STATISTICAL ANALYSIS PLAN

Study Protocol Number: AdvanTIG-205

Study Protocol Title: AdvanTIG-205: A Phase 2, Randomized Study of Ociperlimab (BGB-A1217) and Tislelizumab With Chemotherapy in Patients With Previously Untreated Locally Advanced, Unresectable, or Metastatic Non-Small Cell Lung Cancer (NSCLC)

Date: 06Jun2024

Version: 2.0

[redacted]

[redacted]

[redacted]

Document History

Revision	Effective Date	Brief Description of Change
1.0	Mar 2nd, 2023	Original version
2.0	Jun 6th, 2024	Abbreviated analyses according to study closeout plan, including (not exhausted list): Remove all COVID-19 related analyses; Remove all efficacy sensitivity analyses; Adjustment in variables of subgroup analysis; Adjustment in PFS analysis to align with compound SDD; Remove exploratory analyses of HRQoL; Simplify analyses of imAE, IRR and lab; Add flexible wordings or remove some safety listings; Other minor adjustments and clarifications.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ADA	Antidrug antibody
AE	Adverse event
ALK	Anaplastic lymphoma kinase
AUC	Area under the curve
BOR	Best overall response
CBR	Clinical benefit rate
CI	Confidence interval
CL	Clearance
C_{max}	Maximum observed plasma concentration
C_{min}	Minimum observed plasma concentration
CR	Complete response
CSR	Clinical Study Report
ctDNA	circulating tumor DNA
DCR	Disease control rate
DOR	Duration of response
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report form
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30

EOT	End of treatment
GEP	gene expression profiling
HR	Hazard ratio
HRQoL	Health-related quality of life
ICH	International Conference on Harmonisation
imAE	Immune-mediated adverse event
IRT	Interactive response technology
IRR	Infusion related reaction
ITT	Intent-to-Treat
IV	Intravenous
LLN	Lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NA	Not assessable
NAb	Neutralizing antibody
NE	Not evaluable
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-L1	programmed cell death ligand-1
PFS	Progression-free survival
PK	Pharmacokinetic(s)

PR	Partial response
PRO	Patient-reported outcomes
RECIST	Response Evaluation Criteria in Solid Tumors
ROS1	c-ROS oncogene-1
ROW	Rest of world
Q3W	Once every 3 weeks
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SOC	System Organ Class
$T_{1/2}$	Elimination half-life
T_{max}	Time to maximum plasma concentration
TA	Tumor assessment
TD	Treatment duration
TEAE	Treatment-emergent adverse event
TC	Tumor cells
TIGIT	T-cell immunoglobulin and ITIM domain
TIL	Tumor infiltrating immune cells
TMB	Tumor mutation burden
TTR	Time to response
QLQ-LC13	Quality of Life Questionnaire-Lung Cancer 13
QTcF	Fridericia's correction formula
ULN	Upper limit of normal

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and statistical methods that will be used to analyze and report results for Study AdvanTIG-205: A Phase 2, Randomized Study of Ociperlimab (BGB-A1217) and Tislelizumab With Chemotherapy in Patients Previously Untreated Locally Advanced, Unresectable or Metastatic Non-Small Cell Lung Cancer (NSCLC). This SAP is developed based on AdvanTIG-205 Protocol Amendment 4.0, dated on January 30, 2024. The focus of this SAP is the planned analysis specified in the study protocol. Separate analysis plans for Pharmacokinetic (PK), Pharmacodynamics, Pharmacogenomics and Biomarker analyses that are not described within this SAP may be prepared as needed.

2 STUDY OVERVIEW

2.1 STUDY DESIGN

This is a randomized, investigator- and patient-blinded, sponsor-unblinded, multicenter, Phase 2 study designed to evaluate the efficacy and safety of ociperlimab in combination with tislelizumab and histology-based chemotherapy versus placebo in combination with tislelizumab and histology-based chemotherapy in patients with previously untreated locally advanced, unresectable, or metastatic NSCLC that does not harbor epidermal growth factor receptor (EGFR) mutations, anaplastic lymphoma kinase (ALK) translocations, BRAF V600E mutations, or c-ROS oncogene-1 (ROS1) mutations.

Approximately 270 patients will be enrolled. Eligible participants will be randomized in a 1:1 ratio to receive ociperlimab + tislelizumab + chemotherapy (Arm A) or placebo + tislelizumab + chemotherapy (Arm B). Randomization will be stratified by PD-L1 expression (three levels: < 1% TC versus 1% to 49% TC versus ≥ 50% TC), and histology (squamous versus non-squamous).

