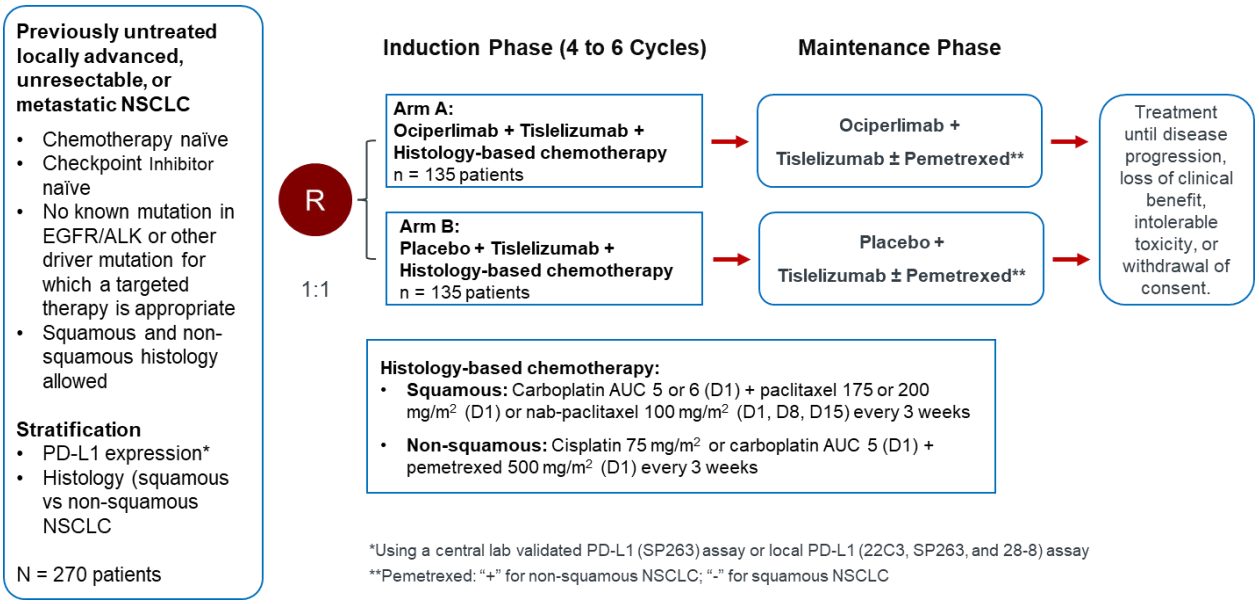
- For patients with non-squamous NSCLC:
  - Arm A: Ociperlimab 900 mg IV + tislelizumab 200 mg IV + pemetrexed 500 mg/m$^2$ once every 3 weeks

- Arm B: Placebo IV + tislelizumab 200 mg IV + pemetrexed 500 mg/m$^2$ once every 3 weeks

- For patients with squamous NSCLC:
  - Arm A: Ociperlimab 900 mg IV + tislelizumab 200 mg IV once every 3 weeks
  - Arm B: Placebo IV + tislelizumab 200 mg IV once every 3 weeks

The study design schematic is presented in Figure 2.

**Figure 2: Study Schema**




Abbreviations: ALK, anaplastic lymphoma kinase; D, day; AUC, area under the concentration-time curve; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand-1; R, randomization; WT, wild type

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

## 3.2. Screening Period

Screening evaluations will be performed within 28 days before randomization. Patients who agree to participate in this study will sign the main ICF before undergoing any screening procedure (refer to Section 7 and Appendix 1 for details). Screening evaluations may be repeated as needed within the screening period; the investigator is to assess preliminary patient eligibility according to the latest screening assessment results.

## 3.3. Treatment Period

After completing all screening activities, eligible patients will be randomized in a 1:1 ratio to receive ociperlimab + tislelizumab + chemotherapy (Arm A) or placebo + tislelizumab + chemotherapy (Arm B).

The study will have 2 phases: an induction phase and a maintenance phase.

During the induction phase (4 to 6 cycles), study treatments will be given as follows:

- Arm A: Ociperlimab 900 mg IV + tislelizumab 200 mg IV + histology-based chemotherapy once every 3 weeks
- Arm B: Placebo IV + tislelizumab 200 mg IV + histology-based chemotherapy once every 3 weeks
- All patients in Arms A and B will receive histology-based chemotherapy:
  - For patients with squamous NSCLC: carboplatin AUC 5 or 6 (D1) + paclitaxel 175 or 200 mg/m$^2$ (D1) or nab-paclitaxel 100 mg/m$^2$ (D1, D8, D15) administered every 3 weeks
  - For patients with non-squamous NSCLC: cisplatin 75 mg/m$^2$ or carboplatin AUC 5 (D1) + pemetrexed 500 mg/m$^2$ (D1) IV administered every 3 weeks

The number of chemotherapy cycles (4 to 6 cycles) and the chemotherapy regimen selection will be at the investigator's discretion.

During the maintenance phase, study treatments will be given as follows:

- For patients with non-squamous NSCLC:
  - Arm A: Ociperlimab 900 mg IV + tislelizumab 200 mg IV + pemetrexed 500 mg/m$^2$ once every 3 weeks
  - Arm B: Placebo IV + tislelizumab 200 mg IV + pemetrexed 500 mg/m$^2$ once every 3 weeks
- For patients with squamous NSCLC:
  - Arm A: Ociperlimab 900 mg IV + tislelizumab 200 mg IV once every 3 weeks
  - Arm B: Placebo IV + tislelizumab 200 mg IV once every 3 weeks

All study treatments will be administered until intolerable toxicity, withdrawal of informed consent, or the timepoint at which, in the opinion of the investigator, the patient is no longer benefiting from study therapy.

No crossover will be allowed between treatment arms because the treatment assignment will remain blinded to investigators and patients until the primary endpoint data are available.

Treatment beyond the initial investigator-assessed, RECIST v1.1-defined disease progression is permitted in both arms provided that the patient has investigator-assessed clinical benefit and is tolerating tislelizumab in combination with ociperlimab (or placebo); the chemotherapy beyond initial progression will be at investigator's discretion (see Section 7.5).

The following criteria must be met to treat patients after initial evidence of radiologic disease progression:

- Absence of clinical symptoms and signs of progressive disease (including clinically significantly worsening of laboratory values)
- ECOG Performance Status ≤ 1

- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, spinal cord compression) that requires urgent alternative medical intervention
- Investigators must obtain written informed consent for treatment beyond radiologic disease progression and inform patients that this practice is not considered standard in the treatment of cancer. Patients must be informed that they may be forgoing treatment that has shown benefit by continuing treatment beyond progression
- The decision to continue study drug(s) beyond initial investigator-assessed progression must be agreed upon with the sponsor medical monitor

Patients who receive study treatment beyond progression will have tumor assessments performed according to the original schedule until study treatment discontinuation.

Tumor assessments are required to be performed on schedule regardless of whether study treatment has been administered or held (ie, their schedule should not be adjusted for delays in cycles). Tumor response will be assessed by investigators using RECIST v1.1 criteria (Eisenhauer et al 2009). Radiologic assessment of tumor-response status will be performed approximately every 9 weeks (± 7 days) from randomization for the first 52 weeks and every 12 weeks (± 7 days) thereafter. Patients who discontinue study treatment early for reasons other than radiologic disease progression (eg, toxicity) will continue to undergo tumor assessments following the original plan until the patient begins a subsequent anticancer treatment, experiences radiologic disease progression or death, withdraws consent, is lost to follow-up, or until the study terminates, whichever occurs first. Details are provided in Section 7.5.

Patient-reported outcomes (PRO; see Section 7.8) will be collected at baseline (Day 1 of Cycle 1), every other cycle through Cycle 13, then every 4 cycles thereafter, and at the End of Treatment (EOT) Visit (Section 3.4). At each visit, PRO will be collected before any procedures or dose administration.

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

Patients will provide blood samples at Cycle 1 Day 1 and Cycle 3 Day 1 for the assessment of mechanism of response or resistance (Section 7.7; Appendix 1).

## 3.4. End of Treatment

The End of Treatment Visit will be conducted when the investigator determines that ociperlimab/placebo or tislelizumab will no longer be used. If routine laboratory tests (eg, hematology, serum chemistry) were completed within 7 days before the EOT Visit, these tests need not be repeated.

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

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

Patients who have progressive disease will be asked to provide an optional biopsy at the EOT Visit for the assessment of mechanism of resistance (Section 7.7).

Patients who have progressive disease will provide blood samples at the EOT Visit for the assessment of mechanism of response or resistance (Section 7.7; Appendix 1).

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

## 3.5. Safety Follow-up

A Safety Follow-up Visit at 30 days (± 7 days) after the last dose of the study drug(s) is required to assess AEs and concomitant medications, unless the time window overlaps with the time window of the EOT Visit; the Safety Follow-up Visit may be a telephone call or an on-site visit if laboratory assessments are necessary. Two additional telephone calls with patients will occur in the safety follow-up period to assess imAEs and concomitant medications if appropriate at 60 and 90 days (± 14 days) after the last dose of ociperlimab (or placebo) and/or tislelizumab regardless of whether the patient starts a new subsequent anticancer therapy. If a patient reports a suspected imAE at a safety follow-up telephone call, the investigator should arrange an unscheduled visit if further assessment is indicated.

For women of childbearing potential (see Appendix 10), an additional follow-up visit for a urine pregnancy test will occur until 120 days after the last dose of ociperlimab and/or tislelizumab or 180 days after the last dose of chemotherapy, whichever comes later.

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

See Appendix 1 for assessments to be performed at the Safety Follow-Up Visit.

## 3.6. Survival Follow-up

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 EOT Visit or as directed by the sponsor until death, withdrawal of consent, loss to follow-up, or end of study.

## 3.7. Discontinuation From the Study Treatment or From the Study

### 3.7.1. Patient Discontinuation From Study Treatment

Patients have the right to discontinue study treatment at any time for any reason. In addition, the investigator has the right to discontinue a patient from the study treatment at any time. Patients who discontinue study treatment for reasons other than disease progression should be followed for assessments of antitumor activity (Section 7.5), safety (Section 7.4) and survival (Section 3.6), if possible.

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

- Disease progression
- Adverse event

- Drug withdrawal by patient
- Pregnancy
- Any medical condition that the investigator or sponsor determines may jeopardize the patient's safety, if he or she were to continue the study treatment
- Use of any concurrent anticancer therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents [including Chinese (or other country) herbal medicine and Chinese (or other country) patent medicines] for the treatment of cancer)
- Patient noncompliance
    - Investigative site staff should first counsel patients who are significantly noncompliant (eg, missing 2 treatment cycles) on the importance of study drug compliance and drug accountability. The investigator may, in consultation with the medical monitor, discontinue patients from treatment who are consistently noncompliant.

Benefits of continuation of ociperlimab (or placebo) and/or tislelizumab beyond 2 years after the start of treatment should be evaluated and discussed with the sponsor's medical monitor (Herbst et al 2020; Kottschade 2019)

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

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

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

## 3.8. End of Study

The end of study is defined as the timepoint when the final data point is collected from the last patient in the study. This is when the last patient dies, withdraws consent, completes all study assessments, or is lost to follow-up. Alternatively, the end of study is when the sponsor decides to terminate the study.

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

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients
- Overall patient enrollment is unsatisfactory
- A rollover study becomes available

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

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

Patients who, in the opinion of the investigator, continue to benefit from ociperlimab in combination with tislelizumab or tislelizumab alone at study termination will be offered the option to continue the treatment as permitted by applicable laws and regulations in a continuous access program, such as but not limited to, a Long-Term Extension study, a Post-Trial Supply program, a Patient Access Program, until the treatment is commercially available in the country of the patient's residence.

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

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

# 4. STUDY POPULATION

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

## 4.1. Inclusion Criteria

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

1. Able to provide written informed consent and can understand and agree to comply with the requirements of the study and the schedule of assessments.
2. Age ≥ 18 years on the day of signing the informed consent form (or the legal age of consent in the jurisdiction in which the study is taking place).
3. Histologically or cytologically documented locally advanced or recurrent NSCLC that is not eligible for curative surgery and/or definitive radiotherapy, with or without chemotherapy, or metastatic non-squamous or squamous NSCLC.
   a. Tumors of mixed non-small cell histology will be categorized by the predominant cell type.
   b. If small cell elements are present, the patient is ineligible.
   c. Patients with Stage IIIa NSCLC are not eligible.
4. No prior systemic therapy for locally advanced or metastatic squamous or non-squamous NSCLC, including but not limited to chemotherapy or targeted therapy. Patients who have received prior neoadjuvant, adjuvant chemotherapy, or chemoradiotherapy with curative intent for nonmetastatic disease must have experienced a disease-free interval of ≥ 6 months from the last dose of chemotherapy and/or concurrent radiotherapy prior to randomization.
5. Archival tumor tissue (formalin-fixed paraffin-embedded block containing tumor [preferred] or approximately 6 to 15 freshly cut unstained slides) or fresh biopsy (if archival tissue is not available) for the determination of PD-L1 levels and retrospective analyses of other biomarkers. PD-L1 expression in tumor cells will be assessed using a central laboratory validated PD-L1 (SP263) assay or local PD-L1 assay. Local PD-L1 results may be utilized under certain circumstances for enrollment.

   Note: If local PD-L1 testing will be used for patient randomization purposes, confirmation of tumor sample receipt by the central laboratory is required before patient randomization (preferably from the same block used for local PD-L1 testing). Local PD-L1 testing must be performed using an approved assay (limited to 22C3, SP263, and 28-8) at a certified laboratory and according to the manufacturer's instructions.
6. At least one measurable lesion by the investigator as defined per RECIST v1.1.

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

8. Adequate organ function as indicated by the following laboratory values during screening.

   Patients must not have required blood transfusion or growth factor support ≤ 14 days before sample collection at screening for the following:

   a. Absolute neutrophil count (ANC) ≥ 1.5 x $10^9$/L
   b. Platelets ≥ 100 x $10^9$/L
   c. Hemoglobin ≥ 90 g/L
   d. Estimated glomerular filtration rate (eGFR) ≥ 45 mL/min/1.73 $m^2$ by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation or calculated creatinine clearance (CrCl) ≥ 45 mL/min/1.73 $m^2$ by Cockcroft-Gault (CG) equation. If using cisplatin, eGFR ≥ 60 mL/min/1.73 $m^2$ by CKD-EPI equation or CrCl ≥ 60 mL/min/1.73 $m^2$ by CG equation (Appendix 9).
      Note: For France only, eGFR ≥ 45 mL/min/1.73 $m^2$ by CKD-EPI equation and CrCl ≥ 45 mL/min/1.73 $m^2$ by CG equation. If using cisplatin, eGFR ≥ 60 mL/min/1.73 $m^2$ by CKD-EPI equation and CrCl ≥ 60 mL/min/1.73 $m^2$ by CG equation.
   e. Serum total bilirubin ≤ 1.5 x ULN (total bilirubin must be < 3 x ULN for patients with Gilberts syndrome).
   f. AST and ALT ≤ 2.5 x ULN or < 5 x ULN if hepatic metastases present.

9. Women of childbearing potential must be willing to use a highly effective method of birth control for the duration of the study, and for ≥ 120 days after the last dose of tislelizumab and ociperlimab/placebo, or ≥ 180 days after the last dose of chemotherapy (14 months after the last dose of cisplatin), whichever occurs later, and must have a negative urine or serum pregnancy test ≤ 7 days before randomization. See Appendix 10.

10. Nonsterile men must be willing to use a highly effective method of birth control for the duration of the study and for ≥ 120 days after the last dose of tislelizumab and ociperlimab/placebo, or ≥ 180 days after the last dose of chemotherapy (11 months after the last dose of cisplatin), whichever occurs later.

    - A sterile man is defined as one for whom azoospermia has been previously demonstrated in a semen sample examination as definitive evidence of infertility.
    - Men with known "low sperm counts" (consistent with "subfertility") are not to be considered sterile for purposes of this study.

11. Eligibility to receive a platinum-based doublet chemotherapy regimen.

    - For patients intended to receive cisplatin: without any hearing impairment.

## 4.2. Exclusion Criteria

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

1. Known mutations in:

   a. *EGFR* gene

      Note: For non-squamous NSCLC, patients with unknown *EGFR* mutation status will be required to have a tissue-based *EGFR* test either locally or at the central laboratory

before enrollment, or endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA)–based *EGFR* test locally. Patients found to have *EGFR*-sensitizing mutations will be excluded. An additional ≥ 6 freshly cut unstained slides are required for non-squamous NSCLC patients with unknown *EGFR* status who will have *EGFR* testing done at the study central laboratory.

b. *ALK* fusion oncogene.

Note: However, testing for *ALK* fusions and *EGFR* mutations can be considered in select patients if they have never smoked, small biopsy specimens were used for testing, or mixed histology was reported.

c. *BRAF V600E*
d. *ROS1*

Note: If no targeted therapy approved by local health authority is available for *BRAF V600E* or *ROS1* mutations, then these patients are eligible.

