BeiGene

STATISTICAL ANALYSIS PLAN

Study Protocol Number:	AdvanTIG-206
Study Protocol Title:	A Phase 2, Randomized, Open-labeled Clinical Study Investigating the Efficacy and Safety of Ociperlimab in Combination With Tislelizumab Plus BAT1706 and of Tislelizumab Plus BAT1706 as First-line Treatment in Patients With Advanced Hepatocellular Carcinoma
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ADA	Antidrug antibody
AE	Adverse event
BOR	Best overall response
CBR	Clinical benefit rate
CI	Confidence interval
CL	Clearance
COVID-19	Coronavirus disease of 2019
CR	Complete response
CSR	Clinical Study Report
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
EHS	Extrahepatic spread
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
imAE	Immune-mediated adverse event
IRT	Interactive Response Technology
IV	Intravenous

MedDRA	Medical Dictionary for Regulatory Activities
MVI	Macrovascular invasion
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PR	Partial response
PT	Preferred term
RECIST	Response Evaluation Criteria in Solid Tumors
Q3W	Once every 3 weeks
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SOC	System Organ Class
TA	Tumor assessment
TE	Treatment-emergent
TEAE	Treatment-emergent adverse event
TIGIT	T-cell immunoreceptor with Ig and ITIM domains
TTR	Time to response
QTcF	Fridericia's correction formula

vCPS	visually-estimated Combined Positive Score

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 study AdvanTIG-206: A Phase 2, Randomized, Open-labeled Clinical Study Investigating the Efficacy and Safety of Ociperlimab in Combination with Tislelizumab Plus BAT1706 and of Tislelizumab Plus BAT1706 as First-line Treatment in Patients with Advanced Hepatocellular Carcinoma. This SAP is based on AdvanTIG-206 Original Protocol 0.0, dated on March 03, 2021. The focus of this SAP is for the planned analysis specified in the study protocol. The analysis details for Pharmacokinetic (PK) and Immunogenicity are described in section 7.6 and 7.7 of this SAP. Analyses of pharmacodynamics and pharmacogenomics are not planned for this study. Other exploratory biomarker analyses may be planned and reported separately.

2. STUDY OVERVIEW

2.1. Study Design

This is a Phase 2, randomized, multicenter, open-label, 2-arm study to investigate the efficacy and safety of ociperlimab in combination with tislelizumab plus BAT1706, and tislelizumab plus BAT1706, as first-line treatment in patients with advanced HCC.

The study will enroll approximately 90 patients randomized in a 2:1 ratio to one of the 2 treatment arms:

- Arm A (n = 60): ociperlimab 900 mg intravenously once every 3 weeks (dosed in 21-day cycles) + tislelizumab 200 mg intravenously once every 3 weeks (dosed in 21-day cycles) + BAT1706 15 mg/kg intravenously once every 3 weeks (dosed in 21-day cycles)
- Arm B (n = 30): tislelizumab 200 mg intravenously once every 3 weeks (dosed in 21-day cycles) + BAT1706 15 mg/kg intravenously once every 3 weeks (dosed in 21-day cycles)

Randomization will be stratified according to the following factors:

- PD-L1 expression (visually estimated combined positive score [vCPS] <1% versus ≥1%) by SP263. The vCPS score is the total percentage of the tumor area covered by tumor cells with PD-L1 membrane staining at any intensity and tumor-associated immune cells with PD-L1 staining at any intensity.
- Macrovascular invasion (MVI)/Extrahepatic spread (EHS) (present versus absent).

The study design schema is shown in Figure 1.

At the beginning of this phase 2 study, a safety run-in period is planned to investigate the safety, tolerability, and PK before expanding the enrollment to additional patients.

The SMC will evaluate the safety data of the study treatments when the first 6 DLT-evaluable patients in Arm A and 3 DLT-evaluable patients in Arm B have completed the first 21 days of treatment. Based on these data, the SMC will recommend whether a dose modification is needed

or whether the current dosing regimen is tolerable. The final decision will be made by the sponsor.