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

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

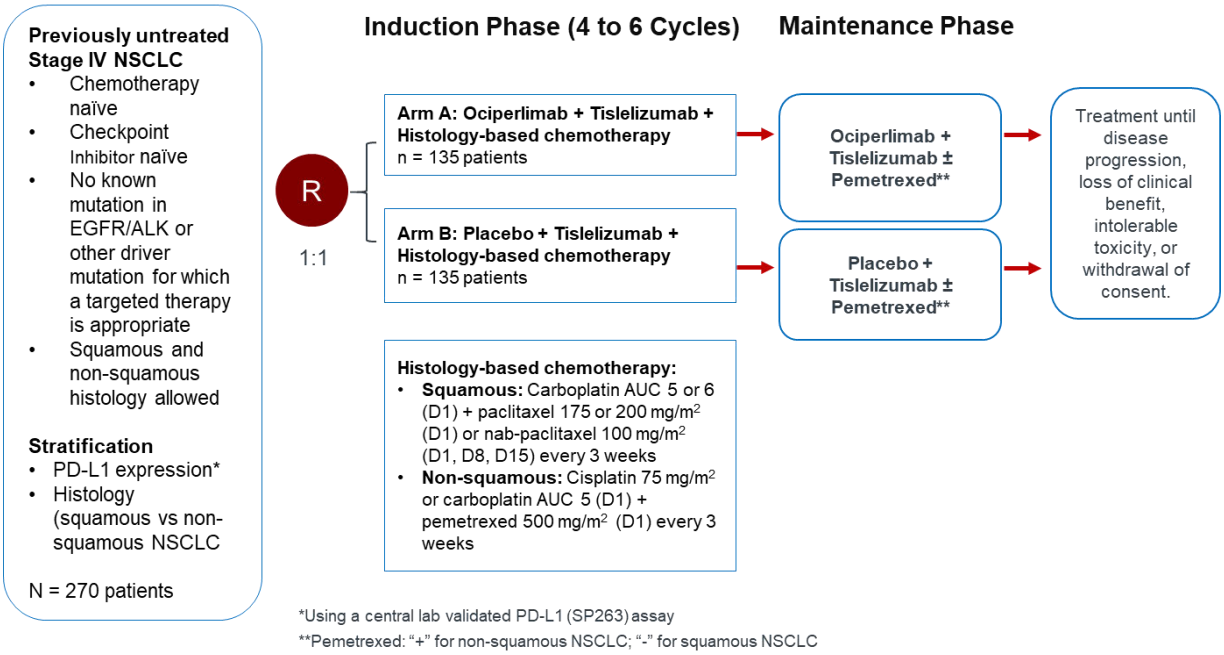
During the maintenance phase, study treatments will be given as follows:

- For patients with non-squamous NSCLC:

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

The study design schema is presented in Figure 1.

Figure 1: Study Schema



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

2.2 STUDY ASSESSMENTS

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

progression or death, withdraws consent, is lost to follow-up, or until the study terminates, whichever occurs first.

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

Safety will be assessed throughout the study by monitoring AEs/SAEs (toxicity grades assigned per NCI-CTCAE v5.0 and laboratory results. Vital signs, physical examinations, ECOG Performance Status change, electrocardiogram (ECG) results, and other examinations will also be used for safety assessment. After initiation of the study drug(s), all AEs and SAEs, regardless of the relationship to the study drug(s), will be reported until either 30 days after last dose of study drug(s) (including chemotherapy) or the initiation of new anticancer therapy, whichever occurs first. Immune-mediated AEs (serious or non-serious) should be reported until 90 days after the last dose of ociperlimab (or placebo) and/or tislelizumab, regardless of whether or not the patient starts a new anticancer therapy. All SAEs considered related to the study drugs that are brought to the attention of the investigator should be reported regardless of time since the last dose of treatment.

3 STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVES

- To compare progression-free survival (PFS) in Arm A and Arm B in the Intent-to-Treat (ITT) Analysis Set, as assessed by investigators per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)

3.2 SECONDARY OBJECTIVES

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

3.3 EXPLORATORY OBJECTIVES

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

4 STUDY ESTIMAND

4.1 PRIMARY ESTIMAND

Primary clinical question of interest: "Will the addition of ociperlimab to tislelizumab in combination with histology-based chemotherapy prolongs time to death/progression in patients with previously untreated locally advanced, unresectable, or metastatic NSCLC that does not harbor EGFR mutations, ALK translocations, BRAF V600E mutations, or ROS1 mutations as first line treatment, had patients not been treated with prior systemic anticancer therapy?"

The primary estimand is described by the following attributes:

1. Treatment of interest:
   Experimental treatment constitutes ociperlimab plus tislelizumab plus histology-based chemotherapy. Control treatment constitutes placebo plus tislelizumab plus histology-based chemotherapy

2. Population:
   All patients with previously untreated locally advanced, unresectable, or metastatic NSCLC that does not harbor EGFR mutations, ALK translocations, BRAF V600E mutations, or ROS1 mutations.

3. Primary variable:
   PFS as assessed by investigator

4. Handling of intercurrent events:
   - Discontinuation of treatment: tumor assessment data collected after discontinuation of study treatment will be used for analysis (treatment policy strategy)
   - New anticancer therapy started prior to disease progression or death: PFS will be censored at the last adequate disease assessment before the new anticancer therapy (hypothetical strategy)

5. Population-level summary:
   Hazard ratio (HR) of PFS and its 95% CI will be estimated from a Cox model stratified by PD-L1 expression (three levels: < 1% TC versus 1% to 49% TC versus ≥ 50% TC) and histology (squamous versus non-squamous NSCLC).

5 STUDY ENDPOINTS

5.1 PRIMARY ENDPOINTS

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

5.2 SECONDARY ENDPOINTS

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

5.3 EXPLORATORY ENDPOINTS

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

6 SAMPLE SIZE CONSIDERATIONS

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

Table 1: Hazard Ratio and Median PFS Assumption, Number of Events, Alpha and Power in the Primary Hypothesis Test

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

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

7 STATISTICAL METHODS

7.1 ANALYSIS SETS

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

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

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

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

7.2 DATA ANALYSIS GENERAL CONSIDERATIONS

7.2.1 Definitions and Computations

Study day:

For analysis of efficacy and baseline characteristics, study day will be calculated with reference to the date of randomization date, unless otherwise specified. For safety analysis, study day will be calculated with reference to the first dose date. For assessments conducted on or after the date of randomization/first dose date, study day will be calculated as (assessment date – randomization/first dose date + 1). For assessments conducted before randomization/first dose date, study day is calculated as (assessment date – randomization/first dose date). 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.

