CLINICAL STUDY PROTOCOL

TITLE PAGE

Protocol Title:	A Randomized, Open-Label, Multicenter, Phase 2, Umbrella Study to Evaluate the Preliminary Efficacy, Safety, and Pharmacodynamics of Tislelizumab Monotherapy and Multiple Tislelizumab-based Immunotherapy Combinations With or Without Chemotherapy as Neoadjuvant Treatment in Chinese Patients with Resectable Stage II to IIIA Non-Small Cell Lung Cancer
Protocol Identifier:	BGB-LC-202
Phase:	2
NCT Number	NCT05577702
Investigational Product(s):	Tislelizumab (BGB-A317) and other investigational agents
Indication:	Neoadjuvant treatment for resectable Stage II to IIIA non-small cell lung cancer
Sponsor:	BeiGene, Ltd. c/o BeiGene USA, Inc. 1840 Gateway Drive, 3rd Floor San Mateo, CA 94404 USA
Sponsor Medical Monitor:	[redacted] Telephone: [redacted] Email: [redacted]
Original Protocol Version 0.0:	18 July 2022
Protocol Amendment Version 1.0:	10 November 2022
Protocol Amendment Version 2.0:	18 July 2023

Confidentiality Statement

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FINAL PROTOCOL APPROVAL SHEET

A Randomized, Open-Label, Multicenter, Phase 2, Umbrella Study to Evaluate the Preliminary Efficacy, Safety, and Pharmacodynamics of Tislelizumab Monotherapy and Multiple Tislelizumab-based Immunotherapy Combinations With or Without Chemotherapy as Neoadjuvant Treatment in Chinese Patients with Resectable Stage II to IIIA Non-Small Cell Lung Cancer

BeiGene, Ltd., Approval:

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

INVESTIGATOR SIGNATURE PAGE

Protocol Title: A Randomized, Open-Label, Multicenter, Phase 2, Umbrella Study to Evaluate the Preliminary Efficacy, Safety, and Pharmacodynamics of Tislelizumab Monotherapy and Multiple Tislelizumab-based Immunotherapy Combinations With or Without Chemotherapy as Neoadjuvant Treatment in Chinese Patients with Resectable Stage II to IIIA Non-Small Cell Lung Cancer

Protocol Identifier: BGB-LC-202

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 Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd., or one of its affiliates.

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

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

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

SYNOPSIS

Name of Sponsor/Company: BeiGene, Ltd.
Investigational Medicinal Product(s): Tislelizumab (BGB-A317) and other investigational agents
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Protocol Identifier: BGB-LC-202
Phase of Development: 2
Number of Patients: In the current protocol, approximately 120 patients will be enrolled. Roughly 60 patients with tumor programmed death protein ligand-1 (PD-L1) expression ≥ 50% will be randomly assigned into Substudy 1 including Arm 1A (tislelizumab monotherapy), Arm 1B (tislelizumab in combination with ociperlimab), and Arm 1C (LBL-007 in combination with tislelizumab) in a 1:1:1 randomization ratio. Roughly 60 patients with tumor PD-L1 expression < 50% will be randomly assigned into Substudy 2 including Arm 2A (tislelizumab in combination with chemotherapy) and Arm 2C (LBL-007 in combination with tislelizumab and chemotherapy) in a 1:2 randomization ratio. With the addition of other investigational agents in combination with tislelizumab over the course of the study, the patient number and randomization ratio can be adjusted.
Study Centers: Approximately 14 centers in China
Study Objectives and Endpoints: **Efficacy Objectives and Endpoints:**

Objectives	**Endpoints**
To evaluate the major pathological response (MPR) rate as assessed by the Blinded Independent Pathology Review (BIPR) in patients receiving investigational agents as neoadjuvant treatment	• The MPR rate as assessed by the BIPR and defined as the proportion of patients with ≤ 10% residual viable tumor in the resected primary tumor and all resected lymph nodes
To evaluate the pathological complete response (pCR) rate of neoadjuvant treatment with investigational agents as assessed by the BIPR	• The pCR rate as assessed by the BIPR and defined as the proportion of patients with absence of residual tumor in the resected primary tumor and all resected lymph nodes

To evaluate the survival related endpoints including event-free survival (EFS), overall survival (OS), disease-free survival (DFS), and milestone endpoints	• EFS is defined as the time from randomization until any of the following events, whichever occurs first: radiographic disease progression that precludes definitive surgery, local or distant recurrence, as assessed by investigator per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, or death due to any cause. The 1-year and 2-year EFS rates will be provided as milestone endpoints. • OS is defined as the time from the date of randomization to the date of death due to any cause. The 1-year and 2-year OS rates will be provided as milestone endpoints. • DFS is defined as the time from the first date of no disease (ie, patients who underwent margin-negative [R0] resection) to local or distant recurrence, as assessed by the investigator according to RECIST v1.1, or death due to any cause, whichever occurs first. The 1-year and 2-year DFS rates will be provided as milestone endpoints.

Safety Objectives and Endpoints:	
Objectives	**Endpoints**
To assess the safety and tolerability of neoadjuvant treatment with investigational agents	• Incidence and severity of treatment-emergent adverse events, including serious adverse events and immune-mediated adverse events (imAEs), with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v5.0)
To assess the feasibility of surgery in patients receiving neoadjuvant treatment with investigational agents	• Proportion of patients who undergo surgical resection within a scheduled period after receiving any dose of investigational agents, delayed or canceled surgery, duration of surgery and surgical approach
Pharmacodynamic/Exploratory Objectives and Endpoints:	
Objectives	**Endpoints**
To evaluate intratumoral, blood-based or draining lymph node-based pharmacodynamics, prognostic biomarkers, and response- or resistance-associated biomarkers seen with neoadjuvant treatment with investigational agents	• Biomarkers assessed in baseline and post-treatment tumor tissue, blood, or draining lymph node samples, which include: - Immune cell quantification and phenotyping via multiplex immunohistochemistry or flow cytometry - Gene expression profile - Gene mutations/tumor mutation burden (TMB)/microsatellite instability (MSI) - T-cell receptor (TCR) profile - Soluble proteins such as cytokines/chemokines - Circulating tumor DNA (ctDNA) or minimal residual disease (MRD) - Target or ligands expression of each investigational agent
To characterize the pharmacokinetics (PK) of the investigational agents	• Serum or plasma concentrations of the investigational agents at specified timepoints
To assess the host immunogenicity to investigational protein therapeutics	• Immunogenic responses to investigational protein therapeutics, evaluated through detection of antidrug antibodies (ADAs)

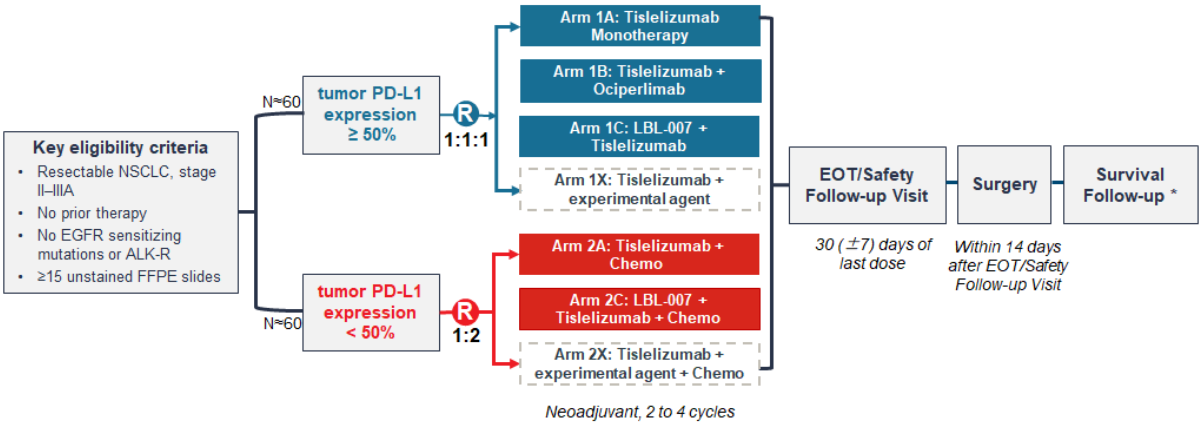
Study Design:

This is a randomized, open-label, multicenter, Phase 2, umbrella study to evaluate the preliminary efficacy, safety, and pharmacodynamics of tislelizumab as monotherapy and in combination with other investigational agents as neoadjuvant treatment in Chinese patients with resectable Stage II to IIIA non-small cell lung cancer (NSCLC).

The study is designed with the flexibility of adding treatment arms as new treatments become available or discontinuing treatment arms that demonstrate minimal clinical activity or unacceptable toxicity, and of modifying the patient population (eg, regarding biomarker status). In the current protocol, Substudy 1 includes Arm 1A (tislelizumab monotherapy), Arm 1B (tislelizumab in combination with ociperlimab), and Arm 1C (LBL-007 in combination with tislelizumab) in patients with tumor PD-L1 expression ≥ 50%; Substudy 2 includes Arm 2A (tislelizumab in combination with chemotherapy) and Arm 2C (LBL-007 in combination with tislelizumab and chemotherapy) in patients with tumor PD-L1 expression < 50%. New tislelizumab-based combination arm(s) may be added in accordance with emerging preclinical or clinical evidence via a protocol amendment.

The total number of patients will depend on the number of experimental arms and the timing when they are added to the study. Arm 1A and Arm 2A may stay open with the corresponding randomization ratio whenever there is at least one combination arm open for enrollment. With the addition of new investigational agents, the patient number and randomization ratio will be adjusted based on the number of experimental arms that are open for enrollment (eg, if an arm is added or enrollment in an arm is suspended for pending analysis of results from the preliminary phase).

The study schema is presented below:



Abbreviations: ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; EOT, End-of-Treatment; FFPE, formalin-fixed paraffin-embedded; NSCLC, non-small cell lung cancer; PD-L1, programmed death protein ligand-1; R, randomization ratio.
*Tumor assessments should be conducted per protocol until disease recurrence or progression that precludes definitive surgery, initiation of new anticancer therapy except the prespecified adjuvant therapy, withdrawal of consent, death, loss to follow-up, or study termination by the sponsor, whichever occurs first. Survival status should be followed per protocol until death, loss to follow-up or the end of study.

Neoadjuvant treatment:

Eligible patients will be assigned randomly in a fixed ratio into one of the active treatment arms.

Substudy 1:

In the current version protocol, eligible patients with tumor PD-L1 expression ≥ 50% will be randomized in a 1:1:1 ratio to 1 of the following treatment arms:

- Arm 1A: tislelizumab on a 3-week cycle for 2 to 4 cycles, followed by surgical resection

- Arm 1B: tislelizumab + ociperlimab on a 3-week cycle for 2 to 4 cycles, followed by surgical resection
- Arm 1C: LBL-007 + tislelizumab on a 3-week cycle for 2 to 4 cycles, followed by surgical resection

Patients randomized to Arm A, Arm B, and Arm C in the original protocol (0.0) and protocol amendment 1.0 will be mapped to Arm 1A, Arm 1B, and Arm 1C in this protocol amendment 2.0, respectively.

Substudy 2:

Eligible patients with tumor PD-L1 expression < 50% will be randomized in a 1:2 ratio to 1 of the following treatment arms:

- Arm 2A: tislelizumab + chemotherapy on a 3-week cycle for 2 to 4 cycles, followed by surgical resection
- Arm 2C: LBL-007 + tislelizumab + chemotherapy on a 3-week cycle for 2 to 4 cycles, followed by surgical resection

The following platinum-based doublet chemotherapy options are permitted for this study:

- Cisplatin/carboplatin + pemetrexed (nonsquamous)
- Cisplatin/carboplatin + paclitaxel (squamous)

For patients with tumors of mixed histology (squamous and nonsquamous), appropriate chemotherapy regimen will be decided by investigators based on the major histological components assessed by pathologists. Carboplatin can replace cisplatin per the investigator's discretion in consideration of patient's tolerability to cisplatin. The reasons for intolerability should be documented. After discontinuation from study treatment due to any reasons (completion of planned neoadjuvant treatment, adverse event, patient's withdrawal, or investigator's decision), the End-of-Treatment (EOT)/Safety Follow-up Visit should be conducted ≤ 30 days (± 7 days) after the last dose of study treatment (refer to Section 3.4 for details). Before surgery, the resectability assessment which is composed of tumor response and safety assessments will be conducted at Presurgical Visit, and the eligible patients will proceed to surgery. Based on the investigator's discretion, patients who are found to have disease progression at scheduled tumor assessments or at any time during neoadjuvant treatment or who discontinued early from neoadjuvant treatment due to intolerable AEs, patient's withdrawal, or investigator's decision may still proceed to undergo surgery if patients are assessed as likely being able to tolerate surgery and their tumor is deemed resectable and nonmetastatic.

For patients who are responding to neoadjuvant therapy but cannot proceed to surgery (eg, because of pulmonary embolism or myocardial infarction), the medical monitor should be consulted.

Surgery:

Upon completion of the neoadjuvant treatment, patients will undergo surgical resection of their tumor. Surgical specimens (primary tumor tissue and dissected lymph nodes) will be assessed for pathological response (MPR and pCR) by the BIPR and biomarker analysis will be performed.

At Presurgical Visit, the investigator will reassess the patient to reconfirm the disease resectability based on tumor response and safety assessments. The Presurgical Visit and associated assessments can be incorporated into the EOT/Safety Follow-up Visit in accordance with local institutional practice. The tumor assessment and other safety assessments at Presurgical Visit should be completed ≤ 14 days before surgery. The surgical procedure should be performed ≤ 14 days after the EOT/Safety Follow-up Visit. If surgery cannot be performed within this time window (eg, because of a prolonged AE), investigator should inform sponsor medical monitor regarding the determination of surgery beyond pre-specified time window as well as the corresponding considerations (refer to Section 5.2.2 for details).

Survival Follow-up:

During the Survival Follow-up period, based on the investigator's benefit-risk assessment for each patient, optional adjuvant regimens per local guideline are allowed after surgery. Disease recurrence status and survival status will be followed periodically during this period.

Blinded Independent Pathology Review:

Independent pathology review will be established for central review of pathologic responses. Tumor and lymph node samples will be submitted for central review. Sites will be trained before enrolling the first patient. Pathology sample acquisition guidelines and the submission process will be outlined in the Pathology Manual for the study, which will be provided by the vendors. For histologic assessment, all tumor and associated lymph node tissues should be sectioned at 1-cm intervals. For assessments of pathological response, the percentage of viable tumor cells in ≥ 1 section per centimeter of the tumor and lymph node tissue resected should be evaluated. The assessment by the BIPR will be used for reporting of the endpoints of MPR and pCR.

Study Assessments

Efficacy assessments:

MPR and pCR will be assessed by the BIPR. Each tumor assessment will include computed tomography (CT) scans (with oral/intravenous contrast, unless contraindicated) of the chest and abdomen (including liver and adrenal glands). In addition, patients will undergo whole body by positron emission tomography (PET) at screening, followed by tumor assessments by CT scans (with oral/intravenous contrast, unless contraindicated) at the EOT/Safety Follow-up Visit after neoadjuvant treatment phase. Tumor assessment at the Presurgical Visit may not be repeated if there is a standard tumor assessment per protocol performed ≤ 14 days before surgery. The first disease follow-up tumor assessment after surgery will be performed at 3 months (± 2 weeks) after surgery, then every 6 months (± 4 weeks) for the first 2 years, and then annually (± 8 weeks) thereafter. Tumor assessments must be conducted per protocol until disease recurrence or progression that precludes definitive surgery, initiation of new anticancer therapy except the prespecified adjuvant therapy, withdrawal of consent, death, loss to follow-up, or study termination by the sponsor, whichever occurs first. Tumor assessment should be performed by investigator per RECIST v1.1, and disease resectability should be assessed by attending thoracic surgeon per local guidelines and best clinical experience. Disease progression that does not preclude definitive surgery is not a criterion for tumor assessment discontinuation. Patients precluded from planned surgery for any reason except disease progression or death will continue to undergo tumor assessment every 6 weeks (± 1 week) until disease progression, death, initiation of new anticancer therapy, withdrawal of consent, loss to follow-up, or study termination by the sponsor, whichever occurs first.

Pharmacodynamic and exploratory assessments:

For biomarker evaluation, formalin-fixed paraffin-embedded (FFPE) specimens (FFPE blocks [preferred] or unstained slides) of the primary tumor and optional lymph node samples will be collected at Screening. If patients undergo surgery, representative tissue samples of the primary tumor will be collected. If accessible, a surgical lymph node sample is recommended to be provided. The surgical specimen for biomarker evaluation is optional for patients who achieve pCR after neoadjuvant treatment. Blood samples will be collected at predose on Day 1 of Cycle 1, on Day 8 of Cycle 1 and at predose on Day 1 of Cycle 2 during the first 2 cycles of the neoadjuvant treatment phase to evaluate PK and ADA biomarkers. Blood samples will also be collected at EOT/Safety Follow-up Visit, 7 days after surgery, and then at the visits for disease follow-up tumor assessment after surgery. Patients who have disease progression/recurrence will be asked to provide an optional biopsy from accessible tumor sites to explore mechanisms of resistance. Biomarker analysis (including PD-L1, immune cell quantification and phenotyping, gene expression profile, gene mutations/TMB/MSI, TCR sequencing and target or

ligands expression of each investigational agent, soluble proteins such as cytokines and chemokines, and ctDNA or MRD) will be performed.

PK samples will be collected for PK characterization of tislelizumab and/or other investigational agents. ADA samples will be collected to detect the development of any ADAs against tislelizumab and/or other investigational agents as appropriate. PK and ADA samples will be collected at times specified in the schedule of assessments.

Safety assessments:

All patients will be assessed for safety and tolerability on Day 1 of each cycle during the neoadjuvant treatment period. Patients will return to the clinic for the EOT/Safety Follow-up Visit as described in Section 3.4.

AEs will be evaluated according to the latest version of National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v5.0). After the informed consent form (ICF) has been signed but before the administration of the study treatment, only serious adverse events should be reported. After initiation of study treatment, all AEs (serious or nonserious), regardless of relationship to treatment, will be reported until either 30 days after the last dose of study treatment or until initiation of prespecified adjuvant treatment or other new anticancer therapy, whichever occurs first. Immune-mediated adverse events (serious or nonserious) should be reported until 90 days after the last dose of study treatment, regardless of whether the patient starts a new anticancer therapy or prespecified adjuvant treatment. All serious adverse events 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.

After the EOT/Safety Follow-up Visit, survival status and any additional anticancer treatment will be evaluated every 6 months (± 4 weeks) via phone contact or in-person contact.

Details about the study assessments are presented in Section 7 and in Appendix 1.

Study Duration:

The study duration varies for each individual patient. After enrollment, each patient is planned to receive neoadjuvant treatment for 2 to 4 cycles, followed by surgery; adjuvant therapy is allowed after surgery at the discretion of the investigator according to local guidelines. A survival follow-up phase is also planned for each patient. Patients have the right to discontinue from the study at any time and for any reason.

Study Population: Patients with resectable, histologically confirmed Stage II to IIIA NSCLC. In the current protocol, approximately 60 patients will be randomly assigned into Substudy 1, including Arm 1A (tislelizumab monotherapy), Arm 1B (tislelizumab in combination with ociperlimab), and Arm 1C (LBL-007 in combination with tislelizumab), for patients with tumor PD-L1 expression ≥ 50% in a 1:1:1 randomization ratio. Approximately 60 patients with tumor PD-L1 expression < 50% will be randomly assigned into Substudy 2, including Arm 2A (tislelizumab in combination with chemotherapy) and Arm 2C (LBL-007 in combination with tislelizumab and chemotherapy), in a 1:2 randomization ratio.

Key Eligibility Criteria:

Key Inclusion Criteria:

- Age ≥ 18 years on the day of signing the informed consent form
- Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1
- Histologically confirmed Stage II-IIIA NSCLC (per the Eighth American Joint Committee on Cancer/Union Internationale Contre le Cancer NSCLC staging system)
- Measurable disease as assessed by the investigator per RECIST v1.1

- Evaluation by an attending thoracic surgeon to confirm eligibility for an R0 resection with curative intent
- Adequate cardiopulmonary function to be eligible for surgical resection with curative intent assessed by investigator
- Adequate hematologic and organ function, defined by protocol-specified laboratory test results, obtained ≤ 7 days before randomization
- Patients must provide at least 15 freshly cut, unstained FFPE slides of the primary tumor, or FFPE block containing equivalent tumor tissues (preferred), for central PD-L1 evaluation during screening and other exploratory biomarker assessments. Only patients with evaluable PD-L1 status assessed by central laboratory are eligible. If local result of epidermal growth factor receptor (EGFR) mutation status (nonsquamous only) is not available, 3 additional slides for central EGFR testing are required.

Key Exclusion Criteria:

- Any prior antineoplastic therapy(ies) for current lung cancer (eg, radiotherapy, targeted therapies, ablation, or other systemic or local antineoplastic treatment)
- Patients with large cell neuroendocrine carcinoma (LCNEC)
- Known EGFR sensitizing mutations and/or anaplastic lymphoma kinase (ALK) rearrangement
- The presence of locally advanced unresectable NSCLC regardless of stage or metastatic disease. Mediastinal lymph node samples are required for clinical staging to assess nodal involvement in patients with contralateral mediastinal adenopathy on CT scan.
- Any condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone or equivalent) or other immunosuppressive medications ≤ 14 days before randomization
  - Adrenal replacement steroids (dose ≤ 10 mg daily of prednisone or equivalent); topical, ocular, intra-articular, intranasal, or inhaled corticosteroid with minimal systemic absorption; and short course (≤ 7 days) of corticosteroid prescribed prophylactically or for the treatment of a nonautoimmune condition are permitted
- Active autoimmune diseases or history of autoimmune diseases that may relapse
  - Patients with controlled type I diabetes, hypothyroidism only requiring hormone replacement, controlled celiac disease by diet alone, skin diseases (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll
- History of interstitial lung disease, pneumonitis, or uncontrolled lung diseases including pulmonary fibrosis, acute lung diseases, etc.
- Severe chronic or active infections requiring systemic antibacterial, antifungal, or antiviral therapy, including tuberculosis infection, etc.
  - Severe infections ≤ 4 weeks before randomization, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
  - Received therapeutic oral or intravenous antibiotics for severe chronic or active infections ≤ 2 weeks before randomization

If applicable, investigational agent-specific eligibility criteria will be provided corresponding to the respective agent-specific appendix.

Investigational Product, Dose, and Mode of Administration:

Substudy 1:

Arm 1A:

Tislelizumab: Day 1 of each 3-week cycle, administered as an intravenous infusion

Arm 1B:

Tislelizumab: Day 1 of each 3-week cycle, administered as an intravenous infusion

Ociperlimab: Day 1 of each 3-week cycle, administered as an intravenous infusion

Arm 1C:

LBL-007: Day 1 of each 3-week cycle, administered as an intravenous infusion

Tislelizumab: Day 1 of each 3-week cycle, administered as an intravenous infusion

Substudy 2:

Arm 2A:

Tislelizumab: Day 1 of each 3-week cycle, administered as an intravenous infusion

Chemotherapy: Day 1 of each 3-week cycle, Cisplatin (75 mg/m^2) (or Carboplatin area under the curve (AUC) = 5 mg/mL/min] + Pemetrexed (nonsquamous, 500 mg/m^2)/Paclitaxel (squamous, 175 mg/m^2), administered as an intravenous infusion.

Arm 2C:

LBL-007: Day 1 of each 3-week cycle, administered as an intravenous infusion

Tislelizumab: Day 1 of each 3-week cycle, administered as an intravenous infusion

Chemotherapy: Day 1 of each 3-week cycle, cisplatin (75 mg/m^2) (or carboplatin [AUC = 5 mg/mL/min)] + pemetrexed (nonsquamous, 500 mg/m^2)/paclitaxel (squamous, 175 mg/m^2), administered as an intravenous infusion.

Carboplatin can replace cisplatin per the investigator's discretion in consideration of patient's tolerability to cisplatin. The reasons for intolerability should be documented.

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

Statistical Methods:

Descriptive statistics will be used to summarize the demographic, disease characteristic, efficacy, and safety data. No statistical hypotheses are planned for this exploratory study.

Analysis sets:

- The Intent-to-Treat (ITT) analysis set includes all enrolled patients. Patients will be analyzed according to their randomized treatment arm.
- The Intent-to-Treat with tumor PD-L1 expression ≥ 50% (ITT-1) analysis set includes all enrolled patients with tumor PD-L1 expression ≥ 50% in Substudy 1. Patients will be analyzed according to their randomized treatment arm. It will be the primary analysis set for the efficacy analysis for patients with tumor PD-L1 expression ≥ 50%.
- The Intent-to-Treat with tumor PD-L1 expression < 50% (ITT-2) analysis set includes all enrolled patients with tumor PD-L1 expression < 50% in Substudy 2. Patients will be analyzed according to their randomized treatment arm. It will be the primary analysis set for the efficacy analysis for patients with tumor PD-L1 expression < 50%.
- The Safety (SAF) analysis set includes all enrolled patients who received ≥ 1 dose of neoadjuvant treatment. Patients will be analyzed according to the treatment they actually received. It will be the analysis set for the safety analyses.

- The Efficacy Evaluable (EE) analysis set includes all patients from the SAF analysis set who have completed surgery as planned; it will be used as supportive analysis set.
- The Biomarker analysis set includes all patients from the SAF analysis set who have ≥ 1 evaluable biomarker measurement; it will be used for the biomarker analysis.

Efficacy analyses:

Primary efficacy analysis of MPR rate will be based on the ITT-1 and ITT-2 analysis sets. All analyses will be descriptive. The rate of MPR along with its 95% Clopper-Pearson CI will be calculated for each arm in each analysis set. In addition, the rate difference between the tislelizumab monotherapy and other tislelizumab-based immunotherapy combinations in the ITT-1 analysis set and the rate difference between tislelizumab in combination with chemotherapy and tislelizumab in combination with LBL-007 and chemotherapy in the ITT-2 analysis set will also be provided using Fisher's exact test.

The efficacy analysis of pCR rate will be summarized similarly to the MPR rate in the ITT-1 and ITT-2 analysis sets.

DFS, EFS, and OS will be estimated using the Kaplan-Meier method in the ITT-1 and ITT-2 analysis sets. The event-free rates at selected timepoints along with 95% CI will be estimated using the Greenwood formula (Greenwood 1926). Hazard ratio and corresponding two-sided 95% CI will be estimated using a Cox proportional hazards model if necessary. Statistical methods will be described in detail in the Statistical Analysis Plan.

Safety analyses:

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

Biomarker analysis:

Exploratory biomarkers will be assessed. Analyses may examine the association between relevant biomarkers and clinically relevant outcomes including patient prognosis, response, and resistance.

Pharmacokinetic Analyses:

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

Immunogenicity Analyses:

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.

Sample size considerations:

This study is designed for the preliminary evaluation of the pharmacodynamics, safety, and efficacy of tislelizumab monotherapy and multiple tislelizumab-based immunotherapy combinations with or without chemotherapy in patients with resectable Stage II to IIIA NSCLC. It is not designed to allow explicit power and Type I error considerations, so there is no formal statistical hypothesis. Approximately 60 patients will be randomly assigned into Substudy 1, including Arm 1A (tislelizumab monotherapy), Arm 1B (tislelizumab in combination with ociperlimab), and Arm 1C (LBL-007 in combination with tislelizumab), in patients with tumor PD-L1 expression ≥ 50% in a 1:1:1 randomization ratio. Approximately 60 patients with tumor PD-L1 expression < 50% will be

randomly assigned into Substudy 2, including Arm 2A (tislelizumab in combination with chemotherapy) and Arm 2C (LBL-007 in combination with tislelizumab and chemotherapy), in a 1:2 randomization ratio. With the defined sample size, the expected 95% CI of the MPR rate difference in patients with tumor PD-L1 expression ≥ 50% between the tislelizumab-based immunotherapy combination arms and the tislelizumab monotherapy arm would be 1% to 59% if the true MPR for tislelizumab-based immunotherapy combinations arm and monotherapy arm is 70% and 40%, respectively. The expected 95% CI of the MPR rate difference in patients with PD-L1 expression < 50% between LBL-007 in combination with tislelizumab and chemotherapy arm and tislelizumab in combination with chemotherapy arm would be -11% to 41% if the true MPR for tislelizumab in combination with LBL-007 and chemotherapy arm and tislelizumab in combination with chemotherapy arm is 49% and 34%, respectively.

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
ADA	antidrug antibody
AE	adverse event
AUC	area under the curve
BGB-A1217	ociperlimab
BGB-A317	tislelizumab
BIPR	Blinded Independent Pathology Review
COVID-19	Coronavirus disease 2019
CT	computed tomography
CYP	cytochrome P-450
DFS	disease-free survival
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
EFS	event-free survival
EOT	End-of-Treatment
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HR	hazard ratio
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
imAE	immune-mediated adverse event
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intention-to-Treat
ITT-1	Intent-to-Treat with tumor PD-L1 expression ≥ 50%
ITT-2	Intent-to-Treat with tumor PD-L1 expression < 50%
MPR	major pathological response

Abbreviation	Definition
MSI	microsatellite instability
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer
NMPA	National Medical Products Administration
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
pCR	pathological complete response
PD-1	programmed death protein-1
PD-L1	programmed death protein ligand-1
PET	positron emission tomography
PK	pharmacokinetic(s)
R0	margin-negative
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
TCR	T cell receptor
TEAE	treatment-emergent adverse event
TIL	tumor-infiltrating lymphocytes
TMB	tumor mutation burden
TPS	Tumor Proportion Score
Treg	regulatory T cell
ULN	upper limit of normal

1. INTRODUCTION

1.1. Background Information on Non-Small Cell Lung Cancer and Unmet Clinical Needs

1.1.1. Background Information on Early-Stage Non-Small Cell Lung Cancer

Lung cancer is the second most commonly diagnosed cancer worldwide, with an estimated 2.2 million new cases and 1.8 million deaths in 2020. During that same year, lung cancer accounted for 1 in 10 (11.4%) cancers diagnosed and for 1 in 5 (18.0%) cancer deaths, making it the leading cause of cancer deaths in 2020 (Siegel et al 2021). Approximately 80% to 85% of lung cancers are non-small cell lung cancer (NSCLC), which includes adenocarcinoma (40%), squamous cell carcinoma (25%), and large cell carcinoma (10%). A few other subtypes of NSCLC, such as adenosquamous carcinoma and sarcomatoid carcinoma, are much less common.

The prognosis for lung cancer patients is relatively poor, although it 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). At diagnosis, about 30% of NSCLC patients have Stage II to IIIA disease. The median 5-year overall survival (OS) rate ranges from 36% to 60% of these patients (defined by the American Joint Committee on Cancer Eighth Edition [Goldstraw et al 2016]). The treatment goal for patients with resectable stage lung cancer is curing their cancer; however, up to 60% of male and up to 50% of female patients with Stage II NSCLC die within 3 years after diagnosis (Araghi et al 2021). As a single modality, surgery for early-stage or locally advanced NSCLC remains associated with high rates of recurrence (Huynh et al 2021a).

1.1.2. Current Treatment Options for Patients With Resectable NSCLC Stage II to IIIA

The most common cause of treatment failure in resectable NSCLC is tumor recurrence (Cruz et al 2017). Local recurrence is associated with poor OS. In Stage I to III NSCLC patients, the local recurrence rate after surgery was 9.4% (median follow-up time 59 months), and the most significant risk factor for local recurrence within 5 years after resection was lymph node metastasis.

The goal of neoadjuvant treatment is to achieve downstaging to enable or facilitate complete resection while preserving lung parenchyma and function to a greater extent, and for an earlier eradication of micrometastases to prevent disease recurrence (Huynh et al 2021a). In the past, chemotherapy was recommended by international treatment guidelines as neoadjuvant or adjuvant treatment for resectable NSCLC (NCCN 2022; CSCO Guidelines 2020). Despite administration of the chemotherapy preoperative treatment, the tumor recurrence and long-term benefit in event-free survival (EFS)/disease-free survival (DFS) or OS in patients with early-stage resectable NSCLC remain unsatisfactory and are associated with significant toxicity, especially hematologic toxicities which may lead to delay of surgical procedures with curative intent or impact the postoperative recovery. According to published clinical studies, the median OS ranged from 93 to 33 months, and the median DFS ranged from 48 to 32 months, and the incidence rate of hematologic toxicity of ≥ Grade 3 ranged from 40% to 85% in patients with early-stage resectable NSCLC treated with preoperative chemotherapy (Douillard et al 2006; Ou

et al 2010; Pisters et al 2010; Scagliotti et al 2012). The major pathological response (MPR) rate achieved from neoadjuvant chemotherapy was only 8.9% to 20% and pathological complete response (pCR) rate ranged from 2.2% to 4% (Hellmann et al 2014).

Anti-programmed cell death protein-1 (PD-1) therapy has emerged as an effective treatment for patients with tumors expressing varying degrees of PD-L1 (Hanna et al 2017). Anti-PD-1 and anti-PD-L1 therapies target the programmed death receptor pathway of T lymphocytes; this checkpoint has been found to be activated in cancers allowing tumors to evade the host immune system. Since the successful development of cancer immunotherapy in advanced NSCLC, creative perioperative treatment regimens containing PD-1/PD-L1 have been conducted in clinical studies recently (Table 1). With emerging data from several pivotal studies in resectable NSCLC recently, the treatment landscape for this patient population is changing. Immune checkpoint inhibitors in combination with platinum-based chemotherapy as neoadjuvant treatment followed by immune checkpoint inhibitors as adjuvant treatment are now recommended as the preferred treatment in the latest international treatment guidelines (NCCN 2023).

For the neoadjuvant treatment setting, patients with resectable NSCLC treated with neoadjuvant immunotherapy plus chemotherapy had higher rates of pathological tumor response and longer EFS compared to chemotherapy alone, which may predict clinical benefit and correlates with improved outcomes (Forde et al 2022; Wakelee et al 2023). Checkmate 816 is the first Phase 3 study to evaluate nivolumab plus chemotherapy as neoadjuvant treatment for Stage IB to IIIA disease. Preliminary result showed a statistically significant and clinically meaningful improvement in the primary endpoint of pCR rate (24% with nivolumab + platinum-doublet chemotherapy versus 2.2% with chemotherapy alone), and the benefit was consistent across disease stages, histologies, tumor mutation burden (TMB), and PD-L1 expression levels. The addition of the neoadjuvant nivolumab to chemotherapy did not impede the feasibility of surgery. The long-term follow-up data appeared that the long-term endpoint was consistently met and the study treatment resulted in a significant improvement in EFS with a 37% risk reduction compared with chemotherapy alone as neoadjuvant (median EFS: 31.6 months versus 20.8 months, hazard ratio [HR] 0.63; 95% CI 0.45 to 0.87; p=0.0052). However, the toxicity of study treatment in the Checkmate 816 study should not be overlooked: treatment-related AEs of any grade were reported in 82.4% and 88.6% of patients in the treatment arm and in the chemotherapy arm, respectively; Grade 3 or 4 treatment-related AEs were reported in 33.5% and 36.9% of patients in the treatment arm and in the chemotherapy arm, respectively (Forde et al 2021; Forde et al 2022). Chemotherapy plus nivolumab is strongly recommended by international treatment guidelines as neoadjuvant treatment for resectable NSCLC, especially for those patients with tumors ≥ 4 cm or node positive and no contraindications to immune checkpoint inhibitors (NCCN 2023). Nivolumab plus platinum-based chemotherapy was granted approval by China National Medical Products Administration (NMPA) as neoadjuvant treatment for operable NSCLC patients in January 2023.

KEYNOTE-671 is a randomized, double-blind Phase 3 trial evaluating neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab as a single agent versus placebo plus neoadjuvant chemotherapy followed by adjuvant placebo in patients with resectable Stage II-IIIB NSCLC. Compared with neoadjuvant chemotherapy alone, adding perioperative pembrolizumab was associated with a significant improvement in EFS (HR 0.58;

95% CI: 0.46 to 0.72; p < 0.001). Patients who received pembrolizumab plus neoadjuvant chemotherapy were also significantly more likely than those who received placebo plus neoadjuvant chemotherapy to attain significantly better MPR (30.2% versus 11.0%; p < 0.0001) and pCR (18.1% versus 4.0%; p < 0.0001) (Wakelee et al 2023).

The AEGEAN study is a randomized, double-blind, multi-center, placebo-controlled, global Phase 3 trial evaluating durvalumab as perioperative treatment for patients with resectable Stage IIA-IIIB NSCLC. Patients treated with the durvalumab plus chemotherapy regimen before and after surgery showed a 32% reduction in EFS versus chemotherapy alone (HR 0.68; 95% CI: 0.53 to 0.88; p = 0.003902). Treatment with neoadjuvant durvalumab plus chemotherapy before surgery resulted in a pCR and MPR rate of 17.2% and 33.3% versus 4.3% and 12.3% for patients treated with neoadjuvant chemotherapy alone (Heymach et al 2023).

The Neotorch study is a randomized, double-blind, placebo-controlled, Phase 3 trial evaluating the efficacy and safety of perioperative toripalimab plus chemotherapy followed by toripalimab maintenance versus chemotherapy alone in patients with resectable Stage II and III NSCLC. With a median follow-up of 18.3 months, interim analysis from the Neotorch trial showed a significant improvement in EFS for patients treated with toripalimab arm (HR 0.40; 95% CI: 0.277 to 0.565; p < 0.0001). In combination with perioperative chemotherapy, toripalimab demonstrated more favorable pCR and MPR of 24.8% versus 1.0% and 48.5% versus 8.4% compared to chemotherapy alone, respectively (Lu et al 2023).

For the adjuvant treatment setting, the IMpower 010 study is a Phase 3 clinical study to investigate adjuvant therapy with atezolizumab versus best supportive care in patients with early-stage NSCLC who had received radical resection followed by adjuvant platinum-based chemotherapy. The results showed that DFS was significantly improved in the study treatment arm compared with best supportive care (HR 0.66; 95% CI: 0.5 to 0.88; p = 0.0039) in patients with resected Stage II to IIIA NSCLC and PD-L1 of 1% or more, and the safety profile was tolerable with an incidence of Grade 3 and 4 treatment-related adverse events of 11% (Felip et al 2021). In March 2022, China NMPA officially approved the use of Atezolizumab as an adjuvant therapy after surgical resection in patients with Stage II-IIIA resectable NSCLC who were evaluated to be PD-L1 positive (Tumor Proportion Score [TPS] ≥ 1%).

Keynote 091 is a multicenter, randomized, triple-blind, placebo-controlled trial in patients with completely resected Stage IB-IIIA NSCLC regardless of tumor PD-L1 expression. Pembrolizumab was shown to significantly improve DFS versus placebo. Median DFS was 53.6 months (95% CI: 39.2 to not reached) in the pembrolizumab group versus 42.0 months (95% CI: 31.3 to not reached) in the placebo group (HR 0.76; 95% CI: 0.63-0.91; p = 0.0014). Atezolizumab and pembrolizumab are both recommended for patients with completely resected NSCLC (Atezolizumab in patients with PD-L1 ≥1%) and negative for EGFR exon 19 deletion or exon 21 L858R mutations or ALK rearrangements who received previous adjuvant chemotherapy and with no contraindications to immune checkpoint inhibitors (NCCN 2023).

Apart from above pivotal studies, some early Phase 1/2 studies exploring neoadjuvant immunotherapy in NSCLC also showed promising outcomes especially in PD-L1 high population, compared with neoadjuvant regimens containing chemotherapy, the PD-1/PD-L1 monotherapy or in combination with other immunotherapy showed notably better safety profile in terms of ≥ Grade 3 treatment-emergent adverse events (TEAEs) (4.5-13% versus 32.3-44.9%)

(Table 1) , which supports the notion that PD-1/PD-L1 monotherapy or in combination with other immunotherapy as neoadjuvant in resectable NSCLC is expected to bring comparable clinical benefit with less safety concern compared with regiments containing chemotherapy in PD-L1 high population.

Table 1: Preliminary Efficacy and Safety Data of PD-1 Pathway-Targeting Immunotherapy or in combination with chemotherapy in Resectable NSCLC Neoadjuvant Treatment

Study name	Phase	Population	Treatment(s)	N	MPR rate	pCR rate	≥ Gr.3 TRAE
Checkmate 159 (Forde et al 2018)	2	I-IIIA	Nivolumab	21	45%	10%	4.5%
NEOSTAR (Cascone et al 2021)	2	I-IIIA	Nivolumab; Nivolumab + ipilimumab	23 21	22% 38%	9% 29%	13% 10%
LCMC3 (Lee JM et al 2021)	2	I-IIIB	Atezolizumab	181	21%	7%	6%
ChiCTR-OIC-17013726 (Gao et al 2020)	1b	IA-IIIB	Sintilimab	40	40.5%	16.2%	10%
NEOpredict-Lung (Schuler et al 2022)	2	I-IIIA	Nivolumab, Nivolumab + Relatlimab	60	27% 30%	13% 17%	N/A
Checkmate 816 (Forde et al 2022)	3	IB-IIIA	Chemotherapy, Nivolumab + Chemotherapy	358	8.9% 36.9%	2.2% 24%	36.9% 33.5%
AEGEAN (Heymach et al 2023)	3	II-IIIB	Chemotherapy, Durvalumab + chemotherapy	799	12.3% 33.3%	4.3% 17.2%	33.1% 32.3%
KEYNOTE-671 (Wakelee et al 2023)	3	II-IIIB	Chemotherapy, Pembrolizumab + Chemotherapy	797	11% 30.2%	4% 18.1%	37.3% 44.9%
Neotorch (Lu et al 2023)	3	II-IIIB	Chemotherapy, Toripalimab + chemotherapy	404	8.4% 48.5%	1% 24.8%	N/A

Abbreviations: Gr, grade; MPR, major pathological response; N/A, not applicable; NSCLC, non-small cell lung cancer; pCR, pathological complete response; PD-1, programmed death protein-1; TRAE, treatment related adverse event.

1.1.3. Unmet Medical Need

Overall, early-stage NSCLC, despite being potentially curable, has a high risk of relapse, or death due to disease progression and unsatisfying current standard of care; exploring neoadjuvant containing novel therapeutic agents is still needed in order to retain the efficacy outcome and minimize safety risk, which may provide more clinical options for patients with early-stage resectable NSCLC.

1.1.4. Background Information on Investigational Agents

Background information on each investigational agent is presented in the appendices:

- Tislelizumab: Appendix 11
- Ociperlimab: Appendix 12
- LBL-007: Appendix 13
- Chemotherapy: Appendix 14

1.2. Study Rationale

1.2.1. Rationale for Patient Population and Treatment Setting

This study will enroll patients with resectable, histologically confirmed Stage II to IIIA NSCLC as determined at screening. In early-stage NSCLC, the 5-year OS rate is only 19% to 43% (Goldstraw et al 2007) with disease recurrence often seen in 30% to 70% of patients who undergo surgical resection (Ponn et al 2005). A rational approach to improve survival in these patients is to eradicate micrometastatic disease and to minimize the risk of relapse with adjuvant or neoadjuvant chemotherapy and immunotherapy. The currently available standard of care in China, including neoadjuvant chemotherapy plus immunotherapy with adjuvant immunotherapy are provided in Section 1.1.2. Despite improvements resulting from the addition of neoadjuvant immunotherapy to chemotherapy agent, the high toxicity should still not be overlooked. Therefore, exploring neoadjuvant therapy containing novel therapeutic agents is still needed in order to retain the efficacy outcome while minimizing the safety risk, which may provide more clinical options for patients with early-stage resectable NSCLC.

Patients with PD-L1 low expression

With nivolumab plus platinum-based chemotherapy approval by China NMPA as neoadjuvant treatment for operable NSCLC patients and results from several other Phase 3 studies of anti-PD-1/PD-L1 inhibitors in combination with chemotherapy as neoadjuvant being conducted in resectable NSCLC, which showed a promising pCR/MPR improvement, neoadjuvant immunotherapy plus chemotherapy is now a preferred regimen over neoadjuvant chemotherapy alone.

Patients with PD-L1 high expression

Previous studies have established the predictive value of tumor PD-L1 expression for evaluating efficacy of anti-PD-1 and anti-PD-L1 therapy in the advanced-stage NSCLC (Borghaei et al 2015, Fehrenbacher et al 2016, Herbst et al 2014, Herbst et al 2016, Rosenberg et al 2016, Topalian et al 2012). Pembrolizumab monotherapy has been approved by the United States (US) Food and Drug Administration (FDA) as the first-line treatment of patients with NSCLC expressing a PD-L1 TPS ≥ 50% in 2016. The approval was expanded to TPS ≥ 1% in 2019 (Keytruda [pembrolizumab] US prescribing information 2021). In February 2021, the FDA approved another checkpoint inhibitor monotherapy, cemiplimab-rwlc, for the first-line treatment of patients with advanced NSCLC whose tumors have high PD-L1 expression (TPS > 50%), which suggests that regimens containing PD-1 inhibitor without chemotherapy may be a potential choice for NSCLC patients with high PD-L1 expression.

Although anti-PD-1/PD-L1 inhibitors in combination with chemotherapy as neoadjuvant showed a promising pCR/MPR improvement, they also showed high toxicity with ≥ Grade 3 AEs assessed as related to the study treatment ranging between 32.3% to 44.9%. On the other hand, several Phase 1b-2 studies evaluating PD-1/PD-L1 inhibitors as monotherapy or in combination with another immunotherapeutic regimen as neoadjuvant in a similar population showed a comparable pCR/MPR, especially in PD-L1 high population, with the incidence of treatment-related adverse events of ≥ Grade 3 only between 4.5% and 13% (Table 1), which suggests that PD-1/PD-L1 monotherapy or in combination with other immunotherapy as neoadjuvant in resectable NSCLC is expected to bring comparable clinical benefit with fewer safety concerns compared with regimens containing chemotherapy in PD-L1 high population.

NEOpredict-Lung was a Phase 2 study that looked at the use of relatlimab plus nivolumab versus nivolumab alone in patients with resectable NSCLC. A total of 60 patients were enrolled in this study and were randomized in a 1:1 ratio to receive nivolumab or in combination with relatlimab prior to surgical resection. MPR was 27% in nivolumab arm versus 30% in nivolumab plus relatlimab arm and was 40% versus 71% in PD-L1 TPS ≥ 50% patients in the 2 arms (Schuler et al 2022). Administering the LAG-3 targeted antibody with PD-1 antibody prior to resection could offer additional clinical benefit for patients with resectable NSCLC, especially patients with PD-1 high expression, which indicates that PD-1 inhibitor or combined immunotherapy regimens containing PD-1 inhibitor may be a potential choice for resectable NSCLC patients, meriting further research on preoperative immune checkpoint inhibitor therapy in the neoadjuvant setting. Besides that, utilizing novel combinations containing other immunotherapeutic agents to improve PD-1/PD-L1 antibody monotherapy is also considered as a promising strategy to identify an optimal neoadjuvant treatment, which could further enhance the recognition and elimination of tumor cells by the host immune system and reduce the impact of the immunosuppressive tumor microenvironment.

1.2.2. Rationale for Tislelizumab or Tislelizumab-Based Immunotherapy Combinations as Neoadjuvant Treatment in Patients With NSCLC

Cancer cells have been found to have intrinsic mechanisms bypassing every step in the cancer immunity cycle to evade anticancer immunity. Across the cancer-immunity cycle, diverse mechanisms of immune escape have been reported, including defective cancer antigen presentation, immune checkpoint mediated exhaustion, decreased sensitivity to immune killing, and enriched immunosuppressive cells/cytokines (Gao et al 2017, Huang et al 2016, Koyama et al 2016, Shayan et al 2016, Topalian et al 2015, Zhu et al 2021). Overcoming above pathways of tumor immune escape may provide a mechanism justification to explore different kinds of immunotherapies or combinations. Several preclinical studies have shown that immunotherapy combinations may bring an additional synergistic effect, eg, PD-1/PD-L1 in combination with TIGIT or LAG-3 (Zhu et al 2021), and in combination therapies are currently being extensively explored in emerging clinical studies to target multiple defects along the immunity cycle and cancer intrinsic alterations and improve the anticancer efficacy.

NSCLC histology is associated with a high frequency of mutation with multiple novel tumor antigens, which may make it more sensitive to immune recognition (Brahmer et al 2010, Iwai et al 2002). Regarding to neoadjuvant treatment for early-stage NSCLC, immunotherapy allows the activated T cells to release cytokines, perforins, granzymes, and others to kill tumor cells. In

terms of mechanisms involved, when the tumor volume is relatively large, antigen presentation cell bears a relatively large antigen load, which elicits a stronger antitumor T cell response, as well as immune memory formation. Therefore, neoadjuvant immunotherapy could theoretically be better than adjuvant immunotherapy and may yield an even greater survival long-term benefit, which is supported by preclinical studies: in animal models, compared with adjuvant immunotherapy, neoadjuvant immunotherapy resulted in better ability to eradicate distant metastases after primary tumor resection, prevent metastasis and lead to greater prolongation of median survival time (Cascone et al 2018, Liu et al 2016).

Breakthrough results from treatment with immune checkpoint inhibitors such as anti-PD-1/PD-L1 antibodies in patients with many types of solid tumors have paved the way to a new era of cancer immunotherapy, leading to a paradigm shift in cancer treatment. The up-regulation of immune checkpoint ligands such as PD-L1 on tumor cells can be induced by tumorigenic alterations and can lead to a prominent immune evasion mechanism. In NSCLC tumors, PD-L1 expression is relatively enriched, with PD-L1 positivity rates ranging from 24% to 60% (Yu et al 2016), and it is associated with poor survival. Since the successful development of cancer immunotherapy, several PD-1/PD-L1 regimens as antibody monotherapy and in combination with chemotherapy have been approved by FDA as standard of care for advanced NSCLC (Gandhi et al 2018, Herbst et al 2020, Langer et al 2016, Reck et al 2016, West et al 2019). The COAST study, a Phase 2, umbrella study investigating efficacy and safety of durvalumab monotherapy or durvalumab-based novel combinations in unresectable, Stage III NSCLC, demonstrated the improved clinical outcomes with durvalumab-based novel combinations, indicating the additional immunomodulation of PD-L1 in combination with other novel biological pathways including anti-CD73 and anti-NKG2A may bring promising clinical benefit (Herbst et al 2022).

Results from several clinical studies including BGB-A317-001, BGB-A317-102, BGB-A317-303, BGB-A317-304 and BGB-A317-307 revealed that tislelizumab and tislelizumab in combination with standard-of-care chemotherapy regimens were generally well tolerated and had favorable efficacy in patients with advanced NSCLC, 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. Besides that, the BGB-A317-315 study, a Phase 3 pivotal study investigating tislelizumab or placebo in combination with chemotherapy as neoadjuvant treatment followed by adjuvant tislelizumab or placebo in patients with Stage II or IIIA NSCLC is in progress. The study already met its primary endpoint (MPR) and key secondary endpoint (pCR) at interim analysis. Significant improvement in MPR and pCR was observed for the tislelizumab in combination with chemotherapy group versus placebo in combination with chemotherapy group. No unexpected safety signals have been observed. Taken together, this evidence supports that tislelizumab could serve as the backbone in novel combinations based on the assessment of its safety and efficacy profile.

The particular rationale of tislelizumab or tislelizumab-based combinations is presented in the investigational agent-specific appendix.

1.2.3. Rationale for Study Design

The BGB-LC-202 study is designed as an umbrella study. Usually, an umbrella study is designed with multiple substudies which may have a similar objective. The study design involves coordinated efforts and a highly efficient manner of initiating/terminating investigational agents according to emerging nonclinical or clinical data, to evaluate multiple investigational agents in the same treatment setting of one disease subtype, as it is supported by FDA guidelines in general, considering the potential advantages in term of flexibility and efficiency in clinical development (US FDA 2022). In comparison, executing multiple individual Phase 2 studies would require longer time and a greater number of patients.

Tislelizumab monotherapy or tislelizumab-based combination therapy arms may be closed or opened during the study based on internal available data from the study or external emerging data.

1.2.4. Rationale for Selection of Investigational Agents

The rationales for selection of investigational agents and corresponding dose selection for each investigational agent are provided in the following agent-specific appendices as follows:

- Tislelizumab: Appendix 11
- Ociperlimab: Appendix 12
- LBL-007: Appendix 13
- Chemotherapy: Appendix 14

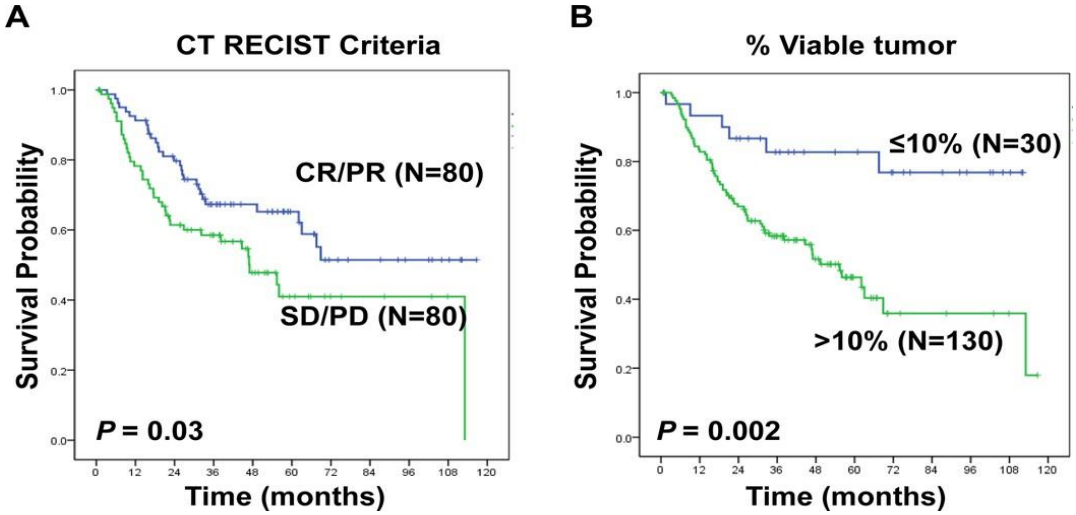
1.2.5. Rationale for Major Pathological Response and Pathological Complete Response as Efficacy Endpoints

In its accelerated approval process, the FDA has adopted a definition of surrogacy, which requires that a surrogate endpoint be reasonably likely to predict clinical benefit (Johnson et al 2003). Pathological response after surgical resection of NSCLC has been proposed as a surrogate endpoint based on 3 findings: 1) pathological response strongly correlates to OS; 2) pathological response is reflective of neoadjuvant treatment; and 3) the degree of pathological response correlates with the degree of OS benefit (Hellmann et al 2014).

The endpoint of pCR, defined as absence of residual tumor in the resected primary tumor and all resected lymph nodes, was widely utilized as an independent or co-primary survival surrogate endpoint in most of recent Phase 3 clinical studies of neoadjuvant treatment in the NSCLC disease field (Huynh et al 2021b). A prospective study of neoadjuvant chemotherapy in NSCLC patients showed a 5-year survival of 54% in patients with Stage IIIA disease who achieved pCR, which is striking when compared with the historical standard (Pisters et al 1993). A randomized, long-term follow-up study which included 179 patients with Stage Ib-IIIa NSCLC treated with neoadjuvant chemotherapy showed that 11% of patients achieved a pCR and had a relative risk of death of 0.42 ($p<0.001$) compared with patients without pCR (Depierre et al 2002). The surrogate endpoint of pCR is adopted from regulatory agencies such as the FDA as an acceptable endpoint for accelerated approval in breast cancer (US FDA 2012). Taken together, this evidence supports the notion that pCR as surrogate endpoint may reasonably predict survival benefit in patients with resectable NSCLC under the neoadjuvant treatment setting.

MPR, defined as ≤10% residual viable tumor tissue, was also proposed as a survival surrogate for patients with resectable NSCLC receiving neoadjuvant chemotherapy treatment (Hellmann et al 2014). This is based on studies in which investigators, in acknowledgment of the rarity of pCR in NSCLC, considered other definitions of pathological response, including residual viable tumor as a surrogate survival endpoint. Junker et al performed pathological analysis of 40 tumors from patients with Stage IIIA and IIIB disease who were given sequential neoadjuvant chemotherapy treatment, chemoradiotherapy, and surgical resection (Junker et al 1997). Patients with ≤ 10% residual tumor in this group had a median survival of 36 months, while patients who had > 10% residual viable tumor tissue had a median survival of 14 months. A retrospective study from the MD Anderson Cancer Center by William and colleagues (William et al 2013) showed that in 160 patients who received neoadjuvant platinum-based doublet chemotherapy, MPR was a stronger predictor of OS than the clinical Response Evaluation Criteria in Solid Tumors (RECIST) response (Figure 1).

Figure 1: Overall Survival by Clinical Response and by Pathological Response



Abbreviations: CT RECIST, computed tomography Response Evaluation Criteria in Solid Tumors; CR/PR, complete response/partial response; SD/PD, stable disease/progressive disease (William et al 2013).

Thus, the sponsor believes that there is significant rationale for the use of pCR and MPR because of their correlation to the magnitude of improvement in OS, with the potential to increase the efficacy benefit of clinical studies and accelerate new treatment options for NSCLC patients.

1.2.6. Biomarker Strategy Rationale

Biomarker analyses will be performed to explore pharmacodynamics of tislelizumab alone or in combination with other investigational agents, as well as the association of biomarkers with patient prognosis, response, and potential resistance to the treatment.

Biomarker analyses in tumor and draining lymph node tissues will include analysis of immune cell quantification and phenotyping, gene expression profiling (GEP), gene mutations/TMB/microsatellite instability (MSI) status, T-cell receptor (TCR) sequencing, and target or ligands expression in each investigational arm at baseline, surgery, and/or disease progression/reoccurrence. In addition, blood-based biomarkers will include periphery immune cell quantification and phenotype change, concentration, and dynamic changes of soluble

proteins such as cytokines/chemokines in blood, circulating tumor DNA (ctDNA) or minimal residual disease (MRD), and TCR sequencing.

Accumulating evidence from mouse models and human patients with cancer has demonstrated the importance of the immune system in recognizing and eliminating transformed malignant cells, as well as the contradictory role in promoting tumor progression by immune system (Yang 2015). Therefore, multiple immunotherapy strategies have been proposed to harness the immune system to battle cancer, including activating antitumor effector cells and/or removing immunosuppressive components. Therefore, the pharmacodynamics will be studied mainly focusing on phenotype changes of immune cells (including effector T cells, regulatory T cells [Tregs], NK cells, myeloid cell, etc) in the tumor microenvironment, peripheral blood, and draining lymph node during treatment based on mechanisms of action of each investigational agent (see the agent-specific appendix). Soluble proteins like cytokines/chemokines released from immune cells, as well as target or ligands of each investigational agent will be investigated.

In addition to immune phenotyping, gene expression profile analysis offers an opportunity to dissect the tumor microenvironment (TME), a crucial mediator of cancer progression and therapeutic outcome. For example, 29 gene signatures covering both anti- and pro-tumor immune cells, angiogenesis/fibrosis and malignant cell properties classified tumors into four distinct TME subtypes and correlated the subtypes with patient response to immunotherapy in multiple cancers (Bagaev et al 2021). Other biomarkers such as TMB (Cristescu et al 2018) may reflect tumor-intrinsic neoantigen generation and the capability to evoke the immune response. In the Phase 2 clinical study of nivolumab neoadjuvant therapy in early-stage NSCLC, a higher TMB level was observed in patients with MPR. Therefore, TMB along with the gene mutations and MSI status should be further explored to understand the clinically relevant genetic biomarkers.

More recently, ctDNA or MRD derived from peripheral blood has shown incredible potential as a highly sensitive and specific cancer biomarker. Particularly, studies of the anti-PD-L1 antibody durvalumab in patients with NSCLC or urothelial carcinoma revealed a correlation between quantitative variations in ctDNA levels and tumor response or patient outcome (Kuziora et al 2017). Therefore, ctDNA of blood samples will be analyzed in this study to provide valuable information on several aspects of exploratory biomarkers, such as prognosis, detection of theranostic mutations, predictive biomarkers, early detection of treatment efficacy or disease relapse, and potential mechanisms of resistance (Cabel et al 2018).

TCR sequencing allows for sensitive tracking of dynamic changes in antigen-specific T cells at the clonal level, giving unprecedented insight into the mechanisms by which immune checkpoint therapy alters T cell responses. Expansion of a greater number of TCR_{β} clonotypes between pre-- and on-treatment samples was observed in responders compared to a smaller number of expanded clonotypes in nonresponders, suggesting antigen-specific T-cell proliferation as a likely to be a key feature of successful responses to immunotherapy (Kidman et al 2020). Some studies have described dynamic changes of TCR repertoire in tumor, blood and draining lymph node, providing insight into how the T cell response changes when immunotherapy is administered. However, the utility of the TCR repertoire as a dynamic biomarker is still limited and requires further exploration.

1.3. Benefit-Risk Assessment

The BGB-LC-202 study will evaluate the efficacy, pharmacodynamics, and safety of the tislelizumab alone and of tislelizumab-based combinations as neoadjuvant treatment in patients with previously untreated, resectable Stage II to IIIA NSCLC. Based on general assessment, the sponsor believes neoadjuvant tislelizumab alone or in combination with novel agents may provide clinical benefit by enhancing the tumor response and reducing disease recurrence after surgery.

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 the data cutoff date of 20 July 2022, tislelizumab has been evaluated in 3220 patients (2173 patients treated with monotherapy and 1047 patients treated with combination therapy), 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, which supports the assessment that the efficacy and safety profile of tislelizumab could serve as backbone therapy in novel combinations.

The risk of observing augmented safety signals, as has been shown for other anti-PD-1-based immuno-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 immune-medicated adverse events (Appendix 7). As shown in Appendix 1, this study includes a comprehensive plan to monitor patient safety. 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.

The design of the current study aims to minimize potential risks to patients, and specifies the rules and procedures to add tislelizumab-based combination arms as follows:

- A rationale for potential synergistic activity of the novel candidate agent in combination with tislelizumab or other PD-1/PD-L1 antibody based on its mechanism of action and supported by nonclinical or clinical evidence at the concept level
- Preliminary evidence of clinical activity of the novel agent in combination with tislelizumab or other PD-1/PD-L1 antibody in certain solid tumor settings
- An established preliminarily, recommended combination dose for the novel agent in combination with tislelizumab with an acceptable safety profile for the target population in this study
- Requirement of a protocol amendment and respective health authority and local Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approvals prior to implementing any new experimental arm
- Updated informed consent form (ICF) with relevant information on the new tislelizumab-based combination arm

The agent-specific benefit-risk assessment is presented in the respective appendix:

- Tislelizumab: Appendix 11
- Ociperlimab: Appendix 12
- LBL-007: Appendix 13
- Chemotherapy：Appendix 14

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives and Endpoints

Table 2: Objectives and Endpoints

Efficacy objectives and endpoints	
Objectives	**Endpoints**
To evaluate the major pathological response (MPR) rate as assessed by the Blinded Independent Pathology Review (BIPR) in patients receiving investigational agents as neoadjuvant treatment	• MPR rate as assessed by the BIPR and defined as the proportion of patients with ≤ 10% residual viable tumor in the resected primary tumor and all resected lymph nodes
To evaluate the pathological complete response (pCR) rate of neoadjuvant treatment with investigational agents as assessed by the BIPR	• The pCR rate as assessed by the BIPR and defined as the proportion of patients with absence of residual tumor in the resected primary tumor and all resected lymph nodes
To evaluate the survival related endpoints including event-free survival (EFS), overall survival (OS), disease-free survival (DFS), and milestone endpoints	• EFS is defined as the time from randomization until any of the following events, whichever occurs first: radiographic disease progression that precludes definitive surgery, local or distant recurrence, as assessed by investigator per RECIST v1.1, or death due to any cause. The 1-year and 2-year EFS rates will be provided as milestone endpoints. • OS is defined as the time from the date of randomization to the date of death due to any cause. The 1-year and 2-year OS rates will be provided as milestone endpoints. • DFS is defined as the time from the first date of no disease (ie, patients who underwent margin-negative [R0] resection) to local or distant recurrence, as assessed by the investigator according to RECIST v1.1, or death due to any cause, whichever occurs first. The 1-year and 2-year DFS rates will be provided as milestone endpoints.
Safety Objectives and Endpoints:	
To assess the safety and tolerability of neoadjuvant treatment with investigational agents	• Incidence and severity of treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs) and immune-mediated adverse events (imAEs), with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v5.0)

Table 2: Objectives and Endpoints (Continued)

Objectives	Endpoints
To assess the feasibility of surgery in patients receiving neoadjuvant treatment with investigational agents	• Proportion of patients who undergo surgical resection within a scheduled period after receiving any dose of investigational agents, delayed or canceled surgery, duration of surgery and surgical approach
Pharmacodynamics/exploratory Objective and Endpoints	
To evaluate intratumoral, blood-based or draining lymph node-based pharmacodynamics, prognostic biomarkers, and response- or resistance-associated biomarkers seen with neoadjuvant treatment with investigational agents	• Biomarkers assessed in baseline and post-treatment tumor tissue, blood, or draining lymph node samples, which include: - Immune cell quantification and phenotyping via multiplex immunohistochemistry or flow cytometry - Gene expression profile - Gene mutations/tumor mutation burden (TMB)/microsatellite instability (MSI) - T cell receptor (TCR) profile - Soluble proteins such as cytokines/chemokines - Circulating tumor DNA (ctDNA) or minimal residual disease (MRD) - Target or ligands expression of each investigational agent
To characterize the pharmacokinetics (PK) of the investigational agents	Serum or plasma concentrations of the investigational agents at specified timepoints
To assess the host immunogenicity to investigational protein therapeutics	Immunogenic responses to investigational protein therapeutics, evaluated through detection of antidrug antibodies (ADAs)

3. STUDY DESIGN

3.1. Summary of Study Design

This is a randomized, multi-center, open-label, Phase 2, umbrella study to evaluate the efficacy, safety, and pharmacodynamics of tislelizumab as monotherapy and in combination with other investigational agents as neoadjuvant treatment in Chinese patients with resectable Stage II to IIIA NSCLC.

The study is designed with the flexibility of adding treatment arms when new treatments become available or discontinuing treatment arms that demonstrate minimal clinical activity or unacceptable toxicity, or modifying the patient population (eg, regarding biomarker status). New tislelizumab-based combination arm(s) may be added in accordance with emerging preclinical or clinical evidence via a protocol amendment. The current protocol includes the following treatment arms:

Substudy 1:

- Arm 1A: tislelizumab monotherapy
- Arm 1B: tislelizumab in combination with ociperlimab
- Arm 1C: LBL-007 in combination with tislelizumab

Substudy 2:

- Arm 2A: tislelizumab in combination with chemotherapy
- Arm 2C: LBL-007 in combination with tislelizumab and chemotherapy

This study consists of a screening phase, a neoadjuvant treatment phase, the End-of-Treatment (EOT)/safety follow-up visit, a surgery phase, and the survival follow-up phase.

Patients will be required to sign an ICF to undergo screening procedures. Local PD-L1 expression results will be acceptable for randomization/enrollment into this study. Patients will also be required to provide tissue samples of the primary tumor and optional lymph node for biomarker evaluation.

The total number of patients depends on the number of experimental arms and the timing when they are added to the study. Arm 1A and Arm 2A may be kept open with the corresponding randomization ratio whenever at least 1 combination arm is open for enrollment. The patient number and randomization ratio will be adjusted based on the number of experimental arms that are open for enrollment (eg, if a new arm is added or enrollment in an existing arm is suspended for pending analysis of results from the preliminary phase). In the current protocol, Substudy 1 includes Arm 1A (tislelizumab monotherapy), Arm 1B (tislelizumab in combination with ociperlimab), and Arm 1C (LBL-007 in combination with tislelizumab) in patients with tumor PD-L1 expression ≥ 50%; Substudy 2 includes Arm 2A (tislelizumab in combination with chemotherapy) and Arm 2C (LBL-007 in combination with tislelizumab and chemotherapy) in patients with tumor PD-L1 expression < 50%.

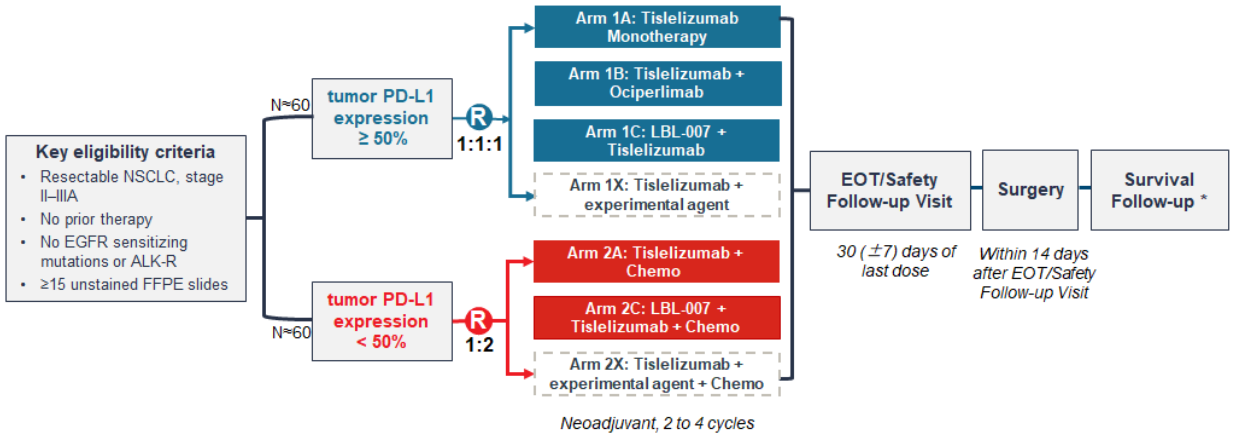
The study design schematic is presented in Figure 2. Eligible patients will be assigned randomly in a certain ratio into 1 of the active treatment arms. In this current version of the protocol, eligible patients with tumor PD-L1 expression ≥ 50% will be randomized in a 1:1:1 ratio to Substudy 1:

- Arm 1A: tislelizumab on a 3-week cycle for 2 to 4 cycles, followed by surgical resection
- Arm 1B: tislelizumab + ociperlimab on a 3-week cycle for 2 to 4 cycles, followed by surgical resection
- Arm 1C: LBL-007 + tislelizumab on a 3-week cycle for 2 to 4 cycles, followed by surgical resection

Eligible patients with tumor PD-L1 expression < 50% will be randomized in a 1:2 ratio to Substudy 2:

- Arm 2A: tislelizumab + chemotherapy on a 3-week cycle for 2 to -4 cycles, followed by surgical resection
- Arm 2C: LBL-007 + tislelizumab + chemotherapy on a 3-week cycle for 2 to 4 cycles, followed by surgical resection

Figure 2: Study Schema



Abbreviations: ALK, anaplastic lymphoma kinase; EOT, End-of-Treatment; EGFR, epidermal growth factor receptor; FFPE, formalin fixed paraffin-embedded; NSCLC, non-small cell lung cancer; PD-L1, programmed death protein ligand-1; R, randomization ratio.
*Tumor assessments should be conducted per protocol until disease recurrence or progression that precludes definitive surgery, initiation of new anticancer therapy except the prespecified adjuvant therapy, withdrawal of consent, death, loss to follow-up, or study termination by the sponsor, whichever occurs first. Survival status should be followed per protocol until death, loss to follow-up or the end of study

Crossover between the experimental arms will not be allowed in this study. After the neoadjuvant treatment, patients will undergo surgical resection and then will enter the Survival Follow-up phase, in which patient may receive optional adjuvant treatment per local guideline at the discretion of investigator.

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

3.2. Screening Period

Screening evaluations will be performed ≤ 28 days before randomization (see Appendix 1). Patients who agree to participate in this study will sign the ICF before undergoing any screening procedure. Screening evaluations may be repeated as needed within the screening period; the investigator is to assess preliminary patient eligibility according to the latest screening assessment results. For rescreening requirements, see Section 7.1.

Patients are required to provide formalin-fixed paraffin-embedded (FFPE) block (preferred) or unstained slides of the primary tumor and optional lymph node sample for biomarker evaluation during screening. Refer to Section 7.7 for more details.

3.3. Neoadjuvant Treatment Phase

Eligible patients will be assigned randomly in a certain ratio into one of the active treatment arms.

In this current version of the protocol, eligible patients with tumor PD-L1 expression ≥ 50% will be randomized in a 1:1:1 ratio to 1 of the following treatment arms in Substudy 1:

- Arm 1A: tislelizumab on a 3-week cycle for 2 to 4 cycles, followed by surgical resection
- Arm 1B: tislelizumab + ociperlimab on a 3-week cycle for 2 to 4 cycles, followed by surgical resection
- Arm 1C: LBL-007 + tislelizumab on a 3-week cycle for 2 to 4 cycles, followed by surgical resection

Eligible patients with tumor PD-L1 expression < 50% will be randomized in a 1:2 ratio to 1 of the following treatment arms in Substudy 2:

- Arm 2A: tislelizumab + chemotherapy on a 3-week cycle for 2 to 4 cycles, followed by surgical resection
- Arm 2C: LBL-007 + tislelizumab + chemotherapy on a 3-week cycle for 2 to 4 cycles, followed by surgical resection

The following platinum-based doublet chemotherapy options are permitted for this study:

- Cisplatin/Carboplatin + Pemetrexed (nonsquamous)
- Cisplatin/Carboplatin + Paclitaxel (squamous)

For patients with tumors of mixed histology (squamous and nonsquamous), appropriate chemotherapy regimen will be decided by investigators based on the major histological components assessed by pathologists. Carboplatin can replace cisplatin per the investigator's discretion in consideration of patient's tolerability to cisplatin. The reasons for intolerability should be documented.

After completion of planned neoadjuvant treatment or discontinuation from study treatment due to any reasons (AE, patient's withdrawal, or investigator's decision), the EOT/Safety Follow-up Visit should be conducted ≤ 30 days (± 7 days) after the last dose of the study treatment (refer to

Section 3.4 for details). The surgical procedure should be performed ≤ 14 days after the EOT/Safety Follow-up Visit. Before surgery, the resectability assessment that composed of tumor response and safety assessments will be conducted at Presurgical Visit, and the eligible patients will proceed to surgery. Based on the investigator's discretion, patients who are found to have disease progression at scheduled tumor assessments or at any time during neoadjuvant treatment or who discontinued early from neoadjuvant treatment due to intolerable AEs, patient's withdrawal, or investigator's decision may still proceed to undergo surgery if patients are assessed as likely being able to tolerate surgery and their tumor is deemed resectable and nonmetastatic. For patients who are responding to neoadjuvant therapy but cannot proceed to surgery (eg, because of pulmonary embolism or myocardial infarction), the medical monitor should be consulted.

A tumor response assessment will be performed at the EOT/Safety Follow-up Visit after the neoadjuvant treatment period. Tumor assessment at the Presurgical Visit may not be repeated if there is a standard tumor assessment per protocol performed ≤ 14 days before surgery (refer to Section 7.5 and Appendix 1 Schedule of Assessments for details).

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

Note: requirements for treatment administration and on-treatment procedures to be performed for a specific experimental arm will be presented in the agent-specific appendix, as applicable.

3.4. End of Treatment and Safety Follow-up Visit

The EOT/Safety Follow-up Visit will be conducted for patients who complete planned neoadjuvant or discontinue from study treatment due to any reason including AE, patient's withdrawal, investigator's decision, and others. Patients will be asked to return to the clinic for the EOT/Safety Follow-up Visit which should occur ≤ 30 (±7) days after the last dose of neoadjuvant treatment or before surgery procedure or the initiation of any new anticancer therapy after neoadjuvant therapy, whichever occurs first.

If routine laboratory tests (eg, hematology, serum chemistry) are performed ≤ 7 days before an EOT/Safety Follow-up Visit, these tests will not need to be repeated. Tumor assessment is not required at the EOT/Safety Follow-up Visit provided that ≤ 2 weeks have passed since the last assessment. However, if the Presurgical Visit has been incorporated into the EOT/Safety Follow-up Visit to assess resectability before surgery, the safety assessment and tumor assessment at this visit should be performed ≤ 14 days before surgery.

In addition, telephone contacts with patients should be conducted to assess immune-mediated adverse events (imAEs) and relevant concomitant medications (ie, those associated with an imAE or any new anticancer therapy), or if a pregnancy test is also required. These contacts should be made at 60 days (± 14 days), and 90 days (± 14 days) after the last dose of study treatment, regardless of whether the patient starts a new anticancer therapy or prespecified adjuvant treatment. Phone contacts should be documented in the patient's source documentation.

If a patient reports a suspected imAE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated. For women of childbearing potential (see Appendix 9), additional pregnancy tests will be required on 90 days (±14 days) and 120 days (±14 days) after the last dose of study drug(s) (in clinic or over the phone, as needed based on assessments required). The timepoint for the additional pregnancy follow-up visit is specified in agent-specified appendix (as applicable).

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

Patients who discontinue study treatment before disease progression will have their tumors assessed as outlined in Section 7.5.

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

3.5. Surgery

Upon completion of neoadjuvant treatment, patients will undergo surgical resection of their tumor. Surgical specimens (primary tumor tissue and dissected lymph nodes) will be assessed for pathological response (MPR and pCR) by the BIPR and biomarker analysis will be performed. Refer to Section 7.7 and Section 10.1 for more details.

At Presurgical Visit, the investigator will reassess the patient to reconfirm disease resectability based on tumor response and safety assessments. The safety assessment and tumor assessment at Presurgical Visit should be completed and reviewed by the investigator ≤ 14 days before surgery. The Presurgical Visit and associated assessments can be incorporated into the EOT/Safety Follow-up Visit if applicable and in accordance with local institutional practice (refer to Section 7.4.8 for details).

The surgical procedure should be performed ≤ 14 days after the EOT/Safety Follow-up Visit. If surgery cannot be performed ≤ this time window (eg, because of a prolonged AE), investigator should inform sponsor medical monitor regarding the determination of surgery beyond pre-specified time window as well as corresponding considerations (refer to Section 5.2.2).

3.6. Survival Follow-up

Patients will be followed for survival status and for information on subsequent anticancer therapy after the EOT/Safety Follow-up Visit. This follow-up will be conducted via telephone call, patient medical records review, and/or clinic visits approximately every 6 months (± 4 weeks) after the EOT/Safety Follow-up Visit or as directed by the sponsor until death, withdrawal of consent, loss to follow-up, or the end of study (see Section 3.7.3).

During the survival follow-up period, based on the investigator's benefit/risk assessment for patients and determination, optional adjuvant therapy per local guidelines is allowed after surgery.

Recurrence status will be monitored and assessed by the investigator per RECIST v1.1 during this period. See Section 7.5 and Appendix 1 for details.

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 recurrence status (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 which include, but are not limited to, the following:

- Radiographic disease progression assessed by the investigator per RECIST v1.1
- AE
- Patient withdrawal from study treatment
- 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
- Except for prespecified study treatment(s) as neoadjuvant, use of any other concurrent antineoplastic therapy(ies) (eg, any systemic anticancer therapy including chemotherapy, targeted therapies, hormonal therapy, immunotherapy, standard anticancer agents and investigational anticancer agents, or any local antineoplastic treatment including radiotherapy, ablation and other resection surgery for any cancer)
- Patient noncompliance:
  Investigative site staff should first counsel patients who are significantly noncompliant on the importance of study treatment compliance and drug accountability. The investigator may, in consultation with the medical monitor, discontinue patients from treatment who are consistently noncompliant.
- Completion of planned neoadjuvant treatment(s)

Patients who discontinue study treatment prior to disease progression will continue to undergo tumor assessments as outlined in Section 7.5.

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

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

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

- Patients have completed all study assessments

The sponsor has the right to terminate any of the experimental arms at any time based on the available data.

3.7.3. 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 and/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/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 the IRBs/ IECs of the early termination of the study.

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.