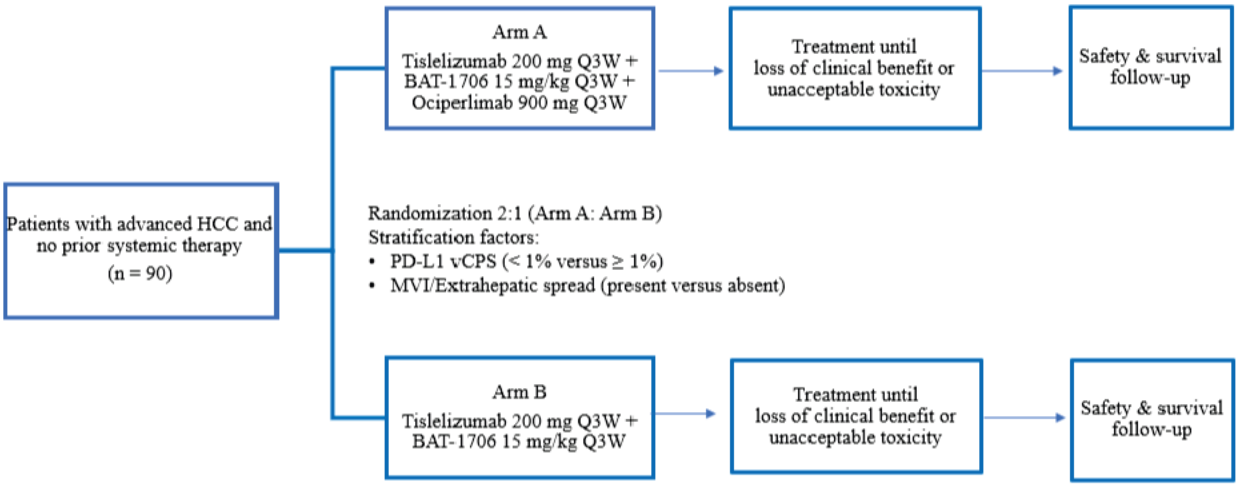
Arm A: For the first 6 patients enrolled in Arm A, if $\leqslant$ 1 in 6 patients experience a DLT, the dosing regimen is tolerable and will be used in subsequent cycles. If $\geqslant$ 2 in 6 patients experience a DLT, the starting dose will be considered as exceeding the MTD, and the sponsor will pause enrollment to allow for further evaluation of the safety data.

Arm B: For the first 3 patients enrolled in Arm B, if no patient experiences a DLT, the dosing regimen is tolerable and will be used in subsequent cycles. If >= 2 patients experience a DLT, the starting dose will be considered as exceeding MTD, and the sponsor will pause enrollment to allow for further evaluation of the safety data. If 1 out of 3 patients experiences a DLT, an additional 3 patients will be enrolled. In this case, if $\leqslant$ 1 in 6 patients experience a DLT, the dosing regimen is tolerable and will be used in subsequent cycles; if $\geqslant$ 2 in 6 patients experience a DLT, the starting dose will be considered as exceeding the MTD.

If a patient discontinues the study within the first 21 days of study due to reasons other than safety, or the clinical examination and/or assessment is incomplete, or the dose intensity of any drug is less than 80%, which leads to non-evaluable safety assessments within the first 21 days, additional patients may be required to be randomized to replace patients whose safety assessment cannot be performed.

Every effort should be made to ensure that each drug is administrated as originally scheduled. Patients who temporarily withhold or permanently discontinue a study drug due to related AEs may continue on the other study drug(s) as long as the patients are experiencing clinical benefit in the opinion of the investigator and after discussion with the medical monitor. However, for patients in Arm A, both ociperlimab and tislelizumab should be withheld or permanently discontinued simultaneously, if necessary.

Figure 1: Study Schema



Abbreviations: HCC, hepatocellular carcinoma; MVI: macrovascular invasion; PD-L1, programmed cell death protein-ligand 1; Q3W, every 3 weeks, vCPS, visually estimated combined positive score.

