STATISTICAL ANALYSIS PLAN

Study Protocol Number: AdvanTIG-204

Study Protocol Title: A Phase 2, Multicenter, Randomized, 3-Arm, Open-Label Study to Investigate the Preliminary Efficacy and Safety of the Anti-TIGIT Monoclonal Antibody Ociperlimab (BGB-A1217) Plus Tislelizumab Plus Concurrent Chemoradiotherapy in Patients with Untreated Limited-Stage Small Cell Lung Cancer

Date: 22 Aug, 2023

Version: 2.0

SIGNATURE PAGE

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ADA	Anti-drug antibody
ADI	Actual dose intensity
AE	Adverse event
AUC	Area under the concentration-time curve
BOR	Best overall response
CI	Confidence interval
CR	Complete response
cCRT	Concurrent Chemo-Radiotherapy
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
FDA	Food and Drug Administration
imAE	Immune-mediated adverse event
LS-SCLC	Limited-Stage Small Cell Lung Cancer
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PK	Pharmacokinetic
PFS	Progression-free survival
PR	Partial response
PS	Performance status
PT	Preferred term
RDI	Relative dose intensity
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment-emergent adverse event

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 AdvanTIG-204 study: a phase 2, multicenter, randomized, 3-arm, open-label study to investigate the preliminary efficacy and safety of the anti-TIGIT monoclonal antibody ociperlimab (BGB-A1217) plus tislelizumab plus concurrent chemoradiotherapy in patients with untreated limited-stage small cell lung cancer. The focus of this SAP is for the planned primary, secondary and exploratory analyses specified in the study protocol.

The analysis details for exploratory biomarker analyses are not described within this SAP. Separate analysis plans will be completed for these analyses.

Reference materials for this SAP include the AdvanTIG-204 protocol amendment (version 3.0, dated as 8Oct2021). If the protocol is amended or updated, then appropriate adjustments to the SAP may be made if they are related to the planned analyses.

The SAP described hereafter is an a priori plan. The SAP will be finalized and approved before any formal analysis. Statistical programming may occur as study data accumulate in order to have analysis programs ready at the time of any formal analysis.

All statistical analyses will be conducted using SAS® (SAS Institute, Inc., Cary, NC, USA), Version 9.3 or higher.

If any analysis defined in the SAP is different from the ones specified in the protocol, analysis defined in the SAP will be performed and reported in the clinical study report.

2 STUDY OVERVIEW

This is a phase 2, multicenter, randomized, 3-arm, open-label study to investigate the preliminary efficacy and safety of the anti-TIGIT monoclonal antibody ociperlimab plus tislelizumab plus cCRT followed by ociperlimab plus tislelizumab (Arm A) and tislelizumab plus cCRT followed by tislelizumab only (Arm B) compared with cCRT only (Arm C) in patients with previously untreated limited-stage small cell lung cancer (LS-SCLC).

Approximately 120 patients will be randomized in a 1:1:1 ratio to receive the study treatment in the following 3 arms:

- Arm A: Ociperlimab 900 mg intravenously once every 3 weeks plus tislelizumab 200 mg intravenously once every 3 weeks combined with cCRT for 4 cycles, followed by ociperlimab 900 mg intravenously once every 3 weeks plus tislelizumab 200 mg intravenously once every 3 weeks
- Arm B: Tislelizumab 200 mg intravenously once every 3 weeks combined with cCRT for 4 cycles, followed by tislelizumab 200 mg intravenously once every 3 weeks
- Arm C: cCRT only for 4 cycles

Randomization will be stratified by disease stage (I/II versus III) by the American Joint Committee on Cancer staging system, 8th edition.

The chemotherapy regimen is cisplatin 75 mg/m^2 on Day 1 of each cycle for 4 cycles. If the patient is unable to tolerate the 1-day administration of cisplatin 75 mg/m^2, at the investigator's discretion (e.g., patients had concurrent superior vena cava syndrome) cisplatin 25 mg/m^2 dosed on Days 1, 2, and 3 is allowed. Etoposide is administered at 100 mg/m^2 on Days 1, 2, and 3 for 4 cycles. Dose adjustment is allowed to address potential renal, hematologic, or other toxicities after the first cycle.

If cisplatin is contraindicated or not tolerated, carboplatin and etoposide will be the alternative regimen. Carboplatin at a dose of area under the plasma or serum concentration-time curve 5 (AUC 5) should be administered as an intravenous infusion once every 3 weeks on Day 1 of each cycle for 4 cycles and etoposide 100 mg/m^2 should be administered on Days 1, 2, and 3 of each cycle for 4 cycles.

For Arm A and Arm B, investigational drug(s) (ociperlimab plus tislelizumab [Arm A] or tislelizumab alone [Arm B]) will be given starting on Cycle 1 Day 1 (C1D1) before chemotherapy and continued for a duration of up to 12 months (a maximum of 17 cycles of treatment) or until disease progression according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1), unacceptable toxicity, death, or another discontinuation criterion is met, whichever occurs first.

Radiation therapy (RT) should start early within cycle 1 or 2 of systemic therapy. The total dose of RT will be 60 to 70 Gy, given in once-daily fractions over 6 to 7 weeks.

Prophylactic cranial irradiation (PCI) is permitted at the investigator's discretion. The preferred total dose for PCI to the whole brain is 25 Gy in 10 daily fractions.

The study is composed of an initial screening phase, a treatment phase (17 cycles maximum), safety follow-up phase (around 30 days), and survival follow-up phase. Screening evaluations will be performed within 28 days before randomization. Screening evaluations may be repeated as needed within the screening period; the investigator assesses preliminary patient eligibility according to the latest screening assessment results. Archival tumor tissue must be collected for the purpose of biomarker analysis. If no archival samples are available, a fresh tumor biopsy at baseline is required. During the study, first tumor imaging will be performed at approximately 12 weeks (± 7 days) from the date of randomization (an additional tumor assessment is allowed if clinically indicated), then every 6 weeks (± 7 days) for the next 54 weeks, and then every 12 weeks (± 7 days) thereafter based on RECIST v1.1. Tumor response will be assessed by investigators. A patient who discontinues study treatment early for reasons other than disease progression (e.g., toxicity) will continue to undergo tumor assessments following the original schedule until disease progression according to RECIST v1.1, withdrawal of consent, loss to follow-up, start of a new anticancer therapy, death, or study termination, whichever occurs first.

The End-of-Treatment (EOT) Visit and Safety Follow-up Visit are planned to be conducted when the investigator determines that study treatment will no longer be used. The EOT visit should be conducted within 7 days after the decision to discontinue study treatment or upon completion of study treatment. Tumor assessment is not specifically required at the EOT or Safety Follow-up Visit and should follow the regular tumor evaluation schedule. However, in some cases, the time window of tumor assessment might overlap with the EOT and/or Safety Follow-up Visit. Patients who discontinue study treatment for any reason will be asked to return to the clinic for the Safety

Follow-up Visit, which is required to be conducted 30 days (± 7 days) after the last dose/last day of study treatment (including cCRT), or initiation of new anticancer therapy, whichever occurs first.

For Arms A and B, patients should return to the site or telephone contacts with patients should be conducted to assess imAEs and concomitant medications (if appropriate, i.e., associated with an imAE or is a new anticancer therapy) at 60 and 90 days (± 7 days) after the last dose of ociperlimab or tislelizumab, regardless of whether patients start a new anticancer therapy. If patients report a suspected imAE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated. The EOT Visit may be used as the Safety Follow-up Visit if it occurred 30 days (± 7 days) after the last dose of study treatment, e.g., at an EOT Visit right after a response assessment showed disease progression resulting in patient discontinuation. Patients who discontinue study treatment or complete study treatment before disease progression will have their tumors assessed. If the EOT Visit is used as the Safety Follow-up Visit, the assessment that has been performed at the EOT Visit does not need to be repeated. Patients who discontinue or complete study treatment before disease progression will need to undergo tumor assessments.