Baseline Measurements:

- For efficacy evaluation: a baseline value is defined as the last non-missing value collected prior to the randomization.
- For non-efficacy evaluation: a baseline value is defined as the last non-missing value prior to the first study drug administration; if no study drug was given, then defined as the last non-missing value prior to the randomization date.

- 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: 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 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.

7.2.2 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 round to 0.0000 will be presented as '< 0.0001' and p-values that round to 1.000 will be presented as '> 0.9999'.
- Time-to-event or duration of event endpoints will be based on the actual date which the radiograph was obtained rather than the associated visit date.
- Missing efficacy or safety data will not be imputed unless otherwise specified.
- 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).

7.2.3 Handling of Missing or Partial Data

Handling of missing data related to primary estimand will be further elaborated in Section 7.4.1. Missing dates or partially missing dates will be imputed conservatively for adverse events and prior/concomitant medications/procedures. Specific rules for handling of missing or partially missing dates for adverse events and prior/concomitant medications/procedures are provided in Appendix 1. Other missing data will not be imputed unless otherwise specified elsewhere in the SAP.

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.

7.2.4 Stratification and Adjustments for Covariates

The value of the stratification factors used at randomization (from Interactive Response Technology [IRT]), including PD-L1 expression (three levels: < 1% TC versus 1% to 49% TC versus ≥ 50% TC) and histology (squamous versus non-squamous NSCLC), will be used in stratified log-rank test and stratified Cox proportional hazard model for primary endpoint PFS, and secondary endpoints OS. For PFS and OS analyses, if the number of events in any stratification cell is low, this cell will be pooled with other adjacent cells. Similarly, these stratification factors will be used in Cochran-Mantel-Haenszel method to analyze ORR. The actual value of the stratification factors (collected in eCRF) and other baseline covariates may be used in the model as covariates as supportive analyses for endpoints.

7.2.5 Multiplicity Adjustment

The type I error will be strongly controlled at 0.025 (1-sided) in the primary analysis of PFS in the ITT analysis set. Only when the superiority of PFS in the ITT analysis set has been demonstrated, its alpha of 0.025 (1-sided) will be shifted sequentially to the hypothesis testing of the secondary endpoints in the order of ORR in the ITT analysis set, followed by OS in ITT analysis set. The inferential test will be stopped at the first non-significant endpoint. Nominal p-values may be computed for other efficacy analyses but should be interpreted with caution. Analyses using nominal p-values will be indicated as such.

7.2.6 Data Integrity

Before any pre-specified statistical analysis begins, the integrity of the data should be reviewed to assure fit-for-purpose. The data set for analysis should be an accurate and complete representation of the patients' relevant outcomes from the clinical database. All data should be complete and reviewed up to a pre-specified cutoff date as specified in the Data Extract and Snapshot Plan. Consistency checks and appropriate source data verification should be completed as specified in the Site Monitoring Plan. For details, refer to the study data integrity protection plan.

7.3 SUBJECT CHARACTERISTICS

7.3.1 Subject Disposition

The number (percentage) of patients randomized, treated, discontinued from treatment and discontinued from the study will be summarized. The primary reason for end of treatment (treatment discontinuation) and end of study (study discontinuation) will be summarized by categories. Study follow up duration will be summarized descriptively.

7.3.2 Protocol Deviations

Protocol deviation criteria will be established together with its category/term of important and not important. Patients with important protocol deviations will be identified and documented before the database lock. Important protocol deviations will be summarized for all patients in the ITT analysis set.

7.3.3 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized in the ITT Analysis Set using descriptive statistics. Continuous variables will be summarized using number of patients, mean, standard deviation, median, minimum, Q1, Q3 and maximum. Categorical variables will be summarized using number of patients and percentage in relevant categories.

Demographic and other baseline characteristics include:

- Age
- Age group (≤ 65 vs > 65 years)
- Sex
- Race
- Ethnicity
- Geographical region (Asia vs ROW)
- Country
- Weight (kg)
- Height (cm)
- BSA (m^2)
- BMI (kg/m^2)
- ECOG performance status at study entry
- Smoking status (never vs current vs former)

7.3.4 Disease History and Baseline Disease Characteristics

The following disease history and baseline disease characteristics will be summarized in ITT population:

- Time since initial cancer diagnosis to randomization date
- Disease stage at study entry
- PD-L1 expression (three levels: < 1% TC vs 1% to 49% TC vs ≥ 50% TC)
- Histological tumor differentiation grade
- Histology (squamous versus non-squamous NSCLC)
- Metastatic disease status at study entry
- Time from metastasis to randomization date
- Location of distant metastases at study entry

In addition, the stratification factors histology (squamous vs non-squamous NSCLC) and PD-L1 expression (< 1% TC vs 1% to 49% TC vs ≥ 50% TC) per IRT versus per eCRF will be tabulated based on ITT population. If there are multiple PD-L1 expression value collected per eCRF, the value from central lab will be used.