2.2. Study Assessments

Tumor imaging must be performed within 28 days prior to randomization. Results of standard-of-care tests or examinations performed before obtaining informed consent and ⩽ 28 days before randomization may be used for the purposes of screening rather than repeating the standard-of-care tests.

On-study tumor assessments will occur every 6 weeks (±7 days) from Day 1 of Cycle 1 for the first 48 weeks and every 12 weeks (±7 days) thereafter based on RECIST v1.1. Tumor assessment should continue as planned in patients receiving study drug(s) after initial investigator-assessed progressive disease (PD). Tumor assessment in such patients should continue until all study drugs are discontinued. A patient who discontinues study drugs for reasons other than PD (eg, toxicity) will continue to undergo tumor assessments in accordance with the original schedule until PD, begins subsequent anticancer therapy, withdrawal of consent, loss to follow-up, death, or until study termination, whichever occurs first.

Patients will be evaluated for any adverse events (AEs) and serious adverse events (SAEs) occurring up to 30 days after the last dose of study drug (all severity grades), per National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] v5.0 or until initiation of new anticancer therapy, whichever occurs first, and for immune-mediated AEs (imAEs) occurring up to 90 days after the last dose of tislelizumab and ociperlimab regardless of whether or not the patient starts a new anticancer therapy. All SAEs considered related to the study drug(s) that are brought to the attention of the investigator should be reported regardless of time since the last dose of study drug, until patient death, withdrawal of consent, or loss to follow-up, whichever occurs first.

3. STUDY OBJECTIVES

3.1. Primary Objective

- To evaluate the efficacy of ociperlimab in combination with tislelizumab plus BAT1706, and tislelizumab plus BAT1706 through the objective response rate (ORR), as assessed by the investigator according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) as first-line treatment in patients with advanced hepatocellular carcinoma

3.2. Secondary Objective

- To assess the efficacy of ociperlimab in combination with tislelizumab plus BAT1706, and tislelizumab plus BAT1706, through duration of response (DOR), time to response (TTR), disease control rate (DCR), clinical benefit rate (CBR) and progression-free survival (PFS) as assessed by the investigators; and overall survival (OS)
- To assess the safety and tolerability of ociperlimab in combination with tislelizumab plus BAT1706, and tislelizumab plus BAT1706

- To characterize the pharmacokinetics (PK) of ociperlimab in combination with tislelizumab plus BAT1706, and tislelizumab plus BAT1706
- To determine host immunogenicity to ociperlimab, tislelizumab, and BAT1706

3.3. Exploratory Objective

- To explore potential biomarkers that may correlate with clinical responses/resistance to ociperlimab in combination with tislelizumab plus BAT1706, and to tislelizumab plus BAT1706

4. DEFINITION OF PRIMARY ESTIMAND

The primary scientific question of interest is: "Will ociperlimab in combination with tislelizumab plus BAT1706 increase the objective response rate (ORR) compared to tislelizumab plus BAT1706 as first-line treatment in patients with advanced hepatocellular carcinoma (HCC), before the patients have PD or start new anticancer therapy whichever occurs first?"

The primary estimand is described by the following attributes:

1) Treatment of interest:
    a. The study experimental treatment is ociperlimab 900 mg + tislelizumab 200 mg + BAT1706 15 mg/kg. The study control treatment for comparison is tislelizumab 200mg + BAT1706 15 mg/kg.
2) Population:
    a. Patients with histologically confirmed advanced HCC who had no prior systemic therapy of the disease and is not amenable to curative treatment.
3) Variable:
    a. The primary variable is a binary response variable of each patient, defined as whether or not the patient achieved objective response, including CR, or PR, as determined by the investigator using the response criteria RECIST v1.1.
4) Handling of remaining intercurrent events:
    a. New anticancer therapy started prior to disease progression or death: Patients starting any new anticancer therapy without achieving an objective response before will be considered as non-responders (composite strategy).
    b. Discontinuation of treatment prior to disease progression or death: response assessment after discontinuation of treatment will be counted and used for analysis (treatment policy strategy).;
5) Population-level summary:
    a. The difference in ORR of the study treatments.