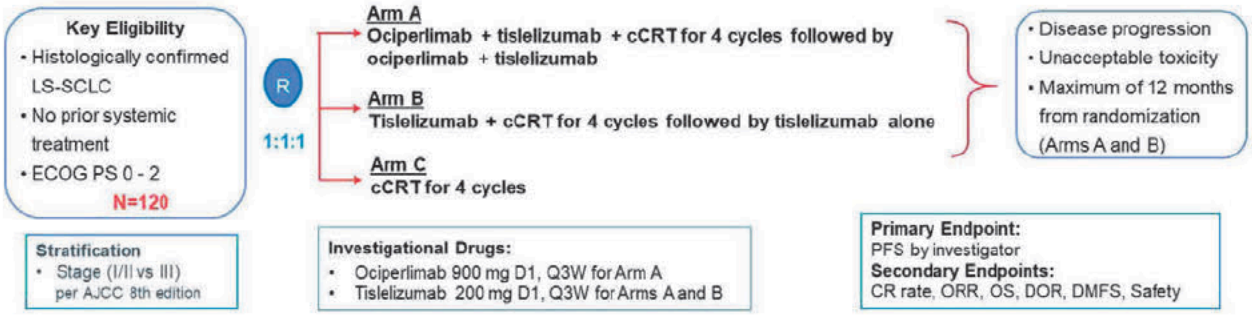
Patients will be followed for survival and to obtain information on subsequent anticancer therapy after discontinuation of study treatment via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (± 14 days) after the Safety Follow-up Visit or as directed by the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

Patients will be evaluated for any AEs and serious adverse events (SAEs) occurring up to 30 days after the last dose of study treatment (all severity grades, per NCI-CTCAE v5.0) or initiation of a new anticancer therapy, whichever occurs first, and immune-mediated AEs (imAEs) occurring up to 90 days after the last dose of ociperlimab or tislelizumab, regardless of initiation of a new anticancer therapy. All treatment-related SAEs will be recorded by the investigator after treatment discontinuation until patient death, withdrawal of consent, or loss to follow-up, whichever occurs first. All study treatment-related SAEs will be followed until they resolve to baseline or ≤ Grade 1, the investigator assesses the AE as stable and unlikely to improve, the patient is lost to follow-up, or the patient withdraws consent, whichever occurs first.

Patient-reported outcomes will be collected using the EORTC QLQ-C30 and QLQ-LC13 questionnaires will be completed at predose on Day 1 of every cycle from Cycle 1 (baseline) through Cycle 4, and then to coincide with scheduled tumor assessments (every 6 weeks [±7 days]) until the EOT visit (Arms A, B, and C).

The study design schema is shown in Figure 1.

Figure 1 Study Schema



Abbreviations: AJCC, American Joint Committee on Cancer; cCRT, concurrent chemoradiotherapy; CR, complete response; D1, Day 1; DMFS, distant metastasis-free survival; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; LS-SCLC, limited-stage small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; Q3W, once every 3 weeks; R, randomization.

3 STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVES

- To compare progression-free survival (PFS) between Arm A (ociperlimab [BGB-A1217] plus tislelizumab plus concurrent chemoradiotherapy [cCRT]) and Arm C (cCRT only) and between Arm B (tislelizumab plus cCRT) and Arm C as assessed by the investigator according to RECIST v1.1 in the Intent-to-Treat (ITT) Analysis Set.

3.2 SECONDARY OBJECTIVES

- To compare the following between Arm A and Arm C and between Arm B and Arm C as assessed by the investigator according to RECIST v1.1 in the ITT Analysis Set:
  - Complete response (CR) rate
  - Overall response rate (ORR)
  - Duration of response (DOR)
  - Overall survival (OS)
  - Distant metastasis-free survival (DMFS)
- To evaluate the correlation of programmed cell death ligand-1 (PD-L1) and T-cell immunoglobulin and ITIM domain (TIGIT) expression with ORR, PFS, and OS
- To evaluate the safety and tolerability of ociperlimab combined with tislelizumab plus cCRT and tislelizumab plus cCRT

3.3 EXPLORATORY OBJECTIVES

- To explore prognostic and predictive effects of tissue- and blood-based biomarkers on efficacy and their association with mechanisms of resistance
- To evaluate health-related quality of life (HRQoL)

- To assess the utility of circulating tumor DNA (ctDNA) level change as a surrogate marker for efficacy
- To assess the pharmacokinetics (PK) of ociperlimab and tislelizumab
- To assess the immunogenicity of ociperlimab and tislelizumab

4 DEFINITION OF PRIMARY ESTIMANDS

4.1 PRIMARY ESTIMAND 1

The primary clinical question of interest 1 is: "Will the addition of tislelizumab and ociperlimab to concurrent chemoradiotherapy prolongs time to death/progression in patients with untreated limited-stage small cell lung cancer?"

The primary estimand is described by the following attributes:

1) Treatment of interest: The study experimental treatment is ociperlimab 900 mg Q3W, tislelizumab 200 mg Q3W, and concurrent chemoradiotherapy which includes cisplatin + etoposide and/or carboplatin + etoposide and radiotherapy. The study control treatment is cCRT.
2) Population: Adult patients with untreated limited-stage small cell lung cancer.
3) Primary variable: Progression-free survival, defined as the time from the date of randomization to the date of the first documented disease progression as determined by the investigator per RECIST v1.1 or death from any cause (whichever occurs first).
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 anti-cancer therapy started prior to progression or death**: data for patients who start to receive new anti-cancer therapy will be censored at the last tumor assessment date prior to the introduction of new therapy or randomization date if no valid tumor assessment before new anti-cancer therapy (hypothetical strategy)
5) Population-level summary: The hazard ratio (HR) for PFS for each comparison (i.e., Arm A versus Arm C) will be estimated using a Cox regression model stratified by disease stage at randomization.

4.2 PRIMARY ESTIMAND 2

The primary clinical question of interest 2 is: "Will the addition of tislelizumab to concurrent chemoradiotherapy prolongs time to death/progression in patients with untreated limited-stage small cell lung cancer?"

The primary estimand is described by the following attributes:

1) Treatment of interest: The study experimental treatment is tislelizumab 200 mg Q3W and concurrent chemoradiotherapy which includes cisplatin + etoposide and/or carboplatin + etoposide, and radiotherapy. The study control treatment is cCRT.
2) Population: Adult patients with untreated limited-stage small cell lung cancer.
3) Primary variable: Progression-free survival, defined as the time from the date of randomization to the date of the first documented disease progression as determined by the investigator per RECIST v1.1 or death from any cause (whichever occurs first).
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 anti-cancer therapy started prior to progression or death**: data for patients who start to receive new anti-cancer therapy will be censored at the last tumor assessment date prior to the introduction of new therapy or randomization date if no valid tumor assessment before new anti-cancer therapy (hypothetical strategy)
5) Population-level summary: The HR for PFS for each comparison (i.e., Arm B versus Arm C) will be estimated using a Cox regression model stratified by disease stage at randomization.

5 STUDY ENDPOINTS

5.1 PRIMARY ENDPOINT

- PFS, defined as the time from the date of randomization to the date of the first documented disease progression as determined by the investigator per RECIST v1.1 or death from any cause (whichever occurs first), in the ITT Analysis Set of Arms A, B, and C

5.2 SECONDARY ENDPOINTS

- CR rate, defined as the proportion of patients who had CR as assessed by the investigator per RECIST v1.1, in the ITT Analysis Set of Arms A, B, and C
- ORR, defined as the proportion of patients who had CR or partial response (PR) as assessed by the investigator per RECIST v1.1, in the ITT Analysis Set of Arms A, B, and C
- DOR, defined as the time from the date of the first occurrence of a documented objective response to the date of documented disease progression as assessed by the investigator per RECIST v1.1 or death from any cause (whichever occurs first), in the ITT Analysis Set of Arms A, B, and C
- OS, defined as the time from the date of randomization to the date of death due to any cause, in the ITT Analysis Set of Arms A, B, and C

- DMFS, defined as the time from the date of randomization to the date of the first documented distant metastasis as assessed by the investigator per RECIST v1.1 or death from any cause (whichever occurs first), in the ITT Analysis Set of Arms A, B, and C
- ORR, PFS, and OS in subgroups based on PD-L1 and TIGIT expression levels
- The incidence and severity of treatment-emergent adverse events (TEAEs) graded according to National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v5.0)

5.3 EXPLORATORY ENDPOINTS

- HRQoL assessment using 2 patient-reported outcomes (PROs) including the European Organisation 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)
- The ctDNA level change before, during, and after treatment as a surrogate marker for efficacy
- Serum concentrations of ociperlimab and tislelizumab at specified timepoints
- Assessment of immunogenicity of ociperlimab and tislelizumab by determining the incidence of antidrug antibodies (ADAs)

6 SAMPLE SIZE CONSIDERATIONS

This study is not designed to make explicit power and type I error consideration but rather to obtain preliminary efficacy and safety data for ociperlimab plus tislelizumab and tislelizumab monotherapy with chemoradiotherapy for patients with untreated LS-SCLC. This study will enroll approximately 120 subjects into 3 arms, with approximately 40 patients in each arm. The contribution of tislelizumab to the efficacy results will be demonstrated by descriptive analysis of PFS, ORR, and DOR in the comparison of Arm B versus Arm C. The contribution of adding ociperlimab will be demonstrated by similarly descriptive analysis in the comparison of Arm A versus Arm B. With a sample size of 40 patients in each arm, the binomial probabilities of detecting ≥ 1 TEAEs with a frequency of 5% and 1% are approximately 0.87 and 0.33, respectively.

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 all efficacy analyses.

The Safety Analysis Set includes all patients who received ≥ 1 dose of any component of study drug; it will be the analysis set used for the safety analysis. Patients in the safety analysis set will be classified according to treatment received, where treatment received is defined as (i) the intended treatment if it was received at least once, or (ii) the first treatment received if intended

treatment is never received. Each patient will be classified into and analyzed consistently within one (and only one) treatment arm.

The PK Analysis Set includes all patients who received ≥ 1 dose of tislelizumab/ociperlimab per the protocol and for whom any quantifiable postbaseline PK data are available.

The ADA Analysis Set, which includes all patients who received ≥ 1 dose of tislelizumab/ociperlimab and for whom both baseline and ≥ 1 postbaseline ADA result are available.

The Biomarker Analysis Set includes all patients who have ≥ 1 evaluable biomarker measurement; it will be used for the biomarker analysis. Specifically, the PD-L1 analysis set includes all patients who have ≥ 1 evaluable PD-L1 measurement, which exclusively includes the measurement derived from tissue samples fixed with 10% formalin; TIGIT analysis set includes all patients who have ≥ 1 evaluable TIGIT measurement.

7.2 Data Analysis General Considerations

All descriptive statistics for continuous variables will be reported using mean, standard deviation (SD), median, 25th percentile (Q1), 75th percentile (Q3), minimum (Min), maximum (Max) and n. Categorical variables will be summarized as number (percentage) of patients. Time-to-event variable: number of non-missing observations (N), median, minimum and maximum. Kaplan-Meier event rates may also be provided if applicable for specific time-to-event variable.

The study Table Listing Graph shells will be provided in a separate document, which will show the content and format of all tables, listings, and graphs in detail.

7.2.1 Definitions and Computations

Baseline Measurements:

- For efficacy evaluation: Unless otherwise specified, a baseline value is defined as the last non-missing value collected prior to or at the time of randomization date. This rule also applies to the stratification factor (baseline disease stage).
- Safety variables: a baseline value is defined as the one which is the latest available valid measurement taken prior to or on the first study drug administration date. If any randomized patients are not treated, the baseline will be the last value on or prior to the randomization date.

Unscheduled Visits: Unscheduled measurements will not be included in by-visit table summaries and graphs but will contribute to best/ worst case value where required (e.g., shift table). Listings will include scheduled and unscheduled data.

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

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.
- *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'.
- For the laboratory safety variables data, if the data below the lower limit of quantification (LLOQ)/limit of linearity, half of the lower limit value (i.e., LLOQ/2) will be used for quantitative analyses. For data above the upper limit of quantification (ULOQ)/limit of linearity, the upper limit value (i.e., ULOQ) will be used for quantitative analyses.

7.2.3 Handling of Missing Data

Missing data will not be imputed unless otherwise specified elsewhere in the SAP. Missing dates or partially missing dates will be imputed conservatively for adverse events, prior or concomitant medications/procedures, disease history, prior therapy, and subsequent anti-cancer therapy collected in the post-treatment page. Please refer to Appendix 11.1 for details.

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 Multiplicity Adjustment

Not applicable.

7.3 Subject Characteristics

7.3.1 Subject Disposition

The number and percentage of patients randomized, treated, permanently discontinued from study treatment, remained on treatment, discontinued from study, and remained on study will be summarized in the ITT Analysis Set. The primary reasons for study treatment discontinuation and study discontinuation will be summarized according to the categories in the eCRF. Study follow-up time will be summarized.

A listing of randomization numbers will be provided.

7.3.2 Protocol Deviations

Important protocol deviation criteria will be established, and patients with important protocol deviations will be identified and documented before the database lock. Important protocol deviations including COVID-19 related will be summarized for all patients in the ITT analysis set. They will also be listed by each category.

7.3.3 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized using descriptive statistics in the ITT Analysis Set. Continuous variables include age, weight, BMI; categorical variables include sex, race, , age group (<65 years, ≥65 years), ECOG performance status at baseline, ethnicity, smoking history, and country.

In addition, the stratification factor (disease stage) per IRT and per eCRF will be summarized based on ITT analysis set.

Patient data listing of demographic and baseline characteristics will be provided.

7.3.4 Disease History

The number and percentage of patients reporting a history of disease and characteristic, as recorded on the eCRF, will be summarized in the ITT Analysis Set. Categorical disease characteristics variables include disease stage, histology, location of local metastases at initial diagnosis, and TNM stage at study entry. Continuous disease history variables include time from initial diagnosis to study entry (day).

7.3.5 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the version of World Health Organization Drug Dictionary (WHO DD) drug codes currently in effect at BeiGene at the time of database lock and will be further classified to the appropriate Anatomical Therapeutic Chemical (ATC) code.

Prior medications are defined as medications that were stopped before the day of the first dose of study drug. Concomitant medications are defined as medications that 1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or 2) started on or after the date of the first dose of study drug up to 30 days after the patient's last dose (as of the Safety Follow-up Visit). In addition, telephone contacts with patients should be conducted to assess imAEs and concomitant medications (if appropriate, i.e., associated with an imAE or is a new anticancer therapy) at 60 days, and 90 days (± 7 days) after the last dose of study treatment, regardless of whether or not the patient starts a new anticancer therapy.

The number and percentage of patients reporting prior and concomitant medications will be summarized by ATC medication class and WHO DD preferred term (PT) in the Safety Analysis Set.

7.3.6 Medical History

Medical History will be coded using MedDRA of the version currently in effect at BeiGene at the time of database lock. The number and percentage of patients reporting a history of any medical condition, as recorded on the eCRF, will be summarized by System Organ Class (SOC) and PT in the ITT Analysis Set.

A listing of medical history will be provided.

7.3.7 Post-Treatment Anti-Cancer Therapy

Flags of start date of new anti-cancer therapy for efficacy and safety analyses are derived separately.

- For efficacy analysis, start date of new anti-cancer therapy could be the earliest of date of prohibited anti-cancer therapy taken during treatment, date of the post-treatment systemic anti-cancer therapy or other anti-cancer therapy such as post-treatment surgery and radiotherapy as deem appropriate.

- The start date of new anti-cancer therapy in defining TEAE for safety is always the first date of new systemic anti-cancer therapy taken after the last study treatment.

Since the tumor response per RECIST or event driven endpoints have not been commonly used for the efficacy evaluation of Tradition Chinese Medicine, the ORR, PFS or OS benefit of Chinese herbal medicines and Chinese patent medicines has not yet been established. Therefore, they will not be considered as new anti-cancer therapy in the efficacy and safety analyses.

Subsequent anti-cancer therapy is defined as the anti-cancer therapy started after the last dose date of study treatment. A summary of number and percentage of patients who received subsequent anti-cancer therapy in procedure or surgery/radiotherapy or systemic anti-cancer therapy/immunotherapy by treatment arm will be provided based on ITT analysis set.

The number (percentage) of patients by regimen number will be summarized. Time to first post-treatment anti-cancer therapy will be summarized descriptively.

Patient data listings of post-treatment systemic therapy will be provided.

7.4 Efficacy Analysis

The efficacy endpoints including PFS, CR rate, ORR, DOR, and OS will be summarized by arm in the ITT Analysis Set. The efficacy endpoints will be compared in Arm A versus Arm C and Arm B versus Arm C. These analyses are descriptive and exploratory; no formal testing was designed for this study.

If not specified otherwise, efficacy analysis described in this section will be based on the ITT analysis set.

7.4.1 Primary Efficacy Endpoint

The final analysis for PFS is estimated to happen approximately 30 months after the enrollment of the first patient.

7.4.1.1 Primary estimand is defined in Sections 4.1 and 4.2.

Variable

PFS per investigator is defined as the time from randomization to the first documented disease progression as assessed by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first. Censoring rules for PFS are specified in Table 6.

Primary efficacy analysis

Kaplan-Meier method (Kaplan and Meier, 1958) will be used to estimate median or other quartiles of PFS along with its 95% confidence interval (CI) which is constructed using Brookmeyer and Crowley method (Brookmeyer and Crowley, 1982). Kaplan-Meier curves will be constructed to provide a visual description of the PFS distribution. Event free rate at selected timepoints (9, 12 and 18 months) will be estimated using Kaplan-Meier method, and the associated standard errors will be estimated using Greenwood's formula (Greenwood, 1926). The $\log(-\log(\cdot))$ transformation will be applied to the 95% CI for event free rate. Median follow-up time will be estimated by the reverse Kaplan-Meier method with 95% CI using the Brookmeyer and Crowley method.

The distribution of PFS will be estimated for Arm A versus Arm C and Arm B versus Arm C using stratified log-rank test based on the stratification factor (disease stage) collected from IRT. One-sided *p*-value will be calculated.

The HR for PFS for each comparison (i.e., Arm A versus Arm C, Arm B versus Arm C) will be estimated using a stratified Cox proportional hazard model with Efron's method of tie handling, with treatment arm as only covariate and stratified by the stratification variable (baseline disease stage) collected from IRT. The 95% CI for the HR will be provided.

Sensitivity analysis and supplementary analysis

In order to evaluate the robustness of the PFS per investigator, we will perform sensitivity analyses with different censoring rules. If the patient met multiple situations in Table 6, the censoring reason will be the earliest situation.

- The sensitivity analysis 1 is the same as the primary analysis except that it uses the actual reported date of progression to define PFS regardless of missing assessments, and any PD or death after more than one missing tumor assessments will be considered as a PFS event. Please refer to Appendix 11.2 for PFS sensitivity analysis censoring rules in details.
- The sensitivity analysis 2 is to assess the impact of stratification factor. Unstratified Cox regression model will also be performed to provide HR and corresponding 95% CI.
- The supplementary analysis is the same as the primary analysis except that it considers initiation of a new anticancer treatment to be a PD event without documented PD or death, and the PFS event date will be derived using the start date of new anticancer therapy.

7.4.2 Secondary Efficacy Endpoints

Complete Response Rate per Investigator

CR rate is the proportion of patients who had a confirmed CR as assessed by investigator per RECIST v1.1 in all randomized patients. Patients without any postbaseline assessment will be considered non-responders. CR rate and its Clopper-Pearson 95% CI (Clopper and Pearson, 1934) will be calculated for each treatment arm in the ITT analysis set. The odds ratio for CR rate between treatment arms will be calculated using the Cochran-Mantel-Haenszel (CMH) test with the stratification factor (baseline disease stage) at randomization, and its two-sided 95% CIs will be provided. Mantel-Haenszel common risk difference in CR rate will be estimated, with its 95% CI constructed by a normal approximation and Sato's variance estimator.

Overall Response Rate per Investigator

ORR with confirmation is the proportion of patients who had a confirmed CR or PR as assessed by the investigator per RECIST v1.1 in all randomized patients. Patients without any postbaseline assessment will be considered non-responders. Similar method used to evaluate CR rate will be applied to the analysis of ORR. In addition, the number and percentage of patients for each of the Best Overall Response (BOR) categories (e.g., CR, PR, SD, PD, NE) will be presented by treatment arm. Similar method used to evaluate ORR with confirmation and confirmed BOR will be applied to the analysis of ORR without confirmation and unconfirmed BOR.

A waterfall plot of best percent change in sum of target lesion diameters from baseline will be provided for each treatment arm. Patients will be ordered by the percentage, from the smallest to the largest in percentages.

Duration of Response per Investigator

DOR is defined for patients with an objective response (confirmed CR or PR) as the time from the first documented objective response to documented disease progression as assessed by the investigator using RECIST v1.1, or death from any cause, whichever occurs first. Only patients who have achieved objective responses (responders) will be included in the analysis of DOR. Similar method used to evaluate PFS will be applied to the analysis of DOR.

Overall Survival

OS is defined as the time from randomization to death from any cause. OS will be analyzed in the ITT Analysis Set. Data for patients who are not reported as having died at the time of analysis will be censored at the date the patients were last known to be alive. 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. Data for patients who do not have postbaseline information will be censored at the date of randomization. Similar method used to evaluate PFS will be applied to the analysis of OS.

Note: 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 patients 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.

Distant Metastasis-Free Survival

The distant metastasis includes separate tumor nodule(s) in a contralateral lobe, tumor with pleural or pericardial nodules or malignant pleural or effusion pericardial, single extrathoracic metastasis in a single organ (including involvement of a single nonregional node), and multiple extrathoracic metastases in a single organ or in multiple organs.

DMFS is defined as the time from the date of randomization to the date of the first documented distant metastasis as assessed by the investigator per RECIST v1.1, or death from any cause, whichever occurs first. Patients who have not developed distant metastasis or died at the time of analysis will be censored at the time of latest date of assessment from their last RECISIT 1.1 assessment. However, if the patient has distant metastasis or dies after 2 or more missed visits, the patient will be censored at the time of the latest RECIST 1.1 assessment prior to the 2 missed visits. If the patient has no visits or does not have baseline data, they will be censored at Day1 unless they die within 2 visits of baseline. Similar method used to evaluate PFS will be applied to the analysis of DMFS.