7.3.5 Prior Anti-Cancer Therapies and Surgeries

The number of patients receiving prior anti-cancer systemic therapies, prior anti-cancer radiotherapy and prior anti-cancer surgery will be summarized. The therapies with the same sequence/regimen number are counted as one prior therapy. The treatment setting, best overall response of the last prior systemic therapy and time from the end of the last prior systemic therapy to randomization. The sites irradiated and the treatment intent and treatment setting of the last prior radiotherapy will be summarized.

7.3.6 Prior and Concomitant Medication

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO DD) drug codes and will be further classified to the appropriate Anatomical Therapeutic Chemical (ATC) code.

The number (percentage) of patients reporting prior and concomitant medications will be summarized by ATC medication class and WHO DD preferred term in the Safety Analysis Set. Prior medications are defined as medications that stopped before the first dose date. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 days after the patient's last dose.

7.3.7 Medical History

Medical history/current medical conditions will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) terminology available at the time of the analyses. The number (percentage) of patients reporting a history of any medical condition, as recorded on the eCRF, will be summarized by system organ class and preferred term in the ITT Analysis Set.

7.3.8 Subsequent Anti-Cancer Therapy

Subsequent anti-cancer therapy is defined as the anti-cancer therapy started after the last dose of study drug(s). A summary of number and percentage of patients who received subsequent systematic anticancer therapy will be provided by treatment arm based on ITT analysis set.

Separate flags of start date of new anti-cancer therapy for efficacy and safety analyses are derived individually.

- As for efficacy analysis, the start date of new anti-cancer therapy will be the earliest date of prohibited anti-cancer therapy taken during treatment, date of the post-treatment systemic anti-cancer therapy and date of other anti-cancer therapy such as post-treatment surgery and radiotherapy as deemed appropriate.
- For non-efficacy analysis, the start date of new anti-cancer therapy is always the first date of new systemic anti-cancer therapy taken after the last study treatment.

Tumor response per RECIST v1.1 or event driven endpoints have not been commonly used for the efficacy evaluation of traditional Chinese medicine. ORR, PFS or OS benefit of Chinese herbal medicines or Chinese patent medicines has not yet been established. Therefore, they will not be taken into account as new anti-cancer therapy in the efficacy and safety analyses.

7.4 EFFICACY ANALYSIS

PFS is the primary endpoint in this study. The primary analyses will be performed when approximately 194 PFS events are observed.

7.4.1 Primary Efficacy Endpoint

The primary estimand is defined in Section 4. Details of the statistical methods used in the derivation and analysis are provided in this section including pre-defined sensitivity analyses of the primary estimand.

Variable

PFS is defined as the time from the randomization date to disease progression or death, whichever occurs first. Clinical or symptomatic progressions without supportive radiologic data will not be considered as PFS events. PFS will be censored at the last adequate tumor assessment if one of the following occurs: absence of event; the event occurred after a new anticancer therapy is given; the event occurred after two or more consecutive tumor assessments. **Table 2** shows the derivation rules for PFS. The algorithm to identify missing TAs are presented in Appendix 2.

Table 2: Censoring Rules for Progression-free Survival Per RECIST Version 1.1

No.	Situation	Date of Progression or Censoring	Outcome
1	No baseline or any post-baseline tumor assessments and without death within 19 weeks from date of first dose of study drug(s)	Date of randomization date	Censored
2	Progression documented between scheduled visits	Date of first radiologic PD assessment	Event
3	No progression at the time of data cut-off or withdrawal from study	Date of last adequate radiologic assessment prior to or on date of data cut-off or withdrawal from study	Censored
4	New anticancer treatment started	Date of last adequate radiologic assessment prior to or on date of new anticancer treatment	Censored
5	Death before first PD assessment	Date of death	Event
6	Death between adequate assessment visits*	Date of death	Event

7	Death or progression after more than one missed visit**	Date of last adequate radiologic assessment before missed tumor assessments	Censored
8	No baseline or any post-baseline tumor assessments and died within 19 weeks from date of first dose of study drug(s)	Date of death	Event

*Adequate tumor assessment is a radiologic assessment of CR, PR, SD, non-CR/non-PD, or PD by investigator.
** More than one missed visit is defined if the duration between the last tumor assessment and death or PD is longer than D2. The D2 is defined as two times protocol specified interval between tumor assessments (TAs) plus the protocol allowed window around the assessments. Since tumor assessment is scheduled as once every 9 weeks for first 52 weeks and once every 12 weeks afterwards with one-week window, D2 is 18 weeks + 1 week in the first 52 weeks and 24 weeks + 1 week afterwards.
Progression date for PFS event will be the earliest date of events defined in 2,5,6,8.

Primary efficacy analysis

Progression Free Survival (PFS) by investigators in the ITT analysis set

The null hypothesis (H_0) to be tested is:

H_0: PFS in Arm A ≤ PFS in Arm B

against the alternative hypothesis (H_1):

H_1: PFS in Arm A > PFS in Arm B

The primary comparison of PFS will be conducted by a stratified log-rank test, using stratification factors of PD-L1 expression (three levels: < 1% TC versus 1% to 49% TC versus ≥ 50% TC) and histology (squamous versus non-squamous NSCLC). This will be the primary analysis once approximately the targeted PFS event number is reached. A significance level of 1-sided alpha of 0.025 will be used in the PFS testing.

PFS as assessed by the investigators per RECIST v1.1 will be estimated using the Kaplan-Meier method in the ITT Analysis Set. The median PFS and 2-sided 95% CI using the method of Brookmeyer and Crowley will be summarized. The cumulative probability of PFS at every 6 months including PFS rate at 6 and 12 months, if estimable, will be calculated for each treatment arm and presented with 2-sided 95% CIs. Standard error for PFS rates will be calculated based on Greenwood's formula. Kaplan-Meier survival probabilities for each arm will be plotted over time.