5. STUDY ENDPOINTS

5.1. Primary Endpoint(s)

- ORR, as assessed by the investigator, defined as the proportion of patients with a confirmed complete response (CR) or partial response (PR) per RECIST v1.1

5.2. Secondary Endpoints

- DOR, TTR, DCR, CBR, and PFS as assessed by the investigator
  - DOR, defined as the time from the first confirmed objective response until the first documentation of disease progression or death, whichever comes first
  - TTR, defined as the time from the randomization date to the first documentation of response
  - DCR, defined as the proportion of patients who achieve CR, PR, or stable disease
  - CBR, defined as the proportion of patients who achieve CR, PR, or durable stable disease (stable disease $\geq$ 24 weeks)
  - PFS, defined as the time from the randomization date to the date of first documentation of disease progression or death, whichever occurs first
- OS, defined as the time from the randomization date until the date of death from any cause
- Incidence and severity of adverse events (AEs), with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v5.0, vital signs, and clinical laboratory test results
- Serum concentrations of ociperlimab, tislelizumab, and BAT1706 at specified timepoints
- Immunogenic responses to ociperlimab, tislelizumab, and BAT1706 evaluated through detection of ADAs

6. SAMPLE SIZE CONSIDERATIONS

This study plans to enroll approximately 90 patients, with 2:1 randomization to

- Arm A (60 patients): tislelizumab + BAT1706 + ociperlimab
- Arm B (30 patients): tislelizumab + BAT1706

These patients will be enrolled to evaluate the preliminary efficacy of tislelizumab plus BAT1706 with or without ociperlimab.

No formal hypothesis testing is planned in the efficacy evaluation.

7. STATISTICAL METHODS

7.1. Analysis Sets

The Intent-to-Treat (ITT) Analysis Set includes all randomized patients. Patients will be analyzed according to their randomized treatment arm (ie, Arm A or Arm B). This will be the primary analysis set for all efficacy analyses.

The Safety Analysis Set (SAS) includes all patients who received ≥ 1 dose of study drugs and will be the primary analysis set for the safety analyses.

The Efficacy Evaluable Analysis Set (EAS) includes all patients in the ITT Analysis Set who had measurable disease at baseline and ≥ 1 evaluable postbaseline tumor response assessment unless discontinued due to any clinical PD or death within 7 weeks after randomization date. This analysis set will be used for supplementary analysis of the primary efficacy endpoint ORR.

The DLT Evaluable Analysis Set includes patients enrolled during the safety run-in period who

- received ≥ 80% of scheduled ociperlimab (if applicable), ≥ 80% of scheduled tislelizumab, and ≥ 80% of scheduled BAT1706 administration during the DLT assessment window (ie, within 21 days of the first dose of study drugs), remained on study during the DLT observation period, and had sufficient safety evaluation performed.

  OR

- experienced a DLT within the DLT observation period.

The PK Analysis Set includes all patients who receive ≥ 1 dose of any component of study drugs (i.e., ociperlimab or tislelizumab or BAT1706) per the protocol, and for whom any postdose PK data are available.

The Immunogenicity Analysis Set includes all patients who receive ≥ 1 dose of any component of study drugs (i.e., ociperlimab or tislelizumab or BAT1706) and for whom both baseline ADA and ≥1 postbaseline ADA results are available.

7.2. Data Analysis General Considerations

7.2.1. Definitions and Computations

Study drugs include ociperlimab (BGB-A1217), tislelizumab (BGB-A317) and BAT1706.

Study day will be calculated in reference to the date of the first dose of study drug. For assessments conducted on or after the date of first dose of study drug, the study day will be calculated as (assessment date – date of the first dose of study drug + 1). For assessments conducted before the date of first dose of study drug, study day is calculated as (assessment date – date of the first dose of study drug). There is no study day 0. In the situation where the event date is partial or missing, the date will appear partial or missing in the listings.

For efficacy evaluation and stratification factors, a baseline value is defined as the last non-missing value collected prior to the randomization.