7.4.3 Exploratory Efficacy Endpoints

Health-Related Quality of Life

EORTC-QLQ-C30

The EORTC-QLQ-C30 (QLQ-C30) consists of 30 questions which can be combined to produce five functional scales (Physical, Role, Cognitive, Emotional, and Social), a global health status/QoL scale, and a number of single items assessing additional symptoms commonly reported by cancer subjects (e.g., dyspnea, loss of appetite, insomnia, constipation, and diarrhea), and financial impact of the disease. The QLQ-C30 will be scored according to the EORTC scoring manual (Fayers et al 2001). Higher scores on the global health status and functioning scales indicate better health status/function but higher scores on symptom scales/items represent greater symptom severity. Please refer to Table 1 for scoring of QLQ-C30 details.

An outcome variable consisting of a score from 0 to 100 will be derived for each of the symptom scales/symptom items, the functional scales and the global health status scale in the QLQ-C30. Each scale of the QLQ-C30 will be transformed so that scale scores will range from 0 to 100. The transformation will proceed in two steps. First, the average of the items contributing to a subscale will be calculated to compute the raw score of the scale. Next, a linear transformation will be applied to 'standardize' the raw score.

- For all scales, the raw score (RS), is the mean of the component items:

$$\text{RS} = (I_1 + I_2 + \cdots + I_n)/n$$

- For functional scales, the derivation formula is as follows:

$$\text{Score} = \left\{1 - \frac{(\text{RS} - 1)}{\text{range}}\right\} \times 100$$

- For symptom scales/items and global health status / QoL, the derivation formula is as follows:

$$\text{Score} = \left\{\frac{(\text{RS} - 1)}{\text{range}}\right\} \times 100$$

For examples, the raw score and the functional scale of emotional functioning are as follows,

$$\text{RS}_{\text{EF}} = (Q_{21} + Q_{22} + Q_{23} + Q_{24})/4, \text{EF score} = \left\{1 - \frac{\text{RS}_{\text{EF}} - 1}{3}\right\} \times 100$$

The raw score and the functional scale of fatigue are as follows,

$$\text{RS}_{\text{FA}} = \frac{Q_{10} + Q_{12} + Q_{18}}{3}, \text{FA score} = \left\{\frac{\text{RS}_{\text{FA}} - 1}{3}\right\} \times 100$$

Table 1 Scoring of QLQ-C30 version 3.0

Scale name	Scale	Number of items	Item range	Items
Global Health Status/ QoL				
Global Health Status/ QoL	QL2	2	6	29, 30
Functional Scales				

Physical Functioning	PF2	5	3	1, 2, 3, 4, 5
Role Functioning	RF2	2	3	6,7
Emotional Functioning	EF	4	3	21, 22, 23, 24
Cognitive Functioning	CF	2	3	20, 25
Social Functioning	SF	2	3	26, 27
Symptom Scales/Items				
Fatigue	FA	3	3	10, 12, 18
Nausea and vomiting	NV	2	3	14, 15
Pain	PA	2	3	9, 19
Dyspnoea	DY	1	3	8
Insomnia	SL	1	3	11
Appetite loss	AP	1	3	13
Constipation	CO	1	3	16
Diarrhoea	DI	1	3	17
Financial difficulties	FI	1	3	28

Item range is the difference between the possible maximum and the minimum response to individual items.

EORTC-QLQ-LC13

The EORTC-QLQ-LC13 (QLQ-LC13) is a lung cancer specific module from the EORTC comprising 13 questions to assess lung cancer symptoms (cough, haemoptysis, dyspnoea and site-specific pain), treatment related side-effects (sore mouth, dysphagia, peripheral neuropathy and alopecia) and pain medication. The QLQ-LC13 incorporates symptom scales including:

- Dyspnoea: (multi-item scale based on 3 questions: were you short of breath when you rested/walked/climbed stairs)
- Cough: 1 item (how much did you cough?)
- Haemoptysis: 1 item (did you cough up blood?)
- Pain: 3 individual items (have you had pain in your chest/your arm or shoulder/other parts of your body?)

The dyspnoea scale is only used if all 3 items have been scored, otherwise the items are treated as single-item measures. The developers of EORTC-QLQ-LC13 indicate that it is highly preferred not to use the LC13 alone (without the core module QLQ-C30), since the module has been designed to be used together with the core questionnaire, and the content validity is based upon this combination. The response options and scoring system are the same as for the QLQ-C30, and the administration is similar. The recall period for items is the past 7 days, and response options include either a 4-point Likert scale or yes/no options. The total score for the instrument ranges from 0 to 100. A high score for a symptom scale or item represents a high level of symptomatology or problems (Fayers et al 2001). Please refer to Table 2 for scoring of QLQ-LC13 details.

Table 2 Scoring of QLQ-LC13

Scale name	Scale	Number of items	Item range	Items
Symptom scales/ items				
Dyspnoea	LCDY	3	3	33, 34, 35
Cough	LCCO	1	3	31

Haemoptysis	LCHA	1	3	32
Sore mouth	LCSM	1	3	36
Dysphagia	LCDS	1	3	37
Peripheral neurophathy	LCPN	1	3	38
Alopecia	LCHR	1	3	39
Pain in the chest	LCPC	1	3	40
Pain in arm or shoulder	LCPA	1	3	41
Pain in other parts	LCPO	1	3	42
Did you take any medicine for pain?		1	2	43
If yes, how much did it help?			4	

Item range is the difference between the possible maximum and the minimum response to individual items.
The dyspnoea scale should only be used if all three items have been answered. Some respondents ignore question 35 because they never climb stairs; in this case, the score for the dyspnoea scale would be biased if it were based upon the other two items. Hence if item 35 is missing then items 33 and 34 should be used as single-item measures.

Missing items: If at least half of the items for a scale are answered, then all the completed items are used to calculate the score. Otherwise, the scale score is set to missing. No imputation will be performed for missing scale score.

Summary statistics (mean, standard deviation, median, and range) of the postbaseline scores and changes from baseline will be reported for the EORTC-QLQ-C30 and QLQ-LC13 questionnaires. Line charts depicting the mean changes (and standard errors) over time from the baseline assessment will be provided for each treatment arm. The clinically meaningful changes postbaseline and a mixed model analysis will be performed to assess the difference in mean changes between Arm A versus Arm C and Arm B versus Arm C at 95% CI using the global health status, physical function, and fatigue domains of QLQ-C30, and dyspnoea, coughing, haemotysis and pain in chest, pain in arms and shoulders and peripheral neuropathy domains of QLQ-LC13. Completion and compliance rates will be summarized at each timepoint by treatment arm. Only patients in the ITT Analysis Set with a non-missing baseline assessment and ≥ 1 in-study non-missing postbaseline assessment will be included in the analyses.

Exploratory efficacy analysis of PFS/ORR in comparison of Arm A vs Arm B

To evaluate the contribution of ociperlimab in combination therapy used in Arm A, exploratory analysis in terms of PFS and ORR will be performed for Arm A versus Arm B.

7.4.4 Subgroup Analysis

Subgroup analysis of primary endpoint of PFS per the investigator will be conducted to determine whether the treatment effect is consistent across various subgroups. The Kaplan-Meier estimates, HR estimates of PFS from an unstratified Cox model and its 95% CI will be estimated within each subgroup. Forest plot of subgroup analysis in PFS per the investigator will be provided, along with the results of the overall primary analysis. Subgroup factors include the followings:

- PD-L1 expression in tumor cells (<1%, ≥1%)
- TIGIT expression level (< 1%, ≥1%)

Note: Clinically meaningful cutoffs of PD-L1 and TIGIT expression level will be selected to divide the biomarker-evaluable patients into subgroups. Subgroup analysis of PD-L1 expression in subgroup defined by different scoring algorithm may also be performed.

- Disease stage (Stage I/II versus Stage III)
- Gender (male versus female)
- Age group (<65 years, ≥65 years)

A subgroup may not be analyzed if it includes <10% of the ITT analysis population.

ORR and OS in PD-L1 and TIGIT Subgroups

ORR and OS analysis by PD-L1 and TIGIT expression subgroups will also be performed to investigate the predictive value of these biomarkers.

7.5 Safety Analysis

Safety will be assessed by monitoring and recording of all TEAEs graded by NCI-CTCAE v5.0. All safety analyses will be performed by treatment arm and by total based on the Safety Analysis Set. Laboratory test results (e.g., hematology, clinical chemistry), vital signs, ECGs, etc. and their changes from baseline will be summarized using descriptive statistics (e.g., n, mean, standard deviation, median, Q1, Q3, minimum, maximum for continuous variables; n [%] for categorical variables. Abnormal values will be flagged.

7.5.1 Extent of Exposure

The following measures of the extent of exposure to each study drug will be summarized. One cycle is defined as 21 days for ociperlimab, tislelizumab, chemotherapy, and radiotherapy.

- Duration of exposure (months): treatment duration will be calculated as last date of exposure – first dose date + 1 and summarized in months descriptively. For duration of exposure of ociperlimab and tislelizumab, it will also be summarized in category of <3 months, 3 to <6 months, 6 to <9 months, ≥9 months.
    - For patients who discontinued from tislelizumab, ociperlimab, and carboplatin duration of exposure is defined as:

      (Minimum (last dose date + 20 days, death date, cutoff date) – first dose date + 1)/ 30.4375
    - For patients who discontinued from cisplatin and etoposide duration of exposure is defined as:

      (Minimum (first dose date in last cycle + 20 days, death date, cutoff date) – first dose date + 1)/ 30.4375
    - For patients who discontinued from radiotherapy duration of exposure is defined as:

    (Minimum (last fraction date, death date, cutoff date) – first fraction date + 1)/ 30.4375
    - For patients who is on treatment is defined as:

(Cutoff date – first dose date + 1)/ 30.4375

- Number of cycles received: for number of cycles received in ociperlimab and tislelizumab sum of all cycles will be summarized, and the number of cycles will also be summarized in category of 1) 1 cycle, 2 cycles, …, 10 cycles, and >10 cycles, and 2) 1-4 cycles, 5-10 cycles and >10 cycles.
- Number of fractions received: the number of fractions taken in radiotherapy will be calculated as the sum of number of completed fractions. Number of fractions received will also be summarized in category of 1-7, 8-14, 15-21, 22-27, 28, and >28.
- Cumulative dose administered: the sum of all actual doses given from first to last administration. The summary will include study drug administration in all scheduled and unscheduled visits prior to the cutoff date. For study treatment of tislelizumab, ociperlimab, and carboplatin, unit of cumulative dose administered is mg; for study treatment of cisplatin and etoposide, the unit is mg/m^2, and it can be calculated using actual dose (mg) divided by baseline body surface area (BSA; m^2); for study treatment of radiotherapy, the unit of cumulative dose administered is Gy.
    - Dose modifications for chemotherapy are required if a patient's body weight changes by ≥10% from baseline (or the new reference body weight). The dose administered (mg/m^2) for chemotherapy with a new body weight will be calculated using the new BSA. This rule is not applicable to carboplatin.
- Actual dose intensity (ADI) is defined as: cumulative dose administered / duration of exposure (cycles), where duration of exposure (cycles) is calculated as (last dose date up to cutoff date* + 20 days - first dose date + 1)/21. ADI will not be summarized for radiotherapy.

  *Use date of last dose for tislelizumab, ociperlimab, and carboplatin; use day 1 of last cycle for etoposide and cisplatin.

- Relative dose intensity (RDI) in % is defined as:

$$\frac{\text{ADI}}{\text{Planned Dose Intensity}} \times 100$$

  where planned dose intensity for tislelizumab is 200 mg/cycle, for ociperlimab is 900 mg/cycle, for cisplatin is 75 mg/m^2/cycle, for carboplatin is the baseline dose intensity (mg/cycle) and for etoposide is 100 mg/m^2/cycle. Relative dose intensity will not be summarized for radiotherapy.
    - The planned dose intensity of carboplatin is calculated for each patient at the baseline. The Calvert formula will be used to calculate the carboplatin dose (GFR+25)×AUC=dose (in mg), where glomerular filtration rate (GFR) can be calculated using the following formula in which serum creatinine concentration (SCr) unit is mg/dL,
        - Creatinine Clearance (C_rC_l) for males (mL/min): $\frac{(140\text{-age})(\text{weight})}{(72)(SC_r)}$

- C_rC_l for females (mL/min): $\frac{(0.85)(140\text{-age})(\text{weight})}{(72)(SC_r)}$

  GFR calculation formula is same as C_rC_l formula as shown above. Baseline weight and baseline SC_r are used in the calculation.

Number of cycles received by patient as a quantitative variable and by category (i.e., number (%) of patient receiving at least 1 cycle, at least 2 cycles etc.), duration of exposure, cumulative dose, ADI and RDI will be summarized by descriptive statistics.

The number and percentage of patients with dose modification to tislelizumab/ociperlimab, to cisplatin plus etoposide, to carboplatin plus etoposide, and to radiotherapy will be summarized, respectively. Reasons for dose modification to tislelizumab and ociperlimab include dose delay, infusion interruption, and infusion rate decreased. Reasons for dose modification to chemotherapy include infusion interruption and dose delay. Reasons for dose modification of radiotherapy only includes dose delay.

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

Examples to calculate ADI, planned dose per cycle and RDI for chemotherapy are provided in the below Table 3.

Table 3 Example Formula to Calculate ADI, Planned Dose and RDI by Cycle when target dose is in the unit of mg/m^2

	ADI	Planned dose per cycle	RDI
Cisplatin	$\frac{\sum_1^{\#\text{of cycles}} \frac{\text{actual dose}}{BSA^*}}{\max(\text{first dose date of last cycle}+20\text{-first dose date}/21, \text{number of cycles in last dosing eCRF page})}$	75 mg/m^2/cycle	$\frac{ADI}{75}$
Carboplatin	$\frac{\sum_1^{\#\text{of cycles}} \text{actual dose}}{\max(\text{first dose date of last cycle}+20\text{-first dose date}/21, \text{number of cycles in last dosing eCRF page})}$	(GFR+25)×AUC at baseline/cycle	$\frac{ADI}{(GFR+25)\times AUC \text{ at baseline}}$
Etoposide	$\frac{\sum_1^{\#\text{of cycles}} \frac{\text{actual dose}}{BSA^*}}{\max(\text{first dose date of last cycle}+20\text{-first dose date}/21, \text{number of cycles in last dosing eCRF page})}$	100 mg/m^2/cycle	$\frac{ADI}{100}$

*BSA (m^2) is calculated as $\sqrt{\frac{[height(cm)\times weight(kg)]}{3600}}$.

7.5.2 Adverse Events

AEs will be graded by the investigators using CTCAE v5.0. The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 25.0 or higher) lower-level term closest to the verbatim term. The linked

MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

7.5.2.1 Treatment-emergent Adverse Events

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

An overall summary of TEAEs will summarize the number (%) of patients with:

- At least one TEAE
- At least one TEAE with grade ≥ 3
- At least one serious TEAE
- At least one TEAE leading to death
- At least one TEAE leading to permanent discontinuation of any component of study drug
  - At least one TEAE leading to permanent discontinuation of ociperlimab/tislelizumab
  - At least one TEAE leading to permanent discontinuation of chemotherapy
  - At least one TEAE leading to permanent discontinuation of radiotherapy
- At least one TEAE leading to treatment modification of any component of study drug
  - At least one TEAE leading to treatment modification of ociperlimab/tislelizumab
  - At least one TEAE leading to treatment modification of chemotherapy
  - At least one TEAE leading to treatment modification of radiotherapy
- At least one TEAE related to any component of study drug
  - At least one TEAE related to ociperlimab/tislelizumab
  - At least one TEAE related to chemotherapy
  - At least one TEAE related to radiotherapy
  - At least one TEAE with grade ≥ 3 and related to any component of study drug
    - At least one TEAE with grade ≥ 3 and related to ociperlimab/tislelizumab
    - At least one TEAE with grade ≥ 3 and related to chemotherapy
    - At least one TEAE with grade ≥ 3 and related to radiotherapy
  - At least one serious TEAE related to any component of study treatment
    - At least one serious TEAE related to ociperlimab/tislelizumab
    - At least one serious TEAE related to chemotherapy

    - At least one serious TEAE related to radiotherapy
- At least one TEAE leading to death related to any component of study drug
    - At least one TEAE leading to death related to ociperlimab/tislelizumab
    - At least one TEAE leading to death related to chemotherapy
    - At least one TEAE leading to death related to radiotherapy
- At least one TEAE leading to treatment discontinuation and related to any component of study drug
- At least one TEAE leading to treatment modification and related to any component of study drug

Summaries of the following TEAE will be provided:

- TEAE by SOC and PT (any grade and grade ≥3)
- TEAE related to any component of study treatment by SOC and PT (any grade and grade ≥3)
- TEAE related to immunotherapy by SOC and PT (any grade and grade ≥3)
- TEAE related to chemotherapy by SOC and PT (any grade and grade ≥3)
- TEAE related to radiotherapy by SOC and PT (any grade and grade ≥3)
- Serious TEAE by SOC and PT
- Serious TEAE related to any component of study treatment by SOC and PT
- Serious TEAE related to immunotherapy by SOC and PT
- Serious TEAE related to chemotherapy by SOC and PT
- Serious TEAE related to radiotherapy by SOC and PT
- TEAE leading to discontinuation of any component of study treatment by SOC and PT (any grade and grade ≥3)
- TEAE leading to death by SOC and PT
- TEAE leading to dose modification of ociperlimab/tislelizumab by SOC and PT
- TEAE leading to dose modification of chemotherapy by SOC and PT
- TEAE leading to dose modification of radiotherapy by SOC and PT

Treatment-related AEs include those events considered by the investigator to be related to study treatment or with missing assessment of the causal relationship. For patients with multiple occurrences of the same event will be counted only once, and the maximum grade per CTCAE v5.0 will be used if CTCAE grade is needed.

Patient data listings of all AEs, SAEs, AE related to COVID-19 will be provided.

7.5.2.2 Immune-mediated Adverse Events

Immune-mediated AEs (imAE) will be identified from all AEs that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to 90 days from the last dose of study drug, regardless of whether the patient starts a new anti-cancer therapy.

Summaries of the following incidence of immune-mediated adverse events will be provided,

- Overview of immune-mediated adverse events
- Immune-mediated adverse events by category and PT (any grade and grade ≥3)
- Immune-mediated adverse events leading to death by category and PT
- Immune-mediated adverse events leading to treatment discontinuation by category and PT
- Immune-mediated adverse events outcome, time to onset, duration by category
- Immune-mediated adverse events treated with systemic corticosteroid by category

7.5.2.3 Infusion-related Adverse Event

For infusion-related reaction (IRR), an overview summary of IRR will be provided. In addition, a summary of incidence by SOC and PT will be provided, sorted by descending order of incidence within each SOC and PT based on Arm A.

7.5.2.4 Deaths

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

Number and causes of deaths, classified by deaths within 30 days of last dose of study drug and deaths more than 30 days after the last dose, will be summarized based on Safety Analysis Set.

Patient data listing of death and reason will be provided.

7.5.3 Laboratory Values

Hematology, serum chemistry, and thyroid function results will be summarized/listed for selected parameters described in Table 4.

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. Plots of laboratory values/change from baseline over time will be provided for selected lab parameters.

Laboratory parameters that are graded in NCI-CTCAE v.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 lab parameters with grades increased in at least 2 from baseline to worst post-baseline will also be summarized.

Potential Hy's Law for liver injury will also be summarized.

Table 4 Clinical Laboratory Assessments

Serum Chemistry	Hematology	Coagulation	Urinalysis	Thyroid Function
Potassium Sodium Chloride Creatinine Blood Urea Nitrogen Urea Albumin Total Protein Total Bilirubin Direct Bilirubin Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Alkaline phosphatase (ALP) Calcium Magnesium Phosphate Glucose Lactate dehydrogenase CK CK-MB (Activity) CK-MB (Mass) Troponin T Troponin I	Hemoglobin Hematocrit White Blood Cell Count Platelet Count Neutrophils Absolute Lymphocytes Absolute	Prothrombin time (PT) PTT aPTT International Normalized Ratio (INR)	Glucose Protein Ketones Blood WBC pH	Free Triiodothyronine (FT3) Free Thyroxine (FT4) Thyroid Stimulating Hormone (TSH)

7.5.4 Vital Signs

Patient data listing of vital signs will be provided.

7.5.5 Electrocardiograms (ECG)

ECG will be performed at the baseline and multiple time points after the start of treatment.

Abnormal post-baseline QTc results will be summarized with the following categories:

- Patients with increase of >30 msec, increase of >60 msec from baseline
- Patients with post-baseline value of >450 msec, value of >480 msec, value of >500 msec

Patient listing of all ECG recordings will be provided.

7.5.6 Eastern Cooperative Oncology Group (ECOG)

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

7.6 PHARMACOKINETIC ANALYSES

Pharmacokinetic samples will be collected in this study as outlined in Appendix 1 of Protocol.

The following analysis plan provides the framework for the summarization of the PK data from study AdvanTIG-204. The objective is to summarize available ociperlimab and tislelizumab PK concentrations following an IV administration. PK parameters will not be characterized as only sparse samples were collected.

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 analysis may be reported separately from the CSR.

7.6.1 Reporting of Pharmacokinetic Concentrations for Descriptive Statistics

The ociperlimab and tislelizumab serum concentration data will be listed and tabulated by visit/cycle at which these concentrations are collected per the study design. Descriptive statistics will include means, medians, ranges, standard deviations, coefficient of variation (CV%), geometric means, and geometric CV%, as appropriate.

7.7 IMMUNOGENICITY ANALYSES

Anti-drug antibodies (ADAs) samples will be collected in this study as outlined in Appendix 1 of 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 and will be reported separately from the CSR.

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 based on Immunogenicity Analysis Set. 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 detected only at one sampling time point during the treatment or follow-up observation period, or 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:** patients with positive NAb.
- **ADA prevalence:** The proportion of all patients that are ADA positive, including pre-existing ADA, at any time point.

8 INTERIM ANALYSIS

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

9 CHANGES IN THE PLANNED ANALYSIS

Table 5 summarizes the major changes in the planned analyses from the last approved version of the SAP including the timing, rational and descriptions of the changes. The changes are all made before final database lock.

Table 5 Statistical Analysis Plan

SAP version	Approval date	Change made from	Rationale of the change	Description of the change
1.0	17Jan2023	N/A	N/A	N/A

2.0	This version	SAP V1.0	1. Introduction: to adjust the biomarker analysis scope in the CSR. 2. Section 7.1: to define the treatment received in the safety analysis set when received wrong treatment; to refine the PD-L1 analysis set. 3. Section 7.3.2: to remove the critical PD summary and align with latest company PD handling SOP in which the critical PD no longer exists. 4. Section 7.3.3: to add a discordance summary of stratification factor between IRT and eCRF; to remove "childbearing potential of female patient" summary as it is not the focus of statistical analysis. 5. Section 7.4.1: to remove "clinical determination of progression" the as it is not applicable to this study; to remove the unstratified log-rank test and the associated p-value from PFS analysis; to move the unstratified Cox regression of PFS analysis in the Section sensitivity and supplementary analysis as it is part of sensitivity analysis; to clarify the PFS event date derivation rule in the supplementary analysis. 6. Sections 5.3 and 7.4.3: to remove the biomarker exploratory endpoint and analysis.	1. Introduction: deleted a language "will be attached to the clinical study report". 2. Section 7.1: added a language: "Patients in the safety analysis set will be classified according to treatment received, where treatment received is defined as (i) the intended treatment if it was received at least once, or (ii) the first treatment received if intended treatment is never received. Each patient will be classified into and analyzed consistently within one (and only one) treatment arm."; added a condition of evaluable PD-L1 measurement which is exclusively includes the measurement derived from tissue samples fixed with 10% formalin. 3. Section 7.3.2: removed the language of critical PD summary. 4. Section 7.3.3: added a language: "In addition, the stratification factor per IRT and per eCRF will be summarized based on ITT analysis set"; removed the category 'childbearing potential of female patient (Yes or No)'. 5. Section 7.4.1: removed the "clinical determination of progression" from the supplementary analysis language; removed the language of unstratified log-rank test "unstratified log-rank test will also be performed to provide p-

SAP version	Approval date	Change made from	Rationale of the change	Description of the change
			7. Section 7.5.1: to add language about the duration of exposure for chemotherapy; to update the algorithm of ADI calculation for chemotherapy. 8. Section 11.2: to correct the early death window algorithm. 9. Administrative changes for clarification.	value"; moved the unstratified Cox regression to the Section Sensitivity Analysis and Supplementary Analysis; replaced "PFS event date will be derived ignoring new anticancer therapy" with "PFS event date will be derived using the start date of new anticancer therapy". 6. Section 7.4.3: removed the exploratory biomarker analysis section. 7. Section 7.5.1: added language about the duration of exposure for chemotherapy when patients discontinue from treatment; updated the language for cisplatin exposure duration; replaced 'date of last dose up to cutoff' with 'first dose date of last cycle up to cutoff' in the denominator of ADI calculation; added the number of cycles in the last dosing eCRF page in the denominator of ADI calculation. 8. Section 11.2: updated the algorithm to define the time window: "19 weeks is defined as protocol specified interval between first two TAs plus the protocol allowed window." 9. Administrative changes for clarification in Sections 2, 4.1, 7.4.1.1, 7.5.1, 11.1, and 11.3.

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11 APPENDIX

11.1 Missing Data Imputation

Missing data will not be imputed unless otherwise specified. Missing data will not be imputed in the listings.

Concomitant Medication/Procedure

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:

If start date of a medication/therapy/procedure is partially missing, the imputation rules are as follows.

- If both month and day are missing, then set to January 01
- If only day is missing, then set to the first day 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, the imputation rules are 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 end date of a medication/therapy/procedure is missing, or the start date or end date is completely missing, do not impute.

Adverse Events

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. The following rules will be applied to impute partial dates for adverse events:

If start date of an adverse event is partially missing, the imputation rules are 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, then set to treatment start date
- If day is missing and month and year ≠ month and year of treatment start date, then set to first day 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)

If end date of an adverse event is partially missing, the imputation rules are 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 > min (death date, end of study date), then set to min (death date, end of study date)

If year of the start date or start date is completely missing, do not impute; if year of the end date or end date is completely missing, do not impute.

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.

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 – 6 months, then set to randomization date – 6 months
- For prior radiotherapy/locoregional therapy, if imputed end date > randomization date, then set to randomization date -1

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.

Subsequent anti-cancer therapy collected in the post-treatment page

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 anti-cancer therapy)

If stop 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 stop > 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.

11.2 Censoring Rules for Primary and Sensitivity Analysis of PFS Per RECIST version 1.1

Table 6 Censoring Rules for Primary and Sensitivity Analysis of PFS

No.	Situation	Date of Progression or Censoring	Primary Analysis	Supplementary Analysis	Sensitivity Analysis 1
1	No baseline or any post-baseline tumor assessments and without death within 19 weeks from reference start date*	Reference start date	Censored	Censored	Censored
2	Progression documented between scheduled visits	Date of first radiologic PD assessment	Progressed	Progressed	Progressed****
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	Censored	Censored
4	New anticancer treatment started	Date of last adequate radiologic assessment prior to or on date of new anticancer treatment	Censored	Progressed	Censored
5	Death before first PD assessment	Date of death	Progressed	Progressed	Progressed****
6	Death between adequate assessment visits**	Date of death	Progressed	Progressed	Progressed****

7	Death or progression after more than one missed visit***	Date of last adequate radiologic assessment before missed tumor assessments	Censored	Censored	Progressed at death or progression
8	No baseline or any post-baseline tumor assessments and died within 19 weeks from reference start date*	Date of death	Progressed	Progressed	Progressed****

The reference start date is the randomization date.
*19 weeks is defined as protocol specified interval between first two TAs plus the protocol allowed window.
**Adequate tumor assessment is a radiologic assessment of CR, PR, SD, non-CR/non-PD or PD as determined by the investigators.
***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 TAs plus the protocol allowed window around the assessments. Since tumor assessment is scheduled at approximately 12 weeks from the date of randomization, then every 6 weeks for the next 54 weeks, and then every 12 weeks thereafter based on RECIST v1.1, D2 is 12 weeks + 1 week in the 54 weeks period and 24 weeks + 1 week afterwards.
****Progression date for PFS event will be the earliest date of events defined in situation 2, 4, 5, 6, 8.

11.3 Rules for Identifying at Least One Missing Tumor Assessments

1) Input scheduled TA visit list:
    a. TA was performed at approximately 12 weeks (±7 days) from the date of randomization (an additional tumor assessment is allowed if clinically indicated), then every 6 weeks (± 7 days) for the next 54 weeks, and then every 12 weeks (± 7 days) thereafter based on RECIST v1.1: week 12, week 18, week 24, week 30, week 36, week 42, week 48, week 54, week 60, week 66, week 78, …
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., week 12 or week 18) as LPTADT_WK. It can be achieved programmatically by following the classification rule (e.g., defining thresholds) depicted in Table 7.
    b. Otherwise (i.e., scheduled TA), use the scheduled visit number (assuming it is coded correctly) to LPTADT_WK
3) Find the assumed 2nd TA visit after LPTADT_WK according to the list in Step 1 (LPTADT_WK_2):
    a. If LPTADT_WK_2 + 1 week < earliest date of PD/death, then PFS is censored at the LPTADT

Table 7 shows how to assign unscheduled TA to a scheduled 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 a 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 7 Example of Scheduled Tumor Assessments with Time Window

Weeks	Scheduled Week - 1	Scheduled Week	Scheduled Week + 1	Threshold
Baseline		Baseline		
TA was performed at approximately 12 weeks (±7 days) from the date of randomization	Week 11	Week 12	Week 13	Week 15
Every 6 weeks (± 7 days) for the next 54 weeks	Week 17	Week 18	Week 19	Week 21
	Week 23	Week 24	Week 25	Week 27
	Week 29	Week 30	Week 31	Week 33
	Week 35	Week 36	Week 37	Week 39
	Week 41	Week 42	Week 43	Week 45
	Week 47	Week 48	Week 49	Week 51
	Week 53	Week 54	Week 55	Week 57
	Week 59	Week 60	Week 61	Week 63
	Week 65	Week 66	Week 67	Week 72
Every 12 weeks (± 7 days) thereafter	Week 77	Week 78	Week 79	…
	…	…	…	…