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

7.4.2 Secondary Efficacy Endpoints

Objective Response Rate

Best overall response (BOR) is defined as the best response recorded from randomization until data cut or the start of new anticancer treatment. The proportion and its corresponding Clopper-Pearson 95% CI for each of the response categories (CR, PR, SD, and PD) will be presented by treatment arm.

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

Overall Survival

Overall survival is defined as 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. The last known alive date will be defined as either the clinical data cutoff date for patients who are still on treatment, or last available date showing patients alive or cut-off date whichever comes first for other alive patients.

Every effort should be made to ensure complete death dates. In the rare case, if day of death date is missing, death date is imputed as the max (last available date showing patient was alive + 1, first day of year/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 patients will be censored at last available date showing that the patient was alive + 1.

The censoring rules for the primary analysis of OS are presented in **Table 3**.

Table 3: Censoring Rules for Primary Analysis of Overall Survival

	Derivation rules	**Outcome**
Intercurrent events		
New anticancer therapy started prior to death	Ignored (treatment policy strategy)	No impact
Patients' withdrawal from the study or loss to follow up	Last known alive date prior to withdrawal. (hypothetical strategy)	Censored
Missing values not related to intercurrent events		
Missing visits	Ignored	No impact

OS will be compared between ociperlimab + tislelizumab + chemotherapy (Arm A) and placebo + tislelizumab + chemotherapy (Arm B) in a 1-sided, stratified log-rank test using stratification

factors of PD-L1 expression (three levels: < 1% TC versus 1% to 49% TC versus ≥ 50% TC) and histology (squamous versus non-squamous NSCLC).

OS will be estimated using the Kaplan-Meier method in the ITT Analysis Set. The median OS and 2-sided 95% CI using the method of Brookmeyer and Crowley will be summarized. The cumulative probability of OS at every 6 months including OS rate at 12 months and 24 months if estimable, will be calculated for each treatment arm and presented with 2-sided 95% CIs. Standard error for survival rates will be calculated based on Greenwood's formula. Kaplan-Meier survival probabilities for each arm will be plotted over time.

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

Duration of Response

Duration of Response (DOR) is defined as progression/death event free time counted from the first objective response date to the first documented radiological PD date/or death date, whichever occurred first. All the censoring rules for PFS will be applied to DOR too. DOR assessed by investigators will be analyzed in the responders only. The median DOR and the cumulative probability of DOR estimated at every 3 months will be calculated using Kaplan-Meier estimates for each treatment arm and presented with 2-sided 95% CIs computed by Brookmeyer and Crowley method using the log-log transformation. No formal testing will be performed to compare DOR between two treatment group as it would be based on a non-randomized subgroup.

Waterfall plots will be provided for the maximum tumor shrinkage based on target lesions. In addition, patients will be flagged in the plot if the percentage change in the sum of diameters of target lesions reflects a non-PD target lesion response but a worsening of non-target lesions or the appearance of a new lesion results in an overall lesion response of PD.

7.4.3 Subgroup Analyses

To determine if the treatment effect is consistent across various subgroups, the median PFS/OS in each subgroup along with unstratified hazard ratio estimates and its 95% CI will be estimated and plotted within each category of the following variables:

- Geographical region (Asia vs ROW)
- Age group (≤ 65 vs > 65 years)
- Sex (Female vs Male)
- Baseline ECOG PS (0 vs 1)
- Histology (squamous vs non-squamous NSCLC)
- PD-L1 expression (< 1% TC vs 1% to 49% TC vs ≥ 50% TC)
- Smoking status (Never vs Current or Former)
- Brain metastasis (Yes vs No)
- Liver metastasis (Yes vs No)
- Number of metastasis sites (<3 vs >=3)

The unstratified risk difference in ORR and its 2-sided 95% CI will be calculated, as well as Clopper- Pearson 95% CIs of ORR for each treatment arm according to aforementioned variables.

7.4.4 Exploratory Efficacy Endpoints

Disease control rate (DCR), clinical benefit rate (CBR) and time to response (TTR)

Disease control rate (DCR) is defined as the proportion of patients whose BOR is CR, PR, or SD. Clinical benefit rate (CBR) is defined as the proportion of patients who have CR, PR, or SD of ≥ 24 weeks in duration. DCR and clinical benefit rate (CBR) assessed by investigators will be analyzed similarly to ORR in the ITT analysis set.

Time to response (TTR) will be summarized using descriptive statistics, such as mean, median, and standard deviation. Only patients who have achieved an objective response will be included in the analysis of TTR.

7.5 SAFETY ANALYSES

Safety will be assessed by monitoring and recording of all AEs graded by NCI-CTCAE v5.0. Laboratory values (e.g., hematology, clinical chemistry), vital signs, ECGs, and PEs, will also be used in determining safety. Descriptive statistics (e.g., n, mean, standard deviation, median, Q1, Q3, minimum, maximum for continuous variables; n [%] for categorical variables) will be used to analyze all safety data in the safety analysis set.

7.5.1 Extent of Exposure

The following exposure parameters will be summarized with descriptive statistics for each study drug. Specifically:

Treatment duration (TD, days) for ociperlimab/placebo, tislelizumab, carboplatin, paclitaxel, nab-paclitaxel, and pemetrexed: The treatment duration will be calculated as (last date of exposure – date of first dose + 1).