For other baseline characteristics, a baseline value is defined as the last non-missing value collected before the first dose of study drug. If no dose was given, use randomization date instead.

All calculations and analyses will be conducted using SAS® Version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina).

7.2.2. Conventions

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'.
- Duration of image-based event endpoints (such as PFS and DFS) will be based on the actual date the radiograph was obtained rather than the associated visit date.
- For laboratory results collected as in numerical range, if lab results >= x or >x then set as x; if < x or <=x, then x/2.
- For by-visit observed data analyses, percentages will be calculated based on the number of patients with non-missing data as the denominator, unless otherwise specified.
- For continuous endpoints, summary statistics will include n, mean, standard deviation, median, Q1, Q3 and range (minimum and maximum).
- For discrete endpoints, summary statistics will include frequencies and percentages.

7.2.3. Handling of Missing Data

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

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

7.2.4. Multiplicity Adjustment

Not applicable.

7.3. Patient Characteristics

7.3.1. Patient Disposition

The summary of patient disposition will be based on ITT Analysis Set.

The number (percentage) of patients who signed informed consent, randomized, and screen-failed will be summarized. The number (percentage) of screen failure reason will also be summarized.

The number (percentage) of patients randomized, randomized but not treated, treated, and discontinued from the study/ the combination therapy/ each compound will be summarized.

Reason for randomized but not treated and discontinued from the study will be summarized. The reason for discontinuation from the combination therapy and each compound will be summarized among patients who were treated. The reasons for treatment/study discontinuation related to COVID-19 will also be presented in the disposition table if any.

Duration of study follow-up 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 time is defined as the time from the randomization date of the last randomized patient to the data cut-off date. Both statistics will be summarized in the disposition table.

A corresponding listing 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. Important protocol deviations will be reviewed and summarized for all patients in the ITT Analysis Set, and also listed by category and subcategory. Deviation categories are not mutually exclusive. Multiple deviations within the same category and subcategory are counted once per patient.

Critical protocol deviation that may significantly impacts efficacy or safety will be reviewed prior to data base lock according to the criteria defined in protocol deviation specification. Critical protocol deviations generally are a subset of the important protocol deviations and will be determined from the final PD listing. Critical protocol deviation should fall in any of the following criteria:

- Patient was enrolled, but had not met the inclusion criteria #3, or #5, or #6, and/or met the exclusion criteria #3.
  - Inclusion Criteria 3

    Has a histologically confirmed HCC, which is either BCLC Stage C disease, or BCLC Stage B disease that is not amenable to or has progressed after locoregional therapy, and is not amenable to a curative treatment approach.
  - Inclusion Criteria 5

Has received no prior systemic therapy for HCC.

Note: Patients who have received prior liver loco-regional therapy (eg, transarterial chemoembolization [TACE]) are not excluded. Neoadjuvant/adjuvant use of small molecule tyrosine kinase inhibitors before/after liver locoregional therapy, eg, liver surgery or TACE, is permitted if progression is documented on or after the locoregional therapy.

- Inclusion Criteria 6

  At least 1 measurable lesion as defined per RECIST v1.1.

  Note: A lesion in an area subjected to prior loco-regional therapy, including previous TACE and radiofrequency ablation (RFA), is not considered measurable unless, since the therapy, there has been evidence of lesion progression as defined by RECIST v1.1.

- Exclusion Criteria 3

  Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2 or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathway; prior treatment with bevacizumab or its biosimilars.

- Using concurrent anticancer therapy, which was prohibited by the protocol.
- Wrong stratum of randomization: Sites provide incorrect stratification data in IRT for subject randomization.

Critical protocol deviations will be summarized for all patients in the ITT Analysis Set, and listed by category and subcategory.

Important protocol deviations and critical protocol deviations related to COVID-19 will also be summarized if any. In addition, missed/delayed visits and tumor assessments due to COVID-19 will be tabulated or listed.