For France only: Patients with non-squamous NSCLC and unknown *ROS1* gene rearrangements status should be tested locally to confirm eligibility. Testing is not required for patients with squamous NSCLC but can be considered if small biopsy samples were used to assess histology or mixed histology was reported.

e. For other genetic mutations, if no targeted therapy approved by local health authority is available, then these patients are eligible.

2. Prior treatment with EGFR inhibitors, ALK inhibitors, or targeted therapy for other driver mutations.
3. Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-TIGIT, or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways in locally advanced or metastatic NSCLC.

Note: Patients who have received prior neoadjuvant, adjuvant, or immuno-oncology therapies in consolidation are eligible, as long as there has been a treatment-free interval of ≥ 6 months from the last dose of immuno-oncology therapy prior to radiologic recurrence of the disease.

4. Active leptomeningeal disease or uncontrolled, untreated brain metastasis.

- Patients with stable central nervous system (CNS) metastases at the time of screening are eligible, provided they meet all the following:

a. Brain imaging at screening shows no evidence of interim progression, patient is clinically stable for at least 2 weeks and without evidence of new brain metastases.
b. Measurable and/or evaluable disease outside the CNS.
c. No ongoing requirement for corticosteroids as therapy for CNS disease; off steroids 3 days before randomization; anticonvulsants at a stable dose are allowed.
d. No stereotactic radiation or whole-brain radiation within 14 days before randomization.

e. Subjects with asymptomatic brain metastases (ie, no neurological symptoms, no requirements for corticosteroids, and no lesion > 1.5 cm) may participate but will require regular imaging of the brain as a site of disease.

5. Active autoimmune diseases or history of autoimmune diseases that may relapse.

   Note: Prospective patients should be carefully questioned to determine whether they have any history of an acquired or congenital immune deficiency or autoimmune disease (Appendix 5). Patients with the following diseases are not excluded and may proceed to further screening:

   a. Controlled Type I diabetes.
   b. Hypothyroidism (provided it is managed with hormone replacement therapy only).
   c. Controlled celiac disease.
   d. Skin diseases not requiring systemic treatment (eg, vitiligo, psoriasis, alopecia).
   e. Any other disease that is not expected to recur in the absence of external triggering factors.

6. Any active malignancy ≤ 5 years before randomization except for the specific cancer under investigation in this study and any locally recurring cancer that has been treated curatively (eg, resected basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix or breast).

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

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

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

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

9. Uncontrollable pleural effusion, pericardial effusion, or ascites requiring frequent drainage

10. History of interstitial lung disease, noninfectious pneumonitis or uncontrolled lung diseases including pulmonary fibrosis, acute lung diseases, etc. Patients with significantly impaired pulmonary function, or who require supplemental oxygen at baseline must undergo an assessment of pulmonary function at screening (see Section 7.1.3).

11. Infection (including tuberculosis infection, etc.) requiring systemic antibacterial, antifungal, or antiviral therapy within 14 days before randomization.

Note: Antiviral therapy is permitted for patients with chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. Patients with symptomatic COVID-19 infection are excluded.

12. Untreated chronic hepatitis B or chronic HBV carriers with HBV DNA > 500 IU/mL (or > 2500 copies/mL) at screening.

    Note: Inactive hepatitis B surface antigen (HBsAg) carriers, treated and stable hepatitis B (HBV DNA < 500 IU/mL or < 2500 copies/mL) can be enrolled. Patients with detectable HBsAg or detectable HBV DNA should be managed per treatment guidelines. Patients receiving antivirals at screening should have been treated for > 2 weeks before randomization.

13. Patients with active hepatitis C.

    Note: Patients with a negative HCV antibody test at screening or positive HCV antibody test followed by a negative HCV RNA test at screening are eligible. The HCV RNA test will be performed only for patients testing positive for HCV antibody. Patients receiving antivirals at screening should have been treated for > 2 weeks before randomization.

14. Known history of human immunodeficiency virus (HIV) infection.

    Note: For sites where required by Health Authority or local guidance, an HIV serology test (including antigen and/or antibodies) will be conducted at baseline for patients with unknown HIV status. Patients with positive HIV test results will be excluded.

15. Any major surgical procedure ≤ 28 days before randomization. Patients must have recovered adequately from the toxicity and/or complications from the intervention before randomization.

16. Prior allogeneic stem cell transplantation or organ transplantation.

17. Any of the following cardiovascular risk factors:

    a. Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living, ≤ 28 days before randomization.
    b. Symptomatic pulmonary embolism ≤ 28 days before randomization.
    c. Any history of acute myocardial infarction ≤ 6 months before randomization.
    d. Any history of heart failure meeting New York Heart Association (NYHA) Classification III or IV (Appendix 6) ≤ 6 months before randomization.
    e. Any event of ventricular arrhythmia ≥ Grade 2 in severity ≤ 6 months before randomization.
    f. Any history of cerebrovascular accident ≤ 6 months before randomization.
    g. Uncontrolled hypertension that cannot be managed by standard antihypertension medications ≤ 28 days before randomization.

    For France only: Systolic pressure ≥ 140 mmHg or diastolic pressure ≥ 90 mmHg on repeated measurements.

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

18. A history of severe hypersensitivity reactions to other monoclonal antibodies or any components of chemotherapy agents.

19. Was administered a live vaccine ≤ 28 days before randomization.

    Note: Vaccines for COVID-19 are allowed except for any live vaccine that may be developed. It is recommended to avoid COVID-19 vaccination within 72 hours before or after study drug administration during the first 2 treatment cycles and within 24 hours before or after study drug administration thereafter (ie, from Cycle 3 onwards). Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed.

20. Underlying medical conditions (including laboratory abnormalities) or alcohol or drug abuse or dependence that will be unfavorable for the administration of study drug, or affect the explanation of drug toxicity or AEs, or result in insufficient or impaired compliance with study conduct.

21. Women who are pregnant, suspected of being pregnant, breastfeeding, or planning to get pregnant during the study.

    Note: Women who are breastfeeding and agree to stop breastfeeding before screening are allowed to enroll. They cannot breastfeed during the study and for at least 120 days after the last dose of study drugs.

22. Concurrent participation in another therapeutic clinical study.

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

23. 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, fatigue, or non-clinically significant laboratory anomalies).

24. Has received any immunotherapy (eg, interleukin, interferon, thymosin, etc.) or any investigational therapies ≤ 14 days or ≤ 5 half-lives (whichever is shorter) before the first dose of study drug.

25. For France, adults protected by law defined in Art. L. 1121-8 of the Public Health Code.

# 5. STUDY TREATMENT

## 5.1. Formulation, Packaging, and Handling

### 5.1.1. Ociperlimab

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

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

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

Refer to the pharmacy manual for details regarding intravenous administration, accountability, and disposal. Refer to the Ociperlimab (BGB-A1217) Investigator's Brochure for other details regarding ociperlimab.

### 5.1.2. Tislelizumab

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

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

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

Refer to the pharmacy manual for details regarding intravenous administration, accountability, and disposal. Refer to the Tislelizumab (BGB-A317) Investigator's Brochure for other details regarding tislelizumab.

### 5.1.3. Chemotherapy Agents

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

For further details, see the manufacturer's prescribing information.

### 5.1.4. Ociperlimab Placebo

Ociperlimab placebo is a sterile, preservative-free solution for infusion formulated in the same buffer as ociperlimab. All excipients used for the manufacture of placebo are of pharmacopeial grade. No animal-derived components are used in the manufacture of placebo. Each vial is packaged into a single carton box.

As with ociperlimab, the contents of the label will be in accordance with all applicable local regulatory requirements.

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

Refer to the pharmacy manual for details regarding intravenous administration, accountability, and disposal.

## 5.2. Dosage, Administration, and Compliance

Dosing schedules for all arms, broken out by individual treatment arm, are provided in Table 3 for the induction phase and Table 4 for the maintenance phase. Dosing administration and monitoring times, broken out by individual treatment arm, are provided in Table 5.

The first dose of study drug is to be administered within 2 business days of randomization.

Patients should receive antiemetics and intravenous hydration for chemotherapy according to the standard of care and manufacturer's instructions. Due to their immunomodulatory effects, premedication with steroids should be limited when clinically feasible. In addition, in the event of chemotherapeutic agent-related skin rash, topical steroid use is recommended as treatment whenever it is clinically feasible.

In special situations (eg, when the administration is prolonged to allow for management of adverse events or in the case of an infusion-related reaction), administration of the subsequent study drugs might be delayed to the second day of each cycle.

Chemotherapy regimen may be switched in consideration of a patient's ability to tolerate the treatment. The reasons for intolerability should be documented.

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

**Table 3: Selection and Timing of Dose for Each Patient (Induction Phase)**

| Treatment arm | Study treatment | Dose | Frequency and sequence of administration | Route of administration | Duration of treatment |
|---|---|---|---|---|---|
| **Arm A** | Tislelizumab | 200 mg | Day 1 of each cycle (21 days) Administer first | Intravenous | See Section 3.3 |
| | Ociperlimab | 900 mg | Day 1 of each cycle (21 days) Administer after tislelizumab | Intravenous | See Section 3.3 |
| | Histology-based Chemotherapy | * | Administer after ociperlimab * | Intravenous | See Section 3.3 |
| **Arm B** | Tislelizumab | 200 mg | Day 1 of each cycle (21 days) Administer first | Intravenous | See Section 3.3 |
| | Placebo infusion | N/A | Day 1 of each cycle (21 days) Administer after tislelizumab | Intravenous | See Section 3.3 |
| | Histology-based Chemotherapy | * | Administer after placebo * | Intravenous | See Section 3.3 |

Abbreviations: AUC, area under the concentration-time curve; D, day; NA, not applicable
* For patients with squamous NSCLC: carboplatin AUC 5 or 6 (D1) + paclitaxel 175 or 200 mg/m$^2$ (D1) or nab-paclitaxel 100 mg/m$^2$ (D1, D8, D15) administered every 3 weeks. For patients with non-squamous NSCLC: cisplatin 75 mg/m$^2$ or carboplatin AUC 5 (D1) + pemetrexed 500 mg/m$^2$ IV (D1) administered every 3 weeks.

**Table 4: Selection and Timing of Dose for Each Patient (Maintenance Phase)**

| Treatment arm | Study treatment | Dose | Frequency and sequence of administration | Route of administration | Duration of treatment |
|---|---|---|---|---|---|
| **Patients with non-squamous NSCLC** | | | | | |
| **Arm A** | Tislelizumab | 200 mg | Day 1 of each cycle (21 days)<br>Administer first | Intravenous | See Section 3.3 |
| | Ociperlimab | 900 mg | Day 1 of each cycle (21 days)<br>Administer after tislelizumab | Intravenous | See Section 3.3 |
| | Pemetrexed | 500 mg/m$^2$ | Day 1 of each cycle (21 days)<br>Administer after ociperlimab | Intravenous | See Section 3.3 |
| **Arm B** | Tislelizumab | 200 mg | Day 1 of each cycle (21 days)<br>Administer first | Intravenous | See Section 3.3 |
| | Placebo infusion | N/A | Day 1 of each cycle (21 days)<br>Administer after tislelizumab | Intravenous | See Section 3.3 |
| | Pemetrexed | 500 mg/m$^2$ | Day 1 of each cycle (21 days)<br>Administer after placebo infusion | Intravenous | See Section 3.3 |
| **Patients with squamous NSCLC** | | | | | |
| **Arm A** | Tislelizumab | 200 mg | Day 1 of each cycle (21 days)<br>Administer first | Intravenous | See Section 3.3 |
| | Ociperlimab | 900 mg | Day 1 of each cycle (21 days)<br>Administer after tislelizumab | Intravenous | See Section 3.3 |
| **Arm B** | Tislelizumab | 200 mg | Day 1 of each cycle (21 days)<br>Administer first | Intravenous | See Section 3.3 |
| | Placebo infusion | N/A | Day 1 of each cycle (21 days)<br>Administer after tislelizumab | Intravenous | See Section 3.3 |

Abbreviations: NSCLC, non-small cell lung cancer.

**Table 5: Administration of Study Treatments and Monitoring Time**

| Cycle | Treatment arm | Study treatment administration and monitoring times |
|---|---|---|
| C1D1 and C2D1 | Arm A | Tislelizumab infusion over 60 (± 5) minutes followed by ociperlimab infusion over 60 (± 5) minutes<br>Patient monitoring for ≥ 120 minutes |
| | Arm B | Tislelizumab infusion over 60 (± 5) minutes followed by placebo infusion over 60 (± 5) minutes<br>Patient monitoring for ≥ 120 minutes |

| Cycle | Treatment arm | Study treatment administration and monitoring times |
|---|---|---|
| C3D1 onwards | Arm A | Tislelizumab infusion over 30 (± 5) minutes followed by ociperlimab infusion over 30 (± 5) minutes<br>Patient monitoring for ≥ 60 minutes |
| | Arm B | Tislelizumab infusion over 30(± 5) minutes followed by placebo infusion over 30 (± 5) minutes Patient monitoring for ≥ 60 minutes |

Abbreviations: C1D1, Cycle 1 Day 1; C2D1, Cycle 2 Day 1; C3D1, Cycle 3 Day 1



**Treatment Administration**

During the induction phase:

- In Arm A, tislelizumab 200 mg will be administered followed by ociperlimab 900 mg and histology-based chemotherapy on Day 1 of each 21-day cycle (once every 3 weeks).
- In Arm B, tislelizumab 200 mg will be administered followed by a placebo infusion and histology-based chemotherapy on Day 1 of each 21-day cycle (once every 3 weeks).

During the maintenance phase in patients with non-squamous NSCLC:

- In Arm A, tislelizumab 200 mg will be administered followed by ociperlimab 900 mg and pemetrexed 500 mg/m$^2$ on Day 1 of each 21-day cycle (once every 3 weeks).
- In Arm B, tislelizumab 200 mg will be administered followed by a placebo infusion and pemetrexed 500 mg/m$^2$ on Day 1 of each 21-day cycle (once every 3 weeks).

During the maintenance phase in patients with squamous NSCLC:

- In Arm A, tislelizumab 200 mg will be administered followed by ociperlimab 900 mg on Day 1 of each 21-day cycle (once every 3 weeks).
- In Arm B, tislelizumab 200 mg will be administered followed by a placebo infusion on Day 1 of each 21-day cycle (once every 3 weeks).

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

The initial infusions (Day 1 of Cycle 1 and Cycle 2) of tislelizumab will be delivered over 60 (± 5) minutes followed by ociperlimab/placebo delivered over 60 (± 5) minutes; if this is well tolerated, then the subsequent infusions of tislelizumab and ociperlimab/placebo may be administered over 30 (± 5) minutes, which is the shortest time period permissible for infusion. Tislelizumab and ociperlimab/placebo must not be concurrently administered with any other drug (Section 6).

Use of a volumetric pump is recommended to control the infusion speed and to avoid potential infusion reactions associated with too rapid administration. The pump may not be needed if the

infusion speed is controlled through alternative means and consistent with approved institutional procedures.

At the end of each infusion period, the line will be flushed with enough normal saline to make sure the complete doses of study drugs are administered.

As a routine precaution, after infusion of all study treatment is complete on Day 1 of Cycle 1 and Cycle 2, patients must be monitored for ≥ 120 minutes afterward in an area with resuscitation equipment and emergency agents. From Cycle 3 onward, a ≥ 60-minute monitoring period is required in an area with resuscitation equipment and emergency agents.

The length of the infusion period for cisplatin, carboplatin, pemetrexed, paclitaxel and nab-paclitaxel may also follow the approved label or local practice. The administered dose may be adjusted within ± 5% of the calculated dose at the investigator's discretion.

If the infusions of tislelizumab, ociperlimab/placebo, chemotherapy, and the premedication for chemotherapy cannot be managed in 1 day, it is acceptable to administer the chemotherapy drug infusions on Day 2 of the cycle.

Guidelines for treatment interruption or discontinuation and for the management of imAEs and infusion-related reactions are provided in detail in Section 8.6 and Appendix 7.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

## 5.3. Overdose or Incorrect Administration

Any incorrect administration of any study drug or overdose of ociperlimab (defined as ≥ 1800 mg in a 24-hour period) or 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 overdose or incorrect administration of study drug will be recorded on the AE eCRF. Any SAEs associated with an overdose or incorrect administration must be reported within 24 hours of awareness via the SAE reporting process described in Section 8.6.2. Supportive care measures should be administered as appropriate.

## 5.4. Investigational Medicinal Product Accountability

The investigational medicinal products (IMPs) required for completion of this study are ociperlimab, ociperlimab placebo, and tislelizumab. Ociperlimab, ociperlimab placebo, and tislelizumab will be provided by the sponsor, as required by local or country-specific guidance. The investigational site will acknowledge receipt of IMPs. Any damaged shipments will be replaced.

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

Chemotherapy drugs (ie, paclitaxel, nab-paclitaxel, carboplatin, cisplatin, pemetrexed) may be locally sourced by the investigational site or, in some circumstances, provided by the sponsor.