- If patients discontinue treatment (with non-missing EOT date), last date of exposure = min (last dose date + 20, death date, clinical data cutoff date) for ociperlimab/placebo, tislelizumab, carboplatin, paclitaxel, and pemetrexed; last date of exposure = min (the first day of the last cycle + 20, death date, clinical data cutoff date) for cisplatin and nab-paclitaxel.
- Otherwise if patient has treatment ongoing, last date of exposure = clinical data cutoff date for calculation of TD

Total Cumulative Dose is calculated as the sum of all actual dosages per administration at all visits prior to the clinical data cutoff date.

Total number of cycles
Total number of cycles is defined as the total number of cycles with non-missing doses.

Actual dose intensity (ADI), planned dose and relative dose intensity (RDI)

Actual Dose Intensity (ADI) for ociperlimab/placebo and tislelizumab (mg/cycle) = 21 * total cumulative dose (mg) / (last dose date prior to cutoff date + 21 – first dose date).

Planned Dose Intensity for ociperlimab/placebo (mg/cycle) = 900 mg/cycle and for tislelizumab (mg/cycle) = 200 mg/cycle.

Relative Dose Intensity (%) for ociperlimab/placebo and tislelizumab = Actual Dose Intensity / Planned Dose Intensity *100%.

The derivations of ADI, planned dose and RDI for chemotherapy drugs are shown in **Table 4**.

Table 4: ADI, Planned dose and RDI for Chemotherapy Drugs

	ADI (mg/mL/min/cycle for carboplatin and mg/m2/cycle for the rest)	Planned dose per cycle	RDI
Carboplatin	$\frac{\sum_1^{\#of\ cycles} \frac{actual\ dose}{eGFR+25} \times 21}{date\ of\ last\ dose\ up\ to\ cutoff + 21 - first\ dose\ date}$	as recorded on eCRF (5 or 6 mg/mL/min)	ADI/planned dose per cycle
Cisplatin	$\frac{\sum_1^{\#of\ cycles} \frac{actual\ dose}{BSA^*} \times 21}{date\ of\ first\ dose\ of\ last\ cycle\ up\ to\ cutoff + 21 - first\ dose\ date}$	75 mg/m^2	$\frac{ADI}{75}$
Paclitaxel	$\frac{\sum_1^{\#of\ cycles} \frac{actual\ dose}{BSA^*} \times 21}{date\ of\ last\ dose\ up\ to\ cutoff + 21 - first\ dose\ date}$	as recorded on eCRF (175 or 200 mg/m^2)	ADI/planned dose per cycle
nab-Paclitaxel	$\frac{\sum_1^{\#of\ cycles} \frac{actual\ dose}{BSA^*} \times 21}{date\ of\ first\ dose\ of\ last\ cycle\ up\ to\ cutoff + 21 - first\ dose\ date}$	100 mg/m^2	$\frac{ADI}{100}$
Pemetrexed	$\frac{\sum_1^{\#of\ cycles} \frac{actual\ dose}{BSA^*} \times 21}{date\ of\ last\ dose\ up\ to\ cutoff + 21 - first\ dose\ date}$	500 mg/m^2	$\frac{ADI}{500}$

* BSA will be calculated based on baseline height and baseline weight unless weight change for a visit is at least 10% greater compared to baseline weight as sqrt(height(cm)*weight (kg)/3600).

The number of patients with dose modifications which includes dose reductions (only applicable to chemotherapy drugs), dose delays (including dose missed) and infusion interruptions and their reasons will be summarized by counts and percentages according to study drug.

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

7.5.2 Adverse Events

The AE verbatim descriptions (Investigator's description from the eCRF) will be classified into standardized medical terminology using Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to MedDRA (Version 25.0 or higher) lower level term closest to the verbatim term. The linked MedDRA System Organ Class (SOC) and Preferred Term are also classified. All adverse event summaries are based on safety analysis set.

In this trial, a TEAE is defined as an AE that has an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to 30 days following study drug discontinuation or the initiation of new anti-cancer therapy, whichever occurs first. Only those AEs that were treatment emergent will be included in summary tables of TEAEs. All AEs, treatment-emergent or otherwise, will be presented in patient data listings.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by SOC and Preferred Term. A patient will be counted only once by the highest severity grade per NCI-CTCAE v 5.0 within an SOC and Preferred Term, even if the patient experienced more than 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 drug.

7.5.2.1 Treatment Emergent Adverse Event

An overall summary and separate summaries of the number (%) of patients with the below types of TEAE will be generated:

- All TEAEs
  - Treatment-related TEAEs by SOC and PT
- Serious TEAEs by SOC and PT
  - Treatment-related serious TEAEs by SOC and PT
- TEAEs with NCI-CTCAE grade ≥3 by SOC and PT
  - Treatment-related TEAEs with NCI-CTCAE grade ≥ 3 by SOC and PT
- TEAEs leading to death by SOC and PT
  - Treatment-related TEAEs leading to death by SOC and PT
- TEAEs leading to treatment discontinuation by SOC and PT
  - Treatment-related TEAEs leading to treatment discontinuation by SOC and PT
- TEAEs leading to dose modification by SOC and PT
  - Treatment-related TEAEs leading to dose modification by SOC and PT

7.5.2.2 Immune-mediated Adverse Event

Immune-mediated adverse events are of special interest and will be recorded until 90 days after discontinuation from Ociperlimab/placebo and/or tislelizumab. Immune-mediated adverse events will be summarized by category within a pre-defined list. The identification of immune-mediated adverse events will be described in immune-mediated adverse event charter.