7.3.3. Demographic and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized using descriptive statistics in the ITT Analysis Set, including:

- Age
- Age Group (< 65 vs ≥ 65 years)
- Sex
- Race
- Ethnicity
- Geographic Region
- Weight
- BMI

- ECOG Performance Status
- Tobacco Use Status
- Alcohol Consumption Status

In addition, the stratification factors per IRT and per central Lab/eCRF will be summarized based on ITT analysis set:

- PD-L1 expression (<1% vs >=1%)
- MVI/EHS status (Present vs Absent)

The value of MVI/EHS status is 'Present' if any of the MVI status and EHS status is 'Present'.

7.3.4. Disease History

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

- BCLC initial staging
- Time From Initial Diagnosis to Randomization Date
- BCLC stage at study entry
- Time From Date of Diagnosis for Staging at Study Entry to Randomization Date
- EHS status (Present vs Absent)
- Time From Date of Initial Diagnosis of Metastatic Disease to Randomization Date
- Location(s) of metastases at study entry
- Number of Metastatic Sites
- Child-Pugh Classification/Score at Study Entry
- Histological type at study entry
- MVI status (Present vs Absent)
- Viral Status (HBV Infected only, HCV Infected only, HBV and HCV Co-infected, Uninfected)
- Alpha-fetoprotein at Baseline (<= 200, > 200 to 400, >400)

The value of EHS status is taken from the question 'Metastatic disease status at study entry?' in disease history page. If 'Metastatic' is chosen, then EHS status = 'present'; otherwise, it is 'absent'. A 'Missing' category will be added to categorical variables if there is any patient has no baseline result of the variable.

A listing of disease history and characteristics will be provided.

7.3.5. Prior Anticancer Therapies

Number (percentage) of patients with any prior therapy for cancer will be summarized in ITT analysis set. Prior anti-cancer drug therapies, prior anti-cancer radiotherapy [except liver], and prior liver local regional therapy will also be summarized in the ITT Analysis Set.

7.3.5.1 Prior Systemic Therapy for cancer

Number (percentage) of patients with any prior systemic therapy for cancer will be summarized.

7.3.5.2 Prior Anti-cancer radiotherapy [except liver]

The number (percentage) of patient with at least one prior anti-cancer radiotherapy [except liver] and treatment setting will be summarized.

7.3.5.3 Prior Liver Local Regional Therapy

Therapy type, number of prior liver local regional therapy, time from last prior liver local regional therapy to randomization date will be summarized. Treatment intent of TACE Therapy (transarterial chemoembolization) and other liver local regional therapies will be summarized respectively.

Patient data listings of prior anti-cancer radiotherapy [except liver], prior liver local regional therapy will be provided accordingly.

7.3.6. Prior and Concomitant Medications

Prior medications are defined as medications that started and stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 days after the patient's last dose. It is noteworthy that the study protocol uses randomization date to defined prior medication and concomitant medication. The definition in this SAP is different from the one in the protocol so that to fine tune the identification of prior and concomitant medications.

Prior and concomitant medications will be coded using drug codes of World Health Organization Drug Dictionary (WHO DD) Global B3 March 1, 2021 or higher. They 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.

7.3.7. Prior and Concomitant Surgeries/Procedures

Prior and concomitant surgeries/procedures may be summarized in the Safety Analysis Set if deemed necessary.

7.3.8. Medical History

Medical History will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 or higher. The number (percentage) of patients reporting a history of any medical condition, as recorded on the CRF, will be summarized by system organ class and preferred term in the ITT Analysis Set.

7.3.9. Subsequent Anti-cancer Therapy

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

- As for efficacy analysis, 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.

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

ORR, PFS or OS benefit of Chinese herbal medicines or Chinese patent medicines (traditional Chinese medicine, TCM) has not yet been established. Therefore, TCM will not be considered as new anti-cancer therapy in the efficacy and safety analysis.

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

The number (percentage) of patients by category, regimen number and treatment intent will be summarized for subsequent systemic anticancer therapy. Time from last dose date to first post-treatment anti-cancer systemic therapy will be summarized descriptively. Patient data listings of post-treatment systemic anti-cancer therapy, procedure/surgery and radiotherapy will be provided.

7.4. Efficacy Analysis

To evaluate the efficacy of the study treatments through ORR is the primary objective of the study. Response assessments will be determined by investigator using RECIST v1.1.

Efficacy Analyses will be provided by subgroups as appropriate, such as PD-L1 subgroups, etc. Per-patient listings may be generated with limited patients for analysis.

The value of the stratification factors used at randomization (collected in IRT), including PD-L1 expression (<1%, >= 1%) and MVI/EHS (present, absent), will be used in the analysis of primary endpoint ORR, secondary endpoints PFS and OS. The actual value of the stratification factors (collected in central Lab/eCRF) may be used for sensitivity analyses if the discrepancy between IRT and central Lab/eCRF is considerable.

7.4.1. Primary Efficacy Analyses

Primary Analysis for Primary Estimand

The primary efficacy endpoint is confirmed ORR as determined by investigator using the RECIST v1.1. ORR is defined as the proportion of patients achieving confirmed BOR of CR or PR. BOR is defined as the best response recorded from the randomization date until progressive disease (PD) or the initiation of new anticancer treatment, whichever occurs earlier. Patients with

no postbaseline response assessment (due to any reason) will be considered as non-responders for BOR. The proportion of patients in each response category will be presented.

ORR will be summarized with a Clopper-Pearson 95% CI constructed to assess the precision of the point estimate. Mantel-Haenszel common odds ratio will be estimated along with its 95% CI constructed by a normal approximation of log odds ratio and the Robins, Breslow, and Greenland variance estimate, stratified by PD-L1 expression and MVI/EHS. Stratified Mantel-Haenszel common risk difference (Mantel and Haenszel, 1959) will be calculated along with its 95% CIs constructed by a normal approximation and Sato's variance estimator (Sato, 1989). A p-value will be obtained using the Cochran-Mantel-Haenszel method stratified by PD-L1 expression and MVI/EHS. It is noteworthy that the p-value is for descriptive purpose only as no formal hypothesis testing was planned in the protocol.

The primary efficacy analysis will be conducted when ORR data are mature, which is 7.5 months (approximately 5 tumor assessments) after the last patient receives the first dose of study drug and will be based on the ITT Analysis Set. Unconfirmed ORR will also be presented for ITT analysis set.

Supplementary Analysis

ORR will be summarized similarly in Efficacy Evaluable Analysis Set as supplementary analysis.

7.4.2. Secondary Efficacy Analyses

Other efficacy endpoints with necessary tumor assessments (ie, DOR, PFS, TTR, DCR and CBR), as well as OS, will be summarized for secondary efficacy analysis. The secondary efficacy analysis will be conducted in ITT analysis set.

Disease Control Rate (DCR)

DCR is defined as the proportion of patients who achieve BOR of CR, PR, or SD. DCR will be estimated with a Clopper-Pearson 95% CI in the ITT Analysis Set and also in Efficacy Evaluable Analysis Set.

Clinical Benefit Rate (CBR)

CBR is defined as the proportion of patients who achieve BOR of CR, PR, or durable SD (SD ≥ 24 weeks). CBR will be estimated with a Clopper-Pearson 95% CI in the ITT Analysis Set and also in the Efficacy Evaluable Analysis Set.

Progression Free Survival (PFS)

PFS is defined as the time from randomization date to disease progression or death due to any cause, whichever occurs first. The definition of PFS in the protocol uses first dose date as the start point. This definition is modified in SAP to facilitate comparison between the two treatment arms.

Medians and other quartiles will be estimated by the Kaplan-Meier method with 95% CIs estimated using the Brookmeyer and Crowley method (Brookmeyer and Crowley, 1982) with

log-log transformation. Event-free rates at selected timepoints, e.g., 3 months, 6 months, 9 months, and 12 months, will be estimated using the Kaplan-Meier method with 95% CIs estimated using the Greenwood formula (Greenwood, 1926).

Hazard ratio of PFS and 95% CIs will be computed using a Cox regression model stratified by PD-L1 expression and MVI/EHS. A log-rank test stratified by PD-L1 expression and MVI/EHS will be applied to obtain the p-value for descriptive purpose. Kaplan Meier curves will be constructed to provide a visual description of the PFS change with time.

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 missing two or more consecutive tumor assessments. Clinical or symptomatic progressions without supporting radiologic data will not be considered as PFS events.

Table 1 shows the derivation rules for PFS.

Table 1: Censoring rules of Progression-free Survival Per RECIST Version 1.1

	Derivation rules	**Outcome**
No progression at the time of data cut-off or withdrawal from study or lost to follow up	Date of last adequate radiologic assessment prior to or on date of data cut-off or withdrawal from study	Censored
New anticancer therapy started prior to disease progression or death	Last adequate disease assessment before the new anticancer therapy	Censored
No baseline or post-baseline tumor assessments and without death within 13 weeks after randomization	Date of randomization	Censored
No baseline or post-baseline tumor assessments and with death within 13 weeks after randomization	Date of death	Event
Death or progression after more than one missed visit	Date of last adequate radiologic assessment before missed tumor assessments	Censored
Progression documented between scheduled visits	Date of first radiologic PD assessment	Event
Death between adequate assessment visits	Date of death	Event

*Adequate tumor assessment is a radiologic assessment of CR, PR, SD, non-CR/non-PD or PD as determined by the reviewers.

** More than one missed visit is identified in Appendix.

Duration of Response (DOR)

DOR is defined as the time from the first confirmed objective response to disease progression documented after randomization or death, whichever occurs first.

DOR will be analyzed among the responders with confirmed PR or CR in the ITT Analysis Set. The censoring rule for DOR will follow the PFS censoring rule. Median and other quantiles of DOR and event-free rates at specific time points will be summarized using the same method as PFS.

Time to Response (TTR)

TTR is defined as the time from randomization date to the first documented response. The definition of TTR in the protocol uses first dose date as the start point. This definition is modified in SAP to facilitate comparison between the two treatment arms.

TTR will be summarized for responders (who have achieved an objective response) only using descriptive statistics such as mean, median, Q1, Q3, min, max and standard deviation.

Other analysis regarding tumor assessments

Waterfall plots will be provided for the maximum tumor shrinkage based on target lesion(s). In addition, patients will be marked out in the plot for those who had tumor reduction in target lesion assessments but contradicted to the PD results in overall response due to new-lesion or non-target lesion.

Overall Survival (OS)

OS is defined as the time from randomization date to death due to any cause. The definition of OS in the protocol uses first dose date as the start point. This definition is modified in SAP to facilitate comparison between the two treatment arms.

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.

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.

OS will be analyzed in the ITT Analysis Set using methods similar to those described for PFS. OS rates at specific time points will be calculated based on Kaplan-Meier method.

7.4.3. Subgroup Analyses

Subgroup analysis on key efficacy endpoints (ORR, PFS, etc.) will be conducted to explore the consistency of efficacy across a variety of subgroups, as appropriate. Subgroup variables at baseline may include but are not limited to Age (< 65 Years, >= 65 Years), Sex (Male, Female), ECOG Performance Status (0, 1), PD-L1 expression (>=1%, <1%), EHS status (present, absent), MVI status (present, absent), EHS/MVI status (present, absent), Viral Status (HBV, HCV,

Uninfected), BCLC stage at study entry (Stage B, stage C), TIGIT expression (>=1%, <1%), Alpha-fetoprotein at Baseline (<= 200, > 200, Missing) , Alpha-fetoprotein at Baseline (<= 400, > 400, Missing) .

7.5. Safety Analyses

Safety will be assessed by monitoring and recording of AEs and laboratory values (e.g., hematology, clinical chemistry). Vital signs, physical examinations, and ECG findings will also be used in determining the safety profile. Descriptive summary statistics (e.g., n, mean, standard deviation, median, minimum, and maximum for continuous variables; n [%] for categorical variables) will be used to analyze all safety data.

All safety analyses will be performed by arm based on the Safety Analysis Set.

7.5.1. Extent of Exposure

The following measures of the extent of exposure will be summarