BeiGene

STATISTICAL ANALYSIS PLAN

Study Protocol Number:	BGB-LC-202
Study 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
Date:	25 Jan 2025
Version:	1.0
NCT Number:	NCT05577702

SIGNATURE PAGE

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Antidrug Antibody
ADI	Actual Dose Intensity
AE	Adverse Event
BGB-A317	Tislelizumab
BGB-A1217	Ociperlimab
BIPR	Blinded Independent Pathology Review
BP	Blood Pressure
CI	Confidence Interval
CV	Coefficient of Variation
CK-MB	Creatine Kinase Cardiac Isoenzyme
CSR	Clinical Study Report
ctDNA	Circulating Tumor DNA
DFS	Disease-Free Survival
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EE	Efficacy Evaluable
EFS	Event-Free Survival
EOT	End of Treatment
imAE	Immune-Mediated Adverse Event
IRR	Infusion-Related Reaction
ITT	Intent-to-Treat
LKADT	Last Known Alive Date
LRT	Likelihood Ratio Test
minFD	Minimum Study Follow-up Duration
MPR	Major Pathological Response
MRD	Minimal Residual Disease
MSI	Microsatellite Instability
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events

NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
pCR	Pathological Complete Response
PK	Pharmacokinetic(s)
PT	Preferred Term
QTcF	QT interval corrected by Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
R0	Pathological Complete Resection of the Primary Tumor
R1	Pathological Resection of Macroscopic Disease with Microscopic Residuals
R2	Pathological Resection of the Primary Tumor with Macroscopic Residuals
R(un)	Uncertain Pathological Resection
SAE	Serious Adverse Event
SAF	Safety
SAP	Statistical Analysis Plan
SFD	Study Follow-up Duration
SOC	System Organ Class
TCR	T Cell Receptor
TEAE	Treatment-Emergent Adverse Event
TMB	Tumor Mutation Burden

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1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for BGB-LC-202: 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. The focus of this SAP is for the final analysis specified in the study protocol. The analysis details for Pharmacogenomics and Biomarker analyses are not described within this SAP. Separate analysis plans will be completed for these analyses and will be attached in addition to this SAP to the clinical study report (CSR).

2. STUDY OVERVIEW

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 (e.g., 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:

Sub-study 1:

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

Sub-study 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. Only Central PD-L1 expression results will be acceptable for randomization/enrollment into this study under protocol version 2.0, while local PD-L1 expression results will be acceptable for randomization/ enrollment into this study under protocol version 1.0. Patients will also be required to provide tissue samples of the primary tumor and optional lymph node

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 (e.g., 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, Sub-study 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%; Sub-study 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 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 Sub-study 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 Sub-study 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

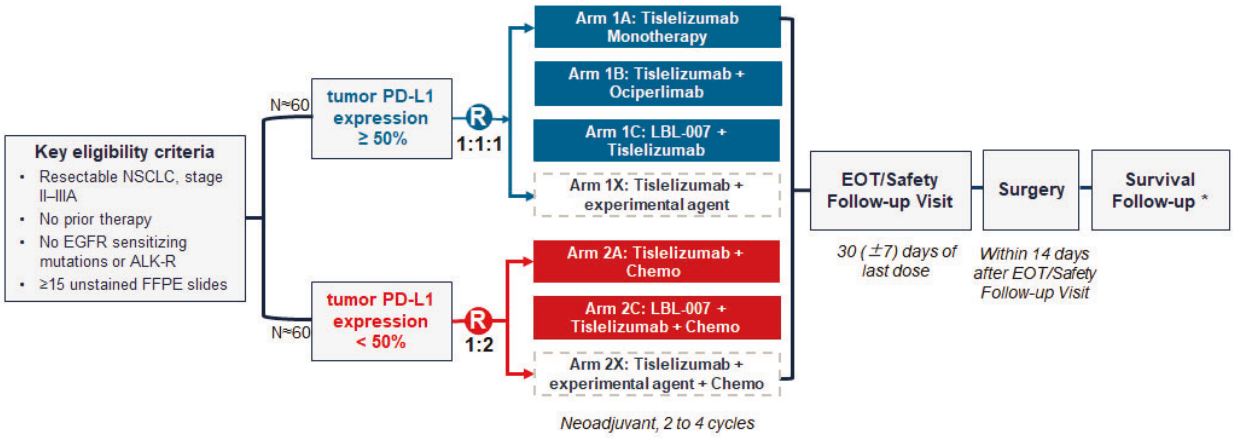
Figure 1. Eligible patients will be assigned randomly in a certain ratio into 1 of the active treatment arms. In this current version of the protocol, eligible patients with tumor PD-L1 expression ≥ 50% will be randomized in a 1:1:1 ratio to Sub-study 1:

- 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 Sub-study 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 1: 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.

Crossover between the experimental arms will not be allowed in this study.

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.

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.

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.

The surgical procedure should be performed ≤ 14 days after the EOT/Safety Follow-up Visit. If surgery cannot be performed ≤ this time window (e.g., 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 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.

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.

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.

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. The first disease follow-up tumor assessment after surgery will be performed after 3 months (± 2 weeks) post-surgery, 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.

Details of study design and clinical visits are specified in study protocol section 3.

3. STUDY OBJECTIVES

3.1. Efficacy Objective

- 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.
- To evaluate the pathological complete response (pCR) rate of neoadjuvant treatment with investigational agents as assessed by the BIPR.
- To evaluate the survival related endpoints including event free survival (EFS), overall survival (OS), disease-free survival (DFS), and milestone endpoints.

3.2. Safety Objective

- To assess the safety and tolerability of neoadjuvant treatment with investigational agents.
- To assess the feasibility of surgery in patients receiving neoadjuvant treatment with investigational agents.

3.3. Pharmacodynamics/Exploratory Objective

- 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.
- To characterize the pharmacokinetics (PK) of the investigational agents.
- To assess the host immunogenicity to investigational protein therapeutics.
- To evaluate objective response rate (ORR) in patients receiving neoadjuvant treatment with investigational agents before surgery as assessed by the investigator.

4. STUDY ENDPOINTS

4.1. Efficacy Endpoint(s)

- 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.
- 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.
- 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 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.

4.2. Safety Endpoints

- 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)
- 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.

4.3. Pharmacodynamics/Exploratory Endpoints

- 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
- Serum or plasma concentrations of the investigational agents at specified timepoints
- Immunogenic responses to investigational protein therapeutics, evaluated through detection of antidrug antibodies (ADAs)
- Objective response rate (ORR), defined as the proportion of patients who had complete response or partial response before surgery as assessed by the investigator per RECIST v1.1 in all randomized patients with measurable disease at baseline.

5. 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 to Sub-study 1, including Arm 1A (tislelizumab monotherapy), Arm 1B (ociperlimab in combination with tislelizumab), 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 Sub-study 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% confidence interval (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.

6. STATISTICAL METHODS

6.1. 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 Sub-study 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 Sub-study 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.
- The Pharmacokinetic analysis set includes all patients who received any dose of the tislelizumab/ociperlimab/LBL-007, for whom any quantifiable postdose PK concentrations are available.
- The ADA analysis set includes all patients who received any dose of tislelizumab/ociperlimab/LBL-007, for whom both baseline ADA and at least 1 post-baseline ADA results are available.

6.2. Multiplicity Adjustment

Not Applicable.

6.3. Data Analysis General Considerations

6.3.1. Definitions and Computations

Study drugs include tislelizumab (BGB-A317), ociperlimab (BGB-A1217), LBL-007, Cisplatin, Carboplatin, Pemetrexed and Paclitaxel.

Study day:
Study day will be calculated in reference to the date of the first dose of study drug (for safety analysis) or randomization date (for efficacy analysis). For assessments conducted on or after the date of the randomization date/first dose of study drug, study day will be calculated as (assessment date – randomization date/date of first dose of study drug + 1). For assessments conducted before the date of the randomization date/first dose of study drug, study day is calculated as (assessment date – randomization date/date of first dose of study drug). There is no study day 0.
In the situation where the event date is partial or missing, the date will appear partial or missing in the listings; Study day and any corresponding durations will be presented based on the imputations specified in Appendix 1.
Surgery:

Surgery is defined as radical surgery described in Section 5.2.2 in study protocol. Exploratory thoracotomy is not considered as surgery in this document.

Baseline Measurements:

- For efficacy evaluation: a baseline value is defined as the last non-missing value collected on or prior to the randomization.
- For safety: a baseline value is defined as the last non-missing value collected on or prior to the first study drug administration.
- For toxicity grade of certain laboratory tests: two baseline toxicity grades should be derived according to the directions lower (Hypo) or higher (Hyper)). For example, a baseline hemoglobin with value between 10.0 g/dL and LLN, two baseline toxicity grades: Grade 1 for Hypo and Grade 0 for Hyper will be derived.

Study Follow-up Duration (SFD): Study follow-up duration is defined as the duration from the randomization date to the study discontinuation date (e.g., death, consent withdrawal, lost to follow-up) or to cutoff date if a patient is still ongoing.

Minimum Study Follow-up Duration (minFD): Minimum study follow up is defined as a difference between the date of analysis cut-off and the date of last patient randomized.

All calculations and analyses will be conducted using SAS version 9.4 or higher and R 4.1.2.

6.3.2. Conventions

Unless otherwise specified, the following conventions will be applied to all analyses:

- 1 year = 365.25 days. Number of years is calculated as (days/365.25) rounded up to 1 significant digit.

- 1 month = 30.4375 days. Number of months is calculated as (days/30.4375) rounded up to 1 significant digit.
- Age will be calculated as the integer part of (date of informed consent – date of birth + 1)/365.25.
- P-values will be rounded to 4 decimal places. P-values that is less than 0.0001 will be presented as '< 0.0001' and p-values that is larger than 0.9999 will be presented as '> 0.9999'.
- Duration of image-based event endpoints (EFS and DFS) will be based on the actual date the radiograph was obtained rather than the associated visit date.
- For laboratory results collected as "< "or ">", a numeric value, 0.0000000001 will be subtracted or added, respectively, to the value.
- For by-visit observed data analyses, percentages will be calculated based on the number of patients with non-missing data as the denominator, unless otherwise specified.
- For continuous endpoints, summary statistics will include n, mean, standard deviation, median, Q1, Q3 and range (minimum and maximum).
- For discrete endpoints, summary statistics will include frequencies and percentages.

6.3.3. Handling of Missing Data

Missing data will not be imputed unless otherwise specified elsewhere in this SAP. Missing dates or partially missing dates will be imputed conservatively for adverse events and prior/concomitant medications/procedures. Specific rules for the handling of missing or partially missing dates for adverse events and prior/concomitant medications/procedures are provided in Appendix 1.

By-visit endpoints will be analyzed using observed data unless otherwise specified. For observed data analyses, missing data will not be imputed, and only the observed records will be included.

6.4. Patient Characteristics

6.4.1. Patient Disposition

The number (percentage) of patients randomized, randomized but not treated, treated, discontinued from the treatment (all treatments), the primary reason for the end of the treatment, discontinued from the study, reasons for discontinued from the study, the number of planned treatment cycles, and the duration of study follow-up, and minimum study follow-up will be summarized by using the ITT-1 analysis set and ITT-2 analysis set in each arm and total in each sub-study.

Treatment discontinuation for each drug component and the reason for treatment discontinuation will be summarized in the ITT-1 analysis set and ITT-2 analysis set in each arm and total in each sub-study.

6.4.2. Demographic and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized using descriptive statistics in the ITT-1 and ITT-2 analysis sets using descriptive statistics. Continuous variables will be summarized using number of patients, mean, standard deviation, median, minimum and maximum. Categorical variables will be summarized using number of patients and percentage in relevant categories.