An overall summary table and separate summaries of the following incidence of immune-mediated adverse events will be provided:

- Immune-mediated adverse events by category and maximum severity
- Immune-mediated adverse events by category, preferred term and maximum severity
- Immune-mediated adverse events leading to death by category and preferred term
- Immune-mediated adverse events leading to treatment discontinuation of ociperlimab/placebo or tislelizumab by category and preferred term

7.5.2.3 Infusion-related Reactions

The PT list of infusion-related reactions (IRRs) includes fever/pyrexia, chills/rigor, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness, hypertension, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, IRR, and transfusion reaction. The following process was used for the final determination of IRRs:

a. The investigator/site must have checked the IRR box on the AE eCRF.

b. The event term must have matched (or been equivalent) to the IRR terms listed above (such as fever or chills), with the exception of events that happened concurrently with one of the terms on this list (such as fever + back pain + chest pain – all would be included).

c. Only events that started on the day of an infusion or the day after an infusion were included.

For IRRs, a summary of incidence by SOC, PT and maximum severity will be provided.

7.5.2.4 Death

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

7.5.3 Laboratory Values

Clinical laboratory (e.g., hematology, serum chemistry, thyroid function, coagulation and urinalysis) values will be evaluated for each laboratory parameter by patient. Abnormal laboratory values will be flagged and identified as those outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be included in the CSR for this protocol. Hematology and serum chemistry laboratory results will be summarized for selected parameters described in **Table 5**.

Laboratory results will be summarized using Système International (SI) units, as appropriate. Hematology and serum chemistry laboratory parameters that are graded in NCI-CTCAE v.5.0 will be summarized by shifts from baseline NCI-CTCAE grade to maximum post-baseline grades. In the summary of laboratory parameters by NCI-CTCAE grade, parameters with NCI-CTCAE grading in both high and low directions (e.g., calcium, glucose, magnesium, potassium, sodium) will be summarized separately.

Laboratory parameters for potential Hy's Law for liver injury and abnormal thyroid function will also be summarized.

Table 5: Clinical Laboratory Parameters

Serum Chemistry	**Hematology**
Alkaline phosphatase	Hemoglobin
Alanine aminotransferase	Hematocrit

Aspartate aminotransferase	White blood cell count
Albumin	Neutrophil count
Total bilirubin	Lymphocyte count
Direct bilirubin	Platelet count
Blood urea nitrogen or urea	
Potassium	
Sodium	
Calcium	
Creatinine	
Glucose	
Lactate dehydrogenase	
Total protein	
Magnesium	
Phosphorus	
Chloride	

7.5.4 Vital Signs

Vital signs will be listed by patient and visit as appropriate.

7.5.5 Electrocardiograms (ECG)

12-lead ECG recordings are required at Screening, Safety Follow-up, and as clinically indicated. Patient listing of ECG will be provided for all ECG recordings as appropriate.

Abnormal post-baseline 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 for each visit by treatment group.

7.5.6 ECOG

A shift table from baseline to worst post-baseline in ECOG performance score will be summarized.

Patient listing of ECOG will be provided for all ECOG findings as appropriate.

7.6 PHARMACOKINETIC ANALYSES

Ociperlimab and tislelizumab PK concentrations following study drug administration will be summarized. PK parameters will not be characterized as only sparse samples were collected. Pharmacokinetic samples were collected as outlined in Appendix 1 of the clinical study protocol.

7.6.1 Reporting of Pharmacokinetic Concentrations for Descriptive Statistics

Ociperlimab (Arm A only) and tislelizumab (Arms A and B) serum concentration data will be tabulated and summarized by visit/cycle at which these concentrations are collected. Descriptive statistics will include means, medians, ranges, standard deviations, coefficient of variation (CV%), geometric means, and geometric CV%, as appropriate and will be based on the PK Analysis Set.

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

7.7 IMMUNOGENICITY ANALYSES

Samples to assess anti ociperlimab antibodies will be collected only in patients randomized to Arm A (ociperlimab in combination with tislelizumab and chemotherapy) while samples to assess anti tislelizumab will be collected in patients randomized to both arms. All anti-drug antibodies (ADA) summaries are based on the Immunogenicity Analysis set.

The scope of anti-drug antibodies calculations used for characterizing clinical immunogenicity depends on the incidence and kinetics of detected ADA. Therefore, not all parameters described below may be derivable.

The immunogenicity results will be summarized using descriptive statistics by the number and percentage of subjects who develop detectable ADAs for ociperlimab and tislelizumab separately. The effect of immunogenicity on PK, efficacy, and safety may be evaluated if data allows and will be reported separately from the CSR. The incidence of positive and neutralizing ADAs (as applicable) will be reported for ADA-evaluable patients according to the following definitions:

- **ADA-evaluable patient**: Number of patients 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 patients as a proportion of the evaluable patient population. This is synonymous with "**ADA Incidence**".
- **Treatment-induced ADA**: ADA-evaluable patients that were ADA-negative at baseline and ADA-positive after study drug administration during the treatment or follow-up observation period.
- **Treatment-boosted ADA**: Baseline-positive ADA-evaluable patients with significant increases (4-fold or higher) in ADA titer after study drug administration during the treatment or follow-up observation period. Baseline-positive ADA-evaluable patient is an ADA-evaluable patient 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.

- **Transient ADA**: Treatment-induced ADA detected only at one sampling time point during the treatment or follow-up observation period, or treatment-induced ADA detected at two or more time points during the treatment, where the first and last ADA-positive samples are separated by a period of less than 16 weeks, and the subject last sampling time point is ADA-negative.
- **Neutralizing ADA**: ADA-evaluable patients with positive neutralizing antibody (NAb).
- **ADA prevalence**: The proportion of all patients that are ADA positive, including pre-existing ADA, at any time point.

7.8 OTHER ANALYSIS

Distribution of PD-L1 expression will be examined in the ITT Population.

Potential association between PD-L1 expression and ociperlimab combined with tislelizumab and chemotherapy effect over tislelizumab combined with placebo and chemotherapy may be explored. Other potential predictive markers may be assessed. Such analyses will be reported separately from the CSR as appropriate.

8 INTERIM ANALYSIS

No formal interim analyses will be conducted, and no formal stopping rules have been specified per protocol for this study. Summaries of efficacy and safety data may be generated to inform subsequent clinical development planning.

9 CHANGES IN THE PLANNED ANALYSIS

The details of the revision have been documented and described in Statistical Analysis Plan v2.0.

10 REFERENCES

Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993 Mar 3;85(5):365-76.

Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials. EORTC Study Group on Quality of Life. Eur J Cancer. 1994;30A(5):635-42

National Cancer Institute Common Toxicity Criteria for Adverse Events Version 5.0. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf. Published 27 November 2017. Accessed 19 March 2021.

Eisenhauer EA, Therasse P, Bogaerts J Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-47.

Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A on behalf of the EORTC Quality of Life Group. EORTC QLQ-C30 Scoring Manual (3rd edition). Brussels: EORTC, 2001.

Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. Washington, DC: United States Food and Drug Administration; 2018.

Robins JM, Tsiatis A. Correcting for non-compliance in randomized trials using rank-preserving structural failure time models. Communications in Statistics. 1991;20: 2609-31.

11 APPENDIX

11.1 APPENDIX 1 IMPUTATION RULES FOR PARTIAL DATES

11.1.1 Impute partial dates for concomitant medication

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

If start date of a medication/therapy/procedure 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 > death date, then set to death date

If end date of a medication/therapy/procedure 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 end date > death date, then set to death 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.

11.1.2 Impute partial dates for adverse events

If year of the start date is missing or start date is completely missing, do not impute. Impute AE end date first if both AE start date and end date are partially missing.

If end date of an adverse event 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 end date > death date, then set to death date

If year of the end date is missing or end date is completely missing, do not impute. If 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 > death date, then set to death date.

11.1.3 Impute partial dates for subsequent anti-cancer surgery/procedure

When the start date of subsequent anti-cancer therapy is partially missing, the following rules will be applied to impute partial dates.

If start 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 end date > death date, then set to death date

If year of the start date is missing, do not impute. If imputed start date is after study discontinuation date, then set to study discontinuation date.

11.1.4 Impute partial dates for prior anti-cancer 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.

- If start date of a disease history or prior therapy 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 > first dose date then set to first dose date – 1

If end date of a disease history or prior 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 end date > first dose date, then set to first dose date -1

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.

11.2 APPENDIX 2 RULES FOR IDENTIFYING MISSING TUMOR ASSESSMENTS

Identifying two missing tumor assessment

1) Input scheduled TA visit list for each study
    a. 9wk-18wk-27wk-36wk-45wk-54wk-66wk- 78wk…
2) Identify last evaluable TA before PD or death (--LPTADT) and map it to the closest scheduled visit (--LPTADT_WK).
    a. In the event of unscheduled TA, choose the closest scheduled visit number (e.g. 9wk or 27wk) as –LPTADT_WK. It can be achieved programmatically by

following the classification rule (e.g. defining thresholds) depicted in **Table S1** below.

b. Otherwise, assign the scheduled visit number (assuming it is coded correctly) to --LPTADT_WK

3) Find the 2nd TA visit after LPTADT_WK according to the list in step 1 (--LPTADT_WK_2)
   a. If LPTADT_WK_2+1wk < earliest of PD/death date, then censor PFS at the –LPTADT

Table 5 shows how to assign unscheduled TA to a schedule visit. The Threshold column is defined as the mid-point between current and next visit (except for baseline); it is the upper limit for LPTADT to be mapped to the prior scheduled assessment (step 2a above). For example, if LPTADT is Week 44 for an unscheduled visit, it will be mapped to Week 42 TA since it is within the Threshold for Week 42. Assuming it is SD and the subsequent TA of the patient is PD after Week 58, PFS will be censored at LPTADT (Week 44); had the PD occurred prior to Week 58, it would be counted as an PFS event.

Table S1: Example of scheduled tumor assessments with time window

Weeks	Scheduled week -1	**Scheduled week**	Scheduled week+1	Threshold
Baseline		Baseline		
Every 9 weeks for the first 52 weeks	Week 8	Week 9	Week 10	Week 14
	Week 17	Week 18	Week 19	Week 23
	Week 26	Week 27	Week 28	Week 32
	Week 35	Week 36	Week 37	Week 41
	Week 44	Week 45	Week 46	Week 50
Every 12 weeks afterwards	Week 53	**Week 54**	Week 55	Week 60
	Week 65	Week 66	Week 67	Week 72
	Week 77	Week 78	Week 79	…
	…	…	…	...