## 5.5. Dose Delay, Interruption, and Modification

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

Every effort should be made to administer the study 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 below. Reasons for dose reductions or delays, the supportive measures taken, and the outcome will be documented in the patient's source documents and recorded in the eCRF.

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

### 5.5.1. General Guidance Regarding Dose Modifications

- Dose modifications for chemotherapy will be performed per local practice and per prescribing information according to the treating physician's clinical judgment (Section 5.5.3).
- Tislelizumab and ociperlimab/placebo might be delayed as defined in Section 5.5.2.
- For any events already apparent at baseline, the dose modifications will apply according to the corresponding shift in toxicity grade, if the investigator considers it is appropriate. For example, if a patient has Grade 1 asthenia at baseline that turns to Grade 2 during treatment, this will be considered a shift of 1 grade and treated as Grade 1 toxicity for dose modification purposes.
- If in the opinion of the investigator, a toxicity is considered to be solely due to 1 component of the study treatment and the dose of that component is delayed or modified in accordance with the guidelines below, other components may be administered if there is no contraindication.
- When treatment is temporarily interrupted because of toxicity, the treatment cycles will be restarted such that the tislelizumab and ociperlimab/placebo infusions ideally remain synchronized and aligned with the chemotherapy schedule.

Dose modification guidelines for chemotherapy, as described below (Section 5.5.3), will depend on the severity of toxicity and an assessment of the risk versus benefit for the patient, with the goal of maximizing the patient's compliance and access to supportive care.

### 5.5.2. Dose Delay or Interruption for Ociperlimab and Tislelizumab

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

In all treatment arms, treatment with study drugs may be temporarily suspended if the patient experiences adverse events and requires a dose to be withheld. If temporary suspension is required, both study drugs (ociperlimab [or placebo] and tislelizumab) must be suspended. Treatment with study drugs should resume as soon as possible after the AEs recover to Grade 1 or baseline (whichever is more severe) and within 12 weeks after the last dose of study drugs. Here the AEs (that cause temporary suspension as mentioned above) refer to AEs related to tislelizumab or ociperlimab as assessed by investigators. If an AE is not related to tislelizumab or

ociperlimab, the decision to delay study drugs is at the discretion of the investigators. If the administration of study drugs can resume within ≤ 10 days of the Day 1 of the cycle, study drugs should be administered in the current cycle. If study drugs need to be withheld for > 10 days within the cycle, study drugs should be omitted from the current cycle and administration should restart in the next cycle. If the toxicity is assessed as not related to chemotherapy, the chemotherapy regimen(s) may be administered as scheduled in the current cycle.

If the patient is unable to resume study drugs within 12 weeks after the last dose of study drugs, then the patient should be discontinued from study treatment. If the patient is not able to resume study drugs ≤ 12 weeks after the last dose for unforeseen non-drug-related reasons, continued treatment may be allowed if approved by the medical monitor.

If a patient is benefiting from the study treatment while meeting the discontinuation criteria, resumption of study treatment may occur after discussion and agreement with the medical monitor.

Specific treatment modifications to manage study drug-related toxicities, such as to imAEs and infusion-related reactions, are described in Section 8.6 and Appendix 7.

### 5.5.3. Dose Delay or Modifications for Chemotherapy

Dose modifications for chemotherapy should be performed per prescribing information and per local practice according to the treating physician's clinical judgment.

If temporary suspension is required for one component of the chemotherapy regimen, the investigator will decide whether the remaining chemotherapy regimen(s) will be administered, taking into consideration the benefits and risks of continuing the regimen(s). 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 is not recommended to be modified for any body weight change of less than 10% except for carboplatin. Dosage of carboplatin should be calculated based on the most recent blood creatinine value per the local approved label.

Chemotherapy-related toxicities must be resolved to baseline or Grade 1 prior to administering the next dose, except for alopecia or Grade 2 fatigue. A maximum of 2 dose reductions is permitted for each chemotherapeutic agent, except for carboplatin for which only one dose reduction is permitted. Once the dose has been decreased, it should remain reduced for all subsequent administrations or further reduced if necessary. 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 should be rescheduled according to the start date of the last chemotherapy cycle.

Patients will be allowed to switch from cisplatin to carboplatin chemotherapy if they become ineligible for cisplatin due to toxicity and if all of the following criteria are met (no more than 6 cycles of chemotherapy will be administered).

- Patients have completed at least one cycle of cisplatin treatment.
- The switch is not due to the reason of suspected of confirmed disease progression by RECIST v1.1.

Switching is allowed only once during the whole study. No switch from carboplatin to cisplatin is allowed. If a dose delay is required for the patients to recover from the cisplatin-related toxicity, carboplatin should be started within 1 cycle (3 weeks) from the anticipated treatment date.

Reasons for platinum switch should be documented in source documents and eCRF.

**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 prior to 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 8. These serve as guidelines and do not replace investigator judgment and applicable local label recommendations.

For anemia and thrombocytopenia that have not recovered to baseline or ≤ Grade 1 (whichever is more severe), chemotherapy should be given as planned when the patient can tolerate it and will have clinical benefit as assessed by the investigator per local practice.

For other situations besides the above, please contact the sponsor medical monitor.

### 5.5.4. Criteria for Discontinuing Chemotherapy Regimens

The drug assessed as not related to the adverse reaction may be continued at the investigator's discretion, provided the current toxicity is resolved. Except where specified above, chemotherapy drug(s) in the platinum-based doublet regimen should be discontinued for any of the following:

- Any Grade 3 or 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
  - Total bilirubin > 5 x ULN
  - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Any cisplatin-related decrease in CrCL to < 30 mL/min requires discontinuation of cisplatin.
- 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.

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

## 5.6. Blinding

This is a randomized, investigator- and patient-blinded, sponsor-unblinded, Phase 2 study. Patients will be randomized in a 1:1 ratio to receive ociperlimab + tislelizumab + chemotherapy (Arm A) or placebo + tislelizumab + chemotherapy (Arm B). Patients, investigators, and site staff will remain blinded to study treatments but the sponsor will be unblinded.

Every effort should be made to avoid unblinding the patient's treatment assignment unless necessary. Unblinding may be indicated and permissible only in specific situations as described below and if necessary for the patient's welfare. Unblinding would occur through Interactive Response Technology (IRT) as per the instructions in the IRT site user manual. If unblinding has occurred, the sponsor must be notified immediately using the Unblinding Event Form. To ensure the continued blinding of blinded study personnel, this form will not include the treatment assignment. Patients will remain on study for safety follow-up and, if applicable, for survival follow-up.

### 5.6.1. Emergency Unblinding

In case of an emergency, such as when a patient has an AE suspected to be related to the investigational drug product and for which management of the AE with one or more drug products with substantial toxicity or invasive procedures is being considered, unblinding can occur. The investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to inform the medical monitor of their intent before unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient. If a patient's treatment assignment is unblinded, the sponsor must be notified immediately.

The investigator performs the emergency unblinding for AEs through an IRT System. Unblinded patients may remain on study treatment at the discretion of the investigator in consultation with the medical monitor and only as permissible per definitions in the study protocol.

### 5.6.2. Nonemergency Unblinding

Nonemergency unblinding to study treatment administration may occur on an individual patient basis when a new anticancer treatment is being considered and only after consultation with and written approval from the medical monitor at the time of 1) confirmed disease progression and EOT, or 2) EOT due to toxicity.

Nonemergency unblinding must be formally requested from the sponsor via the BeiGene Unblinding Form.

### 5.6.3. Inadvertent Unblinding

Every effort will be made to blind both the patient and the investigator/site staff to the identity of the treatment assignment (ie, ociperlimab + tislelizumab + chemotherapy [Arm A] or placebo + tislelizumab + chemotherapy [Arm B]), but the inadvertent unblinding of a patient may occur. Inadvertent unblinding events must be reported using the BeiGene Unblinding Form within 1 business day of awareness. To ensure the continued blinding of study personnel, this form and subsequent CRFs must not include the treatment assignment.

If an investigator, site personnel (eg, those performing assessments), or patient is unblinded, the unblinding will not be a sufficient cause (in and of itself) for that patient to be discontinued from study therapy or excluded from any safety or efficacy analyses.

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

### 5.6.4. Unblinding After Primary Analysis or Completion of the Trial

Investigators, site personnel, and patients will be unblinded to treatment arms and PD-L1 results at the time of primary analysis or the sponsor’s decision to close the trial for safety or non-safety reasons. Placebo administration will be discontinued after unblinding.

# 6. PRIOR AND CONCOMITANT THERAPY

## 6.1. Prior Therapy

As specified in Section 4, patients should not have received prior chemotherapy, targeted therapy, biologic therapy, immunotherapy, or investigational agent used to control locally advanced or metastatic NSCLC, or prior therapy targeting T-cell costimulation or checkpoint pathways in locally advanced or metastatic NSCLC.

## 6.2. Concomitant Therapy

### 6.2.1. Permitted Concomitant Medications/Procedures

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

#### 6.2.1.1. Systemic Corticosteroids

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

#### 6.2.1.2. Hepatitis B Treatment

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

Management of prophylactic antiviral therapy for patients with inactive, treated, and stable hepatitis B (HBV DNA < 500 IU/mL) 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 randomization and continue treatment during the study and for 6 months after study drug treatment discontinuation.

#### 6.2.1.3. Hepatitis C Treatment

Patients with detectable HCV RNA who are receiving treatment at screening should remain on continuous, effective antiviral therapy during the study. Investigators can consider treatment with sofosbuvir alone or in combination with other antivirals following the AASLD guideline or the

local guidelines as appropriate (AASLD/IDSA HCV Guidance Panel 2021). However, interferon-based therapy for HCV is not permitted on study. Patients who are given antiviral therapy must initiate treatment > 2 weeks before randomization.

#### 6.2.1.4. 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 provided 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 the medical monitor agrees that the conditions required to receive palliative radiation are met

Additionally, palliative radiation or other focally ablative therapy for other nontarget sites of the disease is permitted if clinically indicated per investigators' discretion. The medical monitor should be informed of the on-study radiotherapy. These patients should have a tumor assessment of the lesion(s) before receiving the radiotherapy in order to rule out progression of disease.

It is not required to withhold study treatment during palliative radiotherapy.

#### 6.2.1.5. COVID-19 Vaccines

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

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

### 6.2.2. Prohibited Concomitant Medications/Procedures

The following medications are prohibited during screening and through the EOT visit:

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

  Note: Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed.
- Any concurrent anti-cancer therapy, including chemotherapy, hormonal therapy, immunotherapy, standard anticancer agents, or investigational anticancer agents
- Herbal remedies for the treatment of cancer or Chinese patent medicines for use as anticancer treatment (regardless of cancer type) (Appendix 13).

- 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)

### 6.2.3. Restricted Concomitant Medications/Procedures

The following medications are restricted during the study:

- Immunosuppressive agents (except to treat a drug-related AE)
- Systemic corticosteroids > 10 mg daily (prednisone or equivalent), except to treat or control a drug-related AE (per protocol) or for short-term use as prophylactic treatment
- Patients should not abuse alcohol or other drugs during the study
- Use of potentially hepatotoxic drugs in patients with impaired hepatic function should be carefully monitored
- Radiation therapy is not allowed, except for palliative radiation therapy described in Section 6.2.1.4
- Non-steroidal anti-inflammatory drugs (eg, aspirin, ibuprofen, diclofenac, celecoxib, naproxen, indomethacin, or piroxicam) 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.

## 6.3. Potential Interactions Between the Study Drugs and Concomitant Medications

The potential for drug-drug interactions between the study drugs (ociperlimab and tislelizumab), standard chemotherapy, and small-molecule drug products is very low, given that the study drugs are therapeutic monoclonal antibodies. The study drugs are unlikely to have an effect on drug-metabolizing enzymes or transporters because they are expected to degrade into amino acids and recycle into other proteins.

Refer to the drug-drug interaction section in the 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 the list of strong CYP2C8 and CYP3A4 inhibitors (Flockhart 2007; FDA Drug Development and Drug Interactions) 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.

Refer to the drug-drug interaction section in the manufacturer's prescribing information for the influence of the respective chemotherapy agents on drug-metabolizing enzymes or transporters.

# 7. STUDY ASSESSMENTS AND PROCEDURES

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

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

## 7.1. Screening

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

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

Procedures conducted 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 the Safety Assessments (Section 7.4), Tumor and Response Evaluations (Section 7.5) and Biomarkers (Section 7.7) sections. The PK sampling schedule is shown in Appendix 1.

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

### 7.1.1. Informed Consent and Screening Log

Voluntary, written informed consent for participation in the study must be obtained before performing any study-specific procedures at the Screening Visit (Section 7.1, main ICF). Informed consent forms for enrolled patients and for patients who are screened but not enrolled will be maintained at the study site.

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

### 7.1.2. Patient Numbering

After obtaining informed consent, study site personnel will access the IRT system to assign a unique patient number to a potential study participant. Patients who are rescreened (see Section 7.1) will be assigned a new patient number. Screening numbers assigned to the same patient within the IRT system will be linked.

### 7.1.3. Pulmonary Function Tests

Pulmonary function testing including spirometry and assessment of oxygenation, at a minimum, pulse oximetry at rest and with exercise, or alternatively, assessment of diffusion capacity, are to be performed for all patients during the screening period to assist the determination of suitability on the study. Respective test results need to be submitted to the sponsor.

For test results indicative of significantly impaired pulmonary function, eg, resting pulse oximetry < 90% on room air and further desaturation upon exercise, forced expiratory volume (FEV1) < 60% or diffusing capacity of the lungs for carbon monoxide ($D_{LCO}$) (if performed) < 60% of age and sex adjusted predicted performance levels (Pellegrino et al 2005).

Tests may be repeated as clinically indicated while on study.

### 7.1.4. Demographic Data and Medical History

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

Ethnic factors could influence the effects (safety and efficacy) of medicines and the risk/benefit assessment in different populations. Race and Ethnicity data are collected in the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM, Implementation Guide v3.2), in accordance with ICH guidance (ICH E5 1998, ICH E17 2017) adopted by the EMA and FDA, to support population PK analysis, which is a well-established, quantitative method that can quantify and explain the variability in drug concentrations among patients. Variability can be attributed to intrinsic factors (eg, body weight, age, sex, race/ethnicity), or to extrinsic factors (eg, concomitant medications). In some cases, intrinsic or extrinsic factors lead to clinically relevant changes in drug concentrations that require a change in the dose or dosing regimen. Results from population PK analyses will be incorporated into drug product labeling to provide guidance on the dose or dosing regimen including any potential dose adjustment in some subpopulations (eg, race or ethnic group). Therefore, collecting race/ethnicity data in the study is essential to understand whether race/ethnicity could influence the PK, safety, and/or efficacy.

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

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

### 7.1.5. Contraception and Women of Childbearing Potential

Childbearing potential is defined as being physiologically capable of becoming pregnant (ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile). Refer to Appendix 10 for contraception guidelines and definitions of "women of childbearing potential" and "no childbearing potential."

#### 7.1.6. HIV Serology Test

An HIV serology test (antigen and/or antibodies) will be conducted at baseline for patients with unknown HIV status.

#### 7.1.7. COVID-19 Test

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

## 7.2. Enrollment

#### 7.2.1. Confirmation of Eligibility

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 (ICH) E6.

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

#### 7.2.2. Enrollment/Randomization

Site personnel will access the IRT system to randomize to treatment assignment and to enable study drug dispensation. Study treatment must start within 2 business days after randomization/treatment assignment.

## 7.3. Study Drug Dispensation

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

## 7.4. Safety Assessments

#### 7.4.1. Vital Signs, Height, and Weight

Vital signs will include measurements of body temperature (˚C), pulse rate, and blood pressure (systolic and diastolic). Pulse rate and blood pressure will be collected in patients after resting for 10 minutes. Vital signs will be recorded at screening, on Day 1 of each cycle, and at the EOT Visit (Appendix 1).

The patient's vital signs are required to be recorded within 60 minutes before, during, and 30 minutes after completion of study drug infusion on Cycle 1 Day 1. For subsequent infusions, vital signs will be collected within 60 minutes before infusion and, if clinically indicated, during and 30 minutes after the completion of infusion.

Height will be recorded at screening only. Weight will be recorded at screening, on Day 1 of each cycle, and at the EOT Visit.

### 7.4.2. Physical Examinations

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

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

### 7.4.3. Eastern Cooperative Oncology Group Performance Status

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

### 7.4.4. Laboratory Safety Tests

Local laboratory assessments of serum chemistry, hematology, coagulation, and urinalysis described in Appendix 2 will be conducted and collected at the timepoints shown in Appendix 1.

If laboratory tests of serum chemistry (including liver function), hematology, and coagulation at screening are performed > 7 days before randomization, these tests must be repeated within 3 days prior to Cycle 1 Day 1. Hematology, serum chemistry (including liver function tests), and coagulation as specified in Appendix 2 should be performed on Day 1 of each cycle, and at the EOT Visit (Appendix 1).