Demographic and other baseline characteristics include:

- Age (continuously and by categories [≤65 or >65 years])
- Sex (Male and Female)
- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
- Smoking status (Never vs Current vs Former)
- ECOG performance status (0 vs 1)

6.4.3. Disease History

The number (percentage) of patients reporting a history of disease and characteristics, as recorded on the eCRF, will be summarized in the ITT-1 analysis set and ITT-2 analysis set.

Disease characteristics include the following characteristics:

- Time from initial cancer diagnosis to study entry (months)
- Histology (Squamous vs Non-squamous vs Mixed Adeno-Squamous vs Other)
- ALK rearrangement status at study entry (Positive vs Negative vs Unknown)
- EGFR mutation status at study entry (Detected vs Not Detected vs Indeterminate vs Missing)
- Histologic grade (Well Differentiated vs Moderately Differentiated vs Poorly Differentiated vs Not Differentiated vs Cannot be Assessed vs Not Done)
- TNM stages at study entry
    - T stage at study entry (T0 vs T1a vs T1b vs T1c vs T2a vs T2b vs T3 vs T4)
    - N stage at study entry (N0 vs N1 vs N2 vs N3)
    - M stage at study entry (M0 vs M1a vs M1b vs M1c)
- Disease stage at study entry (IIA vs IIB vs IIIA)
- Central confirmed PD-L1 expression level (>= 50% vs 1-49% vs < 1% vs Unknown).

6.4.4. Medical History

Medical History will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 27.0. The number (percentage) of patients reporting a history of any medical condition, as recorded on the CRF, will be summarized by system organ class and preferred term in the ITT-1 analysis set and ITT-2 analysis set.

6.5. Efficacy Analysis

6.5.1. Primary Efficacy Endpoint

Major Pathological Response (MPR) rate as assessed by the BIPR

MPR rate as assessed by the BIPR 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. If patients start new anticancer therapy started prior to surgery, they will be considered as non-responders in analysis. 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.

6.5.2. Secondary Efficacy Endpoints

Pathological Complete Response (pCR) Rate as Assessed by BIPR

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

Event Free Survival 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.

Local recurrence is defined as recurrence in the ipsilateral thorax including lung parenchyma, bronchial stump, main trachea, hilum or mediastinal lymph nodes (including subcarinal lymph nodes), pleura and chest wall diagnosed by radiological examination and/or histopathological confirmation. Ipsilateral thorax means new lesions of lymph node or new lesion in lung is found on same side of baseline location.

Distant recurrence (metastasis) is defined as spread of disease beyond the area of the ipsilateral thorax (including contralateral area and other organs) diagnosed by radiological examination and/or histopathological confirmation.

The efficacy analysis of EFS will be conducted in the ITT-1 and ITT-2 analysis sets separately. The censoring rules for the analysis of EFS are presented in Table 1. 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.

Details of EFS derivation rules are listed as below:

- A disease progression not reaching the RECIST 1.1 criteria by the investigator, but which still precludes surgery (reason for no surgery is progressive disease or tumor unresectability by investigator) is considered as an event.
- Patients who do not undergo surgery due to reasons other than progressive disease and tumor unresectability will be considered to have an event at RECIST 1.1 progression precluding definitive surgery by the investigator or death.
- Patients who died without a reported progression/disease recurrence will be considered to have experienced an event.
- Patients with post-surgery recurrence/progression per RECIST 1.1 by the investigator will be considered as an event.

The following general censoring rules will be applied for the primary analysis of EFS by the investigator:

- A pre-surgical progression (even if reaching the RECIST 1.1 criteria by the investigator) which does not preclude surgery is not considered as an event.
- Patient who did not report progression/recurrence of disease or death will be censored on the date of their last adequate tumor assessment prior to or on date of data cut-off or withdrawal from study or lost to follow up. Secondary primary malignancy tumor discovered other than lung cancer during the study will not be considered as progression/recurrence of disease.

- Patient who did not have any on-study tumor assessments and did not die will be censored on the date of randomization.
- Patient who received subsequent anti-cancer therapy except prespecified optional adjuvant therapy will be censored at the date of the last adequate tumor assessment on or prior to the date of initiation of the subsequent anti-cancer therapy.
- Patient missed more 2 or more consecutive tumor assessment before disease progression, local or distant recurrence or death, its EFS will be censored at the date of last adequate disease assessment before the missing tumor assessments.

The censoring rules for the primary analysis of EFS are presented in Table 1.

Table 1: Event and Censoring Rules of Event Free Survival

No.	Neoadjuvant	Surgery [a]	Survival follow-up	Derivation rules	Outcomes
1	No baseline or post-baseline tumor assessments without death within 15 weeks [b] after randomization			Date of randomization	Censored
2	Death (within 15 weeks [b] after randomization if no baseline or post-baseline tumor assessments)			Date of death	Event
3	Disease progression precluding surgery [c]	No surgery	Any	Date of radiographic progression precluding surgery or date of last presurgical adequate tumor assessment +1 if no radiographic progression	Event
4	No disease progression precluding surgery [c] but progression after presurgical visit	No surgery	Any	Date of radiographic progression before new anti-cancer therapy except prespecified optional adjuvant therapy and not missed 2 or more consecutive tumor assessments [d]	Event
				Otherwise, last adequate radiologic assessment prior to new anti-cancer therapy except prespecified optional adjuvant therapy or missed 2 or more consecutive	Censored

				tumor assessments [d] whichever comes first	
5	No disease progression precluding surgery [c] / No radiographic progression after presurgical visit	No surgery	Any	Date of last adequate radiologic assessment prior to new anti-cancer therapy except prespecified optional adjuvant therapy	Censored
6	Radiographic progression	Surgery (R2 resection)	Any	Date of radiographic progression	Event
7	No radiographic progression	Surgery (R2 resection)	No radiographic progression or local/distant recurrence or death	Last adequate radiologic assessment prior to new anti-cancer therapy except prespecified optional adjuvant therapy	Censored
8	No radiographic progression	Surgery (R2 resection)	Radiographic progression or local/distant recurrence or death	Date of radiographic progression or local/distant recurrence or death before new anti-cancer therapy except prespecified optional adjuvant therapy and not missed 2 or more consecutive tumor assessments [d]	Event
				Otherwise, last adequate radiologic assessment prior to new anti-cancer therapy except prespecified optional adjuvant therapy or missed 2 or more consecutive tumor assessments [d] whichever comes first	Censored

9	Any	Surgery (R0, R1 or R(un) resection)	No tumor assessments	Date of surgery	Censored
10	Any	Surgery (R0, R1 or R(un) resection)	No local/distant recurrence or death	Date of last adequate radiologic assessment prior to new anti-cancer therapy except prespecified optional adjuvant therapy	Censored
11	Any	Surgery (R0, R1 or R(un) resection)	Local/distant recurrence or death	Date of local/distant recurrence or death before new anticancer therapy except pre-specified optional adjuvant therapy and not missed 2 or more consecutive tumor assessments [d]	Event
				Otherwise, last adequate radiologic assessment prior to new anti-cancer therapy except prespecified optional adjuvant therapy or missed 2 or more consecutive tumor assessments [d] whichever comes first.	Censored

[a] Exploratory thoracotomy is not considered as study surgery.
[b] 15 weeks is two consecutive tumor assessment windows in the neoadjuvant treatment period.
[c] Disease progression precluding surgery includes radiographic disease progression per RECIST 1.1 precluding surgery or a disease progression not reaching the RECIST 1.1 criteria but which still precludes surgery (reason for no surgery is progressive disease or tumor unresectable).
[d] Missed 2 or more consecutive tumor assessments missing before disease progression, local or distant recurrence or death.

Overall Survival (OS)

Overall survival is defined as the time from randomization date to the documented death date for patients who died prior to or on the clinical cutoff date. For patients who are alive by the clinical cutoff date, OS will be censored at the last known alive date (LKADT). For patients that are still on treatment at cut-off date, the LKADT will be defined as clinical data cutoff date. For patients who discontinue treatment but are still alive, the LKADT will be defined as the last known alive date or cut-off date, whichever comes first for other patients who are alive.

Every effort should be made to ensure collection of the complete date of death. In the rare case where the day of death is missing, the death date is imputed as the maximum (last available date showing patients alive + 1, first day of month of death date). The patient with imputed death date

will be considered as an event for OS analysis. Death with missing month and/or year will not be imputed for OS analysis and will be censored at LKADT.

The analysis of OS will be conducted in the ITT-1 and ITT-2 analysis sets separately. Hazard ratios and corresponding two-sided 95% CIs of OS for Arm 1C versus Arm 1A, and Arm 1B versus Arm 1A, and Arm 2C versus Arm 2A will be estimated using a Cox proportional hazards model. Kaplan-Meier methodology will be used to estimate median and other quartiles of OS for each treatment arm. OS 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.

Disease Free Survival (DFS) as Assessed by the Investigator

DFS is defined as the time from the first date of no disease (R0 resections as surgery outcome) 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 patients with planned surgery 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 of last known to be alive, and data will be censored on the date they were last known to be alive. Detailed event and censoring rules for DFS are provided in Table 2.

The analysis of DFS will be conducted in the ITT-1 and ITT-2 analysis sets separately. Hazard ratios and corresponding two-sided 95% CIs of DFS for Arm 1C versus Arm 1A, and Arm 1B versus Arm 1A, and Arm 2C versus Arm 2A will be estimated using a Cox proportional hazards model. Kaplan-Meier methodology will be used to estimate median and other quartiles of DFS for each treatment arm. DFS 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.

Table 2: Event and Censoring Rules for Disease-Free Survival

	Derivation rules	**Outcome**
No local/distant recurrence or death at the time of data cut-off or withdrawal from study or lost to follow up	Date of last adequate radiologic assessment on or prior to data cut-off date, withdrawal from study, or lost follow up, whichever comes first.	Censored
New anticancer therapy except prespecified optional adjuvant therapy started prior to local/distant recurrence or death	Last adequate radiological assessment before the subsequent anticancer therapy except prespecified optional adjuvant therapy	Censored
No post-surgery tumor assessments without death within 9.92 months [a] after surgery	First date of no disease	Censored

	Derivation rules	Outcome
No post-surgery tumor assessments with death within 9.92 months after surgery	Date of death	Event
Local/distant recurrence documented between scheduled visits	Date of recurrence	Event
Death before first documented local/distant recurrence	Date of death	Event
Local/distant recurrence or death after two or more consecutive missed visit	Date of last adequate radiologic assessment before missed tumor assessments	Censored

[a] 9.92 months is two consecutive tumor assessment windows after surgery.

6.5.3. Subgroup Analyses

Subgroup analysis on primary efficacy endpoint (MPR) will be conducted by treatment group in the ITT-1 and ITT-2 analysis sets to explore the consistency of efficacy across a variety of subgroups, as appropriate. Subgroup variables may include but are not limited to:

- Age group (< 65 years versus >= 65 years)
- Gender (Male versus Female)
- Disease stage (II vs III)
- ECOG Performance Status (0 versus 1)
- Histologic type of tumor (Squamous versus Non-squamous (including Mixed Adeno-Squamous and Other))
- Smoking status (Former/Current smoker versus Non-smoker)
- Number of planned treatment cycles (2 cycles versus 3 or 4 cycles)
- Central confirmed PD-L1 (< 1% versus 1% to 49% versus >= 50% versus Unknown)

The following subgroup analysis on primary efficacy endpoint, MPR, will be conducted by treatment groups in the ITT-2 analysis set.

- PD-L1 Expression per Enrollment (< 1% versus 1-49%)

The following subgroup analysis on primary efficacy endpoint, MPR, will be conducted by Arm 1A and Arm 1C in the ITT-1 analysis set and treatment groups in the ITT-2 analysis set.

- LAG-3 IHC (>= 10% versus < 10% versus Unknown; >=5 % versus < 5% versus Unknown; >=1% versus <1 % versus Unknown)

6.5.4. Exploratory Efficacy Endpoint

Objective Response Rate (ORR) before Surgery by Investigator

Objective response rate (confirmation not required according to RECIST v1.1) is the proportion of patients who had CR or PR before surgery as assessed by the investigator per RECIST v1.1 in all randomized patients with measurable disease at baseline. Patients without any postbaseline assessment before surgery will be considered as non-responders. The ORR will be summarized with descriptive statistics by arms in each substudy and the corresponding two-sided 95% CIs calculated from Clopper-Pearson exact method will be also presented.

6.5.5. Subsequent Anti-cancer Therapy

Subsequent anti-cancer therapy is defined as the anti-cancer therapy started after the last dose date of study drug.

A summary of number and pecentage of patients who received radiotherapy, procedure or surgery, systemic therapy will be provided by arm based on the ITT-1 and ITT-2 analysis sets.

Patient data listing of subsequent systemic anticancer therapy will be provided.

6.6. Safety Analyses

All safety analyses will be performed by treatment arms based on the safety analysis set in each sub-study unless otherwise specified. Safety and tolerability will be assessed, where applicable, by incidence, severity, and change from baseline values for all relevant parameters including but not limited to AEs, laboratory values, vital signs, and ECG findings.

6.6.1. Extent of Exposure

The following measures of the extent of exposure will be summarized:

- Number of treatment cycles: the total number of treatment cycles in which at least one dose of the study drug is administered.
- Duration of exposure (weeks):
  - For tislelizumab, Ociperlimab, LBL-007, Cisplatin, Carboplatin, Pemetrexed, and Paclitaxel

    If a patient discontinued or completed treatment, the duration of exposure is defined as (min (cutoff date, death date, last dose date + 20) – first dose date at neoadjuvant phase + 1)/7.

  - If a patient is under treatment, the duration of exposure is defined as (cutoff date - first dose date+1)/7.
- Total dose received per patient (mg): defined as the cumulative dose of the study drug during the treatment period of the study.
- Actual dose intensity
  - Actual dose intensity in mg/cycle for tislelizumab/Ociperlimab/LBL-007 = 21*cumulative dose (mg)/(last dose date up to cutoff date + 21 – first dose date)

  - Actual dose intensity (ADI) in mg/cycle for platinum-based chemotherapy is refer to Appendix 2.
  - Actual dose intensity (ADI) of combination therapy will be summarized individually for each component.
- Planned dose intensity:
  - Planned dose intensity (mg/cycle) for tislelizumab is 200 mg/cycle.
  - Planned dose intensity (mg/cycle) for Ociperlimab is 900 mg/cycle.
  - Planned dose intensity (mg/cycle) for LBL-007 is 600 mg/cycle.
  - Planned dose intensity for platinum-based chemotherapy is refer to Appendix 2.
  - Planned dose intensity for combination therapy will be summarized individually for each component.
- Relative dose intensity (%): defined as the ratio of the actual dose intensity and the planned dose intensity.

6.6.2. Adverse Events

AEs will be graded by the investigators using CTCAE version 5.0. The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using MedDRA. Adverse events will be coded to the MedDRA (Version 26.0 or higher) lowest level term closest to the verbatim term, along with the linked MedDRA preferred term (PT) and primary system organ class (SOC).

6.6.2.1 Treatment-emergent Adverse Event

A treatment-emergent adverse event (TEAE) is defined as an AE that has an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of 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. All AEs, treatment-emergent or otherwise, will be presented in patient-level listings.

Safety overview table for each substudy will be provided, including the number and percentage of patients with:

- TEAE
  - Treatment-related
    - Related to Tislelizumab
    - Related to Ociperlimab
    - Related to LBL-007
    - Related to any immunotherapy
    - Related to any component of chemotherapy (in Substudy 2 only)

- TEAE with NCI-CTCAE grade ≥3
  - Treatment-related
    - Related to Tislelizumab
    - Related to Ociperlimab
    - Related to LBL-007
    - Related to any immunotherapy
    - Related to any component of chemotherapy (in Substudy 2 only)
- Serious TEAE
  - Treatment-related
    - Related to Tislelizumab
    - Related to Ociperlimab
    - Related to LBL-007
    - Related to any immunotherapy
    - Related to any component of chemotherapy (in Substudy 2 only)
- TEAE leading to death
  - Treatment-related
    - Related to Tislelizumab
    - Related to Ociperlimab
    - Related to LBL-007
    - Related to any immunotherapy
    - Related to any component of chemotherapy (in Substudy 2 only)
- TEAE leading to discontinuation of study drug
  - TEAE leading to discontinuation of Tislelizumab
  - TEAE leading to discontinuation of Ociperlimab
  - TEAE leading to discontinuation of LBL-007
  - TEAE leading to discontinuation of any immunotherapy
  - TEAE leading to discontinuation of any component of chemotherapy (in Substudy 2 only)
- TEAE leading to dose modification of study drug: Dose modification for tislelizumab, ociperlimab and LBL-007 includes dose interruption, dose delay and infusion rate decrease. Dose modification for chemotherapy includes dose reduction, dose interruption, dose delay and infusion rate decrease.

- TEAE leading to dose modification of Tislelizumab
- TEAE leading to dose modification of Ociperlimab
- TEAE leading to dose modification of LBL-007
- TEAE leading to dose modification of any immunotherapy
- TEAE leading to dose modification of any component of chemotherapy (in Substudy 2 only)

- TEAE leading to surgery withdrawal
  - Treatment-related
    - Related to Tislelizumab
    - Related to Ociperlimab
    - Related to LBL-007
    - Related to any immunotherapy
    - Related to any component of chemotherapy (in Substudy 2 only)
- TEAE leading to surgery delay
  - Treatment-related
    - Related to Tislelizumab
    - Related to Ociperlimab
    - Related to LBL-007
    - Related to any immunotherapy
    - Related to any component of chemotherapy (in Substudy 2 only)

Treatment-related AEs include those events considered by the investigator to be related to study drug or with a missing assessment of the causal relationship.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by SOC, PT and the worst grade. A patient will be counted only once by the highest severity grade within an SOC and PT, even if the patient experienced more than 1 TEAE within a specific SOC and PT. The incidence of following TEAEs will be reported by SOC and/or PT sorted in descending order of SOC and/or PT:

- All TEAEs
  - All TEAEs by SOC and PT (All Grades and >= Grade 3)
  - All TEAEs by PT (All Grades and >= Grade 3)
  - Treatment-related TEAE by SOC and PT (All Grades and >= Grade 3)
    - TEAE related to any immunotherapy by SOC and PT

        - TEAE related to any component of chemotherapy by SOC and PT (in Substudy 2 only)
- Serious TEAEs
    - All SAE by SOC and PT
    - All SAE by PT
    - Serious Treatment-related TEAE by SOC and PT
        - SAE related to any immunotherapy by SOC and PT
        - SAE related to any component of chemotherapy by SOC and PT (in Substudy 2 only)
- TEAEs leading to death
    - TEAE leading to death by SOC and PT
    - TEAE leading to death by PT
- TEAEs leading to treatment discontinuation
    - TEAE leading to treatment discontinuation by SOC and PT
    - TEAE leading to treatment discontinuation by PT
    - TEAE leading to treatment discontinuation of any immunotherapy by SOC and PT
    - TEAE leading to treatment discontinuation of any component of chemotherapy by SOC and PT (in Substudy 2 only)
- TEAEs leading to dose modification
    - TEAE leading to dose modification by SOC and PT
    - TEAE leading to dose modification by PT
    - TEAE leading to dose modification of any immunotherapy by SOC and PT
    - TEAE leading to dose modification of any component of chemotherapy by SOC and PT (in Substudy 2 only)
- TEAEs leading to surgery withdrawal
    - TEAE leading to surgery withdrawal by SOC and PT (All Grades and >= Grade 3)
    - TEAE leading to surgery withdrawal by PT (All Grades and >= Grade 3)
- TEAEs leading to surgery delay
    - TEAE leading to surgery delay by SOC and PT (All Grades and >= Grade 3)
    - TEAE leading to surgery delay by PT (All Grades and >= Grade 3)

6.6.2.2 Immune-mediated Adverse Events (imAE)

Immune-mediated AEs are of special interest and summarized by category within a pre-defined list. The identification of immune-mediated adverse events is described in the immune-mediated adverse event charter.

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.

Summaries of the following incidences of immune-mediated adverse events in each substudy will be provided:

- Overall summary of Immune-mediated adverse events
- Immune-mediated adverse events by category and PT (All Grades and >= Grade 3)
- Serious Immune-mediated adverse events by category and PT (All Grades and >= Grade 3)
- Immune-mediated adverse events leading to death by category and PT (All Grades and >= Grade 3)
- Immune-mediated adverse events leading to treatment discontinuation by category and PT (All Grades and >= Grade 3)
- Immune-mediated adverse events leading to dose modification by category and PT (All Grades and >= Grade 3)
- Immune-mediated adverse events outcome, time to onset, and duration by category

Patient data listings of immune-mediated adverse events will be provided.

6.6.2.3 Infusion-related Reaction (IRR)

IRR is defined as any TEAE checked by the investigator as an IRR in the eCRF IRR checkbox.

For infusion-related reaction, an overview table for each substudy will be provided, including the number and percentage of patients with:

- Infusion-related reaction
  - All infusion-related reaction
  - Infusion-related reaction with NCI-CTCAE grade ≥ 3
  - Serious infusion-related reaction
  - Infusion-related reaction leading to treatment modification
  - Infusion-related reaction leading to treatment discontinuation

Patient data listings of IRRs will be provided.

6.6.2.4 Death

All deaths and causes of death will be summarized by treatment arms in each substudy including those occurred during the study treatment period and those reported during the survival follow-up period after treatment completion/discontinuation.

Patient data listings of deaths will be provided.

6.6.3. Laboratory Value

Laboratory safety tests will be evaluated for selected parameters described in Table 3.

Laboratory parameters (hematology and serum chemistry) that are graded in NCI CTCAE Version 5.0 will be summarized by shifts from baseline CTCAE grades to maximum post-baseline grades. In the summary of laboratory parameters by CTCAE grade, parameters with CTCAE grading in both high and low directions will be summarized separately. The summary tables will report lab assessments up to 30 days of the last dose date.

Patient data listings of hematology, serum chemistry and thyroid function will be provided.

Incidence of patients who meet potential Hy's law criteria will be summarized. A listing of patients who meet Hy's law criteria will be provided.

Table 3: Clinical Laboratory Tests

Serum Chemistry	Hematology	Thyroid function
Alkaline phosphatase	Hematocrit	Free triiodothyronine
Alanine aminotransferase	Hemoglobin	Total triiodothyronine
Aspartate aminotransferase	Lymphocyte count (Absolute)	Free thyroxine
Albumin	Neutrophil count (Absolute)	Thyroid-stimulating hormone
Total bilirubin	Platelet counts	
Direct bilirubin	White blood cell count	
Blood urea nitrogen or urea		
Chloride		
Potassium		
Sodium		
Total calcium [a]		
Creatinine		
Glucose		
Lactate dehydrogenase		
Total Protein		

Serum Chemistry	Hematology	Thyroid function
Creatinine kinase [b]		
CK-MB [b]		

Abbreviations: CK-MB, creatine kinase cardiac isoenzyme.

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

b. 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 in protocol for additional information regarding clinical assessment and management of clinical laboratory abnormalities.

6.6.4. Vital Signs

Descriptive statistics for vital sign parameters (body temperature, pulse rate, systolic and diastolic blood pressure [BP], temperature, and weight) and changes from baseline will be presented by visit.

6.6.5. Electrocardiograms (ECG)

ECG recordings are required at Screening, End of Treatment/Safety Follow-up Visit, at the presurgical Visit, and as clinically indicated.

Abnormal baseline and post-baseline QT interval corrected by Fridericia's formula (QTcF) results will be summarized with the following categories: increase of >30 msec, increase of > 60 msec, value of > 450 msec, value of > 480 msec, value of > 500 msec by treatment group.

6.6.6. Feasibility of Surgery

The following information 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 analysis set and ITT-2 analysis set in each sub-study:

- The number (percentage) of patients randomized but not treated
- The number (percentage) of patients treated but not performed surgery or exploratory thoracotomy and reason.
- The number (percentage) of patients received exploratory thoracotomy
- The number (percentage) of patients received surgery
- The duration of surgery (hours)
- The intent of surgery
- The approach of surgery
- The type of surgery
- Whether all lesions are fully removed
- Surgical margin status
- Residual tumor (R) classification
- Hospital stay after surgery (days)
- The duration of surgery (hours)
- The number (percentage) of patients with delayed surgery and reason.

Patient data listings of surgery withdrawal and delay information will be provided.

6.7. Biomarker Analysis

For the analysis of the biomarker endpoint, which is pharmacodynamic biomarker change (e.g., T-reg 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 logistic regression for binary endpoint, and Cox proportional hazards model for survival endpoints.

These analyses and the results of these analyses may be conducted and reported separately from the CSR.

6.8. Pharmacokinetic Analyses

Serum/plasma concentration data will be tabulated and summarized by visit/cycle at which these concentrations are collected. Descriptive statistics will include mean, median, range, standard deviation, coefficient of variation (CV), geometric mean and geometric CV, as appropriate.

Additional PK analyses may be carried out if supported by data. Additional PK analyses, including population PK analyses and exposure-response analyses (efficacy or safety endpoints), may be conducted as appropriate.

These analyses and the results of these analyses may be conducted and reported separately from the CSR.

6.9. Immunogenicity Analyses

Antidrug Antibody (ADA) samples will be collected for tislelizumab and protein therapeutic investigational agents in this study as outlined in protocol. The scope of ADAs calculations used for characterizing clinical immunogenicity depends on the incidence and kinetics of detected ADA. Therefore, not all parameters described below will be derived or additional parameters may be added. The effect of immunogenicity on PK, efficacy, and safety may be evaluated if data allows.

The immunogenicity results will be summarized using descriptive statistics by the number and percentage of patients who develop detectable ADAs. The incidence of positive and neutralizing ADAs (as applicable) will be reported for ADA-evaluable subjects according to the following definitions:

- **ADA-evaluable subject:** Number of subjects with reportable non-missing baseline result and at least one reportable sample taken after drug administration during the treatment or follow-up observation period with reportable result (used for computing treatment induced ADA incidence).
- **Treatment-emergent ADA:** The sum of both treatment-boosted and treatment-induced ADA-positive subjects as a proportion of the evaluable subject population. Synonymous with "ADA Incidence".
- **Treatment-induced ADA:** ADA-evaluable subjects that were ADA-negative at baseline and ADA-positive following administration of biologic product.
- **Treatment-boosted ADA**: Baseline-positive ADA-evaluable subjects with significant increases (4-fold or higher) in ADA titer after biologic drug administration. Baseline positive ADA-evaluable subject is an ADA-evaluable subject with positive ADA result at baseline.
- **Persistent ADA:** Treatment-induced ADA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period of 16 weeks or longer, or treatment induced ADA incidence only in the last sampling time point of the treatment study period or at a sampling time point with less than 16 weeks before an ADA-negative last sample.
- **Transient ADA:** Treatment-induced ADA that is not considered as persistent ADA.
- **Neutralizing ADA:** patients with positive NAb.

These analyses and the results of these analyses may be conducted and reported separately from the CSR.

7. INTERIM ANALYSES

No formal interim analysis is planned.

8. CHANGES IN THE PLANNED ANALYSIS

Not Applicable.

9. REFERENCES

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Mantel N, Haenszel W. Statistical Aspects of Analysis of Data from Retrospective Studies of Disease. Journal of the National Cancer Institute. 1959;22:719–748.

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APPENDIX 1. IMPUTATION OF MISSING OR PARTIALLY MISSING DATES

In general, missing or partial dates will not be imputed at the data level. The following rules will apply for the specific analysis and summary purposes mentioned below only.

Please note: all the imputed date should be prior to/or by last known alive date. The last known alive date only is based on complete dates without imputation.

1. **Prior/Concomitant Medications/Procedures**

When the start date or end date of medication is partially missing, the date will be imputed to determine whether the medication is prior or concomitant. The following rules will be applied to impute partial dates for medications:

If the start date of medication is partially missing, impute as follows:

- If both month and day are missing, then set to January 01
- If only day is missing, then set to the first of the month

If the end date of medication is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month

If the year of start date or year of end date of a medication/procedures is missing, or the start date or end date is completely missing, do not impute.

If the imputed of a medication end date > last known alive date or end of study date, then set to the last known alive date or end of study date, whichever occurs first.

2. **Adverse Events**

The imputation rule for the safety analyses will be used to address the issues with partial dates. When the start date or end date of an adverse event is partially missing, the date will be imputed to determine whether the adverse event is treatment-emergent. When in doubt, the adverse event will be considered treatment-emergent by default. The following rules will be applied to impute partial dates for adverse events:

If the imputed AE start date is after AE end date (maybe imputed), then update AE start date with AE end date as final imputed AE start date.

If the end date of an AE is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month
- If the imputed AE end date >min(death date, end of study date), then set to min(death date, end of study date)
- If the year of the end date is completely missing, do not impute.

If the start date of an adverse event is partially missing, impute as follows:

- If both month and day are missing and year = year of treatment start date, then set to treatment start date
- If both month and day are missing and year ≠ year of treatment start date, then set to January 01
- If day is missing and month and year = month and year of treatment start date, the set to treatment start date
- If day is missing and month and year ≠ month and year of treatment start date, the set to first of the month
- If the imputed AE start date is after AE end date (maybe imputed), then update AE start date with AE end date as final imputed AE start date
- If the imputed end date > min (death date, end of study date), then set to min(death date, end of study date)

3. **Impute partial dates related to disease history and prior therapy (Drug, surgery/procedure, radiotherapy)**

The following rules will be applied to impute partial dates such as initial diagnosis date, initial BCLC staging date, relapse date, therapy date (start/end date), or surgery date etc.

Impute end date first. If end date is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to the last day of the month
- For prior systemic therapy for cancer, if imputed end date > randomization date-14 days, then set to randomization date – 14 days.

If start date is partially missing, impute as follows:

- If both month and day are missing, then set to January 01
- If only day is missing, then set to the first of the month
- If the imputed start date > end date, then set to the end date

If the year of start date or year of end date of a medication/therapy/procedure is missing, or the start date or end date is completely missing, do not impute.

4. **Subsequent Anti-cancer Therapies**

If start date of subsequent anti-cancer therapy is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month
- If the imputed start date > min (death date, study discontinuation date, data cutoff date, start date of the next subsequent anti-cancer therapy), then set to min (death

date, study discontinuation date, data cutoff date, start date of the next subsequent therapy)

If stop date of is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month
- If the imputed stop date > min (death date, study discontinuation date, data cutoff date, start date of the next subsequent anti-cancer therapy), then set to min (death date, study discontinuation date, data cutoff date, start date of the next subsequent therapy)

The (imputed) stop date must be after or equal to the (imputed)start date

If year of the start date/stop date is missing, do not impute.

APPENDIX 2. ACTUAL DOSE INTENSITY, PLANNED DOSE, and RELATIVE DOSE INTENSITY CALCULATION for CHEMOTHERAPY

	ADI (mg/mL/min/cycle for carboplatin and mg/m^2/cycle for rest)	Planned dose per cycle	RDI
Cisplatin	$\frac{\sum_1^{\#of\ cycles} \frac{actual\ dose}{BSA*} \times 21}{date\ of\ last\ dose\ up\ to\ cutoff + 21 - first\ dose\ date}$	75 mg/m^2	ADI/75
Carboplatin	$\frac{\sum_1^{\#of\ cycles} \frac{actual\ dose}{GFR + 25} \times 21}{date\ of\ last\ dose\ up\ to\ cutoff + 21 - first\ dose\ date}$	5 mg/mL/min	ADI/5
Premetrexed	$\frac{\sum_1^{\#of\ cycles} \frac{actual\ dose}{BSA*} \times 21}{date\ of\ last\ dose\ up\ to\ cutoff + 21 - first\ dose\ date}$	500 mg/m^2	ADI/500
Paclitaxel	$\frac{\sum_1^{\#of\ cycles} \frac{actual\ dose}{BSA*} \times 21}{date\ of\ last\ dose\ up\ to\ cutoff + 21 - first\ dose\ date}$	175 mg/m^2	ADI/175

* To derive BSA at each visit is to use baseline weight unless weight change for one visit is at least 10% greater compared to baseline weight. The general principle is to employ the same drug administration rule as the one specified in the protocol.

The planned dose of chemotherapy is adjusted based on body surface area and glomerular filtration rate. The detailed calculation is specified below:

- BSA_i: Body surface area on i^{th} cycle of chemotherapy. BSA_1 is the BSA at baseline.

  $$\text{BSA}_i(m^2) = 0.0061 * \text{Height}_1 + 0.0128 * \text{Weight}_i\text{-}0.1529$$

  where $\text{Height}_i$is the latest height (centimeter) before and on cycle *i* dosing date, and weight_i is the body weight (kilogram) is the latest weight before and on cycle I dose date.

- GFR_i: Glomerular filtration rate on i^{th} cycle of chemotherapy. GFR_1 is the GFR at baseline.
  - Male: $\text{GFR}_i = (140 - \text{Age}_i) * \text{Weight}_i/(0.81 * \text{SCr}_i)$;
  - Female: $\text{GFR}_i = 0.85 * (140 - \text{Age}_i) * \text{Weight}_i/(0.81 * \text{SCr}_i)$;

  Where SCr_i(Serum Creatinine Concentration) is the latest test result before and on cycle *i* dosing date in μmol/L; $\text{Age}_i = \text{year of SCr}_i \text{ test date} - \text{year of birth} + 1$

- Weight_i: Body weight (kilogram) on i^{th} cycle of chemotherapy. Weight_1 is the weight at baseline.
  - For Cisplatin, Paclitaxel or Pemetrexed, the planned dose for k^{th} cycle is $\text{BSA}'_\text{i} *$ standard dose, where $\text{BSA}'_\text{i} = \text{BSA}_1$ if $(\text{Weight}_\text{i} - \text{Weight}_1)/\text{Weight}_1 < 10\%$; otherwise, $\text{BSA}'_\text{i} = \text{BSA}_\text{i}$.

For carboplatin, the plan dose for k^{th} cycle is $(\mathrm{GFR}_i^{'} + 25) * \text{standard dose}$, where $\mathrm{GFR}_i^{'} = \mathrm{GFR}_1$ if $(\mathrm{Weight}_i - \mathrm{Weight}_1)/\mathrm{Weight}_1 < 10\%$; otherwise, $\mathrm{GFR}_i^{'} = \mathrm{GFR}_i$.