If applicable, additional inclusion/exclusion criteria for a specific experimental arm will be presented in the investigational agent-specific appendix. In addition to the inclusion and exclusion criteria in the protocol body, investigational agent-specific inclusion and exclusion criteria should be met based on patient assignment.

4.1. Inclusion Criteria

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

1. Patient must sign a written ICF and 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 ICF
3. Histologically confirmed Stage II to IIIA NSCLC of squamous or nonsquamous histology (staging should be based on the Eighth Edition American Joint Committee on Cancer/Union Internationale Contre le Cancer NSCLC staging system [Goldstraw et al 2016]):
    a. T4 primary NSCLC will be allowed only on the basis of size (tumors > 7 cm). Invasion of the diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, and separate tumor nodules in a different ipsilateral lobe is not permitted.
    b. Patients with mixed NSCLC histology (squamous and nonsquamous) or NSCLC not otherwise specified are eligible.
    c. Patients may be enrolled based on clinical stage, but pre-operative documentation of nodal involvement by endobronchial ultrasound or mediastinoscopy is strongly encouraged.
4. Patients must provide at least 15 freshly cut unstained FFPE slides of the primary tumor, or FFPE block containing equivalent tumor tissues (preferred), for central PD-L1 evaluation during screening and other exploratory biomarker assessment. Only patients with evaluable PD-L1 status assessed by central laboratory are eligible. If local result of EGFR mutation status (nonsquamous only) is not available, 3 additional slides for central EGFR testing are required.
5. Solid or subsolid appearance of NSCLC on computed tomography (CT) scan with no appearance of purely ground-glass opacity:
    a. For subsolid lesions, the tumor size (ie, clinical T stage) should be measured based on the solid component only, without including the ground-glass opacity component.
6. Evaluation by an attending thoracic surgeon to confirm eligibility for an R0 resection with curative intent (Section 5.2.2)

7. Adequate cardiopulmonary function assessed by an attending thoracic surgeon to be eligible for surgical resection with curative intent
   - If clinically indicated, patients with underlying ischemic, valvular, or other significant heart diseases should be evaluated preoperatively by a cardiologist.
8. Measurable disease as assessed by the investigator per RECIST v1.1
9. ECOG PS ≤ 1
10. Adequate hematologic and organ function, as indicated by the following laboratory values obtained ≤ 7 days before randomization:
    a. Patients must not have required blood transfusion or growth factor support ≤ 7 days before sample collection at screening for the following:
       i. Absolute neutrophil count ≥ 1.5 x 10^9/L
       ii. Platelets ≥ 100 x 10^9/L
       iii. Hemoglobin ≥ 90 g/L
    b. Estimated glomerular filtration rate ≥ 60 mL/min/1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration equation (Appendix 8)
    c. Serum total bilirubin ≤ 1.5 x upper limit of normal (ULN) (total bilirubin must be < 3 x ULN for patients with Gilberts syndrome)
    d. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN
    e. For patients not receiving therapeutic anticoagulation: international normalized ratio or activated partial thromboplastin time ≤1.5 x ULN
11. Women of childbearing potential must be willing to use a highly effective method of birth control (Appendix 9) for the duration of the study or for ≥ 6 months after the last dose of tislelizumab or other investigational agent or chemotherapy, whichever occurs later. They must also have a negative urine or serum pregnancy test result ≤ 7 days before randomization.
12. Nonsterile men must be willing to use a highly effective method of birth control (Appendix 9) for the duration of the study or for ≥ 6 months after the last dose of tislelizumab or other investigational agent or chemotherapy, whichever occurs later.
    a. A sterile man is defined as one for whom azoospermia has been previously demonstrated in a semen sample examination as definitive evidence of infertility.
    b. Men with known “low sperm count” (consistent with “sub-fertility”) are not to be considered sterile for the purposes of this study.

4.2. Exclusion Criteria

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

1. Any prior antineoplastic therapy(ies) for current lung cancer (eg, radiotherapy, targeted therapies, ablation, or other systemic or local antineoplastic treatment)
2. Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4, anti-cell immunoglobulin and ITIM domain (TIGIT), anti-lymphocyte activation gene-3 (LAG-3),

or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways

3. Has mixed small cell lung cancer
4. Patients with large cell neuroendocrine carcinoma (LCNEC)
5. Known EGFR sensitizing mutations and/or ALK rearrangement.
    a. Patients with nonsquamous NSCLC must have been tested for EGFR mutational status locally using a tissue-based or endobronchial ultrasound-guided transbronchial needle aspiration [EBUS-TBNA]–based EGFR test at screening. Patients found to have EGFR-sensitizing mutations are not eligible.
6. Presence of locally advanced unresectable NSCLC regardless of stage or distant metastatic disease. Mediastinal lymph node samples are required for clinical staging to assess nodal involvement in patients with contralateral mediastinal adenopathy on CT scan.
7. Patient with symptomatic coronavirus disease 2019 (COVID-19) infection or asymptomatic patients who tested positive for COVID-19 (through a licensed reverse transcription-polymerase chain reaction [RT-PCR] or antigen testing) during screening should recover from infection or test negative to be eligible for enrollment.
8. Active autoimmune diseases or history of autoimmune diseases that may relapse

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

    a. Controlled type I diabetes
    b. Hypothyroidism (provided it is managed with hormone replacement therapy only)
    c. Celiac disease controlled by diet alone
    d. Skin diseases not requiring systemic treatment (eg, vitiligo, psoriasis, alopecia)
    e. Any other disease that is not expected to recur in the absence of external triggering factors
9. Any malignancy ≤ 2 years before randomization except for the specific cancer under investigation in this study and any locally recurring cancer that has been treated curatively (eg, resected basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix or breast)
10. Any condition that required systemic treatment with either corticosteroids (> 10 mg daily of prednisone or equivalent) or other immunosuppressive medication ≤ 14 days before randomization

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

    a. Adrenal replacement steroid (dose ≤ 10 mg daily of prednisone or equivalent)
    b. Topical, ocular, intra-articular, intranasal, or inhaled corticosteroid with minimal systemic absorption

c. Short course (≤ 7 days) of corticosteroid prescribed prophylactically (eg, for contrast dye allergy) or for the treatment of a nonautoimmune condition (eg, delayed-type hypersensitivity reaction caused by contact allergen)

11. Uncontrolled diabetes or > Grade 1 laboratory test abnormalities in potassium or sodium despite standard medical management or ≥ Grade 3 hypoalbuminemia ≤ 14 days before randomization
12. History of interstitial lung disease, pneumonitis or uncontrolled lung diseases including pulmonary fibrosis, or acute lung diseases.
13. Severe chronic or active infections requiring systemic antibacterial, antifungal or antiviral therapy, including tuberculosis infection, etc.
    a. Severe infections ≤ 4 weeks before randomization, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
    b. Received therapeutic oral or intravenous antibiotics for severe chronic or active infections ≤ 2 weeks before randomization

    Note: Antiviral therapy is permitted for patients with chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. Patients receiving prophylactic antibiotics (eg, for the prevention of urinary tract infection, chronic obstructive pulmonary disease, or for dental extraction) are eligible.
14. Untreated chronic hepatitis B or chronic HBV carriers with HBV DNA ≥ 500 IU/mL (or ≥ 2500 copies/mL) at screening
    Note: Inactive hepatitis B surface antigen (HBsAg) carriers, and patients with treated and stable hepatitis B (HBV DNA < 500 IU/mL or < 2500 copies/mL) may be enrolled. Patients with detectable HBsAg or detectable HBV DNA should be managed per treatment guidelines (see Section 6.2.1.2).
15. 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 with a testing positive test result for HCV antibody. For treatment guidance, see Section 6.2.1.3.
16. Known history of human immunodeficiency virus (HIV) infection. If the status is unknown, an HIV test at screening is required.
17. Any major surgical procedure ≤ 28 days before randomization. Patients must have recovered adequately from the toxicity and/or complications from the intervention prior to randomization.
18. Prior allogeneic stem cell transplantation or organ transplantation
19. Any of the following cardiovascular and cerebrovascular risk factors:
    a. Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living, ≤ 28 days before randomization
    b. Pulmonary embolism ≤ 28 days before randomization
    c. Any history of acute myocardial infarction ≤ 6 months before randomization

d. Any history of heart failure meeting New York Heart Association Classification III or IV (Appendix 6) ≤ 6 months before randomization
e. Any event of ≥ Grade 2 ventricular arrhythmia ≤ 6 months before randomization
f. Any history of cerebrovascular accident ≤ 6 months before randomization
g. Uncontrolled hypertension that cannot be managed with standard antihypertensive medications ≤ 28 days before randomization
h. Any episode of syncope or seizure ≤ 28 days before randomization

20. A history of severe hypersensitivity or intolerance to chimeric or humanized antibodies, fusion proteins, chemotherapy agents, or any of the excipients of study treatment
21. 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
22. Patients with toxicities caused by prior anticancer therapy that have not recovered to baseline or stabilized, except for AEs not considered a likely safety risk (eg, alopecia, neuropathy, and specific laboratory abnormalities)
23. Was administered a live vaccine ≤ 28 days before randomization
    Note: Vaccines for COVID-19 are allowed except for any live vaccine that may be developed. Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed.
24. Underlying medical conditions (including laboratory abnormalities) or alcohol or drug abuse or dependence that will be unfavorable for the administration of study drug or that will affect the explanation of drug toxicity or AEs or result in insufficient or impaired compliance with study conduct
25. Women who are pregnant or who are breastfeeding
26. Concurrent participation in another therapeutic clinical study
    Note: Concurrent participation in observational or noninterventional studies is allowed. In addition, patients who have completed active treatment in a clinical study and are in the follow-up period can be enrolled in this study.

5. STUDY TREATMENT

The specific stipulations of the study treatment for experimental arms including formulation, packaging, handing dosage, administration, dose modification, and overdose are provided in each investigational agent-specific appendix. Only common requirements for study treatment are presented in this section, unless otherwise specified.

5.1. Formulation, Packaging, Labeling, and Handling

- Tislelizumab: Appendix 11
- Ociperlimab: Appendix 12
- LBL-007: Appendix 13
- Chemotherapy: Appendix 14

5.2. Dosage, Administration, and Compliance

5.2.1. Treatment Administration

- Tislelizumab: Appendix 11
- Ociperlimab: Appendix 12
- LBL-007: Appendix 13
- Chemotherapy: Appendix 14

5.2.2. Surgical Treatment Plan

A thoracic surgeon with experience in early-stage resectable NSCLC should evaluate patients at screening to determine eligibility for surgical resection. Patients should be eligible for an R0 resection with curative intent at the time of screening (Rami-Porta et al 2005). Before surgery, the investigator will reassess the patient to reconfirm disease resectability at the Presurgical Visit. The tumor assessment and other safety assessments at Presurgical Visit should be completed ≤ 14 days before surgery. The Presurgical Visit and associated assessments can be incorporated into the EOT/Safety Follow-up Visit if applicable and in accordance with local institutional practice. Safety assessments at the Presurgical Visit, including but not limited to blood tests, coagulation, cardiac or pulmonary tests (if indicated), anesthesia assessment, and other evaluation procedures, should be performed per local standard of care.

The surgical procedure should be performed ≤ 14 days after the EOT/Safety Follow-up Visit. If the surgery cannot be performed within this time window (eg, because of a prolonged AE), investigator should inform sponsor medical monitor regarding the determination of surgery beyond pre-specified time window as well as corresponding considerations. Patients will undergo tumor assessment by CT scan (with oral/intravenous contrast, unless contraindicated) at the EOT/Safety Follow-up Visit after the neoadjuvant treatment period. Tumor assessment at the Presurgical Visit may not be repeated if there is a standard tumor assessment per protocol performed ≤ 14 days before surgery. Resection may be accomplished via an open or minimally

invasive procedure (eg, video-assisted thoracic surgery or robotic video-assisted thoracic surgery).

A complete resection must meet all 4 of the following criteria (Rami-Porta et al 2005):

a. Free resection margins including the bronchial, venous, and arterial stumps, peribronchial soft tissue, and any peripheral margin near the tumor proved microscopically.
b. Systematic nodal dissection in its wider form or, if it is not performed, lobe-specific systematic nodal dissection. Lobe-specific nodal dissection involves dissection and histological examination of intrapulmonary (lobar, interlobar, and segmental) and hilar nodes and ≥ 3 of the following mediastinal nodal stations depending on the lobar location of the primary tumor. The lymph node specimen should include ≥ 6 nodes, ≥ 3 of which should be removed from intrapulmonary and/or hilar stations and ≥ 3 of which should be removed from mediastinal stations. One of the 3 lymph nodes removed from mediastinal stations must be from the subcarinal station.
c. There should be no extracapsular extension of tumor in nodes removed separately or those at the margin of the main lung specimen.
d. The highest mediastinal node that has been removed must be negative microscopically.

Anatomic resection via lobectomy, bilobectomy, or pneumonectomy is strongly preferred. Wedge resections are not allowed.

The performed surgical procedure should be documented and reported in the eCRF. If, after neoadjuvant treatment or during the surgery, the surgeon determines that the patient should not proceed with the planned surgery, the reason should be documented and reported in the eCRF as well.

5.3. Overdose

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

Refer to each investigational agent-specific appendix for details.

5.4. Investigational Medicinal Product Accountability

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

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

5.5. Dose Modification

Every effort should be made to administer the study drugs according to the planned dose and schedule. In the event of significant toxicities, dose modification may be taken. Reasons for dose modification, 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 the protocol are not intended to be a substitute for clinical judgment. Investigators may delay doses for other reasons (eg, AEs or laboratory findings) as appropriate.

Treatment-specific dose modification guidance is presented in Appendix 11 (tislelizumab), Appendix 12 (ociperlimab), Appendix 13 (LBL-007), and Appendix 14 (chemotherapy).

6. PRIOR AND CONCOMITANT THERAPY

6.1. Prior Therapy

The exclusion criteria specify that patients must not have received prior therapy for current lung cancer, including chemotherapy and radiotherapy, and prior treatment with an antibody or drug against immune checkpoint pathways, including but not limited to, anti-PD-1, anti-PD-L1, or anti-CTLA-4 (Section 4.2). All prior cancer related treatments, treatments for underlying active medical conditions, and all medications (eg, prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient ≤ 30 days before randomization must be recorded in the appropriate eCRF.

6.2. Concomitant Therapy

If applicable, additional requirements with respect to concomitant therapy for a particular experimental arm will presented in the investigational agent-specific appendix. In addition to the common stipulations stated this section in the protocol body, investigational agent-specific requirements for concomitant therapy should be met based on patient assignment.

6.2.1. Permitted Concomitant Medications/Procedures

Most concomitant medications and therapies deemed necessary and in keeping with the local standards of medical care at the discretion of the investigator for the supportive care (eg, antiemetics, antidiarrheals, pain medications, and nutritional support) and for a patient's wellbeing are allowed. All concomitant medications will be recorded in the eCRF including all prescriptions, over-the-counter drugs, herbal supplements, and intravenous medications and fluids. If changes (dose, stop, or start) in concomitant medication occur during the study, documentation of drug dosage, frequency, route, date, and reason for use will be recorded in the eCRF. All concomitant medications received ≤ 30 days before the first dose of study drug and 30 days after the last infusion or dose of study treatment should be recorded.

6.2.1.1. Systemic Corticosteroids

Systemic corticosteroids for management 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 treatment administration. The short-term use of steroids as prophylactic treatments (eg, for patients with allergies to diagnostic imaging contrast dyes) is permitted.

6.2.1.2. Hepatitis B Treatment

Management of prophylactic antiviral therapy for patients with inactive, treated, and stable hepatitis B (HBV DNA < 500 IU/mL) is at the discretion of the investigator, as aligned with local guidance. Such medications must be documented in the patient's chart and recorded in the eCRF. Patients receiving antivirals at screening should be managed per treatment guidelines. Once initiated, antiviral treatment should continue until 6 months after the last dose of study treatment or as permitted by local guidance.

6.2.1.3. Hepatitis C Treatment

Patients with detectable HCV RNA who are receiving treatment at screening must meet the criterion of negative HCV RNA to be eligible. If the patients are treated and eligible, they should remain on continuous, effective antiviral therapy during the study. Investigators can consider treatment with antivirals following the international or local guidelines as appropriate.

6.2.1.4. COVID-19 Vaccines

Vaccines for COVID-19 are allowed except for any live vaccine (ie, live SARS-CoV-2 virus) that may be developed. Attenuated (vector) COVID-19 vaccines are inactivated vaccines and as such, are permitted. It is recommended to avoid COVID-19 vaccination ≤ 72 hours before or after study drug administration during the 2 to 4 treatment cycles. Vaccinations are considered a concomitant medication and hence should be entered in the eCRF. The specific COVID-19 vaccine should be recorded instead of generic language, eg, mRNA-1273 vaccine (Moderna), BioNTech vaccine (Pfizer), etc.

6.2.2. Prohibited Concomitant Medications/Procedures

The following medications are prohibited from screening to the EOT/Safety Follow-up Visit:

- Except for study treatment(s), any concurrent antineoplastic therapy(ies) (eg, any systemic anticancer therapy including chemotherapy, targeted therapies, hormonal therapy, immunotherapy, standard anticancer agents and investigational anticancer agents, or any local antineoplastic treatment including radiotherapy, ablation and other resection surgery for any cancer)
- Live vaccines ≤ 28 days before randomization and ≤ 60 days after the last dose of study treatment(s) are prohibited.

6.2.3. Restricted Concomitant Medications/Procedures

The following medications/procedures 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
- Herbal remedies for the treatment of cancer or Chinese patent medicines with approval from the China NMPA for use as anticancer treatment (regardless of cancer type) (Appendix 10)
- Herbal remedies with immune-stimulating properties (eg, mistletoe extract) or that are known to potentially interfere with the liver or other major organ functions (eg, hypericin) (Appendix 10)
- 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.

- Opiates and other medications required for palliative management of patients are allowed. Patients must notify the investigator of all concurrent medications used during the study.

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

6.3. Potential Interactions Between the Study Drugs and Concomitant Medications

Information on potential interactions between study drug and concomitant medications are provided in each investigational agent-specific appendix. The potential for drug-drug interaction between the study drugs (tislelizumab, ociperlimab, or LBL-007), standard chemotherapy, and small-molecule drug products is very low, given tislelizumab, ociperlimab, and LBL-007 are all therapeutic monoclonal antibodies. They are unlikely to have an effect on drug-metabolizing enzymes or transporters because they are expected to be degraded into amino acids and recycled into other proteins. The effect on drug-metabolizing enzymes or transporters for chemotherapy is summarized below.

Cisplatin

During cisplatin use, concurrent therapy with drugs having a potential ototoxic or nephrotoxic effect (eg, aminoglycosides, cefalotin, furosemide, and amphotericin B) should be avoided or closely monitored because this may lead to increased or exacerbated toxicity due to platin-induced changes in renal clearance of these substances.

Carboplatin

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

Pemetrexed

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. Ibuprofen has been shown to increase pemetrexed exposure and poses a potential risk in patients with mild/moderate renal impairment. Hence, ibuprofen usage is discouraged in those patients.

Paclitaxel

The metabolism of paclitaxel is catalyzed by cytochrome P-450 (CYP) 2C8 and CYP3A4. Caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit or induce either CYP2C8 or CYP3A4 (eg, inhibitors ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir or inducers rifampicin, carbamazepine, phenytoin, efavirenz, and nevirapine). When strong CYP2C8 and CYP3A4 inhibitors 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 for more information.

Refer to manufacturer's prescribing information for the respective chemotherapy agents for drug-drug interaction information on the influence of 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. In addition to the common assessments and procedures stated in this section, additional assessment requirements for each particular experimental arm are provided in the respective agent-specific appendix, if applicable. 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 ≤ 28 days before randomization. Patients who agree to participate will sign the ICF before undergoing any screening procedure. The screening period begins on the date the ICF is signed. Screening evaluations may be repeated as needed within the screening period; the investigator will assess patient eligibility according to the latest screening assessment results.

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

For the description of other assessments that are conducted during screening, see Section 7.4 for the safety assessments, Section 7.5 for tumor and response evaluations, and Section 7.7 for biomarkers evaluations.

Patients are required to provide FFPE block (preferred) or unstained slides of the primary tumor and optional lymph node sample for biomarker evaluation during screening. Only patients with evaluable PD-L1 status assessed by central laboratory are eligible. Refer to Section 7.7 for more details.

Rescreening under limited conditions may be allowed after consultation with the sponsor. For example, rescreening may be considered when a patient narrowly misses a laboratory criterion that is correctable and not due to a rapidly deteriorating condition or disease progression. Rescreening is allowed only once. If a patient is rescreened, the patient must provide new informed consent as described in Section 7.1.1, and a new patient number assigned as described in Section 7.1.2.

7.1.1. Informed Consent and Screening Log

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

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

7.1.2. Patient Numbering

After obtaining informed consent, study site personnel will access the Interactive Response Technology (IRT) system to assign a unique patient number to 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. Rescreening is allowed one time per patient.

7.1.3. Demographic Data and Medical History

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

Medical history includes any history of clinically significant disease, surgery, or cancer history; reproductive status (ie, of childbearing potential or no childbearing potential); history of tobacco (ie, former or current or never); and all medications (eg, prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient ≤ 30 days before randomization. Pre-existing AEs at baseline should be recorded as medical history.

Cancer history will include pathologic diagnosis, stage at screening, and tumor location. Radiographic studies performed prior to study entry may be collected for review by the investigator.

7.1.4. Women of Childbearing Potential and Contraception

Childbearing potential is defined as being physiologically capable of becoming pregnant. Refer to Appendix 9 for contraception guidelines and definitions of "women of childbearing potential" and "no childbearing potential." Refer to Appendix 1 for details about pregnancy testing for women of childbearing potential.

7.1.5. HIV Serology Test

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

7.2. Enrollment

7.2.1. Confirmation of Eligibility

The investigator is responsible for ensuring that each patient meets the eligibility criteria for this study. The investigator will assess and confirm the eligibility of each patient. All results from the screening procedures and relevant medical history must be available before eligibility can be determined. All inclusion criteria must be met and none of the exclusion criteria may be met. No eligibility waivers will be granted.

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 in relation to the eligibility criteria.

7.2.2. Enrollment/Randomization

All eligible patients will be randomized to a treatment arm after enrollment according to the randomization ratio specified in Section 9.1.1 to a treatment arm after enrollment.

Site personnel will access the IRT system to randomize patients to a treatment arm and to assign the study drugs. Study treatment must commence ≤ 2 business days after randomization.

7.3. Study Drug Dispensation

Study treatment will be dispensed and administered as described in Section 5.2.

7.4. Safety Assessments

In addition to the common safety assessments described in this section, additional requirements for safety assessments for each particular experimental arm are provided in the respective investigational agent-specific appendix, if applicable.

7.4.1. Vital Signs

See Appendix 1 for vital signs to be collected and the timing of their collection.

Vital signs and weight measurements are required at screening, on Day 1 of the first cycle, on Day 1 of each subsequent cycle, at the EOT/Safety Follow-up Visit, and at the Presurgical Visit. Height measurements are only required at screening.

Vital signs are required to be recorded ≤ 60 minutes before, during, and 30 minutes after the first infusion of study drug(s). For subsequent infusions, vital signs will be collected within 60 minutes before infusion and if clinically indicated, during and 30 minutes after the infusion.

7.4.2. Physical Examinations

At the Screening Visit, the EOT/ Safety Follow up Visit and Presurgical Visit, a complete physical examination will be conducted, including evaluations of 1) the 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 in the eCRF with the appropriate disease/condition terms.

At other 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 in the eCRF. Refer to Section 8.2.1 regarding AE definitions and reporting and follow-up requirements.

7.4.3. Eastern Cooperative Oncology Group Performance Status

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

7.4.4. Laboratory Safety Tests

Local laboratory assessments of serum chemistry, hematology, coagulation, urinalysis, and thyroid function will be conducted as described in Appendix 1. Specific assessments to be performed are listed in Appendix 2.

If laboratory tests at screening are not performed ≤ 7 days before the administration of study drug(s) on Day 1 of Cycle 1, these tests should be repeated and reviewed before the administration of study drug(s). Hematology and serum chemistry (including liver function tests) as specified in Appendix 2 should be performed weekly for the first 2 cycles and within 3 days before Day 1 during Cycle 3 to 4 of neoadjuvant treatment and at EOT/Safety Follow-up Visit and Presurgical Visit. After Cycle 1, the results will be reviewed ≤ 48 hours before the administration of the study drug(s).

Thyroid assessments will be performed as specified in Appendix 1.

7.4.5. Cardiac Enzyme Monitoring

Although immune-mediated myocarditis is a rare complication of immune checkpoint inhibitors, serum creatinine kinase (CK) and CK cardiac isoenzyme (CK-MB) will be monitored to protect study participants and to quantify the risk of muscle inflammation (see Appendix 1 for the blood collection schedule and Appendix 7 for guidelines for the management of suspected immune-mediated myocarditis). Serum troponins may be substituted per local guidelines if used consistently throughout the study.

7.4.6. 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 source documents at the site.

When coinciding with blood draws at the same timepoint, the ECG assessment should be performed prior to the blood draws. Patients should rest in a semirecumbent supine position for ≥ 10 minutes prior to the ECG collection.

7.4.7. 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.

7.4.8. Presurgical Visit and Surgical Complications

Before surgery, the investigator will reassess the eligibility of each patient to reconfirm disease resectability as assessed by tumor response and safety assessments at the Presurgical Visit and in accordance with local institutional practice. Evaluations at the Presurgical Visit will include blood tests, coagulation, cardiac, or pulmonary tests (if indicated), anesthesia assessment, tumor assessment, and other evaluation procedures, that should be performed per local standard of care. The Presurgical Visit and associated assessments could be incorporated into EOT/Safety

Follow-up Visit. The tumor assessment and other safety assessments at the Presurgical Visit should be completed ≤ 14 days before surgery (refer to Appendix 1 and Section 5.2.2 for details).

Data on perioperative complications, including a delay in planned surgery, pneumonitis, acute respiratory distress syndrome, re-admission to the intensive care unit, atrial fibrillation or other supraventricular tachycardias, potential immune-mediated toxicities, and postoperative complications will be collected. Surgical complications occurring ≤ 90 days after surgery will be documented and followed until resolution. Surgical procedure complications will be monitored and recorded at the investigator or designee's discretion.

7.4.9. Hepatitis B and C Testing

Viral hepatitis B and C serologic markers and viral load (if applicable) will be tested by the local laboratory. HBV testing will include hepatitis B surface antibody (HBsAb), HBsAg, and hepatitis B core antibody (HBcAb). In addition, HBV DNA will be quantified in patients with positive test results for HBsAg. HCV testing will consist of HCV antibody plus HCV RNA in patients with positive test results for HCV antibody.

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

7.5. Tumor and Response Evaluations

Tumor imaging will be performed ≤ 28 days before randomization. Results of standard of care tests or examinations performed prior to obtaining informed consent and ≤ 28 days before randomization may be used for the purposes of screening rather than repeating the standard of care tests. Tumor response will be assessed by the investigator using RECIST v1.1 (see Appendix 4).

Each tumor assessment will include CT scans (with oral/intravenous contrast, unless contraindicated) of the chest and abdomen (including liver and adrenal glands). In addition, patients will undergo whole body positron emission tomography (PET) at screening. Other known or suspected sites of disease must be included in the imaging assessments (bone, brain, etc). A CT scan of the chest, abdomen, and pelvis along with a bone scan can be used as an alternative for whole body PET/CT at the investigator's discretion. 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).

After the screening period, tumor assessments using CT scans (with oral/intravenous contrast, unless contraindicated) will be performed in EOT/Safety Follow-up Visit after the neoadjuvant treatment phase. Tumor assessments for the Presurgical Visit may not be repeated if there was a standard tumor assessment per protocol performed ≤ 14 days before surgery. After surgery, each tumor assessment will be performed by CT scans (with oral/intravenous contrast, unless contraindicated) of the chest and abdomen (including liver and adrenal glands), and biopsy (if disease progression is suspected). The first disease follow-up tumor assessment after surgery will

be performed after 3 months (± 2 weeks) postsurgery, then every 6 months (± 4 weeks) for the first 2 years, and annually (± 8 weeks) thereafter.

Tumor assessments must continue according to the schedule until disease recurrence or progression that precludes definitive surgery, withdrawal of consent, initiation of new anticancer therapy except the prespecified adjuvant treatment, death, loss to follow-up, or study termination by the sponsor, whichever occurs first. Tumor assessment should be performed by investigator per RECIST v1.1, and disease resectability should be assessed by attending thoracic surgeon per local guideline and best clinical experience. Disease progression that does not preclude definitive surgery or initiation of prespecified adjuvant treatment is not a criterion of tumor assessment discontinuation. Patients precluded from planned surgery for any reasons except disease progression or death will continue to undergo tumor assessment every 6 weeks (± 1 week) until disease progression, death, initiation of new anti-cancer therapy, withdrawal of consent, loss to follow-up, or study termination by the sponsor, whichever occurs first. If a CT scan with contrast is contraindicated (eg, in patients with impaired renal clearance), a noncontrast CT scan of the chest may be performed and contrast-enhanced MRI scans (if possible) of the abdomen should be performed. If a CT scan for tumor assessment is performed using a PET/CT scanner, the CT scan acquisition must be consistent with the standards of a diagnostic CT scan.

With immunotherapies, pseudoprogression may occur due to immune-cell infiltration and other mechanisms leading to apparent increase of existing tumor masses or appearance of new tumor lesions. Also, some patients may benefit from additional immunotherapies despite evidence of disease progression. Optional biopsy is highly recommended for patients with suspected pseudoprogression, who may not be able to tolerate the surgical procedure. The following criteria must be met to continue neoadjuvant treatment of patients with disease progression assessed by investigator per RECIST v1.1:

- Absence of clinical symptoms and signs of disease progression (including clinically significantly worsening of laboratory values)
- ECOG PS 0 or 1
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, cord compression) that requires urgent alternative medical intervention
- Investigators must obtain written informed consent for treatment after radiologic disease progression and inform patients that this practice is not considered standard in the treatment of cancer.
- The decision to continue study drug(s) beyond initial investigator-assessed progression per RECIST v1.1 must be agreed on the medical monitor and documented in the study records.

7.6. Pharmacokinetic and Antidrug Antibody Testing

Blood samples will be collected for PK characterization of tislelizumab and/or other investigational agents in the original protocol. The serum or plasma (as appropriate) samples will be assayed for tislelizumab and/or other investigational agent concentrations using validated bioanalytical methods. Validated screening and confirmatory assays will be employed to detect ADAs for tislelizumab and other protein therapeutics investigational agents as appropriate.

PK and ADA samples will be collected at the timepoints indicated in Appendix 1. Requirements for collecting PK/ADA of investigational agents included in any new tislelizumab-based combination arm(s) that may be added in the future will be described in the respective protocol amendment(s).

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

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.

7.7.1. Tissue Biomarkers

See Appendix 1 for the tissue biomarker sample collection schedule.

Baseline tissue samples collected during screening and surgery will be shipped to a central laboratory for biomarker testing after local regulatory approval. This may occur after the start of study treatment if necessary.

Patients must provide at least 15 freshly cut unstained FFPE slides of the primary tumor or FFPE block containing equivalent tumor tissues (preferred) for central PD-L1 evaluation during screening and other exploratory biomarker assessments. Only patients with evaluable PD-L1 status as assessed by the central laboratory are eligible. If the local result of EGFR mutation status (nonsquamous only) is not available, 3 additional FFPE slides are required for central EGFR testing. If the first attempt of PD-L1 testing by the central laboratory fail, 3 additional slides may be required for repeat testing. If sufficient baseline tumor tissue is available, around 35 unstained FFPE slides or equivalent FFPE block are strongly recommended to be provided to ensure exploration of all planned biomarkers. If accessible, a baseline lymph node sample (6 to 10 FFPE slides) is recommended to be provided. If fewer slides are available, please contact the sponsor for recommendations.

If patients undergo surgery, tumor tissue and lymph node tissue obtained from surgical resection are required and sent to a central laboratory according to study pathology manuals for pathological response analysis as assessed by BIPR. In addition, representative tissue samples of the primary tumor (at least 20 freshly cut unstained FFPE slides or FFPE block containing equivalent tumor tissues [preferred]) will be collected and sent to a central laboratory for biomarker evaluation. If sufficient tumor tissue is available, around 40 FFPE slides of surgery tumor tissue are recommended to be provided to ensure exploration of all planned biomarkers. If accessible, a surgical lymph node sample is recommended to be provided. The surgical specimen for biomarker evaluation is optional for patients who achieve pCR after neoadjuvant treatment.

Acceptable fresh biopsy samples include core needle biopsies from deep tumor tissue or excisional, incisional, punch, or forceps biopsies from 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, lavage samples, and bone/bone marrow aspirates are not acceptable.

Biomarker analyses in tumor and lymph node tissues will include analyses of PD-L1, immune cell quantification and phenotyping, GEP, gene mutations/TMB/MSI, TCR sequencing and target or ligands expression in each investigational arm, at baseline, surgery, and/or at disease progression/reoccurrence to explore the pharmacodynamics of the therapeutic drugs, as well as potential predictive and prognostic biomarkers and mechanisms of resistance. The analysis may include the association between these biomarkers and clinically relevant outcomes including clinical efficacy, disease status, and resistance.

Patients who have disease progression/recurrence will be asked to provide an optional biopsy (Appendix 1) from accessible tumor sites to explore the mechanism of resistance. If feasible, any follow-up biopsies should ideally be collected from the same tumor lesion used at baseline. Written patient consent is required for fresh tumor biopsies.

7.7.2. Blood Biomarkers

See Appendix 1 for the blood biomarker sample collection schedule.

Blood samples will be collected at predose on Day 1 of Cycle 1, on Day 8 of Cycle 1 and at predose on Day 1 of Cycle 2 of neoadjuvant phase to evaluate PK and ADA biomarkers (Appendix 1). Blood samples will also be collected at the EOT/Safety Follow-up visit; 7 days after surgery, and then at the same visits for disease follow-up tumor assessment after surgery.

Blood-based biomarkers will include periphery immune-cell quantification and phenotype change, concentration and dynamic changes of cytokines/chemokines or soluble proteins such as cytokine/chemokine in the blood, ctDNA or MRD, and TCR sequencing. Changes in those biomarkers may provide evidence of biologic activity of therapeutic drug combination treatment in human. Correlations between these biomarkers and efficacy endpoints will be explored to identify blood-based biomarkers that may help identify patients that are more likely to benefit from investigational agent combination treatment. Analysis may include the association between these biomarkers and clinically relevant outcomes including response, resistance, and prognosis.

7.8. 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 prior to study treatment administration unless otherwise noted. Laboratory results should be reviewed before study treatment administration. The radiograph results from scheduled or unscheduled tumor assessment must be reviewed by the investigator before dosing at the next cycle.

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.

A cycle is defined as having a duration of 21 days. Subsequent visits should be conducted according to the planned schedule every 21 days from Day 1 of last cycle.

7.9. Unscheduled Visits

Unscheduled visits may be performed at any time at the patient's or the investigator's request and may include assessment of vital signs/focused physical examination, ECOG PS, AE review, review of concomitant medications and procedures, radiographic assessments, physical examination of the liver, spleen, and lymph nodes, review of 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's assessment as appropriate, and the results of the diagnostic tests and images should be entered on the unscheduled visit eCRF.

8. SAFETY MONITORING AND REPORTING

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

8.1. Risks Associated With Study Treatment

The information on the risks associated with each investigational agent is provided in the corresponding appendix:

- Tislelizumab: Appendix 11
- Ociperlimab: Appendix 12
- LBL-007: Appendix 13
- Chemotherapy: Appendix 14

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 investigational agent(s) as well as the nonclinical/clinical data from other immunotherapy combination(s) containing PD-L1/PD-1 inhibitors, were considered. Specifically, patients at risk for developing study-emergent active autoimmune diseases or who have a history of autoimmune diseases that may relapse, patients who have undergone allogeneic stem cell or organ transplantation, and patients who have received a live vaccine ≤ 28 days before randomization are excluded from the study (see Section 4.2 for the full list of exclusion criteria).

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 the study treatment or not.

Examples of AEs include:

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

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

Safety will be evaluated in this study through the monitoring of all AEs, defined and graded according to NCI-CTCAE v5.0 (except as noted in Section 8.6.4). 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; physical examinations; laboratory measurements (hematology, chemistry, etc); imaging; consultations (as needed); and other assessments, including those listed in Appendix 1 (Schedule of Assessments) and those listed in each investigational agent-specific appendix, if appliable. 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 treatment will only be administered after clinical laboratory results have been reviewed. Administration of study treatment will be performed in a setting where emergency medical equipment and staff who are trained to respond to medical emergencies are available (see Appendix 11, Appendix 12, Appendix 13, and Appendix 14).

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

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

8.3.4. Assessment of Causality

The investigator is obligated to assess the relationship between the study treatment and the occurrence of each AE or SAE, using best clinical 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 administration of study treatment should be considered and investigated. The investigator should consult the Investigator's Brochure of each study drug in the determination of his/her assessment.

There may be situations when an SAE has occurred and the investigator only has 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 transmitting the SAE report to the sponsor, because the causality assessment is one of the criteria used in determining regulatory reporting requirements. After considering follow-up information, the investigator may subsequently change his/her opinion of causality 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 treatment (ie, there are facts, evidence, or arguments to suggest possible causation). The following factors should be considered in making this assessment, including the following:

- Temporal relationship of the AE to the administration of study treatment or study procedure
- Whether an alternative etiology has been identified
- Mechanism of action of the study treatment
- Biological plausibility
- An AE should be considered "related" to study treatment if any of the following 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 treatment). However, the influence of other factors may have contributed to the AE (eg, the patient's clinical condition or other concomitant AEs).

8.3.5. Follow-up of Adverse Events

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

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

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

8.3.6. 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. Clinically associated events can be reported as a single event (eg, simultaneous occurrence of anemia, thrombocytopenia, and leukopenia may be reported as myelosuppression). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L (or mmol/L) should be recorded as “hyperkalemia.”

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

8.4. Definition of a Serious Adverse Event

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

8.5. Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is a serious adverse reaction that is both unexpected (ie, not present in the 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 that noted in the corresponding Investigator's Brochure for the respective investigational agent(s).

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

8.6.1. Adverse Event Recording Period

After informed consent has been signed but before the administration of the study treatment, only SAEs associated with protocol-defined procedure should be reported to the sponsor.

After initiation of study treatment, all AEs and SAEs, regardless of relationship to the study treatment, will be reported until either 30 days after the last dose of study treatment or until initiation of prespecified adjuvant treatment or other new anticancer therapy, whichever occurs first. Surgical procedure complications will be monitored and recorded at the investigator or designee's discretion. Immune-mediated AEs (serious or nonserious) should be recorded until 90 days after the last dose of study treatment, regardless of whether the patient starts prespecified adjuvant treatment or other new anticancer therapy. SAEs assessed as related to the study treatment that are brought to the attention of the investigator should be reported regardless of time since the last dose of treatment.

AEs and SAEs should be as outlined in Table 3. For the follow-up period for AEs, see Section 8.3.5. For the definition of TEAEs, see Section 9.3.2.

Table 3: 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
SAE associated with protocol-defined procedure	Signing of informed consent	First dose of study drug
All AEs, SAEs [a]	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 AE	First dose of study drug	Up to 90 days after last dose (regardless of initiation of new anticancer therapy), death, withdrawal of consent, or loss to follow-up, whichever occurs first

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

[a] All SAEs considered related to the study treatment(s) that are brought to the attention of the investigator should be reported regardless of time since the last dose of treatment until death, withdrawal of consent, or loss to follow-up, whichever occurs first.

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 (≤ 24 hours after determination) to the sponsor or designee as described in Table 4.

Table 4: Timeframes and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

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

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

a. Report follow-up information that is clinically relevant and pertains to the SAE, which includes but is not limited to the following: Update to the SAE, new additional SAE, outcome, seriousness criteria, investigator-assessed causality, event start date/date of onset, date of death, relationship to each study drug. 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 electronically from within the electronic data capture system. If the electronic submission is not available for any reason, a paper SAE form should be submitted by email or fax.

8.6.2.2. Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a patient, he or she is to report the information to the sponsor ≤ 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 or she must not 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 investigational agent 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. Events that are clearly consistent with the pattern of progression of the underlying disease and are considered unequivocally due to disease progression should not be reported as AEs. However, if there is any uncertainty as to whether an event is due to disease progression, it should be recorded as an AE (see Section 8.6.2).

8.6.5. Deaths

Deaths that occur during the adverse event recording period and which are attributed by the investigator solely to disease progression should not be reported as an AE but recorded on the End of Study eCRF page. For other deaths that occurred during the study safety reporting period (refer to Section 8.6.1), regardless of relationship to study drug, the primary cause of death must be reported as a fatal SAE on the Adverse Event eCRF and immediately reported to the sponsor (see Section 8.6.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown, then the death could be reported as an AE, eg, “Death NOS.”

8.6.6. Pregnancies

If a female patient or the female partner of a male patient becomes pregnant during the pregnancy reporting period, a pregnancy report form must be submitted to the sponsor. The pregnancy reporting period for each arm is specified in Appendix 15. The pregnancy report form is a type of SAE report and must follow the same prompt reporting guidelines described in Section 8.6.2.1. The outcome of the pregnancy, including any premature termination of the pregnancy will also be reported to the sponsor.

While pregnancy itself is not considered an AE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE. An abortion, whether accidental, therapeutic, or spontaneous, should always be reported as an SAE. Similarly, any congenital anomaly or birth defect in a child born to a patient exposed to the study treatment should be recorded and reported as an SAE.

Patients who become pregnant must immediately discontinue treatment (see Section 3.7). For patients who are no longer pregnant, resumption of treatment may be discussed with the medical monitor.

In addition to the common stipulations with respect to pregnancy in this section, additional requirements for the treatment with a particular agent are provided in the investigational agent-specific appendix, if applicable.

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 treatment 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 reference safety information (RSI) in the Investigator's Brochure of each study drug.

8.6.8. Assessing and Recording Immune-Mediated Adverse Events

Treatment with anti-PD-1 therapy and immune checkpoint inhibitors can cause autoimmune disorders. All AEs considered by the investigator to be immune-mediated (see Section 8.7.2) should be classified as imAEs and identified as such in the eCRF adverse event page.

8.6.9. Recording Infusion-Related Reactions

Most anticancer treatments carry a risk for infusion reactions; the incidence may increase when different agents are administered concomitantly. The majority of infusion reactions are characterized by non-specific symptoms, including headache, nausea, fever or chills, dizziness, flush, pruritus, and chest or back pain. These may occur more frequently on initial exposure with less frequent or less severe reactions observed on re-exposure. Severe reactions are uncommon, but may be fatal without appropriate intervention. Any signs or symptoms experienced by patients during the infusion of pharmacologic or biologic agents or any event occurring on the first day of drug administration should be evaluated accordingly.

Any event occurring during or within 24 hours of study drug administration and considered related to the infusion of study treatment should be recorded as a diagnosis (Infusion-related reaction) on the Adverse Event eCRF.

Refer to the eCRF completion guidelines for details. See Appendix 7 for management of infusion-related reactions.

8.6.10. Recording Anaphylaxis

Anaphylaxis is a serious systemic hypersensitivity reaction that is usually rapid in onset and may cause death. It is characterized by the rapid development of airway and/or breathing and/or circulation problems. Intramuscular adrenaline is the most important treatment. Rechallenge is contraindicated. The definition currently accepted by the Agency relies on clinical diagnostic criteria and does not specify a particular immunologic mechanism (US FDA 2014).

It is acknowledged that the distinction between an infusion reaction (refer to Section 8.6.9) and anaphylaxis can be challenging, but nevertheless such distinction is necessary due to the different clinical consequences and the potential option of being rechallenged.

To capture all potential adverse events, it is recommended to report all cases meeting the clinical diagnostic criteria of anaphylaxis as a diagnosis of "Anaphylaxis" with appropriate NCI-CTCAE grading (only Grade 3 through 5 is applicable).

8.7. Management of Events to be Monitored

In addition to the common statements with respect to events to be monitored presented in this section, additional requirements regarding AEs of interest for each particular agent are provided in the investigational agent-specific appendix, if applicable.

8.7.1. Infusion-Related Reactions and Anaphylaxis

Patients should be closely monitored during and after study drug administration for infusion-related reactions and anaphylaxis reactions. See Section 5.2.1 for the monitoring periods required. Immediate access to an intensive care unit or equivalent environment and appropriate medical therapy (including epinephrine, corticosteroids, antihistamines, bronchodilators, and oxygen) must be available to treat infusion-related reactions.

See Appendix 7 for the management of infusion-related reactions and anaphylaxis reactions as well as treatment modifications.

8.7.2. Immune-Mediated Adverse Events

In this study, imAEs are events to be monitored. Potential imAEs are listed in Table 5 below. All AEs similar to those listed in the table should be evaluated in patients receiving the study agent(s) to determine whether the AE is immune-mediated. 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 may not be limited to serologic, immunologic, and histologic (biopsy) data (see Appendix 7). If alternative causes have been ruled out and the AE required the use of systemic steroids, other immunosuppressants, or endocrine therapy, and it is consistent with an immune-mediated mechanism of action, the imAE indicator in the eCRF AE page should be checked.

Recommendations for managing imAEs are detailed in Appendix 7.

Table 5: Examples of Immune-Mediated Adverse Events

Body system affected	Events
Skin	Rash, vitiligo, follicular or urticarial dermatitis, erythematous/lichenoid rash, sweet syndrome, full-thickness necrolysis/Stevens-Johnson syndrome
Gastrointestinal	Colitis (includes diarrhea with abdominal pain or endoscopic/radiographic evidence of inflammation), pancreatitis, hepatitis
Endocrine	Thyroiditis, hypothyroidism, hyperthyroidism, hypophysitis with features of hypopituitarism, insulin-dependent diabetes mellitus, diabetic ketoacidosis, adrenal insufficiency
Respiratory	Pneumonitis/diffuse alveolitis

Body system affected	Events
Eye	Episcleritis, conjunctivitis, iritis/uveitis
Musculoskeletal	Arthritis, arthralgia, myalgia, myasthenic syndrome/myasthenia gravis, myositis
Blood	Anemia, leukopenia, thrombocytopenia
Renal	Interstitial nephritis, glomerulonephritis
Cardiac	Pericarditis, myocarditis
Neurologic	Encephalitis, Guillain-Barré syndrome, meningitis, meningoradiculitis, meningoencephalitis, neuropathy

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. Data will be listed and summarized per sponsor agreed reporting standards, where applicable. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

9.1. Statistical Analysis

9.1.1. Randomization Methods

Patients will be randomly assigned to treatment arms using the IRT system for this study by block randomization.

The randomization ratio will be adjusted to account for fluctuation in the number of experimental arms that are open for enrollment over the course of the study. Arm 1A and Arm 2A may stay open with the corresponding randomization ratio whenever there is at least 1 combination arm open for enrollment.

In the current protocol, approximately 60 patients will be randomly assigned to Substudy 1, including Arm 1A (tislelizumab monotherapy), Arm 1B (tislelizumab in combination with ociperlimab), and Arm 1C (LBL-007 in combination with tislelizumab) in patients with tumor PD-L1 expression ≥ 50% in a 1:1:1 randomization ratio. Patients randomized to Arm A, Arm B, and Arm C in original protocol (0.0) and protocol amendment 1.0 will be mapped to Arm 1A, Arm 1B, and Arm 1C in this protocol amendment 2.0, respectively. Approximately 60 patients with tumor PD-L1 expression < 50% will be randomly assigned to Substudy 2, including Arm 2A (tislelizumab in combination with chemotherapy) and Arm 2C (LBL-007 in combination with tislelizumab and chemotherapy) in a 1:2 randomization ratio.

9.1.2. Analysis Sets

The Intent-to-Treat (ITT) analysis set includes all enrolled patients. Patients will be analyzed according to their randomized treatment arm.

The Intent-to-Treat with tumor PD-L1 expression ≥ 50% (ITT-1) analysis set includes all enrolled patients with tumor PD-L1 expression ≥ 50% in Substudy 1. Patients will be analyzed according to their randomized treatment arm. It will be the primary analysis set for the efficacy analysis of patients with tumor PD-L1 expression ≥ 50%.

The Intent-to-Treat with tumor PD-L1 expression < 50% (ITT-2) analysis set includes all enrolled patients with tumor PD-L1 expression < 50% in Substudy 2. Patients will be analyzed according to their randomized treatment arm. It will be the primary analysis set for the efficacy analysis of patients with tumor PD-L1 expression < 50%.

The Safety (SAF) analysis set includes all enrolled patients who received ≥ 1 dose of neoadjuvant treatment. Patients will be analyzed according to the treatment they actually received. It will be the analysis set for the safety analyses.

The Efficacy Evaluable (EE) analysis set includes all patients from the SAF analysis set who have completed surgery as planned; it will be used as supportive analysis set.

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

9.1.3. Patient Disposition

The number of patients randomized, treated, and discontinued from any study treatment and/or from the study, and those with important protocol deviations will be counted. The primary reason for study treatment and/or study discontinuation will be summarized according to the categories in the eCRF. The end of study status (alive, dead, withdrew consent, or lost to follow-up) at the database 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 in the ITT analysis set, ITT-1 analysis set, and ITT-2 analysis set will be summarized using descriptive statistics. Continuous variables include age, weight, and vital signs. Categorical variables include sex, ECOG PS, race, histology, stage of disease, PD-L1 expression level, smoking status, and number of lesion sites.

9.1.5. Prior and Concomitant Medications

Concomitant medications will be coded using the WHO Drug Dictionary drug codes. Concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical (ATC) code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class in the clinical study report for this protocol. Prior medications will be defined as medications that were stopped before the day of the first dose of study treatment. Concomitant medications will be defined as medications that 1) started before the first dose of study treatment and were continuing at the time of the first dose of study treatment, or 2) started on or after the date of the first dose of study treatment and up to 30 days after the patient's last dose of the study drug (s) (as of the Safety Follow-up Visit).

9.2. Efficacy Analysis

9.2.1. Primary Efficacy Analysis

MPR rate as assessed by the BIPR

MPR rate is defined as the proportion of patients with ≤ 10% residual viable tumor in the resected primary tumor and all resected lymph nodes as assessed by BIPR. The primary analysis of MPR rate will be based on the ITT-1 and ITT-2 analysis sets. Patients that do not have the planned surgery will be considered as failures/non-responders, and will therefore be counted in the denominator, but not in the numerator of the MPR rate. The MPR rate and its Clopper-Pearson 95% CI will be calculated for each arm in each analysis set. The difference in MPR rate will be evaluated using Fisher's exact test between each combination arm and monotherapy arm in the ITT-1 analysis set, and between LBL-007 in combination with tislelizumab and chemotherapy arm and tislelizumab in combination with chemotherapy arm in the ITT-2 analysis set separately. The odds ratio and the difference in MPR rate in each analysis set, as well as their 2-sided 95% CIs, will also be calculated.

The monotherapy arm in the primary efficacy analysis for the ITT-1 analysis set will only include patients randomized to the monotherapy arm who also had the opportunity to be randomized to other combination therapy arms in order to conduct rigorous between-arm comparisons. The tislelizumab in combination with chemotherapy arm in the primary efficacy analysis for the ITT-2 analysis set will only include patients randomized to the tislelizumab in combination with chemotherapy arm who also had the opportunity to be randomized to other immunotherapy in combination with tislelizumab and chemotherapy arms in order to conduct rigorous between-arm comparisons.

9.2.2. Secondary Efficacy Analysis

pCR rate as assessed by the BIPR

pCR rate is defined as the proportion of patients with absence of residual tumor in the resected primary tumor and all resected lymph nodes. The pCR rate will be summarized similarly as the MPR rate in the ITT-1 and ITT-2 analysis sets.

EFS as assessed by the investigator

EFS is defined as the time from randomization until any of the following events, whichever occurs first: radiographic disease progression that precludes definitive surgery, local or distant recurrence, as assessed by the investigator according to RECIST v1.1, or death due to any cause.

The efficacy analysis of EFS will be conducted in the ITT-1 and ITT-2 analysis sets separately. Hazard ratio and corresponding two-sided 95% CI will be estimated using a Cox proportional hazards model. Kaplan-Meier methodology will be used to estimate median and other quartiles of EFS for each treatment arm. EFS rates at selected timepoints (1-year and 2-year) will be estimated using the Kaplan-Meier method with the corresponding 95% CI constructed using Greenwood's formula (Greenwood 1926). Kaplan-Meier curve will be constructed to provide a visual description of the difference among treatment arms.

OS

OS is defined as the time from the date of randomization to the date of death due to any cause. The OS will be summarized similarly as the EFS in the ITT-1 and ITT-2 analysis sets

DFS as assessed by the investigator

DFS is defined as the time from the first date of no disease to local recurrence or distant metastasis or death due to any cause, whichever occurs first, as determined by the investigator. DFS will be analyzed only for patient who have undergone R0 resection in ITT-1 and ITT-2 analysis sets separately. If patients are alive without recurrence, DFS will be determined from the first date of no disease to the date they were last known to be alive, and data will be censored on the date they were last known to be alive. DFS will be summarized similarly as the EFS in the ITT-1 and ITT-2 analysis sets.

9.2.3. Exploratory Efficacy Analysis

The first exploratory efficacy analysis will be based on the EE analysis set with patients with tumor PD-L1 expression ≥ 50% who completed the planned surgery. This analysis set will be used to evaluate the MPR and pCR of the patients with tumor PD-L1 expression ≥ 50%.

The second exploratory efficacy analysis will be conducted by including all patients with tumor PD-L1 expression ≥ 50% from the monotherapy arm for treatment comparison, regardless of whether a monotherapy arm patient had the opportunity or not to be randomized to other experimental arms. Such analysis will be applied to evaluate the difference in MPR and pCR of the patients with tumor PD-L1 expression ≥ 50%.

The third exploratory efficacy analysis will be based on the EE analysis set with patients with tumor PD-L1 expression < 50% who completed the planned surgery. This analysis set will be used to evaluate the MPR and pCR of the patients with tumor PD-L1 expression < 50%.

The fourth exploratory efficacy analysis will be conducted by including all patients with tumor PD-L1 expression < 50% from the tislelizumab in combination with chemotherapy arm for treatment comparison, regardless of whether a tislelizumab in combination with chemotherapy arm patient had the opportunity or not to be randomized to other experimental arms. Such analysis will be applied to evaluate the difference in MPR and pCR of the patients with tumor PD-L1 expression < 50%.

The fifth exploratory efficacy analysis will be an across-study indirect comparison based on the ITT-2 analysis set combined with patients treated with tislelizumab in combination with chemotherapy from Study BGB-A317-315. This analysis set will be used to evaluate the MPR and pCR of the patients with tumor PD-L1 expression< 50%.

9.3. Safety Analyses

Safety will be assessed by monitoring and recording all AEs graded by NCI-CTCAE v5.0. Laboratory values (eg, hematology, clinical chemistry, coagulation, and urinalysis), dosing, vital signs, ECGs, and physical examinations will also be evaluated. All safety data in the SAF analysis set will be summarized descriptively.

9.3.1. Extent of Exposure

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

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

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

9.3.2. Adverse Events

The AE verbatim descriptions (as recorded by the investigator on the eCRF) will be classified into standardized medical terminology using the MedDRA. AEs will be coded to the MedDRA lowest level term closest to the verbatim term, preferred term, and primary System Organ Class (SOC).

A TEAEs 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 the study treatment and during up to 30 days after

study treatment discontinuation, or initiation of new anticancer therapy, or prespecified adjuvant treatment, whichever occurs first. Only those AEs that were treatment-emergent will be included in the summary tables of TEAEs. All AEs, treatment-emergent or otherwise, will be presented in patient-level listings.

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 experimental immunotherapy and up to 90 days after the last dose of study treatment, regardless of whether the patient starts a new anticancer therapy or prespecified adjuvant treatment.

The incidence of TEAEs will be reported by SOC and Preferred Term as the number (percentage) of patients with TEAEs. A patient will be counted only once by the highest severity grade per NCI-CTCAE v5.0 within an SOC and Preferred Term, even if the patient experienced ≥ 1 TEAE within a specific SOC and Preferred Term.

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

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

9.3.3. Laboratory Analyses

Clinical laboratory (eg, hematology, serum chemistry, urinalysis) values will be evaluated for each laboratory parameter. 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, SD, median, minimum, maximum for continuous variables; n [%] for categorical variables) for laboratory parameters will be calculated.

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

9.3.4. Vital Signs

Descriptive statistics for vital sign parameters (body temperature, pulse rate, 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. Electrocardiograms

ECG will be performed at the baseline and at multiple time points after the start of treatment. Clinically significant abnormalities on ECG findings will be presented in a frequency table by visit and arm as appropriate.

9.3.6. Eastern Cooperative Oncology Group Performance Status

A shift table from baseline to worst postbaseline in ECOG PS will be summarized by arm. ECOG PS scores will be summarized by visit and arm, as appropriate.

9.3.7. Feasibility of Surgery

The proportion of patients who undergo surgical resection within the scheduled period after receiving any dose of the investigational agent(s), will be summarized in the ITT-1 and ITT-2 analysis sets. Delayed or canceled surgery, duration of surgery, and surgical approach will also be summarized in ITT-1 and ITT-2 analysis sets.

9.4. Biomarker Analysis

For the analysis of the biomarker endpoint, which is pharmacodynamic biomarker change (eg, Treg reduction) based on mechanisms of action of each investigational agents (see agent-specific appendix) between combination arms versus monotherapy arm, a two-sample t test will be used to compare percentage of biomarker change from baseline to surgery between arms in the Biomarker analysis set. Equal variance assumption will be checked. The percentage of biomarker change within each arm is defined as the change of biomarker at post-treatment from baseline divided by that at baseline. If considerable missing occurs, a linear mixed model with random intercept will be used to estimate biomarker change per arm in the Biomarker analysis set. Treatment assignment, visit, and the interaction of the two will be included as main effects while patient is considered as random effect. Other important demographic or baseline characteristics can be also adjusted, if necessary. Biomarker change will be compared between combination arms and the monotherapy arm using likelihood ratio test (LRT) from linear mixed model. Non-parametric test will be used if the normality assumption is severely violated.

Associations between biomarkers and efficacy endpoints will be examined using logistics regression for binary endpoint, and Cox proportional hazards model for survival endpoints. More details will be provided in Statistical Analysis Plan.

9.5. Pharmacokinetic Analysis

Serum/plasma concentration data will be tabulated and summarized by visit/cycle at which these concentrations are collected. Descriptive statistics will include means, medians, ranges, and SDs, as appropriate. Pharmacokinetic analysis will be conducted.

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

9.6. Immunogenicity Analyses

ADA samples will be collected for tislelizumab and protein therapeutic investigational agents in this study as outlined 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 and will be reported separately from the main study report.

9.7. Sample Size Consideration

This study is designed for the preliminary evaluation of the pharmacodynamics, safety, and efficacy of tislelizumab monotherapy and multiple tislelizumab-based immunotherapy combinations with or without chemotherapy in patients with resectable Stage II to IIIA NSCLC. It is not designed to allow explicit power and Type I error considerations so there is no formal statistical hypothesis.

Approximately 60 patients will be randomly assigned to Substudy 1, including Arm 1A (tislelizumab monotherapy), Arm 1B (tislelizumab in combination with ociperlimab), and Arm 1C (LBL-007 in combination with tislelizumab) in patients with tumor PD-L1 expression ≥ 50% in a 1:1:1 randomization ratio. Approximately 60 patients with tumor PD-L1 expression < 50% will be randomly assigned to Substudy 2, including Arm 2A (tislelizumab in combination with chemotherapy) and Arm 2C (LBL-007 in combination with tislelizumab and chemotherapy) in a 1:2 randomization ratio. For the further emerging experimental drugs to be added into the study, roughly 20 patients with tumor PD-L1 expression ≥ 50% are planned to be enrolled for each corresponding tislelizumab-based immunotherapy combination arm, and roughly 40 patients with tumor PD-L1 expression < 50% are planned to be enrolled for each corresponding tislelizumab in combination with immunotherapy and chemotherapy arm.

Twenty patients in Arms 1A, 1B, 1C, and 2A, and 40 patients in Arm 2C will provide adequate information for estimation precision and safety evaluation. With the defined sample size, the expected 95% CI of the MPR rate difference in patients with tumor PD-L1 expression ≥ 50% between the tislelizumab-based immunotherapy combination arms and the tislelizumab monotherapy arm would be 1% to 59% if the true MPR for the tislelizumab-based immunotherapy combinations arm and monotherapy arm is 70% and 40%, respectively. The expected 95% CI of the MPR rate difference in patients with PD-L1 expression < 50% between the LBL-007 in combination with tislelizumab and chemotherapy arm and the tislelizumab in combination with chemotherapy arm would be -11% to 41% if the true MPR for the LBL-007 in combination with tislelizumab and chemotherapy arm and the tislelizumab in combination with chemotherapy arm is 49% and 34%, respectively. Patients in each arm will be followed for approximately 24 months.

9.8. Interim Analysis

No interim analysis is planned for this study.

10. STUDY COMMITTEES AND COMMUNICATION

10.1. Blinded Independent Pathology Review

A BIPR will be established for central review of pathologic responses. Tumor and lymph node samples will be submitted for central review. Sites will be trained before enrolling the first study patient. Pathology sample acquisition guidelines and the submission process will be outlined in the study pathology manuals to be provided by the vendors. For the histologic assessment, all tumor and associated lymph node tissues should be sectioned at 1-cm intervals. For assessments of pathological response, the percentage of viable tumor cells (TC) in ≥ 1 section per centimeter of the tumor and lymph node tissue resected should be evaluated. The assessment by the BIPR will be used for reporting of MPR and pCR.

10.2. Steering Committee

A steering committee will be established to provide recommendations on safety management and provide guidance to assure that the study is conducted in accordance with GCP and high scientific standards. This Steering Committee meeting will consist of BeiGene representatives and all Steering Committee members (Steering Committee Charter).

11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

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

11.1. Access to Information for Monitoring

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

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

11.2. Access to Information for Auditing or Inspections

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

12. QUALITY ASSURANCE AND QUALITY CONTROL

12.1. Regulatory Authority Approval

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

12.2. Quality Assurance

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

12.3. Study Site Inspections

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

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

12.4. Drug Accountability

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

At study initiation, the monitor will evaluate the site's standard operating procedure for study drug disposal/destruction to ensure that it complies with the sponsor's requirements specified in the Pharmacy Manual. At appropriate times during the conduct of the study or at the end of the study after 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 reviewed periodically 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 investigator and the study center in full conformance with the guidelines for Good Clinical Practice (ICH E6) 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 Definitions and Standards for Expedited Reporting (ICH E2A).

13.2. Institutional Review Board/Independent Ethics Committee

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

The 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 the 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). The sponsor may utilize a protocol amendment to add new experimental arms to this study when new treatments become available, for discontinuing treatment arms that demonstrate minimal clinical activity or unacceptable toxicity, or modifying the patient population (eg, regarding biomarker status). Prior to implementing any new experimental arm, protocol amendment, and respective health authority and IRB/IEC approvals should be obtained.

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

13.3. Informed Consent

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

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

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

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

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

13.4. Patient and Data Confidentiality

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

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

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

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

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

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

Data generated during this study must be available for inspection upon request by representatives of the 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(s), 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 (including any subinvestigators and coinvestigators) 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 is collected or received by the investigator or study team without prior communication with and approval by the sponsor.

14.1.2. Data Collection

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

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

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

14.1.3. Data Management/Coding

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

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

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

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

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

14.2. Data Integrity and In-House Blinding

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

14.3. Study Records Retention

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into ≥ 1 of the following 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.

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

The sponsor will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that study center for the study, as dictated by any institutional requirements, 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 away from the site so that they can be returned sealed to the

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

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

14.4. Protocol Deviations

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

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

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 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 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 IRB/IEC promptly and provide the reason for the suspension or termination.

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

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

14.7. Information Disclosure and Inventions

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

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

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

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

These restrictions do not apply to the following:

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

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

15. REFERENCES

Ahn E, Araki K, Hashimoto M, et al. Role of PD-1 during effector CD8 T cell differentiation. Proc Natl Acad Sci U S A. 2018;115(18):4749-4754.

Ahn M, Niu J, Kim D, et al. Vibostolimab, an anti-TIGIT antibody, as monotherapy and in combination with pembrolizumab in anti-PD-1/PD-L1-refractory NSCLC. Ann Oncol. 2020;31(suppl 4): S887: abstract 1400P.

Amin MB, Greene FL, Edge SB, et al eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017.

Araghi M, Fidler-Benaoudia M, Arnold M, et al. International differences in lung cancer survival by sex, histological type and stage at diagnosis: an ICBP SURVMARK-2 Study. Thorax. 2021;thoraxjnl-2020-216555.

Bagaev A, Kotlov N, Nomie K, et al. Conserved pan-cancer microenvironment subtypes predict response to immunotherapy. Cancer Cell. 2021;39(6):845-865.

Bendell JC, Bedard P, Bang Y-J, et al. Abstract CT302 - Phase Ia/Ib dose-escalation study of the anti-TIGIT antibody tiragolumab as a single agent and in combination with atezolizumab in patients with advanced solid tumors. Presented at: 24-29 April 2020 AACR Virtual Annual Meeting.

Boles KS, Vermi W, Facchetti F, et al. A novel molecular interaction for the adhesion of follicular CD4 T cells to follicular DC. Eur J Immunol. 2009;39(3):695-703.

Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med. 2015;373;1627-39.

Bottino C, Castriconi R, Pende D, et al. Identification of PVR (CD155) and Nectin-2 (CD112) as cell surface ligands for the human DNAM-1 (CD226) activating molecule. J Exp Med. 2003;198:557-67.

Brahmer JR, Drake CG, Wollner I, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol. 2010;28(19):3167-75.

Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2018;36(17):1714-68.

Cabel L, Proudhon C, Romano E, et al. Clinical potential of circulating tumour DNA in patients receiving anticancer immunotherapy. Nat Rev Clin Oncol 2018;15;639-50.

Camisaschi C, Casati C, Rini F, et al. LAG-3 expression defines a subset of CD4(+)CD25(high)Foxp3(+) regulatory T cells that are expanded at tumor sites. J Immunol. 2010;184(11):6545-51.

Camisaschi C, De Filippo A, Beretta V, et al. Alternative activation of human plasmacytoid DCs in vitro and in melanoma lesions: involvement of LAG-3. J Invest Dermatol. 2014;134(7):1893-1902.

Cascone T, Hamdi H, Zhang F, et al. Superior efficacy of neoadjuvant compared to adjuvant immune checkpoint blockade in non-small cell lung cancer. Cancer Res. 2018;78:1719–1719.

Cascone T, William WN Jr, Weissferdt A, et al. Neoadjuvant nivolumab or nivolumab plus ipilimumab in operable non-small cell lung cancer: the phase 2 randomized NEOSTAR trial. Nat Med. 2021;27(3):504-514.

Chauvin J, Pagliano O, Fourcade J, et al. TIGIT and PD-1 impair tumor antigen-specific CD8(+) T cells in melanoma patients. J Clin Invest. 2015;125:2046-58.

Chauvin JM, Zarour H. TIGIT in cancer immunotherapy. J Immunother Cancer. 2020;8(2):e000957.

Chen X, Xue L, Ding X, et al. An Fc-competent anti-human TIGIT blocking antibody Ociperlimab (BGB-A1217) elicits strong immune responses and potent anti-tumor efficacy in pre-clinical models. Front Immunol. 2022;13:828319.

Chiari R, Sidoni A, Metro G. Early stage resectable non-small cell lung cancer: is neoadjuvant immunotherapy the right way forward? J Thorac Dis. 2018;10(Suppl 33):S3890-4.

Clinical Trials Facilitation Group (CTFG). Recommendations related to contraception and pregnancy testing in clinical trials. September 21, 2020. https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2020_09_HMA_CTFG_Contraception_guidance_Version_1.1_updated.pdf. Accessed 30 March 2022.

Cristescu R, Mogg R, Ayers M, et al. Pan-tumor genomic biomarkers for PD-1 checkpoint blockade-based immunotherapy. Science. 2018;362(6411):eaar3593.

Cruz C, Afonso M, Oliveiros B, et al. Recurrence and risk factors for relapse in patients with non-small cell lung cancer treated by surgery with curative intent. Oncology. 2017;92(6):347-52.

Dahan R, Sega E, Engelhardt J, et al. FcγRs Modulate the Anti-tumor Activity of Antibodies Targeting the PD-1/PD-L1 Axis. Cancer Cell. 2015;28(3):285-95.

Datar I, Sanmamed MF, Wang J, et al. Expression Analysis and Significance of PD-1, LAG-3, and TIM-3 in Human Non-Small Cell Lung Cancer Using Spatially Resolved and Multiparametric Single-Cell Analysis. Clin Cancer Res. 2019;25(15):4663-73.

Depierre A, Milleron B, Moro-Sibilot D, et al. Preoperative chemotherapy followed by surgery compared with primary surgery in resectable stage I (except T1N0), II, and IIIa non-small-cell lung cancer. J Clin Oncol. 2002;20(1):247-53.

Dixon KO, Schorer M, Nevin J, et al. Functional anti-TIGIT antibodies regulate development of autoimmunity and antitumor immunity. J Immunol. 2018;200:3000-7.

Dolgin M, New York Heart Association, Fox AC, et al. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. Edition 9. Boston, MA: Lippincott Williams and Wilkins; 1994.

Donia M, Andersen R, Kjeldsen JW, et al. Aberrant Expression of MHC Class II in Melanoma Attracts Inflammatory Tumor-Specific CD4+ T- Cells, Which Dampen $CD8^+$ T-cell Antitumor Reactivity. Cancer Res. 2015;75(18):3747-59.

Douillard JY, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. Lancet Oncol. 2006;7(9):719-27.

Durham NM, Nirschl CJ, Jackson CM, et al. Lymphocyte Activation Gene 3 (LAG-3) modulates the ability of CD4 T-cells to be suppressed in vivo. PLoS One. 2014;9(11):e109080.

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet. 2016;387:1837-46.

Felip E, Altorki N, Zhou C, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. Lancet. 2021;398(10308):1344-57.

Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). https://drug-interactions.medicine.iu.edu/ Accessed 12 July 2023.

Food and Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. U.S. Department of Health and Human Services, Food and Drug Administration. https://www.fda.gov/drugs/drug-interactions-labeling/drug-development- and drug-interactions-table-substrates-inhibitors-and-inducers. Accessed 12 July 2023.

Forde PM, Chaft JE, Smith KN, et al. Neoadjuvant PD-1 Blockade in Resectable Lung Cancer. N Engl J Med. 2018;378(21):1976-1986.

Forde PM, Spicer J, Lu S, et al. Nivolumab (NIVO) + platinum-doublet chemotherapy (chemo) vs chemo as neoadjuvant treatment (tx) or resectable (IB-IIIA) non-small cell lung cancer (NSCLC) in the phase 3 CheckMate 816 trial. Cancer Res. 2021;81(suppl 13): Abstract CT003.

Forde PM, Spicer J, Lu S, et al. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. N Engl J Med. 2022;386(21):1973-1985.

Fourcade J, Sun Z, Chauvin J, et al. CD226 opposes TIGIT to disrupt Tregs in melanoma. JCI Insight. 2018;3(14):e121157.

Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med. 2018;378(22):2078-2092.

Gao J, Ward JF, Pettaway CA, et al. VISTA is an inhibitory immune checkpoint that is increased after ipilimumab therapy in patients with prostate cancer. Nat Med. 2017;23(5):551-555.

Gao S, Li N, Gao S, et al. Neoadjuvant PD-1 inhibitor (Sintilimab) in NSCLC. J Thorac Oncol. 2020;15(5):816-826.

Gettinger S, Choi J, Hastings K, et al. Impaired HLA Class I Antigen Processing and Presentation as a Mechanism of Acquired Resistance to Immune Checkpoint Inhibitors in Lung Cancer. Cancer Discov. 2017;7(12):1420-35.

Ghosh S, Sharma G, Travers J, et al. TSR-033, a Novel Therapeutic Antibody Targeting LAG-3, Enhances T-Cell Function and the Activity of PD-1 Blockade In Vitro and In Vivo. Mol Cancer Ther. 2019;18(3):632-41.

Gil Del Alcazar CR, Huh SJ, Ekram MB, et al. Immune escape in breast cancer during in situ to invasive carcinoma transition. Cancer Discov. 2017;7(10):1098-115.

Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. J Thorac Oncol 2007;2:706-14.

Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. J Thorac Oncol. 2016;11(1):39-51.

Graydon CG, Mohideen S, Fowke KR. LAG3's Enigmatic Mechanism of Action. Front Immunol. 2021;11:615317.

Greenwood M. The natural duration of cancer. Reports on Public Health and Medical Patients. London: Her Majesty's Stationery Office. 1926; 33:1-26.

Guidelines of Chinese Society of Clinical Oncology (CSCO) Non-Small Cell Lung Cancer. 2020.

Gutierrez M, Lam W, Hellmann M, et al. KEYNOTE-495/KeyImPaCT: interim analysis of a randomized, biomarker-directed, phase 2 trial of pembrolizumab-based combination therapy for non–small cell lung cancer (NSCLC). J Immunother Cancer. 2021;9 (Suppl 2):A485.

Haanen JBAG, Carbonnel F, Robert C, et al. Management of toxicities from immunotherapy: ESMO clinical practice guidelines for diagnosis, treatment, and follow-up. Ann Oncol. 2017;28 (suppl 4):iv119-142.

Hanna N, Johnson D, Temin S, et al. Systemic Therapy for Stage IV Non–Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2017;35(30):3484-515.

Hanna GJ, Lizotte P, Cavanaugh M, et al. Frameshift events predict anti-PD-1/L1 response in head and neck cancer. JCI Insight. 2018;3(4):e98811.

He WL, Zhang H, Han F, et al. CD155T/TIGIT signaling regulates $CD8^+$ T cell metabolism and promotes tumor progression in human gastric cancer. Cancer Res. 2017;77:6375-88.

Hellmann MD, Chaft JE, William WN Jr, et al. Pathological response after neoadjuvant chemotherapy in resectable non-small-cell lung cancers: proposal for the use of major pathological response as a surrogate endpoint. Lancet Oncol. 2014;15:e42-50.

Herbst RS, Soria JC, Kowanetz M et al. Predictive correlates of response to the anti-PD-L1 antibody tislelizumab in cancer patients. Nature. 2014;515:563-7.

Herbst RS, Baas P, Kim D-W, et al. Pembrolizumab versus docetaxel for previously treated PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016;387:1540-50.

Herbst RS, Giaccone G, de Marinis F, et al. Atezolizumab for First-Line Treatment of PD-L1-Selected Patients with NSCLC. N Engl J Med. 2020;383(14):1328-1339.

Herbst RS, Majem M, Barlesi F, et al. COAST: An Open-Label, Phase II, Multidrug Platform Study of Durvalumab Alone or in Combination With Oleclumab or Monalizumab in Patients With Unresectable, Stage III Non-Small-Cell Lung Cancer. J Clin Oncol. 2022;22:JCO2200227.

Heymach JV, Harpole D, Mitsudomi T, et al. AEGEAN: A phase 3 trial of neoadjuvant durvalumab+ chemotherapy followed by adjuvant durvalumab in patients with resectable NSCLC. AACR Annual Meeting. 2023.

Huang CT, Workman CJ, Flies D, et al. Role of LAG-3 in regulatory T cells. Immunity. 2004;21(4):503-13.

Huang RY, Eppolito C, Lele S, et al. LAG3 and PD1 co-inhibitory molecules collaborate to limit $CD8^+$ T cell signaling and dampen antitumor immunity in a murine ovarian cancer model. Oncotarget. 2015;6(29):27359-77.

Huang RY, Francois A, McGray AR, et al. Compensatory upregulation of PD-1, LAG-3, and CTLA-4 limits the efficacy of single-agent checkpoint blockade in metastatic ovarian cancer. Oncoimmunology. 2016;6(1):e1249561.

Huard B, Prigent P, Tournier M, et al. CD4/major histocompatibility complex class II interaction analyzed with CD4- and lymphocyte activation gene-3 (LAG-3)-Ig fusion proteins. Eur J Immunol. 1995;25(9):2718-21.

Hsu J, Hodgins JJ, Marathe M, et al. Contribution of NK cells to immunotherapy mediated by PD-1/PD-L1 blockade. J Clin Invest. 2018;128(10):4654-4668.

Hung AL, Maxwell R, Theodros D, et al. TIGIT and PD-1 dual checkpoint blockade enhances antitumor immunity and survival in GBM. Oncoimmunology. 2018;7:e1466769.

Huynh C, Walsh L, Spicer J. Surgery after neoadjuvant immunotherapy in patients with resectable non-small cell lung cancer. Transl Lung Cancer Res. 2021a;10(1):563-80.

Huynh C, Sorin M, Rayes R, et al. Pathological complete response as a surrogate endpoint after neoadjuvant therapy for lung cancer. Lancet Oncol. 2021b;22(8):1056-1058.

International Committee of Medical Journal Editors. Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. 2018. http://www.icmje.org/icmje-recommendations.pdf. Accessed 17 March 2022.

International Council for Harmonisation of Technical Requirements For Pharmaceuticals for Human Use. Structure and content of clinical study reports. E3. 1995. https://database.ich.org/sites/default/files/E3_Guideline.pdf.

International Council for Harmonisation of Technical Requirements For Pharmaceuticals for Human Use. Clinical safety data management: definitions and standards for expedited reporting. E2A. 1994. https://database.ich.org/sites/default/files/E2A_Guideline.pdf.

International Council for Harmonisation of Technical Requirements For Pharmaceuticals for Human Use. Integrated addendum to ICH E6(R1): guideline for good clinical practice. E6(R2). 2016. https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf.

Iwai Y, Ishida M, Tanaka Y, et al. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proc Natl Acad Sci U S A. 2002;99(19):12293-7.

Johnson JR, Williams G, Pazdur R. End points and United States Food and Drug Administration approval of oncology drugs. J Clin Oncol. 2003;21(7):1404-11.

Johnson DB, Nixon MJ, Wang Y, et al. Tumor-specific MHC-II expression drives a unique pattern of resistance to immunotherapy via LAG-3/FCRL6 engagement. JCI Insight. 2018;3(24):e120360.

Johnston R, Comps-Agrar L, Hackney J, et al. The immunoreceptor TIGIT regulates antitumor and antiviral CD8(+) T cell effector function. Cancer Cell. 2014;26:923-37.

Joller N, Lozano E, Burkett PR, et al. Treg cells expressing the coinhibitory molecule TIGIT selectively inhibit proinflammatory Th1 and Th17 cell responses. Immunity. 2014;40:569-81.

Judge SJ, Dunai C, Aguilar EG, et al. Minimal PD-1 expression in mouse and human NK cells under diverse conditions. J Clin Invest. 2020;130(6):3051-3068.

Junker K, Thomas M, Schulmann K, et al. Tumour regression in non small-cell lung cancer following neoadjuvant therapy: histological assessment. J Cancer Res Clin Oncol. 1997;123:469-77.

Kamada T, Togashi Y, Tay C, et al. PD-1+ regulatory T cells amplified by PD-1 blockade promote hyperprogression of cancer. Proc Natl Acad Sci U S A. 2019;116(20):9999-10008.

Kates M, Nirschl TR, Baras AS, et al. Combined Next-generation Sequencing and Flow Cytometry Analysis for an Anti-PD-L1 Partial Responder over Time: An Exploration of Mechanisms of PD-L1 Activity and Resistance in Bladder Cancer. Eur Urol Oncol. 2021;4(1):117-20.

Keytruda [US prescribing information]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp.; 2021.

Kidman J, Principe N, Watson M, et al. Characteristics of TCR repertoire associated with successful immune checkpoint therapy responses. Front Immunol. 2020;11:587014.

Kisielow M, Kisielow J, Capoferri-Sollami G, et al. Expression of lymphocyte activation gene 3 (LAG-3) on B cells is induced by T cells. Eur J Immunol. 2005;35(7):2081-8.

Kong Y, Zhu L, Schell TD, et al. T-cell immunoglobulin and ITIM domain (TIGIT) associates with $CD8^+$ T-cell exhaustion and poor clinical outcome in AML patients. Clin Cancer Res. 2016;22:3057-66.

Kouo T, Huang L, Pucsek A, et al. Galectin-3 Shapes Antitumor Immune Responses by Suppressing $CD8^+$ T Cells via LAG-3 and Inhibiting Expansion of Plasmacytoid Dendritic Cells. Cancer Immunol Res. 2015;3(4):412-23.

Koyama S, Akbay EA, Li YY, et al. Adaptive resistance to therapeutic PD-1 blockade is associated with upregulation of alternative immune checkpoints. Nat Commun. 2016;7:10501. doi: 10.1038/ncomms10501.

Kumagai S, Togashi Y, Kamada T, et al. The PD-1 expression balance between effector and regulatory T cells predicts the clinical efficacy of PD-1 blockade therapies. Nat Immunol. 2020;21(11):1346-1358.

Kuziora M, Higgs BW, Brohawn PZ, et al. Association of early reduction in circulating tumor DNA (ctDNA) with improved progression-free survival (PFS) and overall survival (OS) of patients (pts) with urothelial bladder cancer (UBC) treated with durvalumab (D). Journal of Clinical Oncology 2017;35:15_suppl;11538.

Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol. 2016;17(11):1497-1508.

Lee JM, Chaft J, Nicholas A, et al. Surgical and Clinical Outcomes With Neoadjuvant Atezolizumab in Resectable Stage IB–IIIB NSCLC: LCMC3 Trial Primary Analysis. Journal of Thoracic Oncology 2021; 16 (3_suppl): S59-61.

Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.

Levin SD, Taft DW, Brandt CS, et al. Vstm3 is a member of the CD28 family and an important modulator of T-cell function. Eur J Immunol. 2011;41(4):902-15.

Lichtenegger FS, Rothe M, Schnorfeil FM, et al. Targeting LAG-3 and PD-1 to Enhance T Cell Activation by Antigen-Presenting Cells. Front Immunol. 2018;9:385.

Liu J, Blake SJ, Yong MC, et al. Improved Efficacy of Neoadjuvant Compared to Adjuvant Immunotherapy to Eradicate Metastatic Disease. Cancer Discov. 2016; 6(12):1382-1399.

Lopez A, Tan J, Anderson AE, et al. Characterization of AB154, a humanized, non-depleting α-TIGIT antibody undergoing clinical evaluation in subjects with advanced solid tumors (P260). J Immunother Cancer 2019;7:282.

Lu S, Wu L, Zhang W, et al. Perioperative toripalimab+ platinum-doublet chemotherapy vs chemotherapy in resectable stage II/III non-small cell lung cancer (NSCLC): Interim event-free survival (EFS) analysis of the phase III Neotorch study. 2023.

Mahnke K, Enk AH. TIGIT-CD155 interactions in melanoma: a novel co-inhibitory pathway with potential for clinical intervention. J Invest Dermatol. 2016;136:9-11.

Manieri NA, Chiang EY, Grogan JL, et al. TIGIT: A key inhibitor of the cancer immunity cycle. Trends Immunol. 2017;38:20-8.

Matsuzaki J, Gnjatic S, Mhawech-Fauceglia P, et al. Tumor-infiltrating NY-ESO-1-specific $CD8^+$ T cells are negatively regulated by LAG-3 and PD-1 in human ovarian cancer. Proc Natl Acad Sci U S A. 2010;107(17):7875-80.

McDermott DF, Atkins MB. PD-1 as a potential target in cancer therapy. Cancer Med. 2013:2(5):662-73.

Miller BC, Sen DR, Al Abosy R, et al. Subsets of exhausted $CD8^+$ T cells differentially mediate tumor control and respond to checkpoint blockade. Nat Immunol. 2019;20(3):326-336.

Narayanan S, Ahi PJ, Bijin VA, et al. LAG3 is a central regulator of NK cell cytokine production. doi: https://doi.org/10.1101/2020.01.31.928200

Mimura K, Kua LF, Xiao JF, et al. Combined inhibition of PD-1/PD-L1, Lag-3, and Tim-3 axes augments antitumor immunity in gastric cancer-T cell coculture models. Gastric Cancer. 2021;24(3):611-23.

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. Cancer Therapy Evaluation Program. 27 November 2017.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer (Version 2, 2022).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer (Version 3, 2023).

Niu J, Nagrial A, Voskoboynik HC, et al. Safety and efficacy of vibostolimab, an anti-TIGIT antibody, plus pembrolizumab in patients with anti-PD-1/PD-L1-naive NSCLC. Ann Oncol. 2020;31(suppl 4): S754-840: abstract 1410P.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55.

Ou W, Sun HB, Ye X, et al. Adjuvant carboplatin-based chemotherapy in resected stage IIIA-N2 non-small cell lung cancer. J Thorac Oncol. 2010;5(7):1033-41.

Pauken KE, Torchia JA, Chaudhri A, et al. Emerging concepts in PD-1 checkpoint biology. Semin Immunol. 2021;52:101480.

Pisters KM, Kris MG, Gralla RJ, et al. Pathologic complete response in advanced non-small-cell lung cancer following preoperative chemotherapy: implications for the design of future non-small-cell lung cancer combined modality trials. J Clin Oncol. 1993;11(9):1757-62.

Pisters KM, Vallières E, Crowley JJ,et al. Surgery with or without preoperative paclitaxel and carboplatin in early-stage non-small-cell lung cancer: Southwest Oncology Group Trial S9900, an intergroup, randomized, phase III trial. J Clin Oncol. 2010;28(11):1843-9.

Ponn RB, Lo Cicero J III, Daly BD, et al. Surgical treatment of non-small cell lung cancer. General Thoracic Surgery, Edition 6. Philadelphia, PA. Lippincott Williams & Wilkins. 2005;1548-87.

Preillon J, Cuende J, Rabolli V, et al. Restoration of T-cell Effector Function, Depletion of Tregs, and Direct Killing of Tumor Cells: The Multiple Mechanisms of Action of a-TIGIT Antagonist Antibodies. Mol Cancer Ther. 2021;20(1):121-131.

Rami-Porta R, Wittekind C, Goldstraw P; International Association for the Study of Lung Cancer (IASLC) Staging Committee. Complete resection in lung cancer surgery: proposed definition. Lung Cancer. 2005;49(1):25-33.

Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2016;375(19):1823-1833.

Riley JL. PD-1 signaling in primary T cells. Immunol Rev. 2009;229(1):114-25.

Rodriguez-Abreu D, Johnson ML, Hussein MA, et al. Primary analysis of a randomized, double-blind, phase II study of the anti-TIGIT antibody tiragolumab (tira) plus atezolizumab (atezo) versus placebo plus atezo as first-line (1L) treatment in patients with PD-L1-selected NSCLC (CITYSCAPE). Journal of Clinical Oncology 2020;38:15_suppl;9503.

Rosenberg JE, Hoffman-Censits J, Powles T, et al. Tislelizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet. 2016;387:1909-20.

Scagliotti GV, Pastorino U, Vansteenkiste JF, et al. Randomized phase III study of surgery alone or surgery plus preoperative cisplatin and gemcitabine in stages IB to IIIA non-small-cell lung cancer. J Clin Oncol. 2012;30(2):172-8.

Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. Science. 2011;331:1565-70.

Schuler MHH, Cuppens K, Ploenes T, et al. LBA37 - A randomized, multicentric phase II study of preoperative nivolumab plus relatlimab or nivolumab in patients with resectable non-small cell lung cancer (NEOpredict-Lung). Annals of Oncology. 2022;33:S1404.

Shayan G, Srivastava R, Li J, et al. Adaptive resistance to anti-PD1 therapy by Tim-3 upregulation is mediated by the PI3K-Akt pathway in head and neck cancer. Oncoimmunology. 2016;6(1):e1261779.

Siegel RL, Miller KD, Fuchs HE, et al. Cancer Statistics, 2021. CA Cancer J Clin. 2021;71:7-33.

Soar J, Pumphrey R, Cant A, et al. Emergency treatment of anaphylactic reactions--guidelines for healthcare providers. Resuscitation. 2008;77(2):157-69.

Swann JB, Smyth MJ. Immune surveillance of tumors. J Clin Invest. 2007;117:1137-46.

Stanietsky N, Simic H, Arapovic J, et al. The interaction of TIGIT with PVR and PVRL2 inhibits human NK cell cytotoxicity. Proc Natl Acad Sci USA. 2009;106(42):17858-63.

Tassi E, Grazia G, Vegetti C, et al. Early effector T lymphocytes coexpress multiple inhibitory receptors in primary non-small cell lung cancer. Cancer Res. 2017;77: 851-61.

Tawbi HA, Schadendorf D, Lipson EJ, et al. Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma. N Engl J Med. 2022;386(1):24-34.

Topalian SL, Hodi FS, Brahmer JR, et al. Safety, Activity, and Immune Correlates of Anti-PD-1 Antibody in Cancer. N Engl J Med. 2012;366:2443-54.

Topalian SL, Drake CG, Pardoll DM. Immune checkpoint blockade: a common denominator approach to cancer therapy. Cancer Cell. 2015;27(4):450-61.

Triebel F, Jitsukawa S, Baixeras E, et al. LAG-3, a novel lymphocyte activation gene closely related to CD4. J Exp Med. 1990;171(5):1393-405.

US Food and Drug Administration. Draft Guidance for Industry. Pathologic complete response in neoadjuvant treatment of high-risk early-stage breast cancer: use as an endpoint to support accelerated approval, 2012. Accessed on 13 June 2022. http://www.fda.gov/downloads/Drugs/ Guidance Compliance Regulatory Information/Guidances/ UCM305501.pdf.

US Food and Drug Administration. Guidance for industry: Immunogenicity assessment for therapeutic protein products. Accessed August, 2014. https://www.fda.gov/media/85017/download

US Food and Drug Administration. Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics Guidance for Industry. March 2022.

Wakelee H, Liberman M, Kato T, et al. KEYNOTE-671 Investigators. Perioperative Pembrolizumab for Early-Stage Non-Small-Cell Lung Cancer. N Engl J Med. Accessed 10 July 2023. DOI: 10.1056/NEJMoa2302983.

Wang J, Sanmamed MF, Datar I, et al. Fibrinogen-like Protein 1 Is a Major Immune Inhibitory Ligand of LAG-3. Cell. 2019;176(1-2):334-47.

West H, McCleod M, Hussein M, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2019;20(7):924-937.

William WN Jr, Pataer A, Kalhor N, et al. Computed tomography RECIST assessment of histopathologic response and prediction of survival in patients with resectable nonsmall-cell lung cancer after neoadjuvant chemotherapy. J Thorac Oncol. 2013;8:222-8.

Woo SR, Turnis ME, Goldberg MV, et al. Immune inhibitory molecules LAG-3 and PD-1 synergistically regulate T-cell function to promote tumoral immune escape. Cancer Res. 2012;72(4):917-27.

Workman CJ, Vignali DA. The CD4-related molecule, LAG-3 (CD223), regulates the expansion of activated T cells. Eur J Immunol. 2003;33(4):970-9.

Workman CJ, Cauley LS, Kim IJ, et al. Lymphocyte activation gene-3 (CD223) regulates the size of the expanding T cell population following antigen activation in vivo. J Immunol. 2004;172(9):5450-5.

Workman CJ, Wang Y, El Kasmi KC, et al. LAG-3 regulates plasmacytoid dendritic cell homeostasis. J Immunol. 2009;182(4):1885-91.

Xie J, Wang J, Cheng Sh, et al. Expression of immune checkpoints in T cells of esophageal cancer patients. Oncotarget. 2016;27:63669-78.

Xu F, Liu J, Liu D, et al. LSECtin expressed on melanoma cells promotes tumor progression by inhibiting antitumor T cell responses. Cancer Res. 2014;74(13):3418-28.

Yang Y. Cancer immunotherapy: harnessing the immune system to battle cancer. J Clin Invest. 2015;125(9):3335-7.

Yang ZZ, Kim HJ, Villasboas JC, et al. Expression of LAG-3 defines exhaustion of intratumoral PD-1 + T cells and correlates with poor outcome in follicular lymphoma. Oncotarget. 2017;8(37):61425-39.

Yu X, Harden K, Gonzalez LC, et al. The surface protein TIGIT suppresses T cell activation by promoting the generation of mature immunoregulatory dendritic cells. Nat Immunol. 2009;10(1):48-57.

Yu H, Boyle TA, Zhou C, et al. PD-L1 Expression in Lung Cancer. J Thorac Oncol. 2016;11(7):964-75.

Zhu S, Zhang T, Zheng L, et al. Combination strategies to maximize the benefits of cancer immunotherapy. J Hematol Oncol. 2021;14(1):156.

APPENDIX 1. SCHEDULE OF ASSESSMENTS (FOR ARMS 1A, 1B, 1C, 2A, AND 2C)

Assessment	**Screening [a]**	**Neoadjuvant Treatment**				**EOT/ Safety Follow-up Visit [b, c]**	**Surgery [c]**	**Survival Follow-up**
		Cycle 1 to 2 (Every 21 days)			**Cycle 3 to 4 (Every 21 days)**			
Days (window)	**-28 to -1**	**1 (± 3)**	**8 (± 2)**	**15 (± 2)**	**1 (± 3)**	**30 (± 7) after the last dose**	**Within 14 days from EOT/Safety Follow-up Visit**	**Every 6 months (± 4 weeks) or annual (± 8 weeks) [cc]**
Informed consent [d]	X							
Inclusion/exclusion criteria	X							
Randomization [e]	X[d]							
EGFR assessment (if status is unknown) [f]	X							
Baseline tumor tissue and optional lymph node sample [g]	X							
Surgical tumor tissue and lymph node sample [h]							X	
Pathological response assessment							X	
Demographic data	X							
Medical history and baseline conditions	X							
Thoracic surgery evaluation	X					X (Presurgical)		

Assessment	**Screening [a]**	**Neoadjuvant Treatment**				**EOT/ Safety Follow-up Visit [b, c]**	**Surgery [c]**	**Survival Follow-up**
		Cycle 1 to 2 (Every 21 days)			**Cycle 3 to 4 (Every 21 days)**			
Days (window)	**-28 to -1**	**1 (± 3)**	**8 (± 2)**	**15 (± 2)**	**1 (± 3)**	**30 (± 7) after the last dose**	**Within 14 days from EOT/Safety Follow-up Visit**	**Every 6 months (± 4 weeks) or annual (± 8 weeks) [cc]**
Vital signs/height and weight [i]	X	X			X	X		
Complete physical examination [j]	X					X		
Limited physical examination [k]		X			X			
ECOG PS	X					X		
ECG [l]	X					X		
Hematology [m]	X	X [n]	X	X	X	X		
Chemistry [o]	X	X [n]	X	X	X	X		
Pregnancy test [p]	X	X			X	X (EOT/Safety follow-up visit)		
Coagulation [q]	X	X [n]			X	X		
TSH, free T3 (or total T3), free T4 [r]	X	X [r]				X		
Viral serology [s]	X							
COVID-19 testing [t]	X							
Urinalysis [u]	X	X [n,u]				X		
Pharmacokinetics [v]		X	X (Cycle 1 only)			X (EOT/Safety follow-up visit)		

Assessment	**Screening** [a]	**Neoadjuvant Treatment**				**EOT/ Safety Follow-up Visit** [b, c]	**Surgery** [c]	**Survival Follow-up**
		Cycle 1 to 2 (Every 21 days)			**Cycle 3 to 4 (Every 21 days)**			
Days (window)	**-28 to -1**	**1 (± 3)**	**8 (± 2)**	**15 (± 2)**	**1 (± 3)**	**30 (± 7) after the last dose**	**Within 14 days from EOT/Safety Follow-up Visit**	**Every 6 months (± 4 weeks) or annual (± 8 weeks)** [cc]
Antidrug antibodies [w]		X				X (EOT/Safety follow-up visit)		
Periphery immune cell quantification and phenotyping [x]		X (predose)	X (Cycle 1 only)					
ctDNA/MRD [x] (optional)		X (predose)				X (EOT/Safety follow-up visit)		X (7 days after surgery & the same visits of disease follow-up tumor assessment)
Soluble proteins such as cytokine/chemokine in blood [x]		X (predose)	X (Cycle 1 only)			X (EOT/Safety follow-up visit)		
TCR profile in blood [x]		X (predose)				X (EOT/Safety follow-up visit)		
Optional tumor biopsy at the time of disease progression or recurrence [y]								X
Tumor response and disease recurrence assessments	X [z]					X [aa]		X [bb]

Assessment	**Screening [a]**	**Neoadjuvant Treatment**				**EOT/ Safety Follow-up Visit [b, c]**	**Surgery [c]**	**Survival Follow-up**
		Cycle 1 to 2 (Every 21 days)			**Cycle 3 to 4 (Every 21 days)**			
Days (window)	**-28 to -1**	**1 (± 3)**	**8 (± 2)**	**15 (± 2)**	**1 (± 3)**	**30 (± 7) after the last dose**	**Within 14 days from EOT/Safety Follow-up Visit**	**Every 6 months (± 4 weeks) or annual (± 8 weeks) [cc]**
Prior and concomitant medications [cc]	X	X			X	X (EOT/Safety Follow-up Visit)		
Adverse events [dd]	X	X			X	X (EOT/Safety Follow-up Visit)		
Study treatment administration [ee]		X			X			
Survival follow-up and anticancer treatment								X [ff]

Abbreviations: ADA, antidrug antibody; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the curve; C#D#, Cycle # Day #; CK-MB, creatine kinase cardiac isoenzyme; COVID-19, Coronavirus disease 2019; CT, computed tomography; ECG, electrocardiogram; eCRF, electronic case report form; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EOT, End-of-Treatment; FFPE, formalin-fixed paraffin-embedded; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; imAE, immune-mediated adverse event; IRT, Interactive Response Technology; MPR, major pathological response; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; pCR, pathological complete response; PD-L1, programmed death protein ligand-1; PET, positron emission tomography; PK, pharmacokinetics; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone.

Note: On treatment days, all assessments should be performed before dosing, unless otherwise specified.

a. Results of standard of care tests or examinations performed before obtaining informed consent and ≤ 28 days before randomization may be used for screening assessments rather than repeating these tests unless otherwise indicated (Section 3.2).

b. The EOT/Safety Follow-up Visit will be conducted for patients who discontinue from study treatment due to any reason including completion of planned neoadjuvant, AE, patient's withdrawal, investigator's decision, and others. Patients will be asked to return to the clinic for the EOT/Safety Follow-up Visit which should occur within 30 (±7) days after the last dose of neoadjuvant treatment or before surgery procedure or the initiation of other new anticancer therapy, whichever occurs first. If routine laboratory tests (eg, hematology, serum chemistry) are performed ≤ 7 days before the EOT/Safety Follow-up Visit, these tests will not need to be repeated. Tumor assessment is not required at an EOT/Safety Follow-up Visit provided that ≤ 2 weeks have passed since the last assessment. However, if the Presurgical visit has been

incorporated in to EOT/Safety Follow-up Visit to assess resectability before surgery, the safety assessment and tumor assessment at this visit should be performed ≤ 14 days before surgery.

c. The Presurgical Visit and associated assessments can be incorporated into the EOT/Safety Follow-up Visit and in accordance with local institutional practices. Unless otherwise specified, the assessments for Presurgical Visit are incorporated and presented in the schedule under the EOT/Safety Follow-up Visit. Besides that, per local standard of care the evaluations at Presurgical Visit could also include assessments of blood tests, coagulation, cardiac or pulmonary tests (if indicated), anesthesia assessment, and other evaluation procedures. The safety assessment and tumor assessment at the Presurgical Visit for resectability evaluation should be completed ≤ 14 days before surgery respectively (Section 3.4). Surgery should be performed ≤ 14 days after the EOT/Safety Follow-up Visit (Section 3.5).

d. Informed consent must be documented before any study-specific screening procedure is performed and may be obtained up to 28 days before randomization.

e. Patients with tumor PD-L1 expression ≥ 50% will be randomized into Arm 1A, Arm 1B, or Arm 1C in Substudy 1 via IRT in a 1:1:1 randomization ratio. Patients with tumor PD-L1 expression < 50% will be randomized into Arm 2A and Arm 2C in Substudy 2 via IRT in a 1:2 randomization ratio. The randomization ratio will be adjusted based on the number of experimental arms that are open for enrollment. Study treatment must commence ≤ 2 days after randomization.

f. Patients with nonsquamous NSCLC histology with unknown EGFR status, will be required to be tested locally or at a central laboratory prior to enrollment. Fresh or archival tumor tissues (≥ 3 unstained slides) are required for the assessment of EGFR mutation if at a central laboratory. If archival tissues are insufficient for EGFR testing, a tumor biopsy is mandatory.

g. Patients must provide at least 15 freshly cut unstained FFPE slides of the primary tumor or FFPE block containing equivalent tumor tissues (preferred) for central PD-L1 evaluation during screening and other exploratory biomarker assessments. Only patients with evaluable PD-L1 status as assessed by the central laboratory are eligible. If the local result of EGFR mutation status (nonsquamous only) is not available, 3 additional FFPE slides are required for central EGFR testing. If the first attempt of PD-L1 testing by the central laboratory fail, 3 additional slides may be required for repeat. If sufficient baseline tumor tissue is available, around 35 unstained FFPE slides or equivalent FFPE block are strongly recommended to be provided to ensure exploration of all planned biomarkers. If accessible, a baseline lymph node sample (6 to 10 FFPE slides) is recommended to be provided. If fewer slides are available, please contact sponsor for recommendations. Refer to Section 7.7.1 for more details.

h. If patients undergo surgery, tumor tissue and lymph node tissue obtained from surgical resection are required and sent to a central laboratory according to study pathology manuals for pathological response analysis as assessed by BIPR. In addition, representative tissue samples of the primary tumor (at least 20 freshly cut unstained FFPE slides or FFPE block containing equivalent tumor tissues [preferred]) will be collected and sent to a central laboratory for biomarker evaluation. If sufficient tumor tissue is available, around 40 FFPE slides of surgery tumor tissue are recommended to be provided to ensure exploration of all planned biomarkers. If accessible, a surgical lymph node sample is recommended to be provided. The surgical specimen for biomarker evaluation is optional for patients who achieve pCR after neoadjuvant treatment.

i. Vital signs collected during the study include body temperature, pulse rate, and blood pressure (systolic and diastolic) while the patient is in a seated position after resting for 10 minutes. The patient's vital signs are required to be recorded ≤ 60 minutes before, during, and 30 minutes after the first infusion completed of study drug(s). 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 on Day 1 of the first cycle, on Day 1 of each subsequent cycle, at the EOT/Safety Follow-up Visit, and at the Presurgical Visit. Vital signs collected at the Presurgical Visit include temperature, pulse rate, and blood pressure (systolic and diastolic), and weight.

j. At the Screening Visit and at the EOT/ Safety Follow-up Visit and the Presurgical Visit, a complete physical examination will be conducted, including evaluations of 1) the head, eyes, ears, nose, and throat; and of the 2) cardiovascular, 3) dermatological, 4) musculoskeletal, 5) respiratory, 6) gastrointestinal, and 7) neurological systems. For any abnormality noted at other visits (and as clinically indicated), limited, symptom-directed physical examinations will be performed.

k. Limited, symptom-directed examination should be performed on Day 1 of each cycle and as clinically indicated at other timepoints. New or worsened clinically significant abnormalities should be recorded in the adverse event eCRF.

l. The ECG recordings will be obtained during screening, at the EOT/Safety Follow-up Visit, at the Presurgical Visit, and as clinically indicated at other timepoints. When coinciding with blood draws at the same timepoint, the ECG assessment should be performed before blood draws. Patients should be resting in a semirecumbent supine position for ≥ 10 minutes before ECG recording.

m. Hematology assessments should be performed at screening, during the neoadjuvant phase (weekly during Cycle 1 to 2, ≤ 3 days before Day 1 during Cycle 3 to 4), and at the EOT/Safety Follow-up Visit and the Presurgical Visit. Hematology includes hemoglobin, hematocrit, white blood cell count, platelet count, and differential count (neutrophils, lymphocytes) (Appendix 2).

n. If screening laboratory assessments were performed ≤ 7 days before Day 1 of Cycle 1, they do not have to be repeated. Otherwise, these tests must be repeated and reviewed before study drug administration on Day 1 of Cycle 1.

o. Serum chemistry assessments (including liver function tests) should be performed at screening, during the neoadjuvant phase (weekly during Cycle 1 to 2, ≤ 3 days before Day 1 during Cycle 3 to 4), at the EOT/Safety Follow-up Visit and at the Presurgical visit. The chemistry panel includes sodium, potassium, chloride, glucose, blood urea nitrogen or urea, creatinine, total protein, albumin, total calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, lactate dehydrogenase, creatinine kinase, and CK-MB (Appendix 2). If CK-MB fractionation is not available, troponin I and/or troponin T should be assessed instead. Refer to Section 8.3.6 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.

p. Urine or serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative ≤ 7 days before randomization. Urine pregnancy tests will be performed at each visit before study drug(s) administration, at the EOT/Safety Follow-up Visit. Additional pregnancy tests will be required at 90 (±14) days and 120 (±14) days after the last dose of study treatments for all experimental arms, and at 6 months (±14 days) after the last dose of LBL-007 for Arm 1C and Arm 2C (in the clinic or over the phone, as needed based on assessments required). If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

q. Coagulation parameters should be tested at Screening, ≤ 3 days before Day 1 of each cycle, at the EOT/Safety Follow-up Visit and at the Presurgical Visit. Please refer to Appendix 2 for a list of detailed assessment parameters of coagulation.

r. TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed at screening, ≤ 3 days before Day 1 of Cycle 2, at the EOT/Safety Follow-up Visit and at Presurgical Visit.

s. At screening, patients will be tested for HIV serology (antigen and/or antibodies). Patients will be tested for hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody (HBcAb), and HCV antibody. If a patient has a positive hepatitis B surface antigen at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection. For patients who have detectable HBV DNA or HCV RNA at screening or upon repeat testing, respective viral load testing will be performed every 12 weeks.

t. COVID-19 testing should be performed by a certified local laboratory, which may be located at the study site. Testing may alternatively be performed at a certified offsite laboratory, clinic, or hospital, with the agreement of the investigator. A COVID-19 antigen test should be conducted ≤ 48 hours before Cycle 1 Day 1 if clinically indicated

u. Includes glucose, protein, ketones, and blood; dipstick permitted. Urinalysis should be performed at screening, as clinically indicated during neoadjuvant treatment, at EOT/Safety Follow-up visit and Presurgical Visit (Appendix 2).

v. PK samples for investigational agents will be collected at sites that are able to adequately perform PK sampling and handling. During the neoadjuvant phase, PK samples are required at the following time points: predose Cycle 1 Day 1 (≤ 60 minutes before starting infusion); postdose Cycle 1 Day 1 (≤ 30 minutes after completing infusion); Cycle 1 Day 8; and predose Cycle 2 Day 1 (≤ 60 minutes before starting infusion). A PK sample is required at the EOT/Safety Follow-up Visit during the visit. Should a patient present with any ≥ Grade 3 imAE, an additional blood PK sample may be taken to determine the concentrations. These tests are required when it is allowed by local regulations/IRBs/IECs.

w. ADA samples for protein therapeutic investigational agents will be collected at sites that are able to adequately perform ADA sampling and handling. During the neoadjuvant phase, ADA samples are required at the following time points: predose Cycle 1 Day 1 (≤ 60 minutes before starting infusion), and predose Cycle 2 Day 1 (≤ 60 minutes before starting infusion). An ADA sample is required at the EOT/Safety Follow-up Visit during the 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.

x. Blood samples for biomarker analysis will be collected as follows:
   1) For periphery immune cell quantification and phenotyping analysis: samples will be collected at predose on C1D1, on C1D8, and at predose on C2D1 during the neoadjuvant phase
   2) (Optional) For ctDNA or MRD analysis: samples will be collected at predose on C1D1 and C2D1 during the neoadjuvant phase; at the EOT/Safety Follow-up Visit; at 7 days after surgery; and then at the same visits of disease follow-up tumor assessments after surgery.
   3) For soluble proteins such as cytokine/chemokine analysis: samples will be collected at predose on C1D1, C1D8, predose on C2D1 during the neoadjuvant phase, and at EOT/Safety Follow-up Visit.
   4) For TCR profile analysis: Samples will be collected at predose on C1D1 and C2D1 during the neoadjuvant phase; and at the EOT/Safety Follow-up Visit.

y. Patients will undergo an optional tumor biopsy sample collection, if deemed clinically feasible by the investigator, at the time of first evidence of radiographic disease progression per RECIST v1.1 (Appendix 4) during survival follow-up phase. Biopsies should be performed ≤ 40 days after progression/recurrence or before the prespecified adjuvant or new anticancer therapy, whichever is sooner. Patients must sign a separate Optional Biopsy Informed Consent Form to undergo optional biopsies. See Section 7.1.1 for tissue sample requirements.

z. All measurable and evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care before obtaining informed consent and ≤ 28 days before randomization do not have to be repeated at screening. Screening assessments must include scans of the chest and abdomen by CT scan of the whole body by PET. Tumor assessments after randomization should include CT scans (with oral/intravenous contrast, unless contraindicated) of the chest and abdomen (including liver and adrenal glands). If a CT scan with contrast is contraindicated (eg, in patients with impaired renal clearance), a noncontrast CT scan of the chest may be performed and contrast-enhanced MRI scans (if possible) of the abdomen should be performed. Refer to Section 7.1 for additional details.

aa. Patients will undergo tumor assessments per RECIST v1.1 (Appendix 4) at screening, at the EOT/Safety Follow-up Visit after the neoadjuvant phase and Presurgical Visit. All measurable and evaluable lesions should be reassessed at each subsequent tumor evaluation. The investigator must review radiograph results before dosing at the next cycle. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (eg, the same contrast protocol for CT scans). The investigator will reassess the patient to reconfirm disease resectability, which includes a tumor response assessment and a safety assessment before surgery at the Presurgical Visit. Tumor assessment at the Presurgical Visit may not be repeated if there is standard tumor assessment per protocol performed ≤ 14 days before surgery. Patients precluded from planned surgery for any reason except disease progression or death will undergo tumor assessments every 6 weeks (± 1 week) per RECIST v1.1 until any of the following events, whichever occurs first: radiographic disease progression assessed by the investigator, withdrawal of consent, initiation of new anticancer therapy, death, loss to follow-up, or study termination by the sponsor.

bb. After surgery, disease follow-up tumor assessment will be performed using chest and upper abdominal CT. The first disease follow-up tumor assessment will be performed 3 months (± 2 weeks) after surgery, then every 6 months (± 4 weeks) for the first 2 years, and annually (± 8 weeks) thereafter (Appendix 4). Tumor assessments must continue according to the schedule until disease recurrence or progression that precludes definitive surgery, withdrawal of consent, initiation of new anticancer therapy with the exception of the prespecified adjuvant treatments, death, loss to follow-up, or study termination by the sponsor, whichever occurs first. Tumor assessment should be performed by investigator per RECIST v1.1, and disease resectability should be assessed by attending thoracic surgeon per local guideline and best clinical experience. Disease progression that does not preclude definitive surgery or initiation of prespecified adjuvant treatment is not criterion of tumor assessment discontinuation.

[cc] Information regarding medications (eg, prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment will be collected from 30 days before randomization until 30 days after the last dose of study drug(s) (as of EOT/Safety Follow-up Visit) (Section 6).

[dd] After informed consent has been signed but before the administration of the study drug(s), only SAEs associated with protocol-defined procedure should be reported to the sponsor. After initiation of the study treatment, all AEs and SAEs, regardless of relationship to the study treatment, will be reported until either 30 days after the last dose of study treatment or until initiation of prespecified adjuvant treatment or other new anticancer therapy, whichever occurs first. Surgical procedure complications will be monitored and recorded at the investigator or designee's discretion. Immune-mediated AEs (serious or nonserious) should be recorded until 90 days after the last dose of study treatment, regardless of whether the patient starts pre-specified adjuvant treatment or other new anticancer therapy.

[ee] Tislelizumab 200 mg (Arm 1A), tislelizumab 200 mg plus ociperlimab 900 mg (Arm 1B), LBL-007 600 mg plus tislelizumab 200 mg (Arm 1C), tislelizumab 200 mg plus chemotherapy (cisplatin [75 mg/m^2] or carboplatin [AUC=5 mg/mL/min] + pemetrexed [nonsquamous, 500 mg/m^2]/paclitaxel [squamous, 175 mg/m^2]) (Arm 2A), or LBL-007 600 mg plus tislelizumab 200 mg plus chemotherapy (cisplatin [75 mg/m^2] or carboplatin [AUC=5 mg/mL/min] + pemetrexed [nonsquamous, 500 mg/m^2]/paclitaxel [squamous, 175 mg/m^2]) (Arm 2C) will be given intravenously once every 3 weeks during the neoadjuvant phase (Section 3.3). The specific stipulations of the study treatment of experimental arms including formulation, packaging, dosage handling, administration, dose modification, and overdose are provided in each investigational agent-specific appendix.

[ff] After the EOT/Safety Follow-up Visit, information on survival follow-up and new anticancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, review of patient medical records, and/or clinic visits approximately every 6 months (± 4 weeks) (until the patient withdraws consent, or the sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If a patient withdraws from the study, the study staff may use a public information source (eg, county records) in accordance with local regulations to obtain information about survival status only.

APPENDIX 2. CLINICAL LABORATORY ASSESSMENTS

Serum chemistry	Hematology	Coagulation	Urinalysis	Thyroid function
Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Albumin Total bilirubin Direct bilirubin Blood urea nitrogen or urea Chloride Potassium Sodium Total calcium [b] Creatinine Glucose Lactate dehydrogenase Total protein CK [c] CK-MB [c]	Hematocrit Hemoglobin Lymphocyte count Neutrophil count Platelet counts WBC count	International normalized ratio (INR) Partial thromboplastin time or activated partial thromboplastin time Prothrombin time	Blood Glucose Ketones Protein Random urine protein to creatinine ratio [a] 24-hour protein [a]	Free and total triiodothyronine Free thyroxine Thyroid-stimulating hormone

Abbreviations: CK, creatine kinase; CK-MB, creatine kinase cardiac isoenzyme; WBC, white blood cell.

a. If during routine urinalysis, if urine protein is ≥ 2+ by dipstick, then obtain a 24-hour urine sample for total protein or a random urine sample for total protein and creatinine should be obtained to determine a protein-to-creatinine ratio.

b. Total calcium values will be corrected for patients with hypoproteinemia.

c. All patients will have creatine kinase and CK-MB testing at screening, which is to be repeated at all scheduled visits during the 2 to 4 cycles in the neoadjuvant phase, in the Presurgical Visit and at the EOT/Safety Follow-up Visits. If CK-MB fractionation is not available, assess troponin I and/or troponin T should be assessed instead. Refer to Section 8.3.6 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.

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

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

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

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

Source: Eisenhauer et al 2009.

Definitions

Response and progression will be evaluated in this study 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 RECIST.

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 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 examination (when superficial)

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 to indicate 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) because they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.
- The concept of cystic metastases also applies to metastatic lesions with a necrotic component. Hence, measurable lesions with a necrotic component may be selected as target lesions. However, if non-necrotic lesions are present, these are preferred for selection as target lesions.

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. A maximum of 2 measurable lymph nodes, inclusive of all lymphatic chains involved, may be chosen as target lesions (ie, the lymphatic system is considered one organ). Target lesions should be selected based on size (lesions with the longest diameter), how representative they are of all involved organs, and whether they lend themselves to reproducible repeated measurements.

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

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

Nontarget Lesions

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

these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression" (more details to follow). In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (eg, "multiple enlarged pelvic lymph nodes" or "multiple liver metastases"). If a nontarget lymph node normalizes (< 10 mm in short axis) after baseline, the respective evaluation should be "absent."

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 because it is more objective and may also be reviewed at the end of the study.
- Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, because CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- CT, MRI: Target lesion measurements should be performed in the axial plane. 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). If there is a change from CT to MRI or the reverse, target lesions should continue to be measured provided the imaging parameters do not render measurements incomparable.
- Ultrasound: Ultrasound is not useful in the 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 studies 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. However, if markers are initially above the upper normal limit, they must normalize for a patient to be considered to have CR. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease-specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and prostate-specific antigen response (in recurrent prostate cancer) have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria that are to be integrated with objective tumor assessment for use in first-line studies 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 the criteria for response or stable disease to differentiate between response (or stable disease) and PD.
  New or enlarging fluid collections in an otherwise stable or responding patient should not result in a conclusion of PD. However, if the fluid collection has malignant radiographic features, PD may be declared.
  An increase in the amount of accumulated fluid should not in isolation result in a conclusion of PD but rather be assessed in the context of other disease and evidence of PD.

Response Criteria

Evaluation of Target Lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes 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.
- Both PR and PD: If the change in the sum of diameters is consistent with both PR and PD at a tumor assessment visit, PD should take precedence.
- 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, because a normal lymph node is defined as having a short axis of < 10 mm. The case report form (CRF) may be designed to have target nodal lesions recorded in a separate section where, to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.
- Target lesions that become "too small to measure": While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on a 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 CRF (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 because 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 conclusions of progressions based on 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 timepoints specified in the protocol.

- CR: Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (< 10 mm short axis).
- Non-CR/non-PD: Persistence of one or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits.
- PD: Unequivocal progression (as detailed below) of existing nontarget lesions.

Note: The appearance of one or more new lesions is also considered progression.

- When the patient also has measurable disease: In this setting, to achieve "unequivocal progression" on the basis of the nontarget disease, there must be an overall level of substantial worsening in nontarget disease such that, even in presence of 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 studies when it is not a criterion for study 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 in 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 one that 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 the 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 a flare-up of pre-existing lesions). This is particularly important when the patient's baseline lesions show PR or CR. 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 study 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 in a patient who has visceral disease at baseline and while on study has a CT or MRI brain scan ordered that reveals metastases. The patient's brain metastases are considered to be evidence of 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 that 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 the assessment of progression (particularly possible "new" disease). New lesions can be identified on the basis of FDG-PET imaging according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up, is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not found to be progressing on the basis of the anatomic images, this is not PD.
- Timepoint Response
  - It is assumed that at each protocol-specified timepoint, a response assessment occurs. The following table provides a summary of the overall response status calculation at each timepoint 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

Target lesions	Nontarget lesions	New lesions	Overall response
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 considering any requirement for confirmation. On occasion, a response may not be documented until after the end of therapy, so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's 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 study and the protocol requirements, it may also require confirmatory measurement. Specifically, in nonrandomized studies 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 studies where confirmation of CR or PR IS NOT required: Best response in these studies is defined as the best response across all timepoints (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a 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 timepoint response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not

meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Best response determination in studies where confirmation of CR or PR IS required: CR or PR may be claimed only if the criteria for each are met at a subsequent timepoint 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 an increase in the size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero."

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

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

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on 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 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 a false-positive conclusion of CR due to the 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 studies where response is the primary endpoint, confirmation of PR or CR is required to ensure that responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has

traditionally required confirmation in such studies. However, in all other circumstances such as in randomized studies (Phase 2 or 3) or studies where SD or progression are the primary endpoints, confirmation of response is not required because it will not add value to the interpretation of study results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies that are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6 weeks).

Duration of Overall Response

The duration of overall response is measured from the time the measurement criteria are first met for CR/PR (whichever is first recorded) until the first date when recurrent disease or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study).

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

Duration of Stable Disease

SD is measured from the start of the treatment (in randomized studies, 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 SD varies in different studies and diseases. If the proportion of patients achieving SD for a minimum period of time is an endpoint of importance in a particular study, the protocol should specify the minimal time interval required between 2 measurements for determination of SD.

Note: The duration of response and SD 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 studies 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.

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. INFUSION-RELATED REACTIONS, HYPERSENSITIVITY REACTIONS AND IMMUNE-MEDIATED ADVERSE EVENTS: EVALUATION AND MANAGEMENT

Management of Infusion-Related Reactions

Patients should be closely monitored during and after study drug administration for infusion-related reactions and hypersensitivity reactions. See Appendix 11, Appendix 12, Appendix 13, and Appendix 14 for the monitoring periods required. Immediate access to an intensive care unit or equivalent environment and appropriate medical therapy (including epinephrine, corticosteroids, antihistamines, bronchodilators, and oxygen) must be available to treat infusion-related reactions.

Management of infusion-related reactions are provided in the table below (Rosello et al 2017).

NCI-CTCAE Grade v5.0	Management
Grade 1 Mild transient reaction; infusion interruption not indicated; intervention not indicated	• Decrease infusion rate by 50%. • Closely monitor for worsening signs or symptoms. • Medical management as needed. • Subsequent infusions should be given after appropriate premedication and at the reduced infusion rate.
Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours	• Temporarily stop infusion. • Treatment includes but is not limited to H1/H2 antagonists, corticosteroids. • Restart infusion at 50% rate once infusion-related reaction has resolved or decreased to Grade 1 in severity and titrate to tolerance. • Closely monitor for worsening signs or symptoms. • Appropriate medical management should be instituted. • Subsequent infusions should be given after premedication and at the reduced infusion rate.
Grade 3 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. • Treatment includes but is not limited to H1/H2 antagonists, corticosteroids. • The patient should be withdrawn from study drug(s) treatment.

NCI-CTCAE Grade v5.0	Management
Grade 4 Life-threatening consequences; urgent intervention indicated	• Immediately stop the infusion. • Treatment includes but is not limited to H1/H2 antagonists, corticosteroids. • Proper medical management should be instituted. • The patient should be withdrawn from study drug(s) treatment. • Hospitalization is recommended.

Abbreviations: H1/H2, histamine H1 and H2 receptors; IV, intravenous; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Event; NSAIDS; nonsteroidal anti-inflammatory drugs.

For the prophylaxis of mild events (eg, nasal congestion or flu-like symptoms), a dose of 25 mg indomethacin or a comparable dose of nonsteroidal anti-inflammatory drugs (eg, 600 mg ibuprofen or 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 (eg, paracetamol) may be given to patients at the discretion of the investigator.

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 the treatment.

Management of Anaphylaxis

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

The NCI-CTCAE grading of anaphylaxis starts from Grade 3.

Management and treatment modifications for symptoms of anaphylaxis associated with study drug(s) administration are provided in the table below.

NCI-CTCAE Grade v5.0	Management
Grade 3 Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension **Grade 4** Life-threatening consequences; urgent intervention indicated	• Immediately stop the infusion. • Proper medical management should be instituted. • Treatment includes but is not limited to oral or intravenous antihistamines, antipyretics, glucocorticoids, epinephrine, bronchodilators, and oxygen. • The patient should be withdrawn from study drug(s) treatment. • Rechallenge is prohibited.

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

Evaluation of Immune-Mediated Adverse Events

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

The recommendations for the diagnostic evaluation and management of imAEs are based on European Society for Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) guidelines (Haanen et al 2017, Brahmer et al 2018). For any adverse events not included in the tables below, refer to the ASCO Clinical Practice Guideline (Brahmer et al 2018) for further guidance on the diagnostic evaluation and management of immune-mediated toxicities.

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 diagnosing an imAE:

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

When alternative explanations to autoimmune toxicity have been excluded, the imAE field associated with the adverse event 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. Consider consultation with an endocrinologist if an abnormality is detected.

Immune-Mediated toxicity	Diagnostic evaluation guideline
Pneumonitis	All patients presenting with new or worsened pulmonary symptoms or signs, such as an upper respiratory infection, new cough, shortness of breath, or hypoxia should be assessed by high-resolution CT. Consider pulmonary function test including DLCO. Radiographic appearance is often nonspecific. Depending on the location of the abnormality, bronchoscopy and bronchoalveolar lavage or lung biopsy may be considered. Consult with a respiratory medicine physician for cases of uncertain cause.
Neurological toxicity	Perform a comprehensive neurological examination and brain MRI for all CNS symptoms, review alcohol history and other medications. Conduct a diabetic screen and assess blood B12/folate, HIV status, and TFTs and consider autoimmune serology. Consider the need for brain/spine MRI/MRA and nerve conduction study for peripheral neuropathy. Consult with a neurologist if there are abnormal findings.
Colitis	Review dietary intake and exclude steatorrhea. Consider comprehensive testing, including the following: FBC, UEC, LFTs, CRP, TFTs, stool microscopy and culture, viral PCR, *Clostridium difficile* toxin, and cryptosporidia (drug-resistant organism). In case of abdominal discomfort, consider imaging, eg, X-ray, CT scan. If a patient experiences bleeding, pain, or distension, consider colonoscopy with biopsy and surgical intervention as appropriate.
Eye disorders	If a patient experiences acute, new onset, or worsening of eye inflammation; blurred vision; or other visual disturbances, refer the patient urgently to an ophthalmologist for evaluation and management.
Hepatitis	Check ALT/AST/total bilirubin, INR/albumin; the frequency will depend on severity of the adverse event (eg, daily if Grade 3 to 4; every 2 to 3 days if Grade 2, until recovering). Review medications (eg, statins, antibiotics) and alcohol history. Perform liver screen including hepatitis A/B/C serology, hepatitis E PCR and assess anti-ANA/SMA/LKM/SLA/LP/LCI, iron studies. Consider imaging (eg, ultrasound scan for metastases or thromboembolism). Consult with a hepatologist and consider liver biopsy.
Renal toxicity	Review hydration status and medication history. Test and culture urine. Consider renal ultrasound scan, protein assessment (dipstick/24-hour urine collection), or phase-contrast microscopy. Refer to a nephrologist for further management assistance.
Dermatology	Consider other causes by conducting a physical examination. Consider dermatology referral for skin biopsy.
Joint or muscle inflammation	Conduct musculoskeletal history and perform complete musculoskeletal examination. Consider joint X-ray and other imaging as required to exclude metastatic disease. Perform autoimmune serology and refer to rheumatology for further management assistance. For suspected myositis/rhabdomyolysis/myasthenia include: CK, ESR, CRP, troponin, and consider a muscle biopsy.

Immune-Mediated toxicity	Diagnostic evaluation guideline
Myocarditis	Perform ECG, echocardiogram, CK/CK-MB, troponin (I and/or T), and refer to a cardiologist.

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

Management of Immune-Mediated Adverse Events

imAEs can escalate quickly. Study treatment interruption, close monitoring, timely diagnostic work-up, and treatment intervention, as appropriate, are required. imAEs 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.

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 restarting treatment with the study drug should permanently discontinue treatment.

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.

Management of Immune-Mediated Adverse Events

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
Thyroid disorders	**1 or 2** Asymptomatic TFT abnormality or mild symptoms	Replace thyroxine if hypothyroid, until TSH/T4 levels return to normal range. Thyrotoxic patients should be referred to an endocrinologist. In cases with systemic symptoms: withhold study treatment, treat with a beta blocker, and consider oral prednisolone 0.5 mg/kg/day for thyroid pain. Taper corticosteroids over 2 to 4 weeks. Monitor thyroid function regarding the need for hormone replacement.	Continue study treatment or withhold treatment in cases with systemic symptoms.
	3 or 4 Severe symptoms, hospitalization required	Refer patient to an endocrinologist. If hypothyroid, replace with thyroxine 0.5-1.6 µg/kg/day (for the elderly or those with comorbidities, the suggested starting dose is 0.5 µg/kg/day). Add oral prednisolone 0.5 mg/kg/day for thyroid pain. Thyrotoxic patients require treatment with a beta blocker and may require carbimazole until thyroiditis resolves.	Hold study treatment; resume when resolved/improved to Grade 0 or 1.

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
Hypophysitis	**1 or 2** Mild-moderate symptoms	Refer patient to an endocrinologist for hormone replacement. Add oral prednisolone 0.5-1 mg/kg/day for patients with pituitary inflammation. Taper corticosteroids over at least 1 month. If there is no improvement in 48 hours, treat as Grade 3 or 4.	Continue study treatment.
	3 or 4 Severe or life-threatening symptoms	Refer patient to an endocrinologist for assessment and treatment. Initiate pulse intravenous methylprednisolone 1 mg/kg for patients with headache/visual disturbance due to pituitary inflammation. Convert to oral prednisolone and taper over at least 1 month. Maintain hormone replacement according to endocrinologist's advice.	Hold study treatment for patients with headache/visual disturbance due to pituitary inflammation until resolved/improved to ≤ Grade 2. Discontinuation is usually not necessary.
Pneumonitis	**1** Radiographic changes only	Monitor symptoms every 2 to 3 days. If appearance worsens, treat as Grade 2.	Consider holding study treatment until appearance improves and cause is determined.

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
	2 Symptomatic: exertional breathlessness	Commence antibiotics if infection suspected. Add oral prednisolone 1 mg/kg/day if symptoms/appearance persist for 48 hours or worsen. Consider *Pneumocystis* infection prophylaxis. Taper corticosteroids over at least 6 weeks. Consider prophylaxis for adverse steroid effects: eg, blood glucose monitoring, vitamin D/calcium supplement.	Hold study treatment. Retreatment is acceptable if symptoms resolve completely or are controlled on prednisolone (or its equivalent) ≤ 10 mg/day. If the event recurs upon reintroduction of study treatment, the patient discontinues the study treatment.
	3 or 4 Severe or life-threatening symptoms: breathless at rest	Admit to a hospital and initiate treatment with intravenous methylprednisolone 2-4 mg/kg/day. If there is no improvement, or worsening after 48 hours, add infliximab 5 mg/kg (if no hepatic involvement). Convert to oral prednisolone and taper over at least 2 months. Cover with empiric antibiotics and consider prophylaxis for *Pneumocystis* infection and other adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement.	Discontinue study treatment.
Neurological toxicity	**1** Mild symptoms	–	Continue study treatment.

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
	2 Moderate symptoms	Treat with oral prednisolone 0.5-1 mg/kg/day. Taper over at least 4 weeks. Obtain neurology consultation.	Hold study treatment; resume when resolved/improved to Grade 0 or 1.
	3 or 4 Severe/life-threatening symptoms or Grade 3 or 4 encephalitis, or Guillain-Barré syndrome	Initiate treatment with oral prednisolone or intravenous methylprednisolone 1-2 mg/kg/day, depending on symptoms. Taper corticosteroids over at least 4 weeks. Consider azathioprine, MMF, cyclosporine if no response within 72-96 hours. Guillain-Barré syndrome: Start intravenous immunoglobulin 0.4 g/kg/day for 5 days or plasmapheresis. Consider corticosteroids (methylprednisolone 2 to 4 mg/kg/day) followed by a slow taper. Monitor for concurrent autonomic dysfunction.	Discontinue study treatment.
Colitis/Diarrhea	**1** Mild symptoms: ≤ 4 liquid stools per day over baseline and feeling well	Symptomatic management: fluids, loperamide, avoid high fiber/lactose diet. If Grade 1 persists for > 14 days, manage as a Grade 2 event.	Continue study treatment.

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
	2 Moderate symptoms: 4-6 liquid stools per day over baseline, or abdominal pain, or blood in stool, or nausea, or nocturnal episodes	Oral prednisolone 0.5 mg/kg/day (nonenteric coated). Do not wait for any diagnostic tests to start treatment. Taper steroids over 2 to 4 weeks. Consider endoscopy if symptoms are recurring.	Hold study treatment; resume when resolved/improved to baseline grade.
	3 Severe symptoms: ≥ 7 liquid stools per day over baseline, or if episodic within 1 hour of eating	Initiate intravenous methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Consider prophylaxis for adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement.	Hold study treatment; retreatment may be considered when resolved/improved to baseline grade and after discussion with the study medical monitor.
	4 Life-threatening symptoms	If no improvement in 72 hours or symptoms worsen, consider infliximab 5 mg/kg if no perforation, sepsis, TB, hepatitis, NYHA Class III/IV CHF or other immunosuppressive treatment: MMF or tacrolimus. Consult gastroenterologist to conduct colonoscopy/ sigmoidoscopy.	Discontinue study treatment.
Skin reactions	**1** Skin rash, with or without symptoms, < 10% BSA	Avoid skin irritants and sun exposure; topical emollients recommended.	Continue study treatment.

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
	2 Rash covers 10%-30% of BSA	Avoid skin irritants and sun exposure; topical emollients recommended. Topical steroids (moderate strength cream once a day or potent cream twice a day) ± oral or topical antihistamines for itch. Consider a short course of oral steroids.	Consider holding study treatment and monitor weekly for improvement. If not resolved, interrupt treatment until improved to Grade 1.
	3 Rash covers > 30% BSA or Grade 2 with substantial symptoms	Avoid skin irritants and sun exposure; topical emollients, oral antihistamines, and high-potency topical corticosteroids recommended. Initiate (methyl)prednisolone (or equivalent) 1 to 2 mg/kg, tapering for a period of ≥ 4 weeks.	Hold study treatment. Re-treat after discussion with the study medical monitor, if adverse event has resolved or improved to mild rash (Grade 1 or 2). Do not rechallenge cases of suspected SJS or TEN, unless SJS/TEN has been ruled out in consultation with appropriate specialists.
	4 Skin sloughing > 30% BSA with associated symptoms (eg, erythema, purpura, epidermal detachment), including Stevens-Johnson syndrome (all grades), and toxic epidermal necrolysis	Initiate intravenous methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Admit to a hospital and seek urgent dermatology consultation.	Discontinue study treatment.

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
Hepatitis	**1** ALT or AST > ULN to 3 x ULN	Check LFTs within 1 week and before the next dose; check LFTs to verify that there has been no worsening. If LFTs are worsening, recheck every 48-72 hours until improvement is seen.	Continue study treatment if LFTs are unchanged or improving. Hold study treatment if LFTs are worsening until improvement is seen.
	2 ALT or AST > 3 x to 5 x ULN	Recheck LFTs every 48-72 hours. Administer prednisolone at a dose of 0.5 to 2 mg/kg/day for ≥ Grade 2 liver enzyme elevations, with or without concomitant bilirubin elevations. For Grade 2 hepatitis, withhold tislelizumab until the event has resolved or improved to baseline and prednisolone has been tapered to ≤ 10 mg/day over 2 to 4 weeks.	Hold study treatment; treatment may be resumed when resolved/improved to baseline grade and prednisolone tapered to ≤ 10 mg.
	3 ALT or AST > 5 x to 20 x ULN	Immediately start methylprednisolone 1 to 2 mg/kg (or equivalent). Monitor closely. If no improvement after 3 days, consider additional treatment options (mycophenolate mofetil or azathioprine.	If ALT and AST ≤ 10 x ULN: Hold study treatment until improved to baseline grade; reintroduce only after discussion with the medical monitor. If ALT or AST > 10 x ULN: Discontinue study treatment.

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
	4 ALT or AST > 20 x ULN	Initiate intravenous methylprednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 6 weeks.	Discontinue study treatment.
	Worsening LFTs despite steroids: • If on oral prednisolone, change to pulsed intravenous methylprednisolone. • If on intravenous methylprednisolone, add MMF 500 to 1000 mg twice a day. • If worsens on MMF, consider addition of tacrolimus. Duration and dose of steroid required will depend on severity of event.		
Nephritis	**1** Creatinine 1.5 x baseline or > ULN to 1.5 x ULN	Repeat creatinine test weekly. If symptoms worsen, manage as per criteria below.	Continue study treatment.
	2 Creatinine > 1.5-3 x baseline or > 1.5-3 x ULN	Ensure hydration and review creatinine in 48-72 hours; if not improving, consider creatinine clearance measurement by 24-hour urine collection. Discuss with nephrologist the need for kidney biopsy. If attributed to study drug, initiate oral prednisolone 0.5-1 mg/kg and taper over at least 2 weeks. Repeat creatinine/U&E every 48-72 hours.	Hold study treatment. If not attributed to drug toxicity, restart treatment. If attributed to study drug and resolved/improved to baseline grade, restart study drug if tapered to < 10 mg prednisolone.

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
	3 Creatinine > 3 x baseline or > 3-6 x ULN	Hospitalize patient for monitoring and fluid balance; repeat creatinine test every 24 hours; refer to a nephrologist and discuss need for biopsy. If worsening, initiate intravenous (methyl)prednisolone 1-2 mg/kg. Taper corticosteroids over at least 4 weeks.	Hold study treatment until the cause is investigated. If study drug suspected, discontinue study treatment.
	4 Creatinine > 6 x ULN	As per Grade 3, patient should be managed in a hospital where renal replacement therapy is available.	Discontinue study treatment.
Diabetes/ Hyperglycemia	**1** Fasting glucose value ULN to 160 mg/dL; ULN to 8.9 mmol/L	Monitor closely and treat according to local guideline. Check for C-peptide and antibodies against glutamic acid decarboxylase and islet cells are recommended.	Continue study treatment.
	2 Fasting glucose value 160-250 mg/dL; 8.9-13.9 mmol/L	Obtain a repeat blood glucose level at least every week. Manage according to local guideline.	Continue study treatment.
	3 Fasting glucose value 250-500 mg/dL; 13.9-27.8 mmol/L	Admit patient to hospital and refer to a diabetologist for hyperglycemia management. Corticosteroids may exacerbate hyperglycemia and should be avoided.	Hold study treatment until patient is free of hyperglycemia symptoms, and blood glucose has been stabilized at baseline or Grade 0 or 1.

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
	4 Fasting glucose value > 500 mg/dL; > 27.8 mmol/L	Admit patient to hospital and institute local emergency diabetes management. Refer the patient to a diabetologist for insulin maintenance and monitoring.	Hold study treatment until patient is free of hyperglycemia symptoms, and blood glucose has been stabilized at baseline or Grade 0 or 1.
Ocular toxicity	**1** Asymptomatic eye examination/test abnormality	Consider alternative causes and prescribe topical treatment as required.	Continue study treatment.
	2 Anterior uveitis or mild symptoms	Refer patient to an ophthalmologist for assessment and topical corticosteroid treatment. Consider a course of oral steroids.	Continue study treatment or hold treatment if symptoms worsen or if there are symptoms of visual disturbance.
	3 Posterior uveitis/panuveitis or significant symptoms	Refer patient urgently to an ophthalmologist. Initiate oral prednisolone 1-2 mg/kg and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0 or 1; reintroduce only after discussion with the study medical monitor.
	4 Blindness (at least 20/200) in the affected eyes	Initiate intravenous (methyl)prednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks.	Discontinue study treatment.
Pancreatitis	**2** Asymptomatic, blood test abnormalities	Monitor pancreatic enzymes.	Continue study treatment.

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
	3 Abdominal pain, nausea and vomiting	Admit to hospital for urgent management. Initiate intravenous (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when amylase/lipase improved to Grade 2 and taper over at least 4 weeks.	Hold study treatment; reintroduce only after discussion with the study medical monitor.
	4 Acute abdominal pain, surgical emergency	Admit to hospital for emergency management and appropriate referral.	Discontinue study treatment.
Arthritis	**1** Mild pain with inflammation, swelling	Management per local guideline.	Continue study treatment.
	2 Moderate pain with inflammation, swelling, limited instrumental (fine motor) activities	Management as per local guideline. Consider referring patient to a rheumatologist. If symptoms worsen on treatment, manage as a Grade 3 event.	Continue treatment or, if symptoms continue to worsen, hold study treatment until symptoms improve to baseline or Grade 0 or 1.
	3 Severe pain with inflammation or permanent joint damage, daily living activity limited	Refer patient urgently to a rheumatologist for assessment and management. Initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks.	Hold study treatment unless improved to Grade 0 or 1; reintroduce only after discussion with the study medical monitor.
Mucositis/ stomatitis	**1** Test findings only or minimal symptoms	Consider topical treatment or analgesia as per local guideline.	Continue study treatment.

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
	2 Moderate pain, reduced oral intake, limited instrumental activities	As per local guidelines, treat with analgesics, topical treatments, and oral hygiene care. Ensure adequate hydration. If symptoms worsen or there is sepsis or bleeding, manage as a Grade 3 event.	Continue study treatment.
	3 Severe pain, limited food and fluid intake, daily living activity limited	Admit to hospital for appropriate management. Initiate intravenous (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when symptoms improve to Grade 2 and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0 or 1.
	4 Life-threatening complications or dehydration	Admit to hospital for emergency care. Consider intravenous corticosteroids if not contraindicated by infection.	Discontinue study treatment.
Myositis/ rhabdomyolysis	**1** Mild weakness with/without pain	Prescribe analgesics. If CK is significantly elevated and patient has symptoms, consider oral steroids and treat as Grade 2.	Continue study treatment.
	2 Moderate weakness with/without pain	If CK is 3 x ULN or worse, initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0 to 1.

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
	3 or 4 Severe weakness, limiting self-care	Admit to hospital and initiate oral prednisolone 1 mg/kg. Consider bolus intravenous (methyl)prednisolone and 1-2 mg/kg/day maintenance for severe activity restriction or dysphagia. If symptoms do not improve, add immunosuppressant therapy. Taper oral steroids over at least 4 weeks.	For Grade 3: Hold study treatment until improved to Grade 0 or 1. Discontinue upon any evidence of myocardial involvement.
Myocarditis [a]	**< 2** Asymptomatic but significantly increased CK-MB or increased troponin or clinically significant intraventricular conduction delay	Initiate cardiac evaluation under close monitoring with repeat serum testing and including ECG, cardiac echo/MUGA, and/or other interventions per institutional guidelines; consider referral to a cardiologist. If diagnosis of myocarditis is confirmed, treat as Grade 2.	Hold study treatment. If a diagnosis of myocarditis is confirmed and considered immune-mediated, permanently discontinue study treatment in patients with moderate or severe symptoms. Patients with no symptoms or mild symptoms may not restart tislelizumab unless cardiac parameters have returned to
	2 Symptoms on mild-moderate exertion	Admit to hospital and initiate oral prednisolone or intravenous (methyl)prednisolone at 1-2 mg/kg/day. Consult with a	
	3 Severe symptoms with mild exertion		

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
	4 Life-threatening	cardiologist and manage symptoms of cardiac failure according to local guidelines. If no immediate response, change to pulsed doses of (methyl)prednisolone 1 g/day and add MMF, infliximab, or anti-thymocyte globulin.	baseline and after discussion with the study medical monitor.
Other immune-mediated adverse events	Grade 3 (first occurrence) Grade 4 or recurrent Grade 3; persistent Grade 2 or 3 despite treatment modification; inability to reduce corticosteroid dose to 10 mg prednisone or equivalent per day	NA	Hold study treatment Discontinue study treatment.

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

[a] If clinically significant cardiac enzyme abnormalities are detected during laboratory assessment and serial cardiac enzyme assessments pose logistical hardship for the patient, then patient hospitalization should strongly be considered until immune-mediated myocarditis has been ruled out.

APPENDIX 8. CHRONIC KIDNEY DISEASE EPIDEMIOLOGY COLLABORATION EQUATION

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

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

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

where:

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

κ is 0.7 for women and 0.9 for men,

α is -0.329 for women and -0.411 for men,

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

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

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

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

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

Contraception Guidelines

The Clinical Trials Facilitation Group recommendations related to contraception and pregnancy testing in clinical studies 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 the study drug, and withdrawal are not acceptable methods of contraception.

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

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

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

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

- Surgically sterile (ie, through bilateral salpingectomy, bilateral oophorectomy, or hysterectomy)
- Postmenopausal, defined as:
  - ≥ 55 years of age with no spontaneous menses for ≥ 12 months OR
  - < 55 years of age with no spontaneous menses for ≥ 12 months AND with postmenopausal follicle-stimulating hormone 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 a follicle-stimulating hormone 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 10. LIST OF RESTRICTED CHINESE HERBAL AND PATENT MEDICINES

The following table provides examples of Chinese herbal and patent medications that may be used to treat cancer or that have immune-stimulating properties. **This list is not intended to be all-inclusive.** These medications require a 14-day washout period and should be restricted 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: Gao, ointment; He Ji/Heji, mixture; Jiao Nang/Jiaonang, capsule; Ke Li/Keli, granules; Kou Fu Ye/koufuye, oral liquid; Pian, tablet; Wan, pill/bolus; Zhue She ye/Zhusheye, injections.

APPENDIX 11. TISLELIZUMAB

1. INTRODUCTION - TISLELIZUMAB

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 is being investigated either as monotherapy or in combination with other therapies.

PD-1 is mainly expressed in activated T cells, including cluster of differentiation (CD)8^+ cytotoxic T lymphocytes and $CD4^+$ T-helper lymphocytes (McDermott and Atkins 2013). The PD-1 signaling cascade negatively regulates the T-cell and attenuates T-cell proliferation and functional activities, leading to T-cell exhaustion. PD-1 expression is markedly up-regulated on TILs, while the expression of PD-L1 is significantly increased on tumor cells and tumor-associated immune cells in the presence of stimulating cytokines such as interferon-gamma (IFN-γ) and interferon-alpha in the tumor microenvironment (Riley 2009), which is observed in many types of human solid tumors. This body of evidence provides the basis for cancer immunotherapeutic intervention via the approach of antagonizing PD-1.

Refer to Tislelizumab Investigator's Brochure for additional background.

1.1 Background Information on Tislelizumab

1.1.1. Pharmacology

Tislelizumab binds to the extracellular domain (ECD) of human PD-1 with high specificity and affinity (dissociation constant = 0.15 nM), as demonstrated by receptor binding assays based on surface plasmon resonance. Tislelizumab competitively blocks the binding of both PD-L1 and programmed death ligand-2 (PD-L2). Robust antitumor activity of tislelizumab was also observed in human PD-1 transgenic mice transplanted with B16/F10 mouse melanoma cells overexpressing murine granulocyte-macrophage colony-stimulating factor.

The IgG4-variant antibody has demonstrated very low binding to gamma fragment crystallizable region receptor (FcγR) RI, RIIIA, and complement 1q (C1q) by in vitro assays, suggesting low or no antibody-dependent cellular phagocytosis, antibody-dependent cellular cytotoxicity, and complement-dependent cytotoxicity (CDC) effects in humans.

Tislelizumab binds to the PD-1 of cynomolgus monkey and human with a similar affinity but does not bind to mouse PD-1. The cynomolgus monkey is therefore considered the relevant animal species for nonclinical studies. In single-dose and 13-week repeated-dose toxicology studies in cynomolgus monkeys, no specific concerns were identified in vital organ systems, including the cardiovascular system, central nervous system, and respiratory system.

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

1.1.2 Toxicology

In single-dose toxicity studies in both mice and cynomolgus monkeys, no mortality or apparent toxicity was noted at single doses up to 100 mg/kg.

In a repeated-dose study in cynomolgus monkeys, no apparent toxicity was noted following intravenous infusion of tislelizumab at 3, 10, or 30 mg/kg once every 2 weeks for 13 weeks (7 doses). No test-article-related histopathologic changes were noted in any tissues. No specific concerns were identified for vital organ system functions, including the cardiovascular system, the central nervous system, and the respiratory system. ADAs with neutralization activity were noted but appeared to have no impact on systemic exposure except at the low dose of 3 mg/kg. Thus, with sustained systemic drug exposure, the efficacy of the drug would not be impacted. The no-observed-adverse-effect level (NOAEL) was 30 mg/kg in this study.

Overall, the available toxicological data are considered adequate in support of the clinical development of tislelizumab in patients with advanced cancer.

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

1.1.3. Clinical Pharmacology

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

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

1.1.4. Prior Clinical Experience with Tislelizumab

As of 20 July 2022, 18 studies with tislelizumab are ongoing, and 7 studies have been completed (Tislelizumab Investigator's Brochure). Of the 18 ongoing studies, 10 studies have data available: 5 monotherapy studies and 5 chemotherapy combination therapy studies.

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

1.1.4.1. Pooled Safety Assessment of Monotherapy Studies

A pooled analysis of monotherapy studies was conducted to provide a comprehensive safety assessment separate from combination therapy. Data from patients with solid tumors were analyzed separately from patients with hematologic malignancies.

As of 20 July 2022, data are available from patients treated in 7 pooled solid tumor monotherapy studies (Tislelizumab Investigator's Brochure).

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

(imAEs), ≥ Grade 3 infusion-related AEs, and TEAEs leading to tislelizumab discontinuation was small.

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

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

1.1.4.2. Efficacy Assessment of Tislelizumab

Efficacy data are available from 9 monotherapy studies and 6 combination therapy studies. Among these 15 studies, 13 studies were in patients with solid tumors, and 2 studies were in patients with hematologic malignancies.

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

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

1.2. Tislelizumab Rationales

1.2.1. Rationale for Tislelizumab Monotherapy in the Neoadjuvant Treatment of Patients With Resectable NSCLC

With the successful development of cancer immunotherapy in advanced NSCLC, several studies on neoadjuvant/adjuvant immunotherapy are being conducted in resectable NSCLC. Preclinical studies showed that the immune-suppressive PD-1 axis is activated early in NSCLC; induction of an immune response before surgery may lead to durable protection (Chiari et al 2018). After surgical resection, tumor antigens decrease dramatically and intact blood vessels and lymph nodes for drug delivery are removed, which may influence the effects of immunotherapy. Taking these data into consideration, immunotherapy was given in the neoadjuvant phase. In previous Phase 1b or 2 studies, drugs targeting PD-1 and its ligand, PD-L1, have shown a manageable safety profile and promising preliminary efficacy data, including increased pathological response rate when used for neoadjuvant treatment in patients with resectable NSCLC (Cascone et al 2021, Forde et al 2018, Gao et al 2020, Lee et al 2021).

Tislelizumab monotherapy and the combination of tislelizumab plus platinum-based doublet chemotherapy have demonstrated clinical benefit in advanced NSCLC in 3 Phase 3 studies (BGB-A317-303, BGB-A317-304, and BGB-A317-307) (Tislelizumab Investigator's Brochure).

Overall, above evidence could support sponsor's opinion that tislelizumab neoadjuvant may benefit patients with PD-L1-expression-positive, early-stage, resectable NSCLC and have a tolerable safety profile.

1.2.2. Rationale for Selection of Tislelizumab Dose

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

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

Additionally, tislelizumab is currently approved and marketed in China at the recommended dosage of 200 mg once every 3 weeks for multiple indications either alone or in combination with standard of care chemotherapy. Please refer to the Tislelizumab Investigator's Brochure for additional details.

1.2.3. Biomarker Strategy Rationale

As the most well-known immune checkpoint molecule, the PD-1 pathway has received considerable attention for its role in maintaining T cell exhaustion, a dysfunction state of T cell in the setting of chronic antigen stimulation including cancer. Blockade of the PD-1 pathway using monoclonal antibodies against either PD-1 or the ligand PD-L1 could at least partially restore functions to these T cells with enhanced proliferation, pro-inflammatory cytokine production and killing activity (Pauken et al 2021). However, emerging studies revealed that not all exhausted $CD8^+$ T cells could respond to PD-1 blockade due to large heterogeneity or distinct epigenetic landscapes. Progenitor-like population, which retains the ability to proliferate in response to antigen and produce inflammatory cytokines, is preferentially responsive to PD-1 pathway blockade with a stronger degree of reinvigoration, despite lower PD-1 expression level. Meanwhile, the other more terminally differentiated T cells may not (Miller et al 2019). Besides cytotoxic effector function, the PD-1 pathway may also regulate the differentiation of naive T cells into memory T cells and modulate the responses of existing memory T cell populations (Ahn et al 2018).

Treg cells play a critical role in immune suppression with elevated levels of the PD-1 receptor by at least a fraction of them, suggesting the potential role of PD-1 pathway in regulating this population. It has been reported that PD-1 signaling inhibits Treg cell activation and function, while improved suppressive capacity of Treg is observed after PD-1 blockade (Kamada et al 2019). In tumors, PD-1 blockade leads to both increased PD-1^+ $CD8^+$ T cell function as well as enhanced PD-1+ Treg cell-mediated immunosuppression, with the ratio between them may direct the outcome of the final immune response (Kumagai et al 2020).

Additionally, PD-1 expression has been described on NK cells in some types of cancer and modulating PD-1 can impact NK cell functions. However, other work suggests minimal expression of PD-1 on NK cells (Hsu et al 2018, Judge et al 2020). Consequently, the extent to which PD-1 on NK cells can contribute to regulating host immunity remains an active area of investigation.

In summary, further exploration is needed to clarify the impact of PD-1 on the reinvigoration, formation and maintenance of different T-cell effector/memory subsets, as well as Treg cells and NK cells in this study.

1.3. Benefit-Risk Assessment of Tislelizumab

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 July 2022, tislelizumab has been evaluated in 3220 patients (2173 patients treated with monotherapy and 1047 patients treated with combination therapy), 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. In 2 Phase 3 clinical studies (BGB-A317-304 and BGB-A317-307), tislelizumab in combination with doublet platinum chemotherapy showed statistical and clinical improvement in PFS as the primary endpoint in comparison with chemotherapy, regardless of PD-L1 expression, in treatment-naive metastatic NSCLC patients.

Tislelizumab received approval from China NMPA based on these data for use in the first-line treatment of patients with unresectable, locally advanced, or metastatic squamous and nonsquamous NSCLC in 2021.

The safety profile of tislelizumab is largely consistent with that of other anti-PD-1 antibodies and includes mostly mild or moderate AEs. Very few Grade 3 or Grade 4 imAEs have been observed, and they have been generally reversible and manageable with study drug interruption and/or steroid treatment.

The benefit-risk assessment for tislelizumab monotherapy arm (Arm 1A), based on available tislelizumab data, is considered favorable.

2. STUDY TREATMENT – TISLELIZUMAB

2.1. Formulation, Packaging, Labeling, and Handling

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 and light conditions as specified on the label and in the pharmacy manual. Refer to the pharmacy manual for details regarding reconstitution, intravenous administration, accountability, and disposal. Refer to the Tislelizumab Investigator's Brochure for other details regarding tislelizumab.

2.2. Dosage, Administration, and Compliance

Dosing schedules for the treatment Arm 1A are provided in §Table 1. The first dose of the study drug is to be administered ≤ 2 days after randomization. All patients will be monitored for AEs throughout the study. Treatment modification (ie, dose delay or interruption) or discontinuation will be based on specific laboratory and AE criteria, as described in §Section 2.4.

Refer to §Section 2.2.1 for details on monitoring time.

§Table 1: Selection and Timing of Neoadjuvant Dose in Arm 1A

Treatment arm	Study drug	Dose	Frequency of administration	Route of administration	Duration of treatment
Arm 1A	Tislelizumab	200 mg	Day 1 of each 3-week cycle	Intravenously	2 to 4 Cycles

2.2.1 Tislelizumab Treatment Administration

Tislelizumab will be administered according to the dosing schedule provided in §Table 1. Assigned study drugs will be administered by intravenous infusion through an intravenous line containing a sterile, nonpyrogenic, low-protein-binding 0.2 or 0.22 µm in-line or add-on filter. Specific instructions for product preparation, storage, and administration are provided in the pharmacy manual.

The delivery period of the initial infusion for tislelizumab (Day 1 of Cycle 1) will be over 60 minutes (± 5 minutes); if this is well tolerated, then the delivery period of subsequent infusions may be shortened to over 30 minutes (± 5 minutes), which is the shortest time period permissible for infusion. Tislelizumab must not be concurrently administered with any other drug (§Section 3).

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

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

As a routine precaution, after completion of study treatment on Day 1 of Cycle 1, patients must be monitored ≥ 60 minutes and ≥ 30 minutes from Cycle 2 afterward in an area with resuscitation equipment and emergency agents.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in §Section 2.4. Details for the management of imAEs, infusion-related reactions, and anaphylaxis reactions are provided in detail in Section 8.7 and Appendix 7.

§Table 2: Administration of Tislelizumab and Monitoring Time

Cycle	Tislelizumab Monotherapy
Cycle 1 Day 1	Tislelizumab infusion ≥ 60 minutes followed by patient monitoring for ≥ 60 minutes
Cycle 2 Day 1 onwards	If well tolerated, tislelizumab infusion ≥ 30 minutes followed by patient monitoring for ≥ 30 minutes

Note: The infusion rate of tislelizumab may be decreased or the infusion may be stopped in the event of an infusion-related reaction.

2.3. Overdose

An overdose is defined as ≥ 600 mg of tislelizumab in a 24-hour period. Any overdose or incorrect administration of study drug should be noted in the patient's source documents and in the appropriate eCRF.

2.4. Dose Modification for Tislelizumab

Dose modification for tislelizumab is defined as any of the following: dose delay, dose interruption, and infusion rate decrease. A dose delay is a deviation from the prescribed dosing schedule (ie, the drug is withheld beyond the visit window). A dose interruption is an interruption of an infusion. An infusion rate decrease is a decrease of infusion rate. There will be no dose reduction for tislelizumab in this study.

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

If study treatment is delayed due to treatment-emergent adverse events, study treatment may resume only after the AEs have returned to baseline or ≤ Grade 1 severity except for alopecia or AEs that, in the opinion of the investigator, are not considered a safety risk to the patient. If a treatment delay is due to worsening of laboratory results, eg, hematologic or biochemical parameters, the frequency of relevant blood tests should be increased, as clinically indicated. When several toxicities with different grades of severity occur at the same time, the dose modifications should be according to the highest grade observed.

In general, dose delays for reasons other than management of AEs are prohibited. Total duration of dose delay (ie, the delay duration from first dose of study treatment to actual last dose compared with prescribed dosing schedule) of ≤ 3 weeks is allowed under the following guidance and at the discretion of the investigator. Study treatment should resume as soon as possible after the AEs recover to baseline or Grade 1 (whichever is more severe) if the total delay duration is not more than 3 weeks.

If the patient is unable to resume study treatment ≤ 3 weeks of total delay duration, then the patient should be discontinued from treatment. If the patient is not able to resume study treatment ≤ 3 weeks of total delay duration for unforeseen non-drug-related reasons, continued treatment may be allowed after consolation and approval by the medical monitor.

If a patient is benefiting from the study treatment while meeting the discontinuation criteria, resumption of study treatment may occur upon discussion and agreement with the medical monitor. Specific treatment modifications to manage treatment-related toxicities, such as imAEs, infusion-related reactions, and anaphylaxis reactions, are described in Section 8.7 and Appendix 7.

3. PRIOR AND CONCOMITANT THERAPY – TISLELIZUMAB

3.1. Potential Interactions Between the Study Drugs and Concomitant Medications

The potential for drug-drug interaction between tislelizumab, standard chemotherapy, and small-molecule drug products is very low, given tislelizumab is a therapeutic monoclonal antibody. Tislelizumab is unlikely to have an effect on drug metabolizing enzymes or transporters because it is expected to be degraded into amino acids and recycled into other proteins.

4. SAFETY MONITORING AND REPORTING -TISLELIZUMAB

4.1. Risks Associated With Tislelizumab

Tislelizumab is an investigational agent that is currently in clinical development. The following recommendation is based on results from nonclinical and clinical studies with 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, this type of therapy may increase the risk of imAEs, specifically the induction or exacerbation of autoimmune conditions. AEs observed with anti-PD-1 therapy are presented in Section 8.7.2.

An imAE may occur at any time during or after treatment. Often, the etiology of imAEs is not clear, and other causes should be ruled out. This may require diagnostic testing and consultation with a specialist. Suggested evaluation and management guidelines for suspected imAEs are provided in Appendix 7. Refer to the Tislelizumab Investigator's Brochure for additional details.

APPENDIX 12. OCIPERLIMAB

1. INTRODUCTION - OCIPERLIMAB

Immune surveillance plays a critical role in cancer prevention. However, in situations in which tumors develop resistance mechanisms to suppress the host immune system, tumors eventually grow out of control (Schreiber et al 2011; Swann and Smyth 2007). One such resistance mechanism is up-regulation of immune checkpoint receptors, such as PD-1 and TIGIT (Johnston et al 2014; Chauvin et al 2015).

Ociperlimab (also known as BGB-A1217) is a humanized immunoglobulin G (IgG) 1 monoclonal antibody binding to TIGIT under clinical development for the treatment of human malignancies. TIGIT is an immune checkpoint receptor primarily expressed on immune cells, such as T cells and natural killer (NK) cells (Manieri et al 2017). A large body of literature suggests that TIGIT plays a key role in promoting T-cell exhaustion and maintaining immune tolerance, in both chronic viral infections and the tumor microenvironment (Yu et al 2009; Boles et al 2009; Stanietsky et al 2009; Levin et al 2011; Johnston et al 2014).

When expressed on effector T cells, TIGIT competes with costimulatory receptor cluster of differentiation (CD) 226 (CD226) for binding to its ligands (such as poliovirus receptor [PVR] and poliovirus receptor–related 2 [PVRL2]) and reduces cytokine production, T-cell proliferation, and cytotoxicity (Bottino et al 2003; Stanietsky et al 2009). A similar phenomenon was also observed in NK cells of cancer patients. In addition, regulatory T cells (Tregs) expressing TIGIT demonstrated greater immunosuppressive functions compared with TIGIT-negative Tregs (Joller et al 2014). Some studies have also shown that the interaction between TIGIT and PVR suppresses immune responses mediated by dendritic cells (DCs), especially in the inhibition of type I interferon and IL-12 production and promotion of anti-inflammatory cytokine interleukin (IL) 10 (IL-10) (Yu et al 2009).

Up-regulation of TIGIT expression on tumor-infiltrating lymphocytes (TILs) has been reported in many types of cancers, such as lung (Tassi et al 2017), stomach (He et al 2017), breast (Gil Del Alcazar et al 2017), esophageal (Xie et al 2016), brain (Hung et al 2018), acute myeloid leukemia (Kong et al 2016), and melanoma (Mahnke and Enk 2016). A higher TIGIT/CD226 ratio was associated with poor prognosis in melanoma patients treated with anti-PD-1 and/or anticytotoxic T-lymphocyte–associated protein 4 (anti-CTLA-4) antibodies (Fourcade et al 2018).

Refer to the most recent edition of the Ociperlimab Investigator's Brochure for additional background on ociperlimab.

1.1. Background Information on Ociperlimab

Refer to the Ociperlimab Investigator's Brochure for additional background on Ociperlimab.

1.1.1 Pharmacology

Ociperlimab binds to the extracellular domain of human TIGIT with high specificity and affinity (equilibrium dissociation constant K_D = 0.135 nM), as demonstrated by target-binding assays and surface plasmon resonance (SPR) characterization. In in vitro cell-based assays, ociperlimab consistently and dose-dependently enhances the functional activities of activated human

peripheral blood mononuclear cells (PBMCs). In the MC-38 mouse colon cancer model in TIGIT-humanized mice, ociperlimab in combination with anti–mouse PD-1 enhanced inhibition of tumor growth compared with either monotherapy.

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

1.1.2. Toxicology

The safety profile of ociperlimab was characterized in a 4-week repeat-dose toxicity study in humanized TIGIT knock-in mice and in a 13-week repeat-dose toxicity study in cynomolgus monkeys. Overall, no apparent toxicity was observed in the 13-week cynomolgus monkey or in the 4-week humanized TIGIT knock-in mouse studies. A dose-proportional increase in systemic exposure (AUC and C_{max}) was noted in both species without apparent sex difference while excluding the impact of positive antidrug antibodies (ADAs) in individual animals with lower systemic exposure and/or faster clearance. No accumulation was observed in monkeys after once-every-2-week dosing for 13 weeks, but a trend of accumulation was shown in mice after weekly dosing for 4 weeks. The no-observed-adverse-effect level (NOAEL) of ociperlimab was 50 mg/kg in mice and 100 mg/kg in monkeys, which were the tested high doses in both species. No specific tissue cross-reactivity was detected in normal human tissues.

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

1.1.3. Clinical Pharmacology

Preliminary pharmacokinetics (PK) data are available from 52 patients in the Phase 1 (dose escalation and dose verification in China) portion of Study AdvanTIG-105. Ociperlimab exposures (AUC and C_{max}) increased approximately dose proportionally from the 50 mg to the 1800 mg dose. Across dose groups, serum concentrations of ociperlimab decreased in a biexponential manner after administration. The geometric mean terminal half-life estimate following the first dose ranged from approximately 7 days to 11 days. Postdose PK sampling duration may not be sufficient for robust characterization of elimination half-life using noncompartmental analysis (NCA); hence, the reported half-life values should be interpreted with caution.

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

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

1.1.4. Prior Clinical Experience With Ociperlimab

1.1.4.1. Safety Assessment of Ociperlimab monotherapy or in combination with tislelizumab

As of July 2022, preliminary safety data are available from 4 studies (AdvanTIG-105, AdvanTIG-202, AdvanTIG-204, and AdvanTIG-206). Study AdvanTIG-105 is a Phase 1/1b study investigating the safety, tolerability, PK, and preliminary antitumor activity of the anti-TIGIT monoclonal antibody ociperlimab in combination with the anti-PD-1 monoclonal antibody tislelizumab with or without chemotherapy in patients with unresectable locally advanced or metastatic solid tumors. Study AdvanTIG-202 is a Phase 2 study investigating the efficacy and safety of tislelizumab with or without ociperlimab in patients with previously treated recurrent or metastatic cervical cancer. Study AdvanTIG-204 is a Phase 2 study investigating the preliminary efficacy and safety of ociperlimab plus tislelizumab plus concurrent chemoradiotherapy in patients with untreated limited-stage small cell lung cancer. A total of 126 patients were enrolled in the study across 30 to 40 centers globally. Study AdvanTIG-206 is a Phase 2 study investigating the efficacy and safety of tislelizumab in combination with ociperlimab plus BAT1706 (a bevacizumab biosimilar, a vascular endothelial growth factor [VEGF] inhibitor) and of tislelizumab plus BAT1706 as first-line treatment in patients with advanced hepatocellular carcinoma. A total of 94 patients were enrolled in mainland China/ Taiwan.

As of July 2022, a total of 592 patients had been treated with ociperlimab as monotherapy, in combination with tislelizumab only, in combination with tislelizumab plus chemotherapy, in combination with tislelizumab plus concurrent chemoradiotherapy, or in combination with tislelizumab plus BAT1706 across a variety of tumor types.

Ociperlimab was well tolerated. A pooled analysis of monotherapy and combination therapies conducted to provide a comprehensive safety assessment showed that AEs were generally reversible and manageable. Of 592 patients in the pooled analysis, 65 patients (11.0%) reported ≥ Grade 3 treatment-emergent adverse events assessed as related to ociperlimab, and 59 patients (10.0%) reported AEs leading to discontinuation of ociperlimab. Furthermore, 35 patients (5.9%) experienced a TEAE that led to death, and 5 (0.8%) of them were assessed as related to ociperlimab. Dose-limiting toxicities (DLTs) were assessed in the dose escalation and dose verification parts of AdvanTIG-105 and AdvanTIG-206, and no TEAEs were considered to be a DLT.

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

1.1.4.2. Efficacy Assessment of Tislelizumab in Combination With Ociperlimab

The ociperlimab dose of 900 mg once every 3 weeks combined with tislelizumab 200 mg once every 3 weeks was selected as the recommended Phase 2 dose (RP2D) for further investigation based on data from the ongoing Phase 1/1b Study AdvanTIG-105.

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

1.2. Ociperlimab Rationales

1.2.1. Rationale for Tislelizumab in Combination With Ociperlimab in the Treatment of Patients With Resectable Non-Small Cell Lung Cancer

Upregulation of TIGIT expression in TILs has been reported in NSCLC (Tassi et al 2017). Blockade of TIGIT receptor alone or in combination with PD-1/PD-L1 blockade has been shown to rescue functionally "exhausted" T cells both in vitro and in vivo (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).

Clinically, treatment with anti-TIGIT antibody in combination with anti-PD-L1 therapy has the potential to be more efficacious than anti-PD-L1 therapy alone in metastatic NSCLC without prior checkpoint inhibitor therapy. Improvements in both overall response rate (ORR) and median PFS were reported with tiragolumab plus atezolizumab compared to placebo plus atezolizumab (ORR: 37.31% versus 20.6%; and median PFS: 5.6 months versus 3.9 months) in the first-line treatment of patients with Stage IV NSCLC with a PD-L1 tumor proportion score ≥ 1% (Rodriguez-Abreu et al 2020). Similarly, the combination of vibostolimab, an anti-TIGIT antibody, and pembrolizumab showed unconfirmed and confirmed ORR of 29% and 24%, respectively, in patients who were untreated or had been treated with ≥ 1 line of platinum-containing chemotherapy who had not previously received anti-PD-(L)1 therapy (Ahn et al 2020, Niu et al 2020).

The safety profiles of both the combinations of tiragolumab plus atezolizumab and vibostolimab plus pembrolizumab were found to be tolerable. The rate of imAEs with tiragolumab plus atezolizumab was higher than that with placebo plus atezolizumab (69% versus 47%), but most of the imAEs were manageable Grade 1 or 2 events of infusion-related reaction, including rash. The rate of treatment-related AEs of any grade with vibostolimab plus pembrolizumab was slightly higher than that with vibostolimab monotherapy (71% versus 59%); however, the ≥ Grade 3 treatment-related AE rates were similar between the 2 arms (13% versus 15%), indicating that most of the treatment-related AEs in the combination arm were Grade 1 or 2 in severity (Ahn et al 2020, Niu et al 2020, Rodriguez-Abreu et al 2020).

Study BGB-900-105 showed that the preliminary safety of ociperlimab plus tislelizumab was consistent with that of other anti-TIGIT plus anti-PD-L1 treatment combinations, with no maximum tolerated dose (MTD) reached and no DLT occurring during the treatment period at any dose level (Tislelizumab Investigator's Brochure). Ociperlimab plus tislelizumab appeared to be well tolerated at all the administered doses.

Ociperlimab plus tislelizumab is expected to be tolerable. Ociperlimab and tislelizumab have nonoverlapping anticancer mechanisms and are likely to have synergistic and/or added activity. Adding ociperlimab to tislelizumab will likely further enhance the overall clinical activity of tislelizumab and bring long-term benefits for patients with resectable Stage II to IIIA NSCLC.

1.2.2. Rationale for Selection of Ociperlimab Dose in Combination With Tislelizumab

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

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

As of May 2021, a total of 3 patients were assessed to have a confirmed partial response (PR), 1 patient each in 450 mg, 900 mg, and 1800 mg cohorts. Ociperlimab exposure in all 3 patients with a PR was consistent with that expected at the 900 mg dose level. The confirmed disease control rate (DCR) observed in the 450 mg, 900 mg, and 1800 mg cohorts was 60%, 64.3%, and 60%, respectively.

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

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

1.2.3. Biomarker Strategy Rationale

Cell-surface expression of TIGIT is mainly restricted to lymphocytes including effector $CD4^+$ and $CD8^+$ T, NK cells and Treg cells. Thus, ociperlimab may modulate phenotypes and antitumor activities of these immune cells synergistically in combination with tislelizumab. Moreover, as a Fc-competent TIGIT blocking antibody, ociperlimab may also elicit immune response through Fc-medicated mechanisms of action.

Considering that in patients with cancer, TIGIT is highly expressed by Tregs in peripheral blood mononuclear cells and further upregulated in the tumor microenvironment (TME), compared with other immune populations (Chauvin and Zarour 2020), it is hypothesized that anti-TIGIT mAbs with Fc-binding capability may preferentially induce Treg depletion through antibody-dependent cell-mediated cytotoxicity (ADCC) or antibody-dependent cell-mediated phagocytosis (ADCP). Supportively, it was observed that the higher TIGIT expression in Tregs is correlated with their depletion with an hIgG1 format in PBMCs from patients with cancer, as well as in TILs from mice (Preillon et al 2021). In contrast, no killing of activated $TIGIT^+$ $CD8^+$ T cells was observed (Lopez et al 2019). Accordingly, the ADCC/ADCP–enabling format of the anti-TIGIT mAb had superior antitumor activity, which was dependent upon Fcγ receptor

engagement (Preillon et al 2021). Consistently, in mouse models, the observed antitumor efficacy of ociperlimab is Fc effector function dependent and associated with a pharmacodynamic change of Treg reduction (Chen et al 2022).

Target molecules can be removed from the cell surface through the FcγR-binding induced endocytosis (trogocytosis), thus impacting mAb-based therapies. Through co-culturing purified human T cells with FcγR+ monocytes or DCs, only ociperlimab with competent Fc, rather than the Fc mutant version, induced the trogocytosis of surface TIGIT. Besides, it was also observed in mouse models that ociperlimab treatment decreased the overall TIGIT expression on intra-tumoral T cells and NK cells, suggesting that FcγR trogocytosis may occur in vivo and contribute to the surface removal of TIGIT molecules (Chen et al 2022).

Fc-FcγR interaction may modulate FcγR+ myeloid cells to create a proinflammatory tumor microenvironment (Dahan et al 2015). Supportively, ociperlimab treatment significantly increased the expression of CD86, a co-stimulatory ligand typically found on the surface of antigen-presenting cells (APC) and up-regulated during APC activation, while Fc mutant version showed no effect, suggesting TIGIT mAbs can induce an activation of APC via FcγRs (Chen et al 2022).

Therefore, it is valuable to determine whether ociperlimab can induce Fc-mediated mechanisms including intratumoral Treg depletion, TIGIT downregulation and APC modulation in patients with cancer, as well as its association with clinical outcomes to facilitate drug development and identification of patients who are most likely to benefit from the therapeutic drugs.

1.3. Benefit-Risk Assessment of Tislelizumab in Combination With Ociperlimab

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 with tislelizumab and preliminary results from an anti-TIGIT/anti-PD-L1 competitor combination suggest that ociperlimab has the potential to improve and/or extend the therapeutic benefits of tislelizumab in the treatment-naive setting. 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 those observed with tislelizumab alone. Preliminary data with ociperlimab plus tislelizumab showed that the combination was tolerated in patients with advanced solid tumors. The types and severity of AEs observed were also consistent with those observed with tislelizumab monotherapy. No DLTs were observed at dose levels from 50 mg to 1800 mg in dose escalation in combination with tislelizumab 200 mg (Study BGB-900-105).

The risk of observing augmented safety signals, as has been shown for other anti-PD-1-based immuno-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 of anti-TIGIT and anti-PD-L1 therapies provide an opportunity to specifically augment the activity

of effector T cells in the tumor rather than in the periphery and/or nontumor tissue (Johnston et al 2014), from which the increased systemic toxicity should be limited.

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. The benefit-risk assessment for tislelizumab in combination with ociperlimab arm (Arm 1B), based on available data, is considered favorable.

2. STUDY TREATMENT – TISLELIZUMAB IN COMBINATION WITH OCIPERLIMAB

2.1. Formulation, Packaging, Labeling, and Handling

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. 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 conditions as specified on the label. Shaking should be avoided.

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

2.2. Dosage, Administration, and Compliance

An overview on dosing schedules for the treatment Arm 1B is provided in §Table 1. The first dose of the study drugs is to be administered ≤ 2 days after randomization. All patients will be monitored continuously for AEs. Treatment modification (ie, dose delay or interruption) or discontinuation will be based on specific laboratory and AE criteria, as described in §Section 2.4.

During the neoadjuvant phase, for each cycle, study drug administration in Arm 1B will follow this order: tislelizumab and then ociperlimab. Refer to §Section 2.2.1 for details on monitoring time.

§Table 1: Selection and Timing of Neoadjuvant Dose in Arm 1B

Treatment arm	Study drug	Dose	Frequency of administration	Route of administration	Duration of treatment
Arm 1B	Tislelizumab	200 mg	Day 1 of each 3-week cycle	Intravenously	2 to 4 Cycles
	Ociperlimab	900 mg			

2.2.1. Tislelizumab and Ociperlimab Treatment Administration

Ociperlimab and tislelizumab will be administered according to the dosing schedule provided in §Table 1. The assigned study drugs will be administered by intravenous infusion through an intravenous line containing a sterile, nonpyrogenic, low-protein-binding 0.2 or 0.22 µm in-line or add-on filter. Specific instructions for product preparation, storage, and administration are provided in the pharmacy manual.

The delivery period of the initial tislelizumab and ociperlimab infusion for each study drug (Day 1 of Cycle 1 and Cycle 2) will be over 60 minutes (± 5 minutes); if this is well tolerated, then the delivery period of subsequent infusions for each study drug may be shortened to over 30 minutes (± 5 minutes), which is the shortest time period permissible for infusion. Ociperlimab and tislelizumab must not be concurrently administered with any other drug (refer to §Section 3).

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

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

As a routine precaution, after completion of study treatment on Day 1 of Cycle 1 and Cycle 2, patients must be monitored ≥ 120 minutes and ≥ 60 minutes from Cycle 3 afterward in an area with resuscitation equipment and emergency agents.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in §Section 2.4. Details for the management of imAEs, infusion-related reactions, and anaphylaxis reactions are provided in detail in Section 8.7 and Appendix 7.

§Table 2: Administration of Tislelizumab and Ociperlimab and Monitoring Time

Cycle	Tislelizumab and Ociperlimab Combination
Cycle 1-2 Day 1	Tislelizumab infusion ≥ 60 minutes followed by ociperlimab infusion ≥ 60 minutes Patient monitoring for ≥ 120 minutes after the last infusion
Cycle 3 Day 1 onwards	If well tolerated, tislelizumab infusion ≥ 30 minutes followed by ociperlimab infusion ≥ 30 minutes Patient monitoring for ≥ 60 minutes after the last infusion

Note: The infusion rate of tislelizumab or ociperlimab may be decreased or the infusion may be stopped in the event of an infusion-related reaction.

2.3. Overdose

An overdose is defined as ≥ 600 mg of tislelizumab in a 24-hour period and as ≥ 1800 mg of ociperlimab in a 24-hour period. Any overdose or incorrect administration of study drug should be noted in the patient's source documents and in the appropriate eCRF.

2.4. Dose Modification for Ociperlimab and Tislelizumab

Dose modification for ociperlimab is defined as any of the following: dose delay, dose interruption, and infusion rate decrease. A dose delay is a deviation from the prescribed dosing schedule (ie, the drug is withheld beyond the visit window). A dose interruption is an interruption of an infusion. An infusion rate decrease is a decrease of infusion rate. There will be no dose reduction for ociperlimab in this study.

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

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

If study treatment is delayed due to TEAEs, study treatment may resume only after the AEs have returned to baseline or ≤ Grade 1 severity except for alopecia or AEs that, in the opinion of the investigator, are not considered a safety risk to the patient. If a treatment delay is due to worsening of laboratory results, eg, hematologic or biochemical parameters, the frequency of relevant blood tests should be increased, as clinically indicated. When several toxicities with different grades of severity occur at the same time, the dose modifications should be according to the highest grade observed.

In general, dose delays for reasons other than management of AEs are prohibited. Total duration of dose delay (ie, the delay duration from first dose of study treatment to actual last dose compared with prescribed dosing schedule) of ≤ 3 weeks is allowed under the following guidance and at the discretion of the investigator. Study treatment should resume as soon as possible after the adverse events recover to baseline or Grade 1 (whichever is more severe) if the total delay duration is not more than 3 weeks.

If the patient is unable to resume study treatment ≤ 3 weeks of total delay duration, then the patient should be discontinued from treatment. If the patient is not able to resume study treatment ≤ 3 weeks of total delay duration for unforeseen non-drug-related reasons, continued treatment may be allowed after consolation and approval by the medical monitor

If a patient is benefiting from the study treatment while meeting the discontinuation criteria, resumption of study treatment may occur upon discussion and agreement with the medical monitor. Specific treatment modifications to manage treatment-related toxicities, such as imAEs, infusion-related reactions, and anaphylaxis reactions, are described in Section 8.7 and Appendix 7.

3. PRIOR AND CONCOMITANT THERAPY – OCIPERLIMAB

3.1. Potential Interactions Between the Study Drugs and Concomitant Medications-OCIPERLIMAB

The potential for drug-drug interactions between ociperlimab, standard chemotherapy, and small-molecule drug products is very low given that the ociperlimab is therapeutic monoclonal antibody. Ociperlimab is unlikely to have an effect on drug-metabolizing enzymes or

transporters because it is expected to be degraded into amino acids and recycled into other proteins. Based on the mechanism of action, any therapeutic protein drug-drug interaction is not expected between the investigational agents.

4. SAFETY MONITORING AND REPORTING – OCIPERLIMAB

4.1. Risks Associated With Ociperlimab

Ociperlimab is investigational agent that is currently in clinical development. Limited safety data are available in patients and the full safety profile has not been characterized. The following recommendation is based on results from nonclinical and clinical studies with ociperlimab and published data on other molecules within the same biologic class.

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

Although most imAEs observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. An imAE may occur at any time during or after treatment. Often, the etiology of imAEs is not clear, and other causes should be ruled out. This may require diagnostic testing and consultation with a specialist. Suggested evaluation and management guidelines for suspected imAEs are provided in Appendix 7.

Refer to the Ociperlimab Investigator's Brochure for additional details.

APPENDIX 13. LBL-007

1. Introduction of LBL-007

LBL-007 is a fully human anti-lymphocyte activation gene-3 (LAG-3) monoclonal immunoglobulin (Ig) G4/κ isotype antibody codeveloped by Nanjing Leads Biolabs Co., Ltd. and BeiGene, Ltd. for the treatment of advanced solid tumors. Refer to the LBL-007 Investigator's Brochure for additional information.

1.1. Lymphocyte Activation Gene-3

Lymphocyte Activation Gene-3 (LAG-3 or CD223) is an immune checkpoint protein predominantly expressed on the surface of activated T cells (Huard et al 1995), and natural killer (NK) cells (Triebel et al 1990). LAG-3 expression has also been reported in B cells (Kisielow et al 2005) and plasmacytoid dendritic cells (pDCs) (Workman et al 2009). The main ligand for LAG-3 is the major histocompatibility complex (MHC) Class II protein (Huard et al 1995), and engagement of LAG-3 by MHC II ligand leads to a state of T cell exhaustion, characterized by the attenuation of T-cell activation, inability to proliferate in response to antigen and reduced cytokine production (Huang et al 2004, Workman and Vignali 2003, Workman et al 2004). Liver sinusoidal endothelial cell lectin (LSECtin) (Xu et al 2014), galectin 3 (Kouo et al 2015), and fibrinogen-like protein 1 (FGL1) (Wang et al 2019) are other immune-inhibitory ligands that have been identified to interact with LAG-3 and mediate its inhibitory function in T cells. Consistent with its inhibitory function, LAG-3 expression is high in chronically exhausted or dysfunctional T cells in cancer, particularly in tumor infiltrated T cells (Matsuzaki et al 2010). In addition, LAG-3 is also expressed on regulatory T (Treg) cells and LAG-3^+ Treg cells are highly suppressive compared to their LAG-3- counterparts (Camisaschi et al 2010, Huang et al 2004). A LAG-3 blockade has been shown to promote T cell proliferation and enhance cytotoxic T cells functions (Lichtenegger et al 2018). LAG-3 inhibition can also reduce the immunosuppressive activity of LAG-3^+ Treg cells, resulting in enhanced activation of effector T cells (Huang et al 2004).

LAG-3 is frequently coexpressed with programmed cell death protein-1 (PD-1) on tumor-infiltrating T cells, LAG-3 and PD-1 double positive T cells are in a more severe dysfunctional state than T cells expressing either PD-1 or LAG-3 alone. Moreover, LAG-3 expression is upregulated following anti-PD-1 treatment, and the frequency of LAG-3^+ T cells is significantly upregulated in several solid tumors that are inherently resistant or that become refractory to PD-1 blockade including, non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), melanoma, and bladder cancer (Datar et al 2019, Gettinger et al 2017, Hanna et al 2018, Johnson et al 2018, Kates et al 2021). Preclinical studies in mouse models have shown that a co-blockade of PD-1 and LAG-3 restores the function of exhausted T cells and synergizes to inhibit tumor growth by enhancing antitumor immunity (Mimura et al 2021, Yang et al 2017, Ghosh et al 2019). Those results suggest that the combination of anti-LAG-3 and anti-PD-1 could further improve the clinical outcome of anti-PD-1, and the combination therapy may provide clinical benefit for those patients who are resistant to anti-PD-1 therapy. Indeed, the combination has been proven to be effective in clinic, in patients with previously untreated metastatic or unresectable melanoma in whom a combination of LAG-3 and PD-1 inhibition provided greater benefit than PD-1 blockade alone (Tawbi et al 2022).

1.2. Background Information on LBL-007

1.2.1. Pharmacology

LBL-007 binds to the human LAG-3 extracellular domain with high specificity and affinity ($K_D = 4.39 \times 10^{-10}$ M). LBL-007 effectively blocks the binding of LAG-3 to MHC II molecules, and thereby activates the immune system. An in vitro binding assay showed that LBL-007 also blocks the binding of LAG-3 with other ligands, including FGL-1, LSECtin, and galectin-3. In addition, in vivo studies in human LAG-3 knock-in mice showed LBL-007 significantly inhibiting the tumor growth used alone or in combination with an anti-PD-1 monoclonal antibody.

In vitro studies showed that LBL-007 did not bind to either FcγRIIIA or C1q, indicating weak or no antibody-dependent cell-mediated cytotoxicity (ADCC) or CDC effect in humans. Additionally, in vitro experiments showed that LBL-007 with an S228P modification in the hinge region was more stable than wild-type LBL-007, and did not exchange Fab arms with a wild-type human IgG4 antibody. Therefore, it was predicted that the LBL-007 antibody would be stable in vivo.

1.2.2. Toxicology

Cynomolgus monkey is considered to be the relevant species for nonclinical safety evaluation because it is the pharmacologically relevant species based on sequence homology of LAG-3 and binding affinity activity, and it is a commonly used species for biologic products with a substantial historical toxicology database.

The nonclinical toxicity and toxicokinetic profile of LBL-007 was characterized in a single dose study in cynomolgus monkeys and in repeat-dose studies in rats and cynomolgus monkeys dosed weekly. These toxicity studies were conducted following Good Laboratory Practice regulations.

At the single dose of 150 or 300 mg/kg (3 animals per group), the maximum tolerated dose (MTD) was 300 mg/kg; no mortality or moribundity was observed in cynomolgus monkeys.

In the 3-week repeat dose study in rats, no LBL-007-related abnormal changes were observed in body weight, food consumption, ophthalmological examination, urinalysis, lymphocyte subsets, complement counts, or immunoglobulin counts (IgA, IgG, IgM, IgE) following intravenous infusion of LBL-007 at 20 mg/kg, 60 mg/kg, and 150 mg/kg once a week for 3 consecutive weeks (4 doses). Other abnormalities in hematology and blood chemistry recovered after 4 weeks of dose interruption. The weight coefficient of the liver was increased in female rats in the 150 mg/kg group, and slight to mild hepatocellular necrosis or inflammatory cell infiltration was observed in the histopathological examination. Considering the lack of binding activity of LBL-007 to the LAG-3 in rats, the effects of LBL-007 on the liver were considered to be mostly likely off-target toxicities. Given that in vitro data indicated that cellular and tissue binding with LBL-007 was highly specific to monkey and human, and the absence of LBL-007 pharmacological activity in the rats, the findings in the 3-week repeat-dose study are of uncertain clinical relevance.

The 4-week repeat dose study in cynomolgus monkeys indicated that LBL-007 was well tolerated. Five consecutive weekly doses of LBL-007 at 10, 30, and 100 mg/kg in monkeys between 3 to 5 years old were not associated with any adverse effects. The no-observed-adverse-

effect-level (NOAEL) was 100 mg/kg. LAG-3 receptor occupancy (RO) was increased in female and male cynomolgus monkeys at 1 to 2, 24 to 25, and 168 to 169 hours after the first dose as well as at 24 to 25 and 168 to 169 hours after the last dose. No significant dosage-related increase of LAG-3 RO was observed at all dose levels. At the dose levels of 10, 30, and 100 mg/kg, after the first dose, the increased exposure of LBL-007 in the serum of monkeys in each LBL-007 group was correlated with the increase of the infusion dose. No sex differences in exposure were observed. After 5 consecutive doses, the accumulation factors of LBL-007 ranged from 2.02 to 0.61, indicating a slight accumulation.

The in vitro studies to assess hemolytic potential were conducted in erythrocytes from Japanese white rabbits. There was no evidence of hemolysis or agglutination observed in vitro in rabbit erythrocytes with LBL-007 at a concentration of 5 mg/mL.

The tissue cross-reactivity of LBL-007 was evaluated in healthy cynomolgus monkeys and healthy human frozen tissues using immunohistochemistry. LBL-007 specifically bound to human tissues of colon, ileum, pituitary gland, skeletal muscle, testis, lymph nodes, duodenum, and parathyroid gland, while LBL-007 specifically bound to cynomolgus monkey tissue of the cerebellum.

The in vitro cytokine release study indicated that LBL-007 did not evoke cytokine release in human peripheral blood mononuclear cells.

1.2.3. Clinical Pharmacology

Study WLZB-LBL-007-AST-001:

LBL-007 exhibited dose-dependent increase in exposure over the dose range of 3.0 mg/kg to 10 mg/kg after single intravenous infusion. The time to peak concentration ranged from 1 to 9 hours, and the mean elimination half-life ranged from 182 to 196 hours in the dose range of 3 mg/kg to 10 mg/kg. LBL-007 exhibited non-linear pharmacokinetics (PK) between the 0.05 mg/kg and 1 mg/kg dose levels and linear PK between 3 mg/kg and 10 mg/kg.

The PK characteristics of LBL-007 after multiple dose administration once every 2 weeks were similar to those of a single dose. There was no significant accumulation in exposure of LBL-007 in the lower dose groups (0.05 to 3 mg/kg once every 2 weeks). Little accumulation was observed in higher doses groups (6 and 10 mg/kg once every 2 weeks).

Study LBL-007-CN-002:

After a single intravenous infusion of 0.25 mg/kg, 1 mg/kg, 3 mg/kg, or 6 mg/kg LBL-007 in combination with toripalimab (3 mg/kg), the mean time to maximum LBL-007 concentration ranged from 1.0 to 2.0 hours; $t_{1/2}$ was 43.63, 108.40, 165.89, and 192.30 hours, respectively, with a dose-dependent trend; the mean C_{max} values were 3.350, 9.927, 36.707, and 73.050 μg/mL, respectively; the mean AUC_{0-336} values were 266.264, 1486.522, 5011.602, and 11175.155 h•μg/mL, respectively. The exposure parameter C_{max} increased dose proportionally, while AUC_{0-336} increased slightly more compared with the increase of dosage. Mean changes in V_{ss} ranged from 4.785 to 6.829 L, and mean changes in CL ranged from 0.024 to 0.074 L/h, indicating that the drug was mainly distributed in plasma.

The PK profile of LBL-007 after multiple doses was similar to that after a single dose.

The accumulation ratios for C_{max} and AUC after multiple doses of LBL-007 ranged from 1.018 to 1.553 and 1.019 to 1.543, respectively, suggesting a slight accumulation of LBL-007 in vivo.

1.2.4. Prior Clinical Experience With LBL-007

As of 15 February 2023, the following 5 clinical studies (sponsored by Nanjing Leads Biolabs Co., Ltd.) have been conducted with LBL-007.

Study WLZB-LBL-007-AST-001:

Study WLZB-LBL-007-AST-001 is a recently completed single-arm Phase 1 dose-escalation study to evaluate the safety and tolerability of LBL-007 in patients with advanced solid tumors including lymphoma, and to explore MTD and dose-limiting toxicities (DLTs). The study had been completed with the last patient's last visit on 28 December 2021. As of 15 January 2022, a total of 22 patients were enrolled and received once LBL-007 every 2 weeks at 0.05 mg/kg (n = 2), 0.25 mg/kg (n = 4), 1 mg/kg (n = 3), 3 mg/kg (n = 3), 6 mg/kg (n = 3), or 10 mg/kg (n = 7); of these, 20 patients completed the DLT assessments.

Preliminary safety results showed that the doses were well tolerated with no DLTs in any dose group. MTD was not reached with the maximum-administrated dose of 10 mg/kg in this study. Of the 22 patients, 21 (95.5%) experienced a total of 224 treatment-emergent adverse events (TEAEs); and TEAEs that occurred in ≥ 10% of the patients were anemia (59.1%); hyperglycemia (27.3%); neutrophil count increased, hypocalcemia, upper respiratory tract infection, hyponatremia, and pyrexia (22.7% each); gamma-glutamyltransferase increased (18.2%), white blood cell count increased (18.2%); and weight decreased, platelet count decreased, hypoalbuminemia, hypercalcemia, decreased appetite, asthenia, and sinus tachycardia (13.6% each).

Two patients (9.1%) had TEAEs leading to permanent discontinuation of study treatment, including hypocalcemia (0.25 mg/kg dose group, possibly related to study drug) and gastrointestinal hemorrhage (3 mg/kg dose group, unlikely related to study drug) each in 1 patient, with the outcomes of ongoing and unknown, respectively. No TEAEs leading to death were reported for either.

During the treatment period, 8 patients (36.4%) experienced 13 serious adverse events (SAEs). Of them, 9 SAEs that occurred in 5 patients (22.7%) were considered to be related to the study drug. The 9 SAEs occurred in 1 patient each with an incidence of 4.5% each and included upper gastrointestinal hemorrhage (Grade 2, resolved without sequelae), gastrointestinal hemorrhage (Grade 3, ongoing), hypoalbuminemia (Grade 2, resolving to Grade 1), hypocalcemia (Grade 4, outcome unknown), bronchitis and bronchiectasis (reported by the investigator as one AE term, Grade 3, ongoing), deep vein thrombosis (Grade 3, outcome other: resolving to Grade 2), and anemia (2 events of Grade 3, resolving to Grade 2 and Grade 1, respectively; 1 event of Grade 2, upgraded to Grade 3). The remaining 4 SAEs were considered not to be related to the study drug. The events included enteritis (Grade 2, resolved without sequelae), abdominal pain upper (Grade 3, ongoing), hyponatremia (Grade 3, outcome other: downgraded), and blindness unilateral (Grade 3, outcome unknown), and all occurred in 1 patient with an incidence of 4.5%.

Efficacy results showed that of the 18 evaluable patients (2 patients in the 0.05 mg/kg group, 1 patient in the 0.25 mg/kg group, 3 patients in the 1 mg/kg group, 3 patients in the 3 mg/kg group, 3 patients in the 6 mg/kg group, and 6 patients in the 10 mg/kg group), the objective

response rate (ORR) was 5.6% (1 patient with esophageal cancer in the 10 mg/kg group had partial response [PR]) and the disease control rate (DCR) was 55.6% (1 patient of PR and 9 patients of stable disease [SD]).

Study LBL-007-CN-002:

Study LBL-007-CN-002 is an ongoing single-arm, multicenter Phase 1 dose-escalation and dose-expansion study to evaluate the safety, tolerability, and preliminary efficacy of LBL-007 plus toripalimab or LBL-007 in combination with toripalimab and axitinib (tyrosine kinase inhibitor) for the treatment of unresectable or metastatic melanoma.

As of 11 January 2023, a total of 68 patients were enrolled and treated with LBL-007 at different doses (0.25, 1, 3, 6, and 10 mg/kg, once every 2 weeks) in combination with toripalimab (3 mg/kg, once every 2 weeks). Four patients were enrolled in the 0.25 mg/kg dose group, 3 patients in the 1 mg/kg dose group, 16 patients in the 3 mg/kg dose group, 42 patients in the 6 mg/kg dose group, and 3 patients in the 10 mg/kg dose group. Twenty patients completed the DLT assessment, and no DLT events were observed.

Of the 68 patients, 66 patients (97.1%) experienced ≥ 1 treatment-emergent adverse event. Common TEAEs (incidence ≥ 10%) were aspartate aminotransferase increased (27.9%); blood lactate dehydrogenase increased (27.9%); anemia (26.5%); alanine aminotransferase increased and hypothyroidism (25.0% each); blood creatine phosphokinase increased (20.6%); blood glucose increased, hypokalemia, hyperthyroidism, and COVID-19 (19.1% each); blood triglycerides increased (17.6%); blood bilirubin increased and asthenia (14.7% each); blood cholesterol increased (13.2%); pyrexia (11.8%); and white blood cell count decreased, bilirubin conjugated increased, decreased appetite, nausea, and cough (10.3% each). Most of the events were Grade 1 or 2.

The incidences of TEAEs leading to dose delay and permanent discontinuation were 26.5% and 2.9%, respectively.

Nine SAEs were reported in 6 patients: obstructive jaundice (3.0 mg/kg, Grade 3, unlikely related), T2 bone destruction: melanoma metastasis (suspected; 3.0 mg/kg, Grade 3, definitely not related), hypopituitarism (0.25 mg/kg, Grade 3, possibly related), disease progression (6.0 mg/kg, Grade 5, unlikely related), nausea (3.0 mg/kg, Grade 2, unlikely related), vomiting (3.0 mg/kg, Grade 2, unlikely related), myocarditis (6.0 mg/kg, Grade 2, probably related), severe anemia (6.0 mg/kg, Grade 3, possibly related), and unknown death (3.0 mg/kg, Grade 5, to be evaluated).

A total of 32 patients with melanoma were evaluable for response assessment: 21 had not received anti-PD-(L)-1 antibody therapy (abbreviated as immunotherapy-naive) and 11 had previously received prior anti-PD-(L)-1 antibody therapy (referred to as immunotherapy treated). Four patients achieved PR (3 with acral melanoma and 1 with skin non-acral melanoma; all were immunotherapy-naive patients); 13 patients achieved SD, including 11 immunotherapy-naive patients and 2 immunotherapy-treated patients (1 with mucosal melanoma and 1 with skin non-acral melanoma).

As of 11 January 2023, 11 patients have been enrolled and treated with LBL-007 at 2 dose levels (3.0 mg/kg [n = 4] and 6.0 mg/kg [n = 7]) in combination with toripalimab (3 mg/kg, once every 2 weeks) plus axitinib (5 mg, twice per day, oral). Ten patients (90.9%) experienced

≥ 1 treatment-emergent adverse event. Nine patients (81.8%) experienced LBL-007-related adverse events. Three patients (27.3%) had serious adverse events; 1 patient (9.1%) experienced LBL-007-related serious adverse events. Five patients (45.5%) experienced ≥ Grade 3 treatment-emergent adverse events and none of the events were considered as related to LBL-007. imAEs occurred in 5 patients (45.5%) and none of the events of ≥ Grade 3 were considered as related to LBL-007.

Study LBL-007-CN-003:

Study LBL-007-CN-003 is an ongoing multicenter Phase 1b/2 clinical study to evaluate the safety, tolerability, and preliminary efficacy of LBL-007 in combination with toripalimab in the treatment of advanced malignancies, such as advanced esophageal squamous cell carcinoma (ESCC), HNSCC, cervical cancer, nasopharyngeal cancer, small cell lung cancer, and diffuse large B-cell lymphoma.

As of 11 January 2023, a total of 80 patients received LBL-007 (200 or 400 mg, intravenously, once every 3 weeks) in combination with toripalimab (240 mg, once every 3 weeks). The tolerability evaluation for 400 mg was completed with no DLT events, and the MTD for this study was not reached with the maximum-administrated dose of 400 mg. A total of 12 TEAEs were reported in 7 patients, these AEs included pain in the left lower extremity and anemia (2 events each), and constipation, vomiting, oropharyngeal pain, rash, peripheral neuralgia, back pain, hyperuricemia, and lymphocyte count decreased (1 event for each term). There were no SAEs of any grade. Response assessment was performed in 4 patients, all of which were SD (2 patients with lung adenocarcinoma, 1 patient with nonkeratinizing pleomorphic nasopharyngeal carcinoma, and 1 patient with small cell lung cancer).

Study LBL-007-CN-004:

Study LBL-007-CN-004 is a multicenter, Phase 1b/2 study evaluating the safety, tolerability, and efficacy of LBL-007 in combination with tislelizumab in the treatment of ESCC, hepatocellular carcinoma (HCC), nasopharyngeal carcinoma, urothelial carcinoma, microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR) solid tumors, HNSCC, and melanoma.

As of 11 January 2023, 21 patients received LBL-007 (300 or 600mg, intravenously, once every 3 weeks) in combination with tislelizumab (200 mg, intravenously, once every 3 weeks), including 10 patients in the LBL-007 dose group of 300 mg and 11 patients in the 600 mg dose group. All the 21 patients (100.0%) experienced treatment-emergent adverse events, 17 patients (80.95%) had LBL-007-related treatment-emergent adverse events, 4 patients (19.05%) experienced serious adverse events, and 2 patients (9.5%) had treatment-related serious adverse events. Three patients (14.29%) had ≥ Grade 3 treatment-emergent adverse events and 2 patients (9.52%) had ≥ Grade 3 treatment-emergent adverse events related to LBL-007. Treatment-emergent adverse events leading to dose hold of LBL-007 occurred in 12 patients (57.14%), and adverse event leading to dose hold of LBL-007 and related to LBL-007 occurred in 2 patients (9.52%). One patient (4.76%) experienced treatment-emergent adverse event leading to death. None of the patients experienced treatment-emergent adverse event leading to discontinuation of study drug. imAEs were reported in 6 patients (28.57%). None of the patients experienced infusion-related reactions.

Study BGB-900-102:

Study BGB-900-102 is an open-label, multicenter, nonrandomized Phase 1/2 study evaluating various combinations of BGB-A425 (inhibitor of T-cell immunoglobulin and mucin-domain containing-3 [TIM-3]) and LBL-007 with tislelizumab in advanced solid tumors. This study will consist of 2 phases: Phase 1 dose escalation and Phase 2 with safety lead-in followed by dose expansion. LBL-007 will be initially evaluated in the safety lead-in portion of Phase 2 to confirm the recommended Phase 2 dose (RP2D) of LBL-007 when given in combination with tislelizumab or with tislelizumab plus BGB-A425, and then further evaluated in the dose expansion cohorts of the Phase 2 in various tumor types including HNSCC and NSCLC.

As of 15 February 2023, 11 patients received treatment with LBL-007, including 5 patients who received LBL-007 in combination with tislelizumab (Safety Lead-in: LBL-007+A317), and 6 patients who received LBL-007 in combination with tislelizumab and BGB-A425 (Safety Lead-in: LBL-007+A317+A425).

In the Phase 2 (Safety Lead-in: LBL-007+A317) Cohort A, 5 patients received LBL-007 at 2 dose levels of 300 mg (4 patients) or 600 mg (1 patient) in combination with 200 mg tislelizumab. All the 5 patients (100.0%) experienced ≥ 1 TEAE. Two patients (40.0%) had TEAEs that were assessed as related to the treatment. Three patients (60.0%) experienced ≥ Grade 3 TEAEs; 1 patient (20.0%) had ≥ Grade 3 treatment-related TEAE. Three patients (60.0%) had serious TEAEs; 1 patient (20.0%) experienced serious treatment-related TEAEs. One patient (20.0%) experienced TEAE leading to treatment discontinuation and was considered as related to the treatment. None of the patients experienced fatal adverse events.

In the Phase 2 (Safety Lead-in: LBL-007+A317+A425) Cohort B, 6 patients received LBL-007 at 2 dose levels of 300 mg (3 patients) or 600 mg (3 patients) in combination with 200 mg tislelizumab and 600 mg BGB-A425. Five patients (83.3%) experienced ≥ 1 TEAE. Two patients (33.3%) had TEAEs that were assessed as related to the treatment. One patient (16.7%) experienced ≥ Grade 3 TEAEs; none of the events were considered as related to the treatment. One patient (16.7%) had serious TEAEs, none of the events were considered as related to the treatment. None of patients experienced TEAE leading to treatment discontinuation or fatal adverse events.

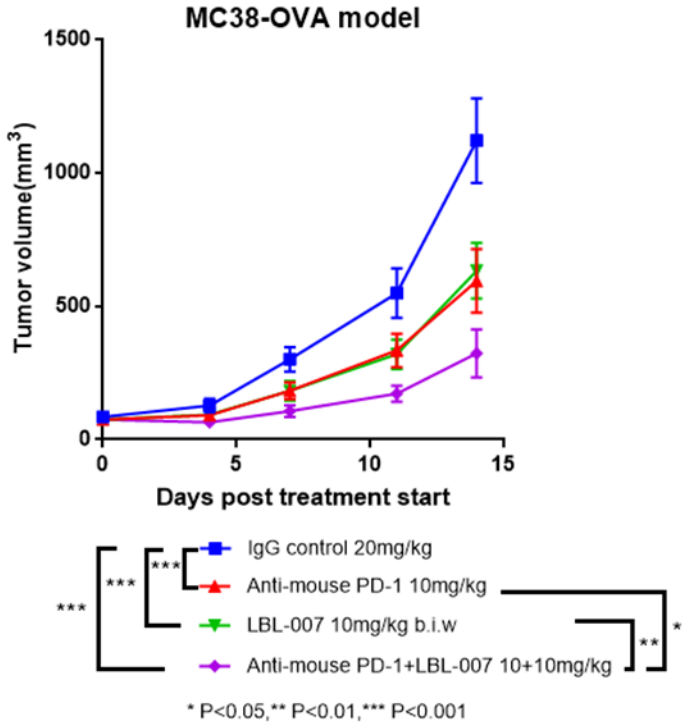
1.3. LBL-007 Rationales

1.3.1. Rationale for LBL-007 in Combination With Tislelizumab as Neoadjuvant Treatment In Patients With NSCLC

Based on multiple preclinical and clinical studies, anti-LAG-3 and anti-PD-1 molecules have synergistic effects across several malignant tumors. Coordinated inhibition of LAG-3 and PD-1 can further enhance the immune response and exert the best antitumor effect of the combination drugs.

In a preclinical mouse study, LBL-007 in combination with anti-PD-1 significantly improved antitumor effect with a tumor growth inhibition (TGI) of 77.63%, superior to LBL-007 (TGI = 56.10%) or anti-PD-1 (TGI = 58.99%) monotherapy in MC38-OVA (mouse colorectal cancer cell line stably expressing OVA protein) syngeneic model in a hLAG-3 knock-in mouse (§Figure 1). Refer to the LBL-007 Investigator's Brochure for additional information.

§Figure 1: Tumor Growth Curve after Treatment With LBL-007, Anti-Mouse PD-1 and the Combination in MC38-OVA Model

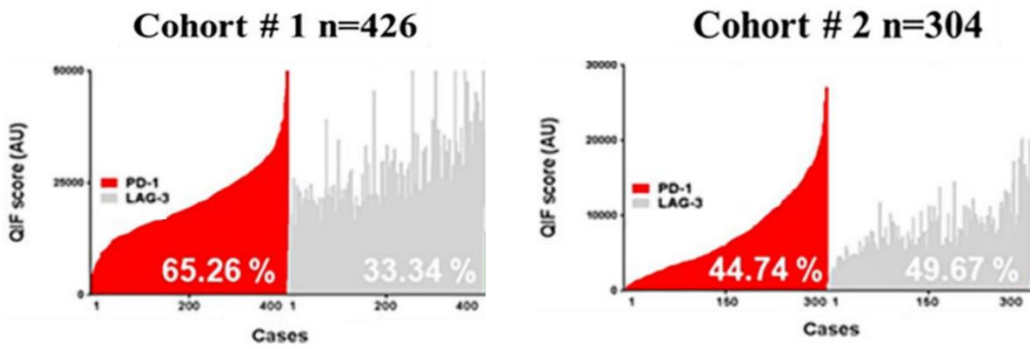


Abbreviations: MC38-OVA, mouse colorectal cancer cell line stably expressing OVA protein; PD-1, programmed cell death protein-1.

The synergic antitumor efficacy for anti-LAG-3 antibody in combination with anti-PD-1 antibody has been preliminarily validated in a clinical study. The first anti-LAG-3 antibody (relatlimab, Bristol Myer Squibb, Princeton, NJ) was recently approved by the FDA based on the significant clinical benefit of LAG-3/PD-1 combinational therapy compared to anti-PD-1 alone in unresectable metastatic melanoma (Tawbi et al 2022). In the study of LBL-007 in combination with anti-PD-1 antibody toripalimab in melanoma (LBL-007-CN-002), a total of 32 EE patients had an ORR of 12.5% and a DCR of 53.1% (4 PRs and 13 SDs). Of the 11 evaluable patients with cutaneous acral melanoma who had not received anti-PD-(L)-1 antibody treatment, the ORR was 27.3% and the DCR was 81.8%. In the study of LBL-007 in combination with toripalimab in the treatment of advanced malignancies (Study LBL-007-CN-003), efficacy was assessed in 4 patients, all of whom had SD.

LAG-3 plays an important role in the immunosuppression of tumor-infiltrating lymphocytes (TILs) in NSCLC. Analysis from the TCGA database showed LAG-3 expression also ranked high in NSCLC, compared with all the indications. Multiplex quantitative immunofluorescence data from 730 clinically annotated NSCLC tissue analyses showed that LAG-3 was detected in TILs from 41.5% of NSCLC cases (Datar et al 2019), indicating high LAG-3 expression frequency in NSCLC. Besides, elevated LAG-3 ligands (FGL1 or galectin-3) are associated with resistance to anti-PD-(L)1 therapy (Wang et al 2019).

§Figure 2: Distribution and Frequency of T-cell PD-1 and LAG-3 Expression in NSCLC



Source: Datar et al 2019
Abbreviations: LAG-3, lymphocyte activation gene-3; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein-1.
Note: Level of the markers measured using quantitative immunofluorescence (QIF) in 2 retrospective NSCLC cohorts- Cohort #1 (n=426) and #2 (n=304). The frequency of expression of each marker is indicated with white-colored text within the charts. Detectable LAG-3 was seen in 33.34% and 49.67% in Cohorts 1 and 2 separately, and 41.5% in the overall set.

KEYNOTE-495 [NCT03516981] is a group-sequential, adaptively randomized, multisite, open-label, Phase 2 study, including a subgroup investigating first-line pembrolizumab plus LAG-3 inhibitor favezelimab (MK-4280) in patients with advanced NSCLC, with the primary endpoint of investigator-assessed ORR per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. At the data cutoff date of 11 January 2021, 30 patients were treated with pembrolizumab 200 mg + favezelimab 200 mg once every 3 weeks; and 34 patients were treated with pembrolizumab 200 mg + favezelimab 800 mg once every 3 weeks. Although sample sizes were small, the $Tcell_{inf}GEP^{high}TMB^{high}$ subgroup demonstrated the best response among the biomarker subgroups for all pembrolizumab plus LAG-3 inhibitor favezelimab (MK-4280) therapies as demonstrated in §Table 1. which supports the benefit of LAG-3 combined with PD-1 as neoadjuvant in patients with early-stage, resectable NSCLC.

§Table 1: Confirmed ORR by Therapy and Biomarker Status in KEYNOTE-495

Arm	**Total** **% (n/N)** **(95% CI)**	**$Tcell_{inf}GEP^{high}$ TMB ^{high} subgroup** **% (n/N)** **(95% CI)**
Pembrolizumab + Favezelimab 200 mg Q3W	23% (7/30) (95% CI: 10-42)	60% (3/5) (95% CI: 15-95)
Pembrolizumab + Favezelimab 800 mg Q3W	26% (9/34) (95% CI: 13-44)	42% (5/12) (95% CI: 15-72)

Source: Gutierrez et al 2021
Abbreviations: ORR, overall response rate; Q3W, once every 3 weeks; $Tcell_{inf}GEP$, T-cell-inflamed gene expression profile; TMB, tumor mutational burden.

Moreover, PD-(L)1 combined with LAG-3 pathway targeting antibodies are under active investigation in the first-line treatment setting for NSCLC. CA224-104 (NCT04623775) is a Phase 2, randomized, double-blind study of relatlimab plus nivolumab in combination with chemotherapy versus nivolumab in combination with chemotherapy as first line treatment for participants with Stage IV or recurrent NSCLC, with estimated enrollment of 520 participants and projected primary completion date of February 2024. No data from this study has been released yet.

In conclusion, as indicated by both nonclinical research and clinical studies as well as the high expression level of LAG-3 in NSCLC tumors along with supporting pharmacological toxicology and clinical PK data of LBL-007, the synergistic blockade effect of LAG-3 and PD-(L)1 pathways provided a strong scientific rationale to expand the investigation of tislelizumab in combination with LBL-007 as neoadjuvant in patients with early-stage, resectable NSCLC.

1.3.2. Rationale for Selection of LBL-007 Dose in Combination With Tislelizumab

In the single-agent dose escalation trial of WLZB-LBL-007-AST-001, the highest dose of 10 mg/kg (once every 2 weeks) was tested in 7 patients with no DLT and was generally well tolerated. Limited drug accumulation was observed at steady-state due to its short half-life. The dose of 10 mg/kg (once every 2 weeks) provides exposure coverage up to 600 mg (for an average body weight of 60 kg) LBL-007 dosed once every 3 weeks.

In Study BGB-900-102, Study LBL-007-CN-004, and BGB-A317-LBL-007-201, 300 and 600 mg once every 3 weeks LBL-007 in combination with tislelizumab 200 mg once every 3 weeks in patients with solid tumor will be evaluated for tolerability, PK, and clinical activity. The RP2D identified from these studies will be used as LBL-007 regimen in this study.

The PK, safety, and efficacy data obtained from the first-in-human study AST-001, and from combination study with toripalimab (PD-1) CN-002, were analyzed in aggregate to determine the recommended dose for studies of LBL-007. The dose of 300 and 600 mg intravenously once every 3 weeks was selected for further evaluation.

In Study AST-001, doses of LBL-007 0.05, 0.25, 1, 3, 6, and 10 mg/kg once every 2 weeks were evaluated. Concentration-time profiles from 0.05 mg/kg up to 1 mg/kg exhibited a typical Target-mediated Drug Disposition (TMDD) pattern, suggesting lack of target saturation. Once doses reached 3 mg/kg and above, PK of LBL-007 became linear, indicating of target saturation. The observed mean trough concentration of 5.63 µg/mL at 3 mg/kg was selected as the at target concentration that overcomes TMDD.

A preliminary population PK analysis was conducted pooling PK results from AST-001 and CN-002. The results of this analysis reveal that LBL-007 has a clearance of 0.022 L/hr with a half-life of approximately 12 days. Simulation suggests that at 600 mg once every 3 weeks, approximately 85% patients will achieve steady-state trough concentration of 5.63 µg/ml.

1.3.3. Biomarker Strategy Rationale

Early studies suggested that LAG-3 was a negative regulator of T cells and blockade of LAG-3 would boost human T-cell proliferation with elevated cytokine productions (Huard et al 1995). In multiple mouse tumor models, LAG-3 co-expresses with PD-1 on tumor-infiltrating $CD4^+$ and $CD8^+$ T cells, in which LAG-3 was shown to control T-cell proliferation and maintain

exhaustion. Although LAG-3 monotherapy in mice tumors was largely ineffective, interestingly, dual LAG-3/PD-1 co-blockade synergistically limited the tumor growth and resulted in tumor clearance better than anti-PD-1 monotherapy. Dual targeting increased $CD4^+$ and $CD8^+$ T-cell infiltration, as well as increased the frequency of single-and double-producing $IFN\gamma^+/TNF\alpha^+$ $CD8^+$ T cells in this model (Huang et al 2015, Woo et al 2012).

Given that LAG-3 was predicted to be highly structurally homologous to CD4 with structure similarities, it is not surprising that MHC class II molecule is one of ligands for LAG-3. A recent study showed that MHC class II-expressing tumor cells (eg, melanoma cells) attracts tumor-specific $CD4^+$ T cell infiltration, perhaps mediated by interaction with LAG-3, which in turn negatively influences $CD8^+$ T-cell responses (Donia et al 2015).

As LAG-3 impacts $CD8^+$ T-cell function as well, it is speculated that there may be additional LAG-3 ligands for $CD8^+$ T cells interacting with target cells that do not express MHC class II molecules. Several alternative ligands for LAG-3 are identified, including FGL-1, Gal-3, and LSECtin, which have each been shown to induce LAG-3-mediated inhibition of T-cell activation (Graydon et al 2021).

In human cancer patients, LAG-3 has been found to be preferentially expressed on tumor-infiltrating Tregs in a number of tumor subtypes. LAG-3 has also been shown to be required for maximal activity of Tregs, whose blockade abrogates Treg suppressive function in vitro (Huang et al 2004). More recent study also showed that blockade or genetic deletion of LAG-3 skewed $CD4^+$ T cells into a Th1 phenotype, with LAG-3 limiting IL-2 and STAT5 signaling that modulates the ability to be suppressed by Tregs (Durham et al 2014).

LAG-3 is constitutively expressed at a much greater level on pDCs than any other cell type, yet its functional role on these cells is not well understood. $Lag3^{-/-}$ pDCs show enhanced in vivo expansion without activation marker alteration or differential cytokine production compared with wildtype pDCs (Workman et al 2009). In humans, LAG-3+ pDCs were found to infiltrate the melanoma environment and interact with HLA-DR-expressing tumor cells in vivo (Camisaschi et al 2014).

Additionally, LAG-3 was expressed in a subset of NK cells with high expression of activation and maturation markers, while its functional role is not well understood. LAG-3 blockade on NK cells resulted in enhanced secretion of pro-inflammatory cytokines, but not affecting the cytotoxic activity (Narayanan et al 2020).

In summary, it is of great significance to explore whether LBL-007 could synergistically reinvigorate T cells with tislelizumab better in patients with cancer, as well as its impact on Treg, NK, and pDC cells. The association of pharmacodynamics induced by LBL-007 and LAG-3 ligand expression with clinical outcomes will be assessed to identify the potential predictive or resistant biomarkers.

1.4. Benefit-Risk Assessment

As described previously, both preclinical and clinical studies of LBL-007 or other anti-LAG-3 antibodies combined with PD-1 inhibitors have shown the synergistic effect and improved antitumor activity along with a favorable safety profile. It is therefore expected that tislelizumab + LBL-007 will potentially have a favorable benefit- risk ratio and will demonstrate clinical efficacy in patients with NSCLC.

As of the cutoff date of 20 July 2022, tislelizumab has been evaluated in 3220 patients (2173 patients treated with monotherapy and 1047 patients treated with combination therapy, Tislelizumab Investigator's Brochure) with a safety and efficacy profile similar to what has been reported for other anti-PD-1 therapies. However, based upon their mechanism(s) of action, preclinical, as well as clinical data, treatment with LBL-007 and tislelizumab is expected to increase the rate of immune-mediated toxicities as compared to treatment with tislelizumab monotherapy. A comprehensive practice guideline has been established to monitor, diagnose, and manage such immune-mediated toxicities (Appendix 7). This monitoring plan will be utilized to evaluate patient safety during the course of the study. The totality of the data in the study as well as external information including available data from the two Phase 1/2 studies of BGB-900-102 and Study LBL-007-CN-004 which will evaluate safety of LBL-007 in combination with tislelizumab in patients with solid tumors, may also be reviewed for the decision making.

2. STUDY DESIGN

2.1. End of Treatment and Safety Follow-up Visit

In addition to common requirements with respect to pregnancy testing after study treatment as described in Section 3.4, an additional pregnancy test should be performed at 6 months (± 14 days) after the last dose of LBL-007 (in clinic or over the phone, as needed based on assessments required).

3. STUDY TREATMENT- LBL-007 in combination with tislelizumab

3.1. Formulation, Packaging, Labeling, and Handling

LBL-007 is a recombinant monoclonal antibody formulated for intravenous infusion and is provided as a preservative-free, single-use vial, containing a minimum of 5 mL of a 17 mg/mL concentrated solution (85 mg) of antibody in a buffered isotonic solution. LBL-007 is aseptically filled in single-use vials (6 mL, United States Pharmacopeia [USP] Type I glass) with a coated butyl rubber stopper and sealed with an aluminum flip-off 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 stored as specified on the label. Do not freeze. Shaking should be avoided.

Refer to the Pharmacy Manual for details regarding intravenous administration, accountability, and disposal. Please also refer to the LBL-007 Investigator's Brochure for additional information.

3.2. Dosage, Administration and Compliance

Dosing schedules for Arm 1C are provided in §Table 2. The first dose of the study drug(s) is to be administered within 2 business days after randomization. All patients will be monitored throughout the study for AEs. Treatment modification (ie, dose delay or interruption) or discontinuation will be based on specific laboratory and AE criteria, as described in §Section 3.3.

During the neoadjuvant phase, for each cycle, study drug administration in Arm 1C will follow this order: LBL-007 and then tislelizumab. Refer to §Section 3.2.1 for details on monitoring time.

§Table 2: Selection and Timing of Neoadjuvant Dose in Arm 1C

Treatment arm	Study Drug	Dose	Frequency of Administration	Route of Administration	Duration of Treatment
Arm 1C	LBL-007	600 mg	Day 1 of every 3 weeks	IV	2 to 4 Cycles
	Tislelizumab	200 mg			

Abbreviation: IV, intravenous.

3.2.1. LBL-007 and Tislelizumab Treatment Administration

Tislelizumab and LBL-007 will be administered separately by intravenous infusion, through an intravenous line containing a sterile, nonpyrogenic, low-protein-binding 0.2 micron in line or add-on filter. Tislelizumab and LBL-007 must be prepared and administered as separate infusions and may not be administered with any other drug (§Section 4). Refer to the Pharmacy Manual for detailed instructions on drug preparation, storage, and administration.

Dosing administration and monitoring times are provided in §Table 3. For the first cycle, LBL-007 will be infused ≥ 60 minutes followed by patient monitoring for ≥ 60 minutes followed by tislelizumab infusion ≥ 60 minutes. After final infusion of the study drug, patients must be monitored for ≥ 60 minutes in an area with resuscitation equipment and emergency agents.

If infusions of LBL-007 and tislelizumab are well tolerated in the first cycle, from Day 1 of Cycle 2, infusion of LBL-007 will remain ≥ 60 minutes followed by patient monitoring for ≥ 30 minutes followed by the administration of tislelizumab ≥ 30 minutes. Thereafter, patients must be monitored for ≥ 30 minutes in an area with resuscitation equipment and emergency agents.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in §Section 3.3. Details for the management of imAEs, infusion-related reactions, and anaphylaxis reactions are provided in detail in Section 8.7 and Appendix 7.

§Table 3: Administration of LBL-007 and Tislelizumab and Monitoring Time

Cycle	LBL-007 and Tislelizumab Combination
Cycle 1 Day 1	LBL-007 infusion ≥ 60 minutes followed by patient monitoring for ≥ 60 minutes followed by tislelizumab infusion ≥ 60 minutes Patient monitoring for ≥ 60 minutes after the last infusion
Cycle 2 Day 1 onwards	If well tolerated, LBL-007 infusion ≥ 60 minutes followed by patient monitoring for ≥30 minutes followed by tislelizumab infusion ≥ 30 minutes Patient monitoring for ≥ 30 minutes after the last infusion

Note: The infusion rate of tislelizumab or LBL-007 may be decreased or the infusion may be stopped in the event of an infusion-related reaction.

3.3. Dose modification for LBL-007 and Tislelizumab

Dose modification for LBL-007 is defined as any of the following: dose delay, dose interruption, and infusion rate decrease. A dose delay is a deviation from the prescribed dosing schedule (ie, the drug is withheld beyond the visit window). A dose interruption is an interruption of an infusion. An infusion rate decrease is a decrease of infusion rate. There will be no dose reduction for LBL-007 in this study.

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

If a dose delay is required, both LBL-007 and tislelizumab are to be delayed (ie, LBL-007 and tislelizumab must both be delayed and if applicable restarted at the same time). Exceptions may be considered following consultation between the investigator and the medical monitor.

If study treatment is delayed due to TEAEs, study treatment may resume only after the AEs have returned to baseline or ≤ Grade 1 severity except for alopecia or AEs that, in the opinion of the investigator, are not considered a safety risk to the patient. If a treatment delay is due to worsening of laboratory results, eg, hematologic or biochemical parameters, the frequency of relevant blood tests should be increased, as clinically indicated. When several toxicities with different grades of severity occur at the same time, the dose modifications should be according to the highest grade observed.

In general, dose delays for reasons other than management of AEs are prohibited. Total duration of dose delay (ie, the delay duration from first dose of study treatment to actual last dose compared with prescribed dosing schedule) of ≤ 3 weeks is allowed under the following guidance and at the discretion of the investigator. Study treatment should resume as soon as possible after the AEs recover to baseline or Grade 1 (whichever is more severe) if the total delay duration is not more than 3 weeks.

If the patient is unable to resume study treatment ≤ 3 weeks of total delay duration, then the patient should be discontinued from treatment. If the patient is not able to resume study treatment ≤ 3 weeks of total delay duration for unforeseen non-drug-related reasons, continued treatment may be allowed after consolation and approval by the medical monitor

If a patient is benefiting from the study treatment while meeting the discontinuation criteria, resumption of study treatment may occur upon discussion and agreement with the medical monitor. Specific treatment modifications to manage treatment-related toxicities, such as imAEs, infusion-related reactions, and anaphylaxis reactions, are described in Section 8.7 and Appendix 7.

4. PRIOR AND CONCOMITANT THERAPY – LBL-007

4.1. Potential Interactions Between LBL-007 and Concomitant Medications

A PK drug-drug interaction of LBL-007 with other therapeutics is not anticipated given that the primary elimination pathways are protein catabolism via the reticuloendothelial system or target-mediated disposition. LBL-007 is not expected to induce or inhibit the major drug metabolizing CYP pathways. Because LBL-007 is expected to be degraded into amino acids and

recycled into other proteins, it is unlikely to have an effect on drug metabolizing enzymes or transporters. Based on the mechanism of action, any therapeutic protein drug-drug interaction is not expected between the investigational agents.

5. SAFETY MONITORING AND REPORTING – LBL-007

5.1. Risks Associated With LBL-007

LBL-007 is an investigational agent that is currently in clinical development. Limited clinical information is available for LBL-007 (§Section 1.4). Safety data is available from 22 patients treated with LBL-007 (§Section 1.4; LBL-007 Investigator's Brochure). The following recommendation is based primarily upon results from clinical data of LBL-007.

According to clinical studies for which safety results are currently available, the possible toxicities of LBL-007 include immune-mediated endocrine disorders (acute hypophysitis and thyroid disease), gastrointestinal disorders, anaemia, immune-mediated myocarditis (dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, and syncope), and immune-mediated lung disease (pneumonia, cough, dyspnea, and respiratory failure).

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. To assist with this, management guidelines for suspected imAEs are provided in Appendix 7.

Refer to the LBL-007 Investigator's Brochure for additional details.

5.2. Pregnancies

In addition to common requirement with respect to pregnancy related SAE report stated in Section 8.6.6 , if a female patient or the female partner of a male patient becomes pregnant ≤ 6 months after the last dose of LBL-007, a pregnancy report form must be submitted to the sponsor.

APPENDIX 14. CHEMOTHERAPY

1. RATIONALE FOR CHOICE OF CHEMOTHERAPY

Standard guidelines for the neoadjuvant and adjuvant treatment of resectable non-small cell lung cancer recommend platinum-based doublet chemotherapy with either cisplatin or carboplatin for patients with comorbidities or who are not able to tolerate cisplatin (NCCN 2023). Either platinum may be combined with a variety of chemotherapeutics, including vinorelbine, etoposide, gemcitabine, docetaxel, paclitaxel, and pemetrexed, with demonstrated comparable efficacy. In this study, neoadjuvant chemotherapy will consist of platinum in combination with either pemetrexed or paclitaxel for patients with nonsquamous and squamous histology, respectively.

2. STUDY TREATMENT- CHEMOTHERAPY

2.1. Formulation, Packaging, Labeling, and Handling

Management (ie, labeling, 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 for the respective chemotherapy agents.

2.2. Dosage, Administration and Compliance

Patients will receive treatment with platinum-based doublet chemotherapy in combination with tislelizumab (Arm 2A) or LBL-007 and tislelizumab (Arm 2C) during the neoadjuvant phase . An overview on dosing schedules for the treatment Arm 2A and 2C is provided in §Table 1. The first dose of the study drugs is to be administered ≤ 2 working days after randomization. All patients will be monitored continuously for AEs. Treatment modification (ie, dose delay or interruption) or discontinuation will be based on specific laboratory and AE criteria, as described in §Section 2.3 and §Section 2.4. For each cycle, tislelizumab and LBL-007 will be administered before chemotherapy drugs. The order of chemotherapy drugs administration will be conducted in accordance with the relevant local guidance and/or clinical practice. Refer to §Section 2.2.1 for details on the administration of chemotherapy.

§Table 1 Selection and Timing of Neoadjuvant Dose in Arm 2A and 2C

Treatment Arm	Study Drug	Dose	Frequency of Administration	Route of Administration	Duration of Treatment
Arm 2A	Tislelizumab	200 mg	Day 1 of every 3 weeks	IV	2 to 4 Cycles
	Cisplatin	75 mg/m^2			
	Carboplatin*	AUC of 5 mg/mL/min			
	Pemetrexed	500 mg/m^2			
	Paclitaxel	175 mg/m^2			
Arm 2C	LBL-007	600 mg	Day 1 of every 3 weeks	IV	2 to 4 Cycles
	Tislelizumab	200 mg			
	Cisplatin	75 mg/m^2			

	Carboplatin*	AUC of 5 mg/mL/min			
	Pemetrexed	500 mg/m^2			
	Paclitaxel	175 mg/m^2			

Abbreviations: AUC, area under the curve; IV, intravenous(ly).
Chemotherapy options for Arm 2A and Arm 2C are: Cisplatin/Carboplatin + Pemetrexed (nonsquamous), Cisplatin/Carboplatin + Paclitaxel (squamous). For patients with tumors of mixed histology (squamous and non-squamous), appropriate chemotherapy regimen will be decided by investigators based on the major histological components assessed by pathologists.
*Carboplatin can replace cisplatin per the investigator's discretion in consideration of patient's tolerability to cisplatin. The reasons for intolerability should be documented.

2.2.1 Chemotherapy Treatment Administration

Patients should receive antiemetics and intravenous hydration for chemotherapy according to the standard of care and manufacturer's instruction. 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 delayed due to management of AEs or in the case of an infusion-related reaction), administration of the subsequent study drugs including chemotherapy might be delayed to the second day of each cycle.

Cisplatin 75 mg/m^2 will be administered as an intravenous infusion over 4 hours on Day 1 of each 3-week cycle for 2 to 4 cycles. All patients should receive adequate hydration (including pretreatment hydration) and diuretics. Urinary output > 2000 mL must be maintained in the following 24 hours of the infusion.

Carboplatin area under the curve (AUC) of 5 mg/mL/min will be administered as an intravenous infusion over 1 hour on Day 1 of each 3- week cycle for 2 to 4 cycles. Carboplatin can replace cisplatin per the investigator's discretion in consideration of patient's tolerability to cisplatin. The reasons for intolerability should be documented.

For nonsquamous: Pemetrexed 500 mg/m^2 will be administered as an intravenous infusion over 10 minutes on Day 1 of each 3-week cycle for 2 to 4 cycles. All patients should receive the appropriate supplementation of vitamin B12 and folic acid according to the approved product label and/or standard practice. In addition, all patients should receive the appropriate corticosteroid premedications as per the local approved label. Additional premedications should be administered as per standard practice.

For squamous: Paclitaxel 175 mg/m^2 will be administered as an intravenous infusion over 3 hours on Day 1 of each 3-week cycle for 2 to 4 cycles. In addition, all patients should receive the appropriate premedications as per the local approved labels. Additional premedications should be administered as per standard practice.

Patients will be monitored continuously for AEs and will be instructed to notify their physician immediately for any and all AEs. Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of each therapy. The infusion and monitoring of cisplatin, carboplatin, pemetrexed, and paclitaxel may also follow approved drug labels or

clinical practice. Please refer to Appendix 11 and Appendix 13 for the details of administration of tislelizumab and LBL-007.

2.3 Dose Delay or Modification

Effort should be made to administer the study drug(s) according to the planned dose and schedule. In the event of significant toxicities, dose modifications for chemotherapy agents are permitted according to the respective local prescribing information, guidelines, or clinical standard practice. Reasons for dose modifications or delays, the supportive measures taken, and the outcome will be documented in the patient's chart and recorded in the electronic case report form.

There will be no dose reduction for tislelizumab or LBL-007 in Arms 2A and 2C. Dose modification or chemotherapy depends on the severity of toxicity and an assessment of the risk versus benefit for the patient, with the goal of maximizing the patient's benefit. Dose modifications for chemotherapy should be performed per prescribing information and per local practice according to investigator's clinical judgment. In a case of dose reduction of chemotherapy, all further chemotherapy doses will decrease by 25% for the next cycle. A maximum of 2 dose reductions for each chemotherapeutic agent is allowed, except that carboplatin is only permitted to decrease by 20% doses once. Once the dose has been decreased, it should remain reduced for all subsequent administrations or further reduced if necessary. There will be no dose escalations in this study. If additional reductions are required, that chemotherapeutic agent should be discontinued. Study drug-related toxicities must be resolved to baseline level, or Grade 1 before administering the next dose of study drug, except for alopecia or Grade 2 fatigue.

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

Administration of chemotherapy should ideally remain synchronized with predefined cycles and tislelizumab and LBL-007 infusions. When a treatment cycle is delayed or interrupted because of toxicity resulting from either component of the chemotherapy regimen, other study drugs (tislelizumab and LBL-007) generally be withheld and resumed together to remain synchronized. At the subsequent cycle, if chemotherapy still cannot be given due to prolonged AE and toxicities, then tislelizumab and LBL-007 could be given as scheduled for that cycle alone, if clinically appropriate. If chemotherapy has been withheld for 42 days (delayed cycle + subsequent cycle), then it should permanently be discontinued.

Risks Associated with Chemotherapy

Cisplatin

Cisplatin is known to cause myelosuppression, ototoxicity, and nephrotoxicity.

Cisplatin-based chemotherapy is considered to be moderately emetogenic. Patients will be monitored for cisplatin-related AEs.

Carboplatin

Carboplatin is known to cause bone marrow suppression including myelosuppression, anemia, and thrombocytopenia. Carboplatin-based chemotherapy is considered to be moderately emetogenic. Patients will be monitored for carboplatin-related AEs.

Pemetrexed

The most common side effects of pemetrexed include gastrointestinal symptoms (nausea, vomiting, diarrhea, or constipation), myelosuppression, infection, fatigue, stomatitis, loss of appetite, and rash.

Paclitaxel

Common side effects of paclitaxel include: hypotension, nausea, and vomiting, arthralgia, myalgia, alopecia, diarrhea, hypersensitivity condition, mucositis, skin rash, electrocardiogram abnormality, increased serum alkaline phosphatase, increased serum aspartate aminotransferase (AST), infusion site reaction, peripheral neuropathy, and flushing.

For more details regarding the safety profiles of the respective chemotherapy agents, refer to the manufacturer's prescribing information.

Selected Precautions:

- Neutropenia: Fever or other evidence of infection must be assessed promptly and treated aggressively following the local clinical practice and/or the guidelines.
- Renal Toxicity:
  - Nephrotoxicity is common with cisplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside antibiotics.
  - Patients should not be given cisplatin or carboplatin if their creatinine clearance is 60 mL/min or 45 mL/min, respectively.
- Ototoxicity and sensory neural damage should be assessed before each cycle. Cisplatin is contraindicated in patients with a pre-existing hearing deficit.

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 below 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 25% of both drugs doses. If there is a second episode despite dose reduction, the patient must receive prophylactic antibiotics during the subsequent cycles. If there is a third episode, the chemotherapy will be discontinued.

Adverse Event		Treatment
Neutropenia	Grade 3 (0.5-0.99 × 10^9/L)	Chemotherapy delay until ≤ Grade 1 (≥ 1.5 × 10^9/L); restart with the full dose
	Grade 4 (< 0.5 × 10^9/L)	Chemotherapy delay until recovered to ≤ Grade 1; dose reduction of all further doses by 25%
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 25%

Abbreviations: AUC, area under the curve.
[a] If considered in the best interest of the patient and consistent with local practice, the 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. Carboplatin is only permitted to decrease by 20% doses once (from AUC 5 to AUC 4).

Recommended Dose Modifications for Non-Hematologic Toxicities

The dose adjustments of chemotherapy for non-hematologic toxicity are described in §Table 2. All dose modifications should be made based on the worst grade toxicity.

§Table 2. Chemotherapy Dose Modifications for Non-Hematological Toxicity

Toxicity	Grade	Treatment
Renal toxicity	≥ Grade 1	Delay chemotherapy until recovered to Grade 0 or baseline, change cisplatin to carboplatin, if possible; dose reduction by 25% for other drug; if recur, stop chemotherapy
Ototoxicity	Grade 2	Dose reduction of all further doses of cisplatin by 25%
	Grade 3 or 4	Delay chemotherapy until recovered to ≤ Grade 2, change cisplatin to carboplatin
Sensory neuropathy	Grade 2	Dose reduction for all further doses of cisplatin by 25%
	Grade 3	Stop cisplatin, change cisplatin to carboplatin
	Grade 4	Stop cisplatin/carboplatin
Total bilirubin	Grade 2	Two dose reduction level for all further doses of chemotherapy (each dose level requires a deduction by 25%)
	Grade 3 or 4	Stop chemotherapy
AST or ALT Elevation	Grade 3	Dose reduction for all further doses of by 25%
	Grade 4	Stop chemotherapy
Other organ toxicity	Grade 2	Delay chemotherapy until ≤ Grade 1 or baseline [a]
	Grade 3 or 4	Delay chemotherapy until recovered to ≤ Grade 1 or baseline [a], dose reduction of all further dose by 25%

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

Note: If considered in the best interest of the patient and consistent with local practice, the 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.
[a] Skin reactions, paronychia, alopecia, fatigue, nausea/vomiting which may have resolved to Grade 2 or baseline.

2.4. Discontinuation of Chemotherapy Regimens

Chemotherapy drugs could be discontinued for any of the following:

- Any Grade 3 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 alanine aminotransferase (ALT) > 5 to 10 × upper limit of normal (ULN) for > 2 weeks
  - AST or ALT > 10 × ULN or
  - Total bilirubin > 5 × ULN or
  - Concurrent AST or ALT > 3 × ULN and total bilirubin > 2 × ULN
- Any cisplatin-related decrease in creatinine clearance to < 30 mL/min (using the Cockcroft-Gault formula) requires discontinuation of cisplatin.
- Any drug-related AE that recurs after 2 prior dose reductions for the same drug-related AE requires discontinuation of the drug(s).
- Any Grade 3 or 4 drug-related hypersensitivity reaction or infusion reaction requires discontinuation of the drug(s) assessed to be causing the reaction. If the drug is assessed as not related to the hypersensitivity reaction or infusion reaction, it may be continued.
- Any Grade 4 AE that the investigator considers related to study drug(s) and inappropriate to be managed by dose reduction(s) requires discontinuation of drug(s). If the drug is not assessed to be related to the event it may be continued.
- If any toxicity which led to treatment discontinuation does not resolve within 21 days, that component will be discontinued.

For toxicities not listed above, the investigator's medical judgment would determine whether chemotherapy regimen should be discontinued, in accordance with patient's wellbeing and local standards.

APPENDIX 15. PREGNANCY REPORTING PERIOD

If a female patient or the female partner of a male patient becomes pregnant during the following period for each arm, the pregnancy must be reported as specified in Section 8.6.6.

Arm	Treatment	Pregnancy Reporting Period
Experimental Arm 1A	Tislelizumab	On treatment or ≤ 180 days after the last dose of tislelizumab
Experimental Arm 1B	Tislelizumab + ociperlimab	On treatment or ≤ 180 days after the last dose of tislelizumab or ociperlimab, whichever occurs later
Experimental Arm 1C	LBL-007 + Tislelizumab	On treatment or ≤ 180 days after the last dose of LBL-007 or tislelizumab, whichever occurs later
Experimental Arm 2A	Tislelizumab + chemotherapy	On treatment or ≤ 180 days after the last dose of tislelizumab or chemotherapy, whichever occurs later
Experimental Arm 2C	LBL-007 + Tislelizumab + chemotherapy	On treatment or ≤ 180 days after the last dose of LBL-007 or tislelizumab or chemotherapy, whichever occurs later

Signature Page

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