In addition, for patients with squamous NSCLC receiving nab-paclitaxel during the induction phase (first 4 to 6 cycles), hematology will also be performed weekly on Day 8 and Day 15 of each cycle before the administration of nab-paclitaxel.

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's source documents and the medical monitor must be notified. Only test results from previously approved hospitals/clinicals will be accepted.

After Cycle 1, lab assessments are to be done, results are to be reviewed within 48 hours before study drug administration.

Furthermore, the following tests will be performed as specified in Appendix 1:

- Urine or serum pregnancy test
- Thyroid function testing (thyroid stimulating hormone [TSH], free T3, free T4)
- Hepatitis serology (Section 7.4.7)
- Cardiac enzyme monitoring (Section 7.4.4.1)

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

#### 7.4.4.1. Cardiac Enzyme Monitoring

Although immune-related myocarditis is a rare complication of immune checkpoint inhibitors, serum creatinine kinase (CK) and CK cardiac muscle isoenzyme (CK-MB) is monitored (Appendix 2) to protect study participants and to quantify the risk of muscle inflammation (see Appendix 1 for the blood collection schedule and Appendix 7 for guidelines for management of suspected immune-related myocarditis). If laboratory tests of cardiac enzymes at screening are performed > 7 days before randomization, these tests must be repeated within 3 days prior to Cycle 1 Day 1. Serum troponins may be substituted per local guidelines if used consistently throughout the study.

### 7.4.5. Electrocardiograms

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

The ECG recordings will be obtained during screening, the EOT Visit, and as clinically indicated at other timepoints (Appendix 1). When coinciding with blood draws at the same timepoint, ECG assessment should be performed before blood draws. Patients should rest in a semi-recumbent supine position for at least 10 minutes before ECG collection.

### 7.4.6. Adverse Events

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

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

### 7.4.7. Hepatitis B and C Testing

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

Inactive hepatitis B surface antigen (HBsAg) carriers and patients with treated and stable hepatitis B (HBV DNA < 500 IU/mL or < 2500 copies/mL) can be enrolled. Patients with detectable HBsAg or detectable HBV DNA should be managed per treatment guidelines. Patients receiving antivirals at screening should have been treated for > 2 weeks before randomization. Patients who have detectable HBV DNA at screening will perform a viral load test every 4 cycles (eg, Day 1 of Cycles 5, 9, 13).

Patients with a negative HCV antibody test at screening or positive HCV antibody test followed by a negative HCV RNA test at screening can be enrolled. The HCV RNA test will be performed only for patients testing positive for HCV antibody. Patients receiving antivirals at screening should have been treated for > 2 weeks before randomization. Patients who had a positive

antibody test at screening will perform a viral load test every 4 cycles (eg, Day 1 of Cycles 5, 9, 13).

## 7.5. Tumor and Response Evaluations

Tumor imaging will be performed within 28 days before randomization. Radiologic images captured as standard of care before obtaining written informed consent and ≤ 28 days before randomization may be used rather than repeating tests. During the study, tumor imaging will be performed every 9 weeks (± 7 days) from randomization for the first 52 weeks and then every 12 weeks (± 7 days) based on RECIST v1.1. Tumor assessments are required to be performed on schedule regardless of whether study treatment has been administered or held; they should not be adjusted for possible delays in cycles. Tumor assessments should continue until radiologic disease progression as determined by the investigators. Patients who discontinue study treatment early for reasons other than radiologic disease progression (eg, toxicity) will continue to undergo tumor assessments following the original plan until the patient begins a subsequent anticancer treatment, experiences radiologic disease progression or death, withdraws consent, is lost to follow-up, or until the study terminates, whichever occurs first.



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

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 is required to be used throughout the study (eg, the same contrast protocol for CT scans or MRI).

- Imaging of the brain (preferably MRI) at baseline is required for all screened patients. Screening evaluations will be performed within 28 days before randomization.
- If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the study, a non-contrast CT of the chest plus a contrast-enhanced MRI (if possible) of the abdomen and pelvis should be performed.
- If a CT scan for tumor assessment is performed on a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards of a diagnostic CT scan.
- Bone scans (Technetium-99m [Tc-99m]) or PET should be performed at screening if clinically indicated. If bone metastases are present at screening and cannot be seen on CT or MRI scans, Tc-99m or PET bone scans should be repeated when a CR is suspected in target lesion or when progression in bone is suspected.
- CT scans of the neck or extremities should be performed at screening only if clinically indicated and should be 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 nontarget lesions per RECIST v1.1 may be used.

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

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

At the investigator's discretion, patients may continue their assigned treatment after PD has been confirmed by the investigator per RECIST v1.1. To continue treatment, the criteria for treatment beyond disease progression in Section 3.3 must be met. In both arms, tislelizumab in combination with ociperlimab (or placebo) treatment beyond the initial investigator-assessed, RECIST v1.1-defined PD is permitted provided that the patient has investigator-assessed clinical benefit and is tolerating the treatment. Continuation of chemotherapy treatment after initial disease progression will be at the discretion of the investigator.

Tumor assessment should continue as planned in patients receiving tislelizumab in combination with ociperlimab (or placebo) beyond initial investigator-assessed progression. Tumor assessment in such patients should continue until study treatment discontinuation.

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

## 7.6. Pharmacokinetic and Antidrug Antibody Testing

Blood samples will be collected for characterization of ociperlimab and tislelizumab PK. The serum samples will be assayed for ociperlimab and tislelizumab concentrations using validated immunoassays. Checkpoint inhibitor drugs may elicit an immune response. Patients with signs of any potential immune response to study drug will be closely monitored (Appendix 7). Validated screening and confirmatory assays will be employed to detect ADAs at multiple timepoints throughout the study (see Appendix 1). The immunogenicity evaluation will utilize a risk-based immunogenicity strategy (Koren et al 2008; Worobec and Rosenberg 2004a; Worobec and Rosenberg 2004b) to characterize ADA responses to tislelizumab and ociperlimab in support of the clinical development program.

Shipping, storage, and handling of samples for the assessment of ociperlimab and tislelizumab PK and ADA assays will be managed through a central laboratory. Refer to the laboratory manual for instructions.

PK and ADA samples will be collected at the timepoints indicated in Appendix 1.

## 7.7. Biomarkers

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

Biomarker analyses in tumor tissues will include but not be limited to the expression of TIGIT, CD226, CD155, CD112, PD-L1, GEP, TMB, gene mutations, MSI, and TILs to explore potential predictive and prognostic biomarkers and mechanisms of resistance. For sites in mainland China, tissue sample testing will be limited to the expression of TIGIT, CD226, CD155, CD112, PD-L1, GEP, TMB, gene mutations, MSI, and TILs at baseline and at disease progression/reoccurrence.

Archival tumor tissues (formalin-fixed paraffin-embedded blocks or approximately 6 to 15 freshly cut unstained slides) need to be sent to the central laboratory during Screening for central immunohistochemistry assay of PD-L1 status using the central laboratory-validated PD-L1 (SP263) assay (preferably from the same block used for local PD-L1 testing). Archival tissue sample for retrospective biomarkers testing can be delivered after the screening period. An additional ≥ 6 freshly cut unstained slides are required if non-squamous NSCLC patients with unknown *EGFR* status will be tested at a central laboratory.

If no archival samples are available, a fresh tumor biopsy at baseline is mandatory. For fresh biopsy specimens, acceptable samples include core needle biopsies for deep tumor tissue or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.

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

Patients who have progressive disease will be asked to provide an optional biopsy at the EOT Visit (Appendix 1) from accessible tumor sites to obtain samples to explore the mechanism of resistance. If feasible, any follow-up biopsy should be ideally taken from the same tumor lesion as the baseline biopsy if one was provided. Written patient consent is required for fresh tumor biopsies.

Blood samples will be taken predose on Day 1 of Cycle 1, predose on Day 1 of Cycle 3, and at the EOT Visit after disease progression to evaluate biomarkers including, but not limited to, circulating tumor DNA (ctDNA), TMB, MSI, gene mutations, and EVs in blood (Appendix 1). For sites in mainland China, blood-based biomarkers will be limited to ctDNA, TMB, MSI, gene mutations, and EVs.

## 7.8. Patient-Reported Outcomes

Patients will be asked to complete questionnaires before any clinical activities (including blood draws or imaging scans) are performed during on-study clinic visits according to the schedule in Appendix 1. These questionnaires will include the EORTC-QLQ-C30 (Appendix 11) and its lung cancer module QLQ-LC13 (Appendix 12). The questionnaires will be provided in the patient's preferred language.

## 7.9. Visit Windows

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

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other event, the visit should be scheduled on the nearest feasible date (the visit window is provided in Appendix 1).

A cycle is defined as every 21 days. In the induction phase, subsequent visits should be conducted according to a new 21-day schedule based on the starting date of the patient's last

cycle of chemotherapy. In the maintenance phase, subsequent visits should be conducted according to the last tislelizumab infusion in the induction phase.

## 7.10. Unscheduled Visits

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

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

# 8. SAFETY MONITORING AND REPORTING

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

## 8.1. Risks Associated With Study Drugs

### 8.1.1. Risks Associated With Ociperlimab and Tislelizumab

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

The PD-L1/PD-1 pathway is involved in peripheral immune tolerance; therefore, such therapy may increase the risk of imAEs, specifically the induction or enhancement of autoimmune conditions. AEs observed with anti PD-1 therapy are presented in Section 8.6.12.

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

### 8.1.2. Risks Associated With Chemotherapy Agents

For NSCLC patients who were treated with paclitaxel in a first-line setting, frequent (> 5%) Grade 3 or 4 drug-related toxicities were neutropenia, anemia, nausea, vomiting, and fatigue (Scagliotti et al 2008). For NSCLC patients who were treated with carboplatin in a first-line setting, frequent (> 5%) Grade 3 or 4 toxicities were leukopenia, neutropenia, anemia, thrombocytopenia, febrile neutropenia, nausea, vomiting, anorexia and constipation (Ohe et al 2007). Although not life threatening, these AEs can severely impact the physical, psychological, and social well-being of patients receiving chemotherapy and can lead to dose reductions and discontinuations.

Please refer to Table 6 below for the reported toxicity of the respective chemotherapeutic agents.

**Table 6. Commonly and Specific Reported Toxicity of the Chemotherapeutic Agents**

| Agents | Common toxicity | Specific toxicity |
|---|---|---|
| Cisplatin | Myelosuppression with leukopenia, thrombocytopenia, and anemia; infectious complications; nausea/vomiting and other gastrointestinal toxicity; hepatic impairment; fatigue; anorexia; constipation | Nephrotoxicity, ototoxicity, peripheral neuropathies |
| Carboplatin | | Ototoxicity and peripheral neuropathies |
| Paclitaxel | | Hypersensitivity reaction, peripheral neuropathy, myalgia, arthralgia, cardiovascular disorders |
| Pemetrexed | | Nephrotoxicity, skin rash, pneumonitis, radiation recall |
| *Nab*-paclitaxel | | Peripheral neuropathy, alopecia |

Refer to the manufacturer's prescribing information for additional details.

## 8.2. General Plan to Manage Safety Concerns

### 8.2.1. Eligibility Criteria

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

### 8.2.2. Safety Monitoring Plan

Safety will be evaluated in this study through the monitoring of all AEs, which will be defined and graded according to NCI-CTCAE v5.0. All enrolled patients will be evaluated clinically and with standard laboratory tests at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of AEs (see Table 7), physical examinations, laboratory measurements (eg, hematology or chemistry) and other assessments including those listed in Appendix 1. In addition, patients will be closely monitored for the development of any signs or symptoms of infections or autoimmune conditions.

At the start of each cycle, study drugs 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 (Section 5.2).

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

The potential safety issues anticipated in this study, as well as measures intended to avoid or minimize such toxicities, are outlined in Section 8.6.

## 8.3. Adverse Events

### 8.3.1. Definitions and Reporting

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

Examples of AEs include:

- Worsening of a chronic or intermittent preexisting condition, including an increase in severity, frequency, duration, and/or has an association with a significantly worse outcome
- Detection or diagnosis of a new condition after study drug administration, even though the condition may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concurrent medication (overdose per se should not be reported as an AE or SAE)

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



### 8.3.2. Assessment of Severity

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

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

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

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

### 8.3.3. Assessment of Causality

The investigator is obligated to assess the relationship between the study drug and the occurrence of each AE or SAE, using best clinical judgment. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the AE or SAE to the study drug should be considered and investigated. The investigator should consult the Tislelizumab (BGB-A317) Investigator’s Brochure, the Ociperlimab (BGB-A1217) 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 only limited information to include in the initial report to the sponsor. However, it is very important that the investigator always assesses causality for every SAE before transmission of the SAE report to the sponsor, because the causality assessment is one of the criteria used when determining

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

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

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



### 8.3.4. Follow-up of Adverse Events

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

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

All AEs and SAEs (only SAEs in case of patients who did not meet screening criteria) will be followed until resolution, the condition stabilizes or is considered chronic, the AE or SAE is otherwise explained, the patient is lost to follow-up or the patient withdraws consent. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, radiographic imaging, or consultation with other health care professionals.

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

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

### 8.3.5. Laboratory Test Abnormalities

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

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

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

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

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

## 8.4. Definition of a Serious Adverse Event

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

- Results in death
- Is life-threatening
  Note: The term “life-threatening” in the definition of “serious” refers to an AE in which the patient was at risk of death at the time of the AE. It does not refer to an AE that hypothetically might have caused death if it were more severe.
- Requires hospitalization or prolongation of existing hospitalization
  Note: In general, hospitalization signifies that the patient was admitted (usually involving at least an overnight stay) to the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting.

- Results in disability/incapacity
  Note: The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere with or prevent everyday life functions, but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
- Is considered a significant medical AE by the investigator based on medical judgement (eg, may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The following are NOT considered to be SAEs:

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

## 8.5. Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is a serious adverse reaction that is both unexpected (ie, not present in the product's Reference Safety Information [RSI]) and meets the definition of a serious adverse drug reaction (SADR), the specificity or severity of which is not consistent with those noted in the Tislelizumab (BGB-A317) Investigator's Brochure, Ociperlimab (BGB-A1217) Investigator's Brochure, and chemotherapy prescribing information.

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

### 8.6.1. Adverse Event Recording Period

After informed consent has been signed but prior to the administration of the study drug(s), only SAEs should be reported.

After initiation of the study drug(s), all AEs and SAEs, regardless of the relationship to the study drug(s), will be reported until either 30 days after last dose of study drug(s) (including chemotherapy) or the initiation of new anticancer therapy, whichever occurs first. Immune-mediated AEs (serious or nonserious) should be reported until 90 days after the last dose of ociperlimab (or placebo) and/or tislelizumab, regardless of whether or not the patient starts a new anticancer therapy. All SAEs considered related to the study drugs 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 7. For the follow-up period for AEs, see Section 8.3.4. For the definition of TEAEs, see Section 9.3.2.

**Table 7: Guidance for Duration of Recording New or Worsening Adverse Events in All Treatment Arms**

| Event type | Record new or worsening events that occur during this period | |
|---|---|---|
| | Begin | End |
| SAEs [a] | Signing of informed consent | Up to 30 days after last dose, initiation of new anticancer therapy, death, withdrawal of consent, or loss to follow-up, whichever occurs first |
| Nonserious AEs due to PD | Do not record (see Section 8.6.4) | |
| All nonserious AEs, except those due to PD | First dose of study drug | Up to 30 days after last dose, initiation of new anticancer therapy, death, withdrawal of consent, or loss to follow-up, whichever occurs first |
| Immune-mediated AEs (serious or nonserious) | First dose of study drug | Up to 90 days after last dose of ociperlimab (or placebo) and/or tislelizumab (regardless of initiation of new anticancer therapy), death, withdrawal of consent, or loss to follow-up, whichever occurs first |

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

### 8.6.2. Reporting Serious Adverse Events

#### 8.6.2.1. Prompt Reporting of Serious Adverse Events

As soon as the investigator determines that an AE meets the protocol definition of an SAE, the event must be reported promptly (within 24 hours) to the sponsor or designee as described in Table 8.

**Table 8: Timeframes and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee**

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

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

#### 8.6.2.2. Completion and Transmission of the Serious Adverse Event Report

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

SAE Report will always be completed as thoroughly as possible with all available details of the event and forwarded to the sponsor or designee within the designated time frames.

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

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

The sponsor will provide contact information for SAE receipt.

#### 8.6.2.3. Regulatory Reporting Requirements for Serious Adverse Events

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

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

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

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

### 8.6.3. Eliciting Adverse Events

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

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

### 8.6.4. Disease Progression

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

### 8.6.5. Deaths

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

### 8.6.6. Pregnancies

If a female patient or the partner of a male patient becomes pregnant while receiving study drug treatment or within 120 days after the last dose of ociperlimab and/or tislelizumab or 180 days after the last dose of chemotherapy, a pregnancy report form is required to be completed and expeditiously submitted to the sponsor to facilitate outcome follow-up. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

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

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

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

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

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

- Tislelizumab (BGB-A317) Investigator's Brochure
- Ociperlimab (BGB-A1217) Investigator's Brochure
- Nab-paclitaxel label
- Cisplatin label
- Carboplatin label
- Paclitaxel label
- Pemetrexed label

### 8.6.8. Assessing and Recording Immune-Mediated Adverse Events

Because treatment with anti-PD-1 or immune checkpoint inhibitors can cause autoimmune disorders, AEs considered by the investigator to be immune-mediated (see Section 8.6.12) should be classified as imAEs and identified as such on the eCRF AE page until 90 days after the last dose of ociperlimab (or placebo) and/or tislelizumab.

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

An extensive list of potential imAEs appears in Section 8.6.12, Table 10. 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 7.

### 8.6.9. Recording Infusion-Related Reactions

The symptoms of infusion-related reactions may include but are not limited to fever, chills/rigor, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness, or hypertension. Severe reactions may include acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, or cardiogenic shock. Each individual sign and symptom of an infusion reaction should be recorded as a separate AE in the eCRF and identified as an infusion-related reaction. Refer to the eCRF completion guidelines for details.

As a routine precaution, after completing the infusion of study drugs on Day 1 of Cycle 1 and Cycle 2, patients must be monitored for ≥ 120 minutes afterward in an area with resuscitation equipment and emergency agents. From Cycle 3 onward, a ≥ 60-minute monitoring period is required in an area with resuscitation equipment and emergency agents.

The management of infusion-related reactions, severe hypersensitivity reactions, and imAEs according to the NCI-CTCAE v5.0 criteria are outlined below.

### 8.6.10. Managing Infusion-Related Reactions

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

Treatment modifications for symptoms of infusion-related reactions due to study drug(s) is provided in Table 9.

**Table 9: Treatment Modifications for Symptoms of Infusion-Related Reactions Due to Study Drug(s)**

| NCI-CTCAE grade | Treatment modification for all study arms |
|---|---|
| **Grade 1 – mild**<br>Mild transient reaction; infusion interruption not indicated; intervention not indicated. | Decrease infusion rate by 50%. Any worsening is closely monitored. Medical management as needed.<br>Subsequent infusions should be given after premedication and at the reduced infusion rate. |
| **Grade 2 – moderate**<br>Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, intravenous fluids); prophylactic medications indicated for ≤ 24 hours. | Stop infusion. Infusion may be resumed at 50% of previous rate once infusion-related reaction has resolved or decreased to Grade 1 in severity. Any worsening is closely monitored. Proper medical management should be instituted as described below.<br>Subsequent infusions should be given after premedication and at the reduced infusion rate. |

| | |
|---|---|
| **Grade 3 – severe**<br>Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. | Immediately stop the infusion. Proper medical management should be instituted as described below.<br>The patient should be withdrawn from study drug(s) treatment. |
| **Grade 4 – life threatening**<br>Life-threatening consequences; urgent intervention indicated. | Immediately stop the infusion. Proper medical management should be instituted as described below.<br>The patient should be withdrawn from study drug(s) treatment.<br>Hospitalization is recommended. |

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

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

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

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

### 8.6.11. Severe Hypersensitivity Reactions and Flu-Like Symptoms

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

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

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

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

### 8.6.12. Immune-Mediated Adverse Events

Immune-mediated AEs are of special interest in this study. If the events listed below or similar events occur, the investigator should exclude alternative explanations (eg, combination drugs, infectious disease, metabolic, toxin, disease progression, or other neoplastic causes) with appropriate diagnostic tests that may include, but are not limited to, serologic, immunologic, and histologic (biopsy) data. The imAE indicator in the eCRF AE page should be checked 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.

A list of potential imAEs is shown below in Table 10. All conditions similar to those listed should be evaluated in patients receiving study drugs to determine whether they are immune-mediated.

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

**Table 10: Examples of Immune-Mediated Adverse Events**

| Body system affected | Events |
|---|---|
| Skin (mild-common) | pruritus or maculopapular rash; vitiligo |
| Skin (moderate) | follicular or urticarial dermatitis; erythematous/lichenoid rash; Sweet syndrome |
| Skin (severe-rare) | full-thickness necrolysis/Stevens-Johnson syndrome |
| Gastrointestinal | colitis (includes diarrhea with abdominal pain or endoscopic/radiographic evidence of inflammation); pancreatitis; hepatitis; aminotransferase (ALT/AST) elevation; bowel perforation |
| Endocrine | thyroiditis, hypothyroidism, hyperthyroidism; hypophysitis with features of hypopituitarism, eg, fatigue, weakness, weight gain; insulin-dependent diabetes mellitus; diabetic ketoacidosis; adrenal insufficiency |
| Respiratory | pneumonitis/diffuse alveolitis |

| | |
|---|---|
| Eye | episcleritis; conjunctivitis; iritis/uveitis |
| Musculoskeletal | arthritis; arthralgia; myalgia; neuropathy; myasthenic syndrome/myasthenia gravis, myositis |
| Blood | anemia; leukopenia; thrombocytopenia |
| Renal | interstitial nephritis; glomerulonephritis; acute renal failure |
| Cardiac | pericarditis; myocarditis; heart failure |
| Neurologic | encephalitis, meningitis, meningoradiculitis, meningoencephalitis, Guillain-Barré syndrome |

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

Recommendations for managing imAEs are detailed in Appendix 7.

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

# 9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

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

## 9.1. Statistical Analysis

### 9.1.1. Randomization Methods

As discussed in Section 7.2.2 , patients will be randomized using the IRT system for this study by stratified permuted block randomization.

### 9.1.2. Analysis Sets

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

The Per-Protocol (PP) Analysis Set includes all randomized patients who received ≥ 1 dose of the assigned study drug and had no critical protocol deviations. Critical protocol deviations will be determined and documented before the database lock for the primary analyses.

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

The PK Analysis Set includes all patients who received ≥ 1 dose of any component of study drug per the protocol and for whom any postdose PK data are available.

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

### 9.1.3. Patient Disposition

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

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

### 9.1.4. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics of patients in the ITT Analysis Set will be summarized using descriptive statistics. Continuous variables include age, weight, vital signs, time since initial cancer diagnosis, and time since advanced/metastatic disease diagnosis. Categorical variables include sex, ECOG Performance Status at study entry, geographical region, country, race, histological subtype, metastatic site, PD-L1 expression, and tobacco use.

### 9.1.5. Prior and Concomitant Medications

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

## 9.2. Efficacy Analyses

The primary analyses will be performed when approximately 194 PFS events have been observed.

### 9.2.1. Primary Efficacy Analysis

PFS in ITT Analysis Set:

The null hypothesis ($H_0$) to be tested is:

$H_0$: PFS in Arm A ≤ PFS in Arm B

against the alternative hypothesis ($H_1$):

$H_1$: PFS in Arm A > PFS in Arm B

A stratified log-rank test to compare PFS distribution between ociperlimab + tislelizumab + chemotherapy (Arm A) and placebo + tislelizumab + chemotherapy (Arm B) will be the primary efficacy analysis, stratified by PD-L1 expression (three levels: < 1% TC versus 1% to 49% TC versus ≥ 50% TC) and histology (squamous versus non-squamous NSCLC). It will be performed once the targeted PFS event number is reached. A significance level of 1-sided alpha of 0.025 will be used in the PFS testing.

PFS as assessed by the investigators per RECIST v1.1 will be estimated using the Kaplan-Meier method in the ITT Analysis Set. PFS will be censored at the last adequate tumor assessment if one of the following occurs by the time of analysis: absence of event, a new anticancer therapy is given, or the event occurred after ≥ 2 missing tumor assessments. For cases with missing baseline tumor assessment, a death occurring ≤ 19 weeks from the randomization date will be considered a PFS event. Clinical or symptomatic progressions without supportive radiologic data will not be considered as PFS events.

The median PFS and 2-sided 95% CI using the method of Brookmeyer and Crowley will be summarized. The cumulative probability of PFS at every 6 months including PFS rate at 6 and 12 months, if estimable, will be calculated for each treatment arm and presented with 2-sided

95% CIs. Standard error for PFS rates will be calculated based on Greenwood's formula. Kaplan-Meier survival probabilities for each arm will be plotted over time.

The treatment effect will be estimated by fitting a Cox regression model to the PFS times, including treatment arm as a factor and PD-L1 expression (three levels: < 1% TC versus 1% to 49% TC versus ≥ 50% TC) and histology (squamous versus non-squamous NSCLC) as strata. From this model, the HR of PFS will be estimated and presented with a 2-sided 95% CI.

Subgroup analysis of PFS will be performed by PD-L1 expression, histology, region, and other key risk factors that are to be described in the SAP.



### 9.2.2. Secondary Efficacy Analysis

Best overall response (BOR) is defined as the best response per RECIST v1.1 recorded from randomization until data cut, progressive disease, or start of a new anticancer treatment. The null hypotheses of no difference in ORR per RECIST v1.1 assessed by the investigators between ociperlimab + tislelizumab + chemotherapy (Arm A) and placebo + tislelizumab + chemotherapy (Arm B) will be tested in a Cochran-Mantel-Haenszel (CMH) test adjusting for stratification factors (PD-L1 expression [three levels: < 1% TC versus 1% to 49% TC versus ≥ 50% TC] and histology [squamous versus non-squamous NSCLC]) in the ITT Analysis Set. Patients with no postbaseline response assessment (for any reason) will be considered non-responders. The odds ratio in ORR and its 2-sided 95% CI will be calculated, as well as ORR and its Clopper-Pearson 95% CIs for each treatment arm.

DOR as assessed by the investigators will be derived using the similar censoring rule as for PFS and summarized descriptively in the responders receiving ociperlimab + tislelizumab + chemotherapy (Arm A) versus placebo + tislelizumab + chemotherapy (Arm B).

OS will be compared between ociperlimab + tislelizumab + chemotherapy (Arm A) and placebo + tislelizumab + chemotherapy (Arm B) in a 1- sided, stratified log-rank test using stratification factors of PD-L1 expression (three levels: < 1% TC versus 1% to 49% TC versus ≥ 50% TC) and histology (squamous versus non-squamous NSCLC).

In absence of confirmation of death, patients will be censored either at the date that the patient was last known to be alive or the date of data cutoff, whichever comes earlier. The median OS and 2-sided 95% CI using the method of Brookmeyer and Crowley will be summarized. The cumulative probability of OS at every 3 months including OS rate at 12 months and 24 months if estimable, will be calculated for each treatment arm and presented with 2-sided 95% CIs. Standard error for survival rates will be calculated based on Greenwood's formula. Kaplan-Meier survival probabilities for each arm will be plotted over time.

The treatment effect will be estimated by fitting a Cox regression model to the OS times including treatment arm as a factor and PD-L1 expression (three levels: < 1% TC versus 1% to 49% TC versus ≥ 50% TC) and histology (squamous versus non-squamous NSCLC) as strata. From this model, the HR of OS will be estimated and presented with a 2-sided 95% CI.

The secondary endpoints of ORR and OS will be tested sequentially once PFS superiority of Arm A over Arm B has been demonstrated.

### 9.2.3. Exploratory Efficacy Analysis

The proportion and its corresponding Clopper-Pearson 95% CI for each of the response categories (eg, CR, PR, SD, PD, NE, and NA) will be presented for ociperlimab + tislelizumab + chemotherapy (Arm A) and placebo + tislelizumab + chemotherapy (Arm B). DCR and CBR as assessed by the investigators will be analyzed similarly to ORR. Proportion of response categories with unconfirmed CR and PR may be presented as well. TTR will be summarized using descriptive statistics, such as mean, median, and standard deviation. Only patients who have achieved an objective response will be included in the analysis of TTR.

HRQoL is assessed via EORTC QLQ-C30's global health status/QoL (GHS) and functional and symptom scale scores and single item scores and symptoms measured by QLQ-LC13. Observed values and changes from baseline will be summarized using descriptive statistics. Graphic method will be used for treatment comparison.

Postbaseline scores of GHS and physical function (PF) of the QLQ-C30 and dyspnea, coughing, hemoptysis, pain in chest, peripheral neuropathy, and pain in the arms and shoulders symptoms of the QLQ-LC13 will be furthered analyzed using a mixed-model analysis at prespecified timepoints and compare between the Treatment Arms A and B.

## 9.3. Safety Analyses

### 9.3.1. Extent of Exposure

Extent of exposure to each study drug will be summarized descriptively by the number of doses received (number and percentage of patients), duration of exposure (weeks), 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 by reason will be summarized for each study drug. Frequency of the above dose adjustments and discontinuation will be summarized by category.

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

### 9.3.2. Adverse Events

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

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by System Organ Class and Preferred Term. A patient will be counted only once by the highest

severity grade per NCI-CTCAE v5.0 within a System Organ Class and Preferred Term, even if the patient experienced more than 1 TEAE within a specific System Organ Class and Preferred Term. The number (percentage) of patients with TEAEs will also be summarized by relationship to the study drug. Treatment-related AEs include those events considered by the investigator to be related to a study drug or with missing assessment of the causal relationship. SAEs, deaths, TEAEs of all grades, TEAEs with ≥ Grade 3 severity, imAEs, treatment-related TEAEs, and TEAEs that led to treatment discontinuation or dose modification will be summarized.



### 9.3.3. Laboratory Analyses

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

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

### 9.3.4. Vital Signs

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

### 9.3.5. Pulmonary Function Test

Pulmonary function test results will be listed by patient.

## 9.4. Pharmacokinetic Analysis

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

## 9.5. Immunogenicity Analyses

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

## 9.6. Sample Size Considerations

The sample size calculation is driven by the primary efficacy analysis of PFS in the comparison between ociperlimab + tislelizumab + chemotherapy (Arm A) and placebo + tislelizumab + chemotherapy (Arm B) in the ITT Analysis Set. The number of PFS events needed is based on the assumption of an exponential distribution with the targeted median PFS improvement. The 1-sided overall Type I error in the study is set at 0.025. Table 11 summarizes the statistical assumption and power in the sample size calculation. Assuming an approximately 10% dropout rate for PFS, 1:1 randomization and 14 months enrollment time, approximately 270 patients will be enrolled in order to observe targeted PFS events approximately 33 months after study start.

**Table 11: Hazard Ratio and Median PFS Assumption, Number Of Events, Alpha and Power in the Primary Hypothesis Test**

| Endpoint | HR | Median in Arm A (months) | Median in Arm B (months) | Number of events | 1-Sided Alpha | Power |
|---|---|---|---|---|---|---|
| PFS | 0.65 | 13.7 | 8.9 | 194 | 0.025 | 85% |

Abbreviations: HR, hazard ratio; PFS, progression-free survival

## 9.7. Interim Analyses

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

# 10. STUDY COMMITTEES AND COMMUNICATION

Not applicable.

# 11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

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



## 11.1. Access to Information for Monitoring

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

The study 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 study monitor should have access to any patient records needed to verify the entries on the eCRFs. The investigator agrees to cooperate with the study monitor to ensure that any problems detected during these monitoring visits are resolved.

## 11.2. Access to Information for Auditing or Inspections

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

# 12. QUALITY ASSURANCE AND QUALITY CONTROL

## 12.1. Regulatory Authority Approval

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



## 12.2. Quality Assurance

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

## 12.3. Study Site Inspections

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

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

## 12.4. Drug Accountability

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

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

for disposal, arrangements will be made between the site and the sponsor or its representative for destruction or return of unused study drug supplies.

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

# 13. ETHICS/PROTECTION OF HUMAN PATIENTS

## 13.1. Ethical Standard

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

## 13.2. Institutional Review Board/Independent Ethics Committee

This protocol, the ICFs, any information to be given to the patient, and any relevant supporting information must be submitted, reviewed, and approved by the IRB/IEC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/IEC. Copies of the IEC/IRB correspondence and approval of the amended ICF/other information and the approved amended ICF/other information must be forwarded to the sponsor promptly.

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

### 13.2.1. Protocol Amendments

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

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

## 13.3. Informed Consent

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

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

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

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

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

## 13.4. 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 Good Clinical Practice 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 [SFTPs]) 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 the United States Food and Drug Administration (US FDA), the China National Medical Products Administration (China NMPA), and all other national and local health authorities; by sponsor monitors, representatives, and collaborators; and by the IRBs/IECs for each study site, as appropriate.

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

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

## 13.5. Financial Disclosure

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

# 14. DATA HANDLING AND RECORD KEEPING

## 14.1. Data Collection and Management Responsibilities

### 14.1.1. Data Entry in the Electronic Case Report Form

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

### 14.1.2. Data Collection

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

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

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

### 14.1.3. Data Management/Coding

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

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

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

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

The AE verbatim descriptions (the investigator's description from the eCRF) will be coded using MedDRA. AEs will be coded to MedDRA by Lowest Level Term, Preferred Term, and primary System Organ Class (SOC). Concomitant medications will be coded using the WHO Drug Dictionary. Concomitant diseases/medical history will be coded using MedDRA.

## 14.2. Data Integrity and In-house Blinding

Functions/persons with access to the EDC system shall be prohibited from using the EDC system to generate unnecessary listings/summaries that may introduce unwanted bias or to share such outputs from the EDC system with other functions/persons who do not have access to the EDC system. Analyses or summaries generated by randomized treatment assignment and actual treatment received will be limited and documented.



## 14.3. Study Records Retention

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

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

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

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

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

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

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

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



## 14.4. Protocol Deviations

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

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

## 14.5. Study Report and Publications

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

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

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

## 14.6. Study and Study Center Closure

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

- Return of all study data to the sponsor
- Resolution and closure of all data queries
- Accountability, reconciliation, and arrangements for unused study drug(s)
- Review of study records for completeness
- Collection of all study documents for the trial master file filing according to GCP and local regulation
- Shipment of samples (including, but not limited to, those for PK, ADA, and biomarkers) to the assay 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 reason. Potential reasons for suspension or discontinuation include but are not limited to safety or ethical issues or noncompliance with this protocol, GCP, the sponsor's written instructions, the clinical study agreement, or applicable laws and regulations. If the sponsor determines that such action is needed, the sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. When feasible, the sponsor will provide advance notification to the investigator of the impending action before it takes effect.

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

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

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

## 14.7. Information Disclosure and Inventions

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

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

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

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

These restrictions do not apply to:

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

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

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# APPENDIX 1. SCHEDULE OF ASSESSMENTS

| Assessment | Screening [a] | Treatment cycles | | | | End-of-Treatment Visit [b] | Safety Follow-Up[c] | Survival Follow-Up[d] |
|---|---|---|---|---|---|---|---|---|
| | | Induction Phase Cycles 1 up to 4 to 6 (every 21 days) | | | Maintenance Phase Subsequent Cycles (every 21 days) | | | |
| **Days (window)** | **-28 to ~ -1** | **1 (± 3)** | **8 (± 2)** | **15 (± 2)** | **1 (± 3)** | **0 to 7 days** | **30 (± 7), 60 (± 14), and 90 (± 14) days after last dose** | **Every 3 months (± 14 days)** |
| Main informed consent [a] | X | | | | | | | |
| Inclusion/exclusion criteria | X | | | | | | | |
| Randomization [e] | X | | | | | | | |
| Demographics/medical history/prior medications [f] | X | | | | | | | |
| Collection of *EGFR/ALK/BRAF V600E/ROS1* mutation status and local PD-L1 testing results [g] | X | | | | | | | |
| Vital signs/ height and weight [h] | X | X | | | X | X | | |
| Physical examination [i] | X | X | X | X | X | X | | |
| ECOG Performance Status | X | X | | | X | X | | |
| 12-lead ECG [j] | X | As clinically indicated | | | | X | | |

| Assessment | Screening [a] | Treatment cycles | | | | End-of-Treatment Visit [b] | Safety Follow-Up[c] | Survival Follow-Up[d] |
|---|---|---|---|---|---|---|---|---|
| | | Induction Phase Cycles 1 up to 4 to 6 (every 21 days) | | | Maintenance Phase Subsequent Cycles (every 21 days) | | | |
| **Days (window)** | **-28 to ~ -1** | **1 (± 3)** | **8 (± 2)** | **15 (± 2)** | **1 (± 3)** | **0 to 7 days** | **30 (± 7), 60 (± 14), and 90 (± 14) days after last dose** | **Every 3 months (± 14 days)** |
| Adverse events [k] | X | X | X [k] | X [k] | X | X | X | |
| Concomitant medications | X | X | X [k] | X [k] | X | X | X | |
| Hematology[l] | X | X | X [l] | X [l] | X | X | X[c] | |
| Serum chemistry [l] | X | X | | | X | X | X[c] | |
| CK and CK-MB [m] | X | X | | | X | X | X[c] | |
| Coagulation parameters[l] | X | X | | | X | X | X[c] | |
| Urinalysis [l] | X | As clinically indicated | | | | | X[c] | |
| Pregnancy test [n] | X | X | | | X | X | X | |
| Thyroid function [o] | X | X [o] | | | X [o] | X | X[c] | |
| COVID-19 testing [p] | X | | | | | | | |
| Viral serology [q] | X | As clinically indicated | | | | | X[c] | |
| Pulmonary function tests [r] | X | As clinically indicated | | | | | | |
| Pharmacokinetics [s] | | X | | | X | X | | |
| Antidrug antibodies [t] | | X | | | X | X | | |
| Tumor assessment [u] | X | Every 9 weeks (± 7 days) from randomization for the first 52 weeks, then every 12 weeks (± 7 days) | | | | X [t] | | |

| Assessment | Screening [a] | Treatment cycles | | | | End-of-Treatment Visit [b] | Safety Follow-Up[c] | Survival Follow-Up[d] |
|---|---|---|---|---|---|---|---|---|
| | | Induction Phase Cycles 1 up to 4 to 6 (every 21 days) | | | Maintenance Phase Subsequent Cycles (every 21 days) | | | |
| **Days (window)** | **-28 to ~ -1** | **1 (± 3)** | **8 (± 2)** | **15 (± 2)** | **1 (± 3)** | **0 to 7 days** | **30 (± 7), 60 (± 14), and 90 (± 14) days after last dose** | **Every 3 months (± 14 days)** |
| Archival tumor tissue [v] | X | | | | | | | |
| Fresh tumor tissue [w] | X | | | | | X[w] | | |
| Blood collection for biomarker analysis [x] | | X | | | | X | | |
| Ociperlimab administration [y] | | X | | | X | | | |
| Tislelizumab administration [z] | | X | | | X | | | |
| Ociperlimab placebo infusion [aa] | | X | | | X | | | |
| Chemotherapy administration [bb] | | X | X[bb] | X[bb] | X | | | |
| EORTC QLQ-C30 and QLQ-LC13 [cc] | | X | | | X | X | | |
| Survival status | | | | | | | | X |

Abbreviations: AE, adverse event; ALK, anaplastic lymphoma kinase; AUC, area under the concentration-time curve; CK, creatine kinase; CK-MB, creatine kinase cardiac muscle isoenzyme; CT, computed tomography; D, day; DLCO, diffusing capacity of the lungs for carbon monoxide; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13; EOT, End-of-Treatment; EV, extracellular vesicle; FEV1, forced expiratory volume; FFPE, formalin-fixed paraffin-embedded; FT3, free triiodothyronine; FT4, free thyroxine; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; ICF, informed consent form; IEC, Independent Ethics Committee; imAE, immune-mediated adverse event; IRB, Institutional Review Board; IRT, Interactive Response Technology; IV, intravenous(ly); MRI, magnetic resonance imaging; MSI, microsatellite instability;

NCI-CTCAE v5.0, National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand-1; PET, positron emission tomography; PK, pharmacokinetic(s); RECIST v1.1, Response Evaluation Criteria in Solid Tumors, Version 1.1; SAE, serious adverse event; ctDNA, circulating tumor DNA; TMB, tumor mutation burden; TSH, thyroid-stimulating hormone; v, version.

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

[b] The End of Treatment Visit will be conducted when the investigator determines that ociperlimab or tislelizumab will no longer be used. (Section 3.4). If routine laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the EOT Visit, tests need not be repeated.

[c] A Safety Follow-Up Visit at 30 days (± 7 days) after the last dose of the study drug(s) is required to assess AEs and concomitant medications, unless the time window overlaps the time window of the EOT Visit; the Safety Follow-Up Visit may be a telephone call or an on-site visit if laboratory assessments are necessary. Two additional telephone calls with patients will occur in the safety follow-up period to assess imAEs and concomitant medications if appropriate (ie, if associated with an imAE or a new anticancer therapy) at 60 and 90 days (± 14 days) after the last dose of ociperlimab (or placebo) and/or tislelizumab regardless of whether the patient starts a new subsequent anticancer therapy. If a patient reports a suspected imAE at a safety follow-up telephone call, the investigator should arrange an unscheduled visit if further assessment is indicated. Patients who discontinue study treatment before disease progression will need to undergo tumor assessments as outlined in Section 7.5.

[d] Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (± 14 days) after the EOT Visit or as directed by the sponsor until death, loss to follow-up, withdrawal of consent, or study termination by sponsor. All patients will be followed for survival and subsequent anticancer therapy information unless a patient requests to be withdrawn from survival follow-up.

[e] Patients will be randomized in a 1:1 ratio to either Arm A (ociperlimab + tislelizumab + chemotherapy) or Arm B (placebo + tislelizumab + chemotherapy via IRT. All patients are required to receive study treatment within 2 business days of randomization.

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

[g] *EGFR*, *ALK*, *BRAF V600E*, and *ROS1* mutational status, if known, will be collected. Patients with non-squamous NSCLC and unknown *EGFR* mutational status will be required to have a tissue-based *EGFR* test performed either locally or centrally at screening. Local PD-L1 testing may be used for patient randomization purposes, in which case, the local PD-L1 testing results will be collected in the eCRF. If local PD-L1 testing will not be used for patient randomization purposes, local PD-L1 testing results, if available, will not be collected in the eCRF.

[h] Vital signs collected on study include body temperature (°C), pulse rate, and blood pressure (systolic and diastolic) after patients have rested for 10 minutes. Vital signs will be recorded at screening, on Day 1 of each cycle, and at the EOT Visit. The patient's vital signs are required to be recorded within 60 minutes before, during, and 30 minutes after completion of study drug infusion on Cycle 1 Day 1. For subsequent infusions, vital signs will be collected within 60 minutes before infusion and, if clinically indicated, during and 30 minutes after the infusion. Height will be recorded at screening only. Weight will be recorded at screening, on Day 1 of each cycle, and at the EOT Visit.

[i] A complete physical examination is required at screening; subsequent visits will entail limited, symptom-directed physical examinations (as detailed in Section 7.4.2). For patients with squamous NSCLC receiving nab-paclitaxel during the induction phase (first 4-6 cycles), a symptom-directed physical examination will also be performed weekly on Day 8 and Day 15 of each of these cycles.

[j] The ECG recordings will be obtained during screening, the EOT Visit, and as clinically indicated at other timepoints. Patients should be resting in a semi-recumbent supine position for at least 10 minutes before each ECG collection.

[k] The AEs and laboratory abnormalities will be graded per NCI-CTCAE v5.0. All AEs will also be evaluated for seriousness. After the main ICF has been signed, but before the first administration of the study drug(s), only SAEs should be recorded. After the initiation of the study drug(s), all AEs and SAEs, regardless of relationship to study drug(s), will be reported until either 30 days after last dose of all study drug(s) or the initiation of new anticancer therapy,

whichever occurs first. Immune-mediated AEs (serious or non-serious) should be reported until 90 days after the last dose of ociperlimab and tislelizumab, regardless of whether or not the patient starts a new anticancer therapy. All SAEs considered related to the study drug(s) that are brought to the attention of the investigator should be reported regardless of time since the last dose of treatment. For non-squamous NSCLC receiving nab-paclitaxel, review of AEs and concomitant medications may be conducted by telephone on Days 8 and 15. The patient should be asked if any new symptoms have been observed or existing symptoms may have worsened, and if there have been any changes to medications. The investigators should remind patients to return to the clinical study site for further assessment if new AEs arise or worsen.

[l] Local laboratory assessments of serum chemistry, hematology, coagulation, and urinalysis will be conducted, of which certain elements will be collected as specified in Appendix 2. If laboratory tests of serum chemistry (including liver function), hematology, and coagulation at screening are performed > 7 days before randomization, these tests must be repeated within 3 days prior to Cycle 1 Day 1. Hematology and serum chemistry (data collected as specified in Appendix 2) will be performed on Day 1 of each cycle. For patients with squamous NSCLC receiving nab-paclitaxel during the induction phase (first 4 to 6 cycles), hematology will also be performed weekly on Day 8 and Day 15 of each of these cycles before the administration of nab-paclitaxel. After Cycle 1, results are to be reviewed within 48 hours before study drug administration. Coagulation assays will be performed at screening, on Day 1 of each cycle, and at the EOT Visit. Urinalysis is to be conducted during the treatment period only if clinically warranted. Refer to Section 8.3.5 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.

[m] All patients will have CK and CK-MB testing at screening, each cycle assessments, the EOT Visit, and the safety follow-up visits. If laboratory tests of cardiac enzymes at screening are performed > 7 days before randomization, these tests must be repeated within 3 days prior to Cycle 1 Day 1. If CK-MB fractionation is not available, troponin I and/or troponin T may be tested instead. Refer to Section 8.3.5 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.

[n] Urine or serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 7 days before randomization. Urine pregnancy tests will be performed at each visit before dosing, and at the EOT 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. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.

[o] Analysis of FT3 (or total T3 for sites where free T3 testing is not performed), FT4, and TSH will be performed by a local study site laboratory. Thyroid function tests will be performed at screening or on C1D1 prior to dosing, and then every 2 cycles (ie, Day 1 of Cycles 3, 5, and 7, etc.), and at the EOT Visit.

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

[q] At screening, patients will be tested for HIV serology (antigen and/or antibodies) for patients with unknown HIV status, hepatitis B surface antigen, hepatitis B surface antibody, total hepatitis B core antibody (HBcAb), and HCV antibody. Viral load assessment (HBV DNA or HCV RNA) will be performed only when HBsAg or HCV antibody is positive, respectively. Patients who have detectable HBV DNA or HCV RNA at screening will perform the respective viral load test every 4 cycles (ie, Day 1 of Cycle 5, 9, and 13, etc.).

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

[s] Procedures for collection of blood samples to evaluate ociperlimab and tislelizumab PK are described in the laboratory manual. Predose samples (within 60 minutes before starting infusion) are required to be collected on Day 1 of Cycles 1, 2, 5, 9, and 17. Postdose samples (within 30 minutes after completing study drug infusion) are required to be collected on Day 1 of Cycles 1 and 5. An additional PK sample is required to be collected at the EOT Visit. Should a patient present with any ≥ Grade 3 imAE, an additional blood PK sample may be taken. These tests are required when it is allowed by local regulations/IRBs/IECs.

[t] Blood used to test for anti-ociperlimab and anti-tislelizumab antibodies will be collected within 60 minutes before beginning the Day 1 infusion of Cycles 1, 2, 5, 9, and 17 and at the EOT Visit. All samples should be collected at the same time as blood collection for predose PK analysis. These tests are required when it is allowed by local regulations/IRBs/IECs.

[u] Radiologic images that are captured as standard of care before obtaining written informed consent and ≤ 28 days before randomization may be used rather than repeating tests. All measurable and evaluable lesions are required to 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 is required to be used throughout the study (eg, the same imaging protocol for CT or MRI). Imaging of the brain (preferably MRI) is required for all patients during screening. Bone scan or PET is required if clinically indicated. During the study, tumor imaging will be performed every 9 weeks (± 7 days) from randomization for the first 52 weeks and then every 12 weeks (± 7 days) based on RECIST v1.1. Tumor assessments are required to be performed on schedule regardless of whether study treatment has been administered or held; they should not be adjusted for possible delays in cycles. Tumor assessment should continue until radiologic disease progression as determined by the investigator. Patients who discontinue study treatment early for reasons other than radiologic disease progression (eg, toxicity) will continue to undergo tumor assessments following the original plan until the patient experiences disease progression or death, withdraws consent, is lost to follow-up, or until the study terminates, whichever occurs first. See also Section 7.5.

[v] Patients are required to provide archival tumor tissues during screening period if available (FFPE blocks or approximately 6 to 15 freshly cut unstained slides) for prospective analysis of PD-L1 status, or retrospective analysis of PD-L1 status for subjects that are randomized using the local PD-L1 results, and for retrospective analysis of other biomarkers (Section 7.7) and for *EGFR* testing if the patient has non-squamous NSCLC and unknown *EGFR* status. Note: For sites in mainland China, tissue samples will be obtained to test biomarkers limited to the expression of TIGIT, CD226, CD155, CD112, and PD-L1, GEP, TMB, gene mutations and MSI, and TILs at baseline and at disease progression/reoccurrence.

[w] In the absence of archival tumor tissues, a fresh biopsy of a tumor lesion at baseline is required. See Section 7.7 for more information. Patients who have progressive disease will be asked to provide an optional biopsy at the EOT Visit for the assessment of mechanism of resistance (written informed consent is required before obtaining an optional fresh tumor biopsy).

[x] Blood samples are required to be collected predose on Day 1 of Cycle 1, predose on Day 1 of Cycle 3, and at the EOT Visit after disease progression to evaluate biomarkers including, but not limited to, ctDNA, TMB, MSI, gene mutations, and EVs in blood. Note: Blood-based biomarkers, including ctDNA, TMB, MSI, gene mutations, and EVs will be explored for blood samples collected at sites in mainland China.

[y] Ociperlimab will be given intravenously once every 3 weeks in Arm A. On Day 1 of Cycles 1 and 2, ociperlimab will be delivered over 60 minutes. If well tolerated, subsequent infusions can be administered over ≥ 30 minutes. The first dose will be given on Cycle 1 Day 1 and subsequent dosing will continue on the scheduled 21-day intervals. Ociperlimab infusion must always occur after the infusion of tislelizumab has been completed. Patients must be monitored after study treatment infusions are complete as shown in Table 5.

[z] Tislelizumab will be given intravenously once every 3 weeks. On Day1 of Cycles 1 and 2, tislelizumab will be delivered over 60 (± 5) minutes. If well tolerated, subsequent infusions can be administered over ≥ 30 (± 5) minutes. The first dose will be given on Cycle 1 Day 1 and subsequent dosing will continue on the scheduled 21-day intervals. Note: Tislelizumab must not be concurrently administered with any other drug. Patients must be monitored after study treatment infusions are complete as shown in Table 5.

[aa] Ociperlimab placebo infusions will be given intravenously once every 3 weeks in Arm B. On Day 1 of Cycles 1 and 2, placebo infusions will be delivered over 60 (± 5) minutes. If well tolerated, subsequent infusions can be administered over 30 (± 5) minutes. The first dose will be given on Cycle 1 Day 1 and subsequent dosing will continue on the scheduled 21-day intervals. Placebo infusions must always occur after the infusion of tislelizumab has been completed. Patients must be monitored after study treatment infusions are complete as shown in Table 5.

[bb] Doublet chemotherapy will be given for 4 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). For patients with non-squamous NSCLC whose disease has not progressed after 4 to 6 cycles of doublet chemotherapy, maintenance treatment of pemetrexed is permitted. For patients with squamous NSCLC,

the histology-based chemotherapy regimen will be carboplatin AUC 5 or 6 (D1) + paclitaxel 175 or 200 mg/m$^2$ (D1) or nab-paclitaxel 100 mg/m$^2$ (D1, D8, D15) administered every 3 weeks. For patients with non-squamous NSCLC, the histology-based chemotherapy regimen will be cisplatin 75 mg/m$^2$ or carboplatin AUC 5 (D1) + pemetrexed 500 mg/m$^2$ (D1) IV administered every 3 weeks.
During maintenance, patients with non-squamous NSCLC only will receive pemetrexed 500 mg/m$^2$ (D1) IV administered every 3 weeks.

[cc] To be completed before any clinical activities during on-study site visits. EORTC QLQ-C30 and QLQ-LC13will be completed at baseline (Day 1 of Cycle 1), at every other cycle through Cycle 13, then every 4 cycles thereafter, and at the EOT Visit, whichever comes first.

# APPENDIX 2. CLINICAL LABORATORY ASSESSMENTS

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

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

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

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

[c] On routine urinalysis, if urine protein is ≥ 2+ by dipstick, 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.

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

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

Source: Oken et al 1982. Eastern Cooperative Oncology Group, Robert Comis MD, Group Chair.

# APPENDIX 4. THE RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) GUIDELINES, VERSION 1.1

Source: Eisenhauer et al 2009.

**Definitions**

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

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

Measurable Disease

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

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

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

Nonmeasurable Disease

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

Bone lesions:

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

- Blastic bone lesions are nonmeasurable.

Cystic lesions:

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

Lesions with prior local treatment:

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

Target Lesions

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

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

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

Nontarget Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as nontarget lesions and should also be recorded at baseline. Measurements are not required and

these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression" (more details to follow). In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (eg, "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

**Guidelines for Evaluation of Measurable Disease**

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

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

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

- Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in CR. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA125 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 CA125 progression criteria which are to be integrated with objective tumor assessment for use in firstline trials in ovarian cancer.
- Cytology, histology: These techniques can be used to differentiate between partial response (PR) and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

**Response Criteria**

Evaluation of Target Lesions

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

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

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

Evaluation of Nontarget Lesions

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

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

discontinuation of therapy. A modest "increase" in the size of one or more nontarget lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in nontarget disease in the face of SD or PR of target disease will therefore be extremely rare.

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

New Lesions

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

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

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

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

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

- Negative FDGPET at baseline, with a positive FDGPET at follow-up, is a sign of PD based on a new lesion.
- No FDGPET at baseline and a positive FDGPET at follow-up: If the positive FDGPET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDGPET 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 FDGPET scan). If the positive FDGPET at follow-up corresponds to a preexisting site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

- Timepoint Response
  - It is assumed that at each protocol specified time point, a response assessment occurs. The following table provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline:

| Target Lesions | Nontarget Lesions | New Lesions | Overall Response |
|---|---|---|---|
| CR | CR | No | CR |
| CR | Non-CR/non-PD | No | PR |
| CR | Not evaluated | No | PR |
| PR | Non-PD or not all evaluated | No | PR |
| SD | Non-PD or not all evaluated | No | SD |
| Not all evaluated | Non-PD | No | NE |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

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

When patients have nonmeasurable (therefore nontarget) disease only, the following table is to be used:

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

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

Evaluation of Best Overall Response

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

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

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

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

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

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

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

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

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

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

**Confirmation of Measurement/Duration of Response**

Confirmation

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

In the case of SD, measurements must have met the SD criteria at least once after trial entry at a minimum interval (in general not less than 6 weeks).

Duration of Overall Response

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

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

Duration of Stable Disease

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

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

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

# APPENDIX 5. PREEXISTING IMMUNE DEFICIENCIES OR AUTOIMMUNE DISEASES

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

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



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

# APPENDIX 6. NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

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

Adapted from Dolgin et al 1994.
Original source: Criteria Committee, New York Heart Association, Inc. Diseases of the Heart and Blood Vessels. Nomenclature and Criteria for diagnosis, 6th edition Boston, Little, Brown and Co. 1964, p 114.

# APPENDIX 7. IMMUNE-MEDIATED ADVERSE EVENT EVALUATION AND MANAGEMENT

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

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

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

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

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

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

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

| Immune-mediated Toxicity | Diagnostic Evaluation Guideline |
|---|---|
| Neurological toxicity | Perform a comprehensive neurological examination and brain MRI for all CNS symptoms; review alcohol history and other medications. Conduct a diabetic screen and assess blood B12/folate, HIV status, TFTs, and consider autoimmune serology. Consider the need for brain/spine MRI/MRA and nerve conduction study for peripheral neuropathy. Consult with a neurologist if there are abnormal findings. |
| For France only:<br>Guillain-Barré syndrome | Clinical findings resemble classical ascending Guillain-Barré syndrome symptoms, including bilateral proximal weakness, ataxia, distal sensory, autonomic disturbances, and cranial nerve involvement. Referral to a neurologist should be considered for symptoms of Guillain-Barré syndrome. Consider checking for antiganglioside antibodies. |
| 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).<br>In case of abdominal discomfort, consider imaging, eg, X-ray, CT scan. If a patient experiences bleeding, pain, or distension, consider colonoscopy with biopsy and surgical intervention as appropriate. |
| Eye disorders | If a patient experiences acute, new onset, or worsening of eye inflammation; blurred vision; or other visual disturbances, refer the patient urgently to an ophthalmologist for evaluation and management. |
| Hepatitis | Check ALT/AST/total bilirubin, INR/albumin; the frequency will depend on severity of the AE (eg, daily if Grade 3 to 4; every 2 to 3 days if Grade 2, until recovering). Review medications (eg, statins, antibiotics) and alcohol history. Perform liver screen including Hepatitis A/B/C serology, Hepatitis E PCR and assess anti-ANA/SMA/LKM/SLA/LP/LCI, iron studies. Consider imaging (eg, ultrasound scan for metastases or thromboembolism). Consult with a hepatologist and consider liver biopsy. |
| Renal toxicity | Review hydration status and medication history. Test and culture urine. Consider renal ultrasound scan, protein assessment (dipstick/24-hour urine collection), or phase-contrast microscopy. Refer to a nephrologist for further management assistance. |
| Dermatology | Consider other causes by conducting a physical examination. Consider dermatology referral for skin biopsy. |
| For France only:<br>Toxic epidermal necrolysis and Stevens-Johnson syndrome | For signs or symptoms of Stevens-Johnson syndrome or toxic epidermal necrolysis, withhold study drugs and refer the patient for specialized assessment and treatment. |

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

| Immune-mediated Toxicity | Diagnostic Evaluation Guideline |
|---|---|
| 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.<br>For suspected myositis/rhabdomyolysis/myasthenia include: CK, ESR, CRP, troponin, and consider a muscle biopsy. |
| Myocarditis | Perform ECG, echocardiogram, CK/CK-MB, troponin (I and/or T), and refer to a cardiologist. |

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

### Treatment of Immune-Mediated Adverse Events

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

| Autoimmune Toxicity | Grade | Treatment Guidelines (Subject to Clinical Judgement) | Study Drug Management (All Arms) |
|---|---|---|---|
| **Thyroid Disorders** | **1-2**<br>Asymptomatic TFT abnormality or mild symptoms | Replace thyroxine if hypothyroid, until TSH/T4 levels return to normal range.<br>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.<br>Taper corticosteroids over 2-4 weeks. Monitor thyroid function regarding the need for hormone replacement. | Continue study treatment or withhold both study drugs in cases with systemic symptoms. |
| | **3-4**<br>Severe symptoms, hospitalization required | Refer patient to an endocrinologist.<br>If hypothyroid, replace with thyroxine 0.5-1.6 µg/kg/day (for the elderly or those with comorbidities, the suggested starting dose is 0.5 µg/kg/day). Add oral prednisolone 0.5 mg/kg/day for thyroid pain.<br>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 (All Arms) |
|---|---|---|---|
| **Hypophysitis** | **1-2**<br>Mild-moderate symptoms | Refer patient to an endocrinologist for hormone replacement.<br>Add oral prednisolone 0.5-1 mg/kg/day for patients with pituitary inflammation. Taper corticosteroids over at least 1 month.<br>If there is no improvement in 48 hours, treat as Grade 3-4. | Continue study treatment. |
| | **3-4**<br>Severe or life-threatening symptoms | Refer patient to an endocrinologist for assessment and treatment.<br>Initiate pulse intravenous methylprednisolone 1 mg/kg for patients with headache/visual disturbance due to pituitary inflammation. Convert to oral prednisolone and taper over at least 1 month.<br>Maintain hormone replacement according to endocrinologist's advice. | Hold study treatment for patients with headache/visual disturbance due to pituitary inflammation until resolved/improved to ≤ Grade 2. Discontinuation is usually not necessary. |
| **Pneumonitis** | **1**<br>Radiographic changes only | Monitor symptoms every 2-3 days.<br>If appearance worsens, treat as Grade 2. | Consider holding both study drugs until appearance improves and cause is determined. |

| Autoimmune Toxicity | Grade | Treatment Guidelines (Subject to Clinical Judgement) | Study Drug Management (All Arms) |
|---|---|---|---|
| | **2**<br>Symptomatic: exertional breathlessness | Commence antibiotics if infection suspected. Add oral prednisolone 1 mg/kg/day if symptoms/appearance persist for 48 hours or worsen.<br>Consider *Pneumocystis* infection prophylaxis. Taper corticosteroids over at least 6 weeks.<br>Consider prophylaxis for adverse steroid effects: eg, blood glucose monitoring, vitamin D/calcium supplement. | Hold both study drugs. 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**<br>Severe or life-threatening symptoms: breathless at rest | Admit to a hospital and initiate treatment with intravenous methylprednisolone 2-4 mg/kg/day. If there is no improvement, or worsening after 48 hours, add infliximab 5 mg/kg (if no hepatic involvement).<br>Convert to oral prednisolone and taper over at least 2 months.<br>Cover with empiric antibiotics and consider prophylaxis for *Pneumocystis* infection and other adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement. | Discontinue both study drugs. |
| **Neurological Toxicity** | **1**<br>Mild symptoms | – | Continue study treatment. |

| Autoimmune Toxicity | Grade | Treatment Guidelines (Subject to Clinical Judgement) | Study Drug Management (All Arms) |
|---|---|---|---|
| | **2**<br>Moderate symptoms | Treat with oral prednisolone 0.5-1 mg/kg/day. Taper over at least 4 weeks.<br>Obtain neurology consultation. | Hold both study drugs; resume both study drugs when resolved/improved to Grade 0-1. |
| | **3-4**<br>Severe/life-threatening symptoms | Initiate treatment with oral prednisolone or intravenous methylprednisolone 1-2 mg/kg/day, depending on symptoms. Taper corticosteroids over at least 4 weeks.<br>Consider azathioprine, MMF, cyclosporine if no response within 72-96 hours. | Discontinue both study drugs. |
| **For France only:**<br>**Guillain-Barré syndrome** | **All grade** | There is no Grade 1 symptoms. For Grade 2 symptoms, consider oral or intravenous methylprednisolone (2 to 4 mg/kg/day) followed by a slow taper. For grade 3 or 4 symptoms, more intensive immune modulation may be required in addition to Corticosteroids or by exchanging CSs for IVIG (0.4 g/kg/day for 5 days) or plasma exchange or selective separation.<br>Monitor for concurrent autonomic dysfunction.<br>Referral to a neurologist should be considered for symptoms of Guillain-Barré syndrome. | Discontinue both study drugs. |

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

| Autoimmune Toxicity | Grade | Treatment Guidelines (Subject to Clinical Judgement) | Study Drug Management (All Arms) |
|---|---|---|---|
| **Skin reactions** | **1**<br>Skin rash, with or without symptoms, < 10% BSA | Avoid skin irritants and sun exposure; topical emollients recommended.<br>For France only: Topical steroids (mild to moderate strength) and oral antihistamines for itch. | Continue study treatment. |
| | **2**<br>Rash covers 10%-30% of BSA | Avoid skin irritants and sun exposure; topical emollients recommended.<br>Topical steroids (moderate strength cream once a day or potent cream twice a day) ± oral or topical antihistamines for itch. Consider a short course of oral steroids. | Continue study treatment.<br>For France only: Consider holding both study drugs. Re-treat when AE is resolved or improved to mild rash (Grade 1). |
| | **3**<br>Rash covers > 30% BSA or Grade 2 with substantial symptoms | Avoid skin irritants and sun exposure; topical emollients recommended.<br>Initiate steroids as follows based on clinical judgement:<br>For moderate symptoms: oral prednisolone 0.5-1 mg/kg/day for 3 days then taper over 2-4 weeks.<br>For severe symptoms: intravenous methylprednisolone 0.5-1 mg/kg/day; convert to oral prednisolone and taper over at least 4 weeks. | Hold both study drugs.<br>Re-treat when AE is resolved or improved to mild rash (Grade 1-2, for France only: Grade 1) after discussion with the study medical monitor. |

| Autoimmune Toxicity | Grade | Treatment Guidelines (Subject to Clinical Judgement) | Study Drug Management (All Arms) |
|---|---|---|---|
| | **4**<br>Skin sloughing > 30% BSA with associated symptoms (eg, erythema, purpura, epidermal detachment) | Initiate intravenous methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks.<br>Admit to a hospital and seek urgent dermatology consultation. | Discontinue both study drugs.<br>For France only: Permanently discontinue both study drugs. |
| **For France only:**<br>**Toxic epidermal necrolysis and Stevens-Johnson syndrome** | **Any grade** | Refer the patient for specialized assessment and treatment. | Permanently discontinue both study drugs. |
| **Hepatitis** | **1**<br>ALT or AST > ULN to 3 x ULN | Check LFTs within 1 week and before the next dose; check LFTs to verify that there has been no worsening.<br>If LFTs are worsening, recheck every 48-72 hours until improvement is seen. | Continue study treatment if LFTs are unchanged or improving.<br>Hold both study drugs if LFTs are worsening until improvement is seen. |
| | **2**<br>ALT or AST 3-5 x ULN | Recheck LFTs every 48-72 hours.<br>For persistent ALT/AST elevation: consider oral prednisolone 0.5-1 mg/kg/day for 3 days, then taper over 2-4 weeks.<br>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 both study drugs; treatment with both study drugs may be resumed when resolved/improved to baseline Grade and prednisolone tapered to ≤ 10 mg. |

| Autoimmune Toxicity | Grade | Treatment Guidelines (Subject to Clinical Judgement) | Study Drug Management (All Arms) |
|---|---|---|---|
| | **3**<br>ALT or AST 5-20 x ULN | ALT/AST < 400 IU/L and normal bilirubin/INR/albumin: Initiate oral prednisolone 1 mg/kg and taper over at least 4 weeks.<br>ALT/AST > 400 IU/L or raised bilirubin/INR/low albumin: Initiate intravenous (methyl)prednisolone 2 mg/kg/day.<br>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.<br>For France only: Reintroduce only after a positive advice of a hepatologist and after discussion with the study medical monitor. |
| | **4**<br>ALT or AST > 20 x ULN | Initiate intravenous methylprednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 6 weeks. | Discontinue both study drugs. |
| | For France only: For patients with Grade 3 or 4 immune-related liver injury, hospitalization and initiation of corticosteroid 1-2 mg/kg/day should be considered.<br>If there is no response to corticosteroid within 2-3 days, alternative immunosuppressive therapy should be considered, such as MMF (1000 mg twice daily), tocilizumab (8 mg/kg), tacrolimus, azathioprine, cyclosporine, or anti-thymocyte globulin.<br>**Global:**<br>**Worsening LFTs despite steroids:**<br>• If on oral prednisolone, change to pulsed intravenous methylprednisolone.<br>• If on intravenous methylprednisolone, add mycophenolate mofetil (MMF) 500 to 1000 mg twice a day.<br>• If worsens on MMF, consider addition of tacrolimus.<br>Duration and dose of steroid required will depend on severity of event. | | |
| **Nephritis** | **1**<br>Creatinine 1.5 x baseline<br>or > ULN to 1.5 x ULN | Repeat creatinine weekly.<br>If symptoms worsen, manage as per criteria below. | Continue study treatment. |

| Autoimmune Toxicity | Grade | Treatment Guidelines (Subject to Clinical Judgement) | Study Drug Management (All Arms) |
|---|---|---|---|
| | **2**<br>Creatinine > 1.5-3 x baseline or > 1.5-3 x ULN | Ensure hydration and review creatinine in 48-72 hours; if not improving, consider creatinine clearance measurement by 24-hour urine collection.<br>Discuss with nephrologist the need for kidney biopsy.<br>If attributed to study drug, initiate oral prednisolone 0.5-1 mg/kg and taper over at least 2 weeks.<br>Repeat creatinine/U&E every 48-72 hours. | Hold study treatment.<br>If not attributed to drug toxicity, restart treatment.<br>If attributed to study drug and resolved/improved to baseline grade: Restart study drug if tapered to < 10 mg prednisolone. |
| | **3**<br>Creatinine > 3 x baseline or > 3-6 x ULN | Hospitalize patient for monitoring and fluid balance; repeat creatinine every 24 hours; refer to a nephrologist and discuss need for biopsy.<br>If worsening, initiate intravenous (methyl)prednisolone 1-2 mg/kg. Taper corticosteroids over at least 4 weeks. | Hold study treatment until the cause is investigated.<br>If study drug suspected: Discontinue study treatment. |
| | **4**<br>Creatinine > 6 x ULN | As per Grade 3, patient should be managed in a hospital where renal replacement therapy is available. | Discontinue study treatment. |
| **Diabetes/ Hyperglycemia** | **1**<br>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. |

| Autoimmune Toxicity | Grade | Treatment Guidelines (Subject to Clinical Judgement) | Study Drug Management (All Arms) |
|---|---|---|---|
| | **2**<br>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**<br>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 both study drugs until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1. |
| | **4**<br>Fasting glucose value > 500 mg/dL; > 27.8 mmol/L | Admit patient to hospital and institute local emergency diabetes management.<br>Refer the patient to a diabetologist for insulin maintenance and monitoring. | Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1. |
| **Ocular Toxicity** | **1**<br>Asymptomatic eye examination/test abnormality | Consider alternative causes and prescribe topical treatment as required. | Continue study treatment. |
| | **2**<br>Anterior uveitis or mild symptoms | Refer patient to an ophthalmologist for assessment and topical corticosteroid treatment.<br>Consider a course of oral steroids. | Continue study treatment or hold both drugs if symptoms worsen or if there are symptoms of visual disturbance. |
| | **3**<br>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 both study drugs until improved to Grade 0-1; reintroduce only after discussion with the study medical monitor. |
| | **4**<br>Blindness (at least 20/200) in the affected eyes | Initiate intravenous (methyl)prednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. | Discontinue both study drugs. |

| Autoimmune Toxicity | Grade | Treatment Guidelines (Subject to Clinical Judgement) | Study Drug Management (All Arms) |
|---|---|---|---|
| **Pancreatitis** | **2**<br>Asymptomatic, blood test abnormalities | Monitor pancreatic enzymes. | Continue study treatment. |
| | **3**<br>Abdominal pain, nausea and vomiting | Admit to hospital for urgent management. Initiate intravenous (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when amylase/lipase improved to Grade 2 and taper over at least 4 weeks. | Hold both study drugs; reintroduce both study drugs only after discussion with the study medical monitor. |
| | **4**<br>Acute abdominal pain, surgical emergency | Admit to hospital for emergency management and appropriate referral. | Discontinue both study drugs. |
| **Arthritis** | **1**<br>Mild pain with inflammation, swelling | Management per local guideline. | Continue study treatment. |
| | **2**<br>Moderate pain with inflammation, swelling, limited instrumental (fine motor) activities | Management as per local guideline. Consider referring patient to a rheumatologist.<br>If symptoms worsen on treatment, manage as a Grade 3 event. | Continue treatment or, if symptoms continue to worsen, hold both study drugs until symptoms improve to baseline or Grade 0-1. |
| | **3**<br>Severe pain with inflammation or permanent joint damage, daily living activity limited | Refer patient urgently to a rheumatologist for assessment and management.<br>Initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks. | Hold both study drugs unless improved to Grade 0-1; reintroduce only after discussion with the study medical monitor. |
| **Mucositis/ stomatitis** | **1**<br>Test findings only or minimal symptoms | Consider topical treatment or analgesia as per local guideline. | Continue study treatment. |

| Autoimmune Toxicity | Grade | Treatment Guidelines (Subject to Clinical Judgement) | Study Drug Management (All Arms) |
|---|---|---|---|
| | **2**<br>Moderate pain, reduced oral intake, limited instrumental activities | As per local guidelines, treat with analgesics, topical treatments, and oral hygiene care.<br>Ensure adequate hydration.<br>If symptoms worsen or there is sepsis or bleeding, manage as a Grade 3 event. | Continue study treatment. |
| | **3**<br>Severe pain, limited food and fluid intake, daily living activity limited | Admit to hospital for appropriate management.<br>Initiate intravenous (methyl)prednisolone 1-2 mg/kg/day.<br>Convert to oral prednisolone when symptoms improve to Grade 2 and taper over at least 4 weeks. | Hold both study drugs until improved to Grade 0-1. |
| | **4**<br>Life-threatening complications or dehydration | Admit to hospital for emergency care. Consider intravenous corticosteroids if not contraindicated by infection. | Discontinue both study drugs. |
| **Myositis/ Rhabdomyolysis** | **1**<br>Mild weakness with/without pain | Prescribe analgesics.<br>If CK is significantly elevated and patient has symptoms, consider oral steroids and treat as Grade 2. | Continue study treatment. |
| | **2**<br>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 both study drugs until improved to Grade 0-1. |

| Autoimmune Toxicity | Grade | Treatment Guidelines (Subject to Clinical Judgement) | Study Drug Management (All Arms) |
|---|---|---|---|
| | **3-4**<br>Severe weakness, limiting self-care | Admit to hospital and initiate oral prednisolone 1 mg/kg. Consider bolus intravenous (methyl)prednisolone and 1-2 mg/kg/day maintenance for severe activity restriction or dysphagia.<br>If symptoms do not improve, add immunosuppressant therapy.<br>Taper oral steroids over at least 4 weeks. | For Grade 3: Hold study treatment until improved to Grade 0-1. Discontinue upon any evidence of myocardial involvement. |
| **Myocarditis**[a] | **< 2**<br>Asymptomatic but significantly increased CK-MB or increased troponin OR clinically significant intraventricular conduction delay | Initiate cardiac evaluation under close monitoring with repeat serum testing and including ECG, cardiac echo/MUGA, and/or other interventions per institutional guidelines; consider referral to a cardiologist.<br>If diagnosis of myocarditis is confirmed, treat as Grade 2. | Hold both study drugs.<br>If a diagnosis of myocarditis is confirmed and considered immune-mediated, permanently discontinue study treatment in patients with moderate or severe symptoms.<br>Patients with no symptoms or mild symptoms may not restart study drugs unless cardiac parameters have returned to baseline and after discussion with the study medical monitor. |
| | **2**<br>Symptoms on mild-moderate exertion | Admit to hospital and initiate oral prednisolone or intravenous (methyl)prednisolone at 1-2 mg/kg/day. Consult with a | |
| | **3**<br>Severe symptoms with mild exertion | | |

| Autoimmune Toxicity | Grade | Treatment Guidelines (Subject to Clinical Judgement) | Study Drug Management (All Arms) |
|---|---|---|---|
| | **4**<br>Life-threatening | cardiologist and manage symptoms of cardiac failure according to local guidelines.<br>If no immediate response, change to pulsed doses of (methyl)prednisolone 1 g/day and add MMF, infliximab, or anti-thymocyte globulin. | |
| **Other immune-mediated adverse events** | **≤ 2** | Clinical management per local guideline based on adverse event type and severity. | Continue study treatment. |
| | **3** | | Hold study treatment until improved to Grade 0-1.<br>For recurrent Grade 3: Discontinue study treatment. |
| | **4** | | Discontinue study treatment. |

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

[a] If clinically significant cardiac enzyme abnormalities are detected during laboratory assessment and serial cardiac enzyme assessments pose logistical hardship for the patient, then patient hospitalization should strongly be considered until immune-mediated myocarditis has been ruled out.

# APPENDIX 8. DOSE MODIFICATION FOR 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<br>If there is a second episode despite dose reduction, the patient must receive prophylactic antibiotics during the subsequent cycles<br>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 ($\geq 1.5 \times 10^9$/L); restart with the full dose |
| | Grade 4 ($< 0.5 \times 10^9$/L) | Chemotherapy delay until recovered to ≤ Grade 1; 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. Resume nab-paclitaxel and carboplatin at reduced doses when peripheral neuropathy improves to Grade 1 or completely resolves.

# APPENDIX 9. CHRONIC KIDNEY DISEASE EPIDEMIOLOGY COLLABORATION (CKD-EPI) EQUATION, COCKCROFT-GAULT EQUATION, AND CALVERT FORMULA

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

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

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

where:

$S_{cr}$ is serum creatinine in mg/dL,
$\kappa$ is 0.7 for females and 0.9 for males,
$\alpha$ is -0.329 for females and -0.411 for males,
min indicates the minimum of $S_{cr}/\kappa$ or 1, and
max indicates the maximum of $S_{cr}/\kappa$ 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

**COCKCROFT-GAULT EQUATION:**

$$\text{CrCl (male; mL/min)} = \frac{(140 - \text{age}) \times (\text{weight in kg})}{72 \times \text{serum creatinine (mg/dL)}}$$

CrCl (female; mL/min) = 0.85 x CrCl (male)

**CALVERT FORMULA:**

Total Dose (mg) = (target AUC) x (CrCl + 25)

The CrCl used in the Calvert formula should not exceed 125 mL/min.

When using eGFR instead of CrCl for calculation, generate with actual body surface area (BSA) instead of 1.73 $m^2$.

Maximum carboplatin dose (mg) = target AUC 5 (mg•min/mL) x (125 + 25) = 5 x 150 mL/min = 750 mg

Abbreviations: AUC, area under the concentration-time curve; BSA, body surface area; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; $S_{cr}$, serum creatinine concentration.

# APPENDIX 10. CONTRACEPTION GUIDELINES AND DEFINITIONS OF "WOMEN OF CHILDBEARING POTENTIAL," "NO CHILDBEARING POTENTIAL"

Contraception Guidelines

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

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

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

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

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

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

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

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

Adapted from Clinical Trials Facilitation and Coordination Group (CTFG) 2020.

# APPENDIX 11. EUROPEAN ORGANISATION FOR RESEARCH AND TREATMENT OF CANCER QUALITY OF LIFE CANCER QUESTIONNAIRE QLQ-C30

## EORTC QLQ-C30 (version 3)

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

Please fill in your initials: ____

Your birthdate (Day, Month, Year): ____

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

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

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

Please go on to the next page

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

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

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

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

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

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

# APPENDIX 12. EUROPEAN ORGANISATION FOR RESEARCH AND TREATMENT OF CANCER QUALITY OF LIFE QUESTIONNAIRE LUNG CANCER QLQ-LC13



## EORTC QLQ - LC13

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

| During the past week : | | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|---|
| 31. | How much did you cough? | 1 | 2 | 3 | 4 |
| 32. | Did you cough up blood? | 1 | 2 | 3 | 4 |
| 33. | Were you short of breath when you rested? | 1 | 2 | 3 | 4 |
| 34. | Were you short of breath when you walked? | 1 | 2 | 3 | 4 |
| 35. | Were you short of breath when you climbed stairs? | 1 | 2 | 3 | 4 |
| 36. | Have you had a sore mouth or tongue? | 1 | 2 | 3 | 4 |
| 37. | Have you had trouble swallowing? | 1 | 2 | 3 | 4 |
| 38. | Have you had tingling hands or feet? | 1 | 2 | 3 | 4 |
| 39. | Have you had hair loss? | 1 | 2 | 3 | 4 |
| 40. | Have you had pain in your chest? | 1 | 2 | 3 | 4 |
| 41. | Have you had pain in your arm or shoulder? | 1 | 2 | 3 | 4 |
| 42. | Have you had pain in other parts of your body? | 1 | 2 | 3 | 4 |
| | If yes, where _____ | | | | |
| 43. | Did you take any medicine for pain? | | | | |
| | **1 No 2 Yes** | | | | |
| | If yes, how much did it help? | 1 | 2 | 3 | 4 |

# APPENDIX 13. LIST OF PROHIBITED CHINESE HERBAL AND PATENT MEDICINES

The following table provides examples of Chinese herbal and patent medications that may be used to treat cancer or have immune-stimulating properties. **This list is not intended to be all-inclusive.** These medications require a 14-day wash-out and should be prohibited during the study.

| **Drug Name (Chinese)** | **Drug Name (English)** |
|---|---|
| Rg3 参一胶囊 | Ginsenoside-Rg3 capsule |
| **养正消**积胶囊 | Yangzheng Xiaoji Jiaonang |
| **化癥回生口服液** | Huazheng Huisheng Koufuye |
| **十全大**补汤 | Juzentaihoto |
| 华蟾素注射液 | Cinobufacini/Huachansu injection |
| 华蟾素片/**胶囊** | Cinobufacini/Huachansu Pian/Capsules |
| **博**尔宁**胶囊** | Boerning capsule |
| **去甲斑蝥素片** | Norcantharidin Pian |
| **参丹散**结胶囊 | Shendan Sanjie Jiaonang |
| **参芪扶正注射液** | Shengqi Fuzheng Zhusheye |
| **参**莲胶囊/颗粒 | Shen Lian Jiao Nang/Ke Li |
| 吗特灵注射液 | Ma Te Ling injection |
| **回生口服液** | Hui Sheng Kou Fu Ye |
| **复方斑蝥胶囊** | Fufang Banmao Jiaonang |
| **复方**红豆杉胶囊 | Fufang Hongdoushan Jiaonang |
| **复方苦参注射液** | Fufang Kushen Zhusheye |
| **天仙胶囊** | Tian Xian capsule |
| **奇宁注射液** | Qining injection |
| **威麦宁胶囊** | Weimaining Jiao Nang |
| **安**尔欣注射液 | Anerxin/Ginseng polysaccharide injection |
| **安康欣胶囊** | Ankangxin Jiaonang |
| **安替可胶囊** | Antike capsule |
| **岩舒注射液** | Yanshu injection |
| **平消片/胶囊** | Ping Xiao Pian/Jiao Nang |
| **康力欣胶囊** | Kanglixin Jiaonang |

| Drug Name (Chinese) | Drug Name (English) |
|---|---|
| 康艾注射液 | Kang'ai Zhusheye |
| 康莱特注射液 | Kanglaite Injection |
| 康莱特软胶囊 | Kanglaite Soft Capsules |
| 慈丹胶囊 | CIDAN Capsule |
| 槐耳颗粒 | Huaer Keli |
| 海生素注射液 | Haishengsu injection |
| 消癌平丸/片/胶囊/颗粒 | Xiaoaiping Wan/Pian/Jiao Nang/Ke Li |
| 消癌平注射液 | Xiaoaiping Zhusheye |
| 牛黄醒消丸 | Niuhuang Xingxiao pill |
| 猪苓多糖注射液 | Polyporus polysaccharide injection |
| 白花蛇舌草注射液 | Hedyotis Dissusa wild injection |
| 紫龙金片 | Zi Long jin pian |
| 肝复乐片/胶囊 | Ganfule Jiaonang/GFL tablet |
| 肿节风片 | Zhongjiefeng tablet |
| 胃复春片 | Weifuchun pill |
| 艾迪注射液 | Ai Di Zhu She Ye |
| 芪珍胶囊 | Qizhen Jiaonang |
| 莪术油注射液 | Zedoary turmeric oil injection |
| 金复康口服液 | Kanglixin Jiaonang |
| 金蒲胶囊 | Jinpu capsule |
| 金龙胶囊 | Jinlong Capsules |
| 香菇多糖 | Lentinan |
| 鸦胆子油乳注射液 | Yadanzi/Brucea javanica Youru Zhusheye |
| 鸦胆子油软胶囊/口服乳液 | Yadanziyou Ruan jiao nang/Kou Fu Ru Ye |

Terminology list: Pian = tablet; Jiao Nang/Jiaonang = capsule; Ke Li/Keli = granules; Zhue She ye/Zhusheye = injections; Kou Fu Ye/koufuye = oral liquid; Wan = Pill/bolus; He Ji/Heji = mixture; Gao = ointment.

[redacted]

| | |
|---|---|
| Approval with eSignature | [redacted] |

[redacted]

Approved Date 1/30/2024

[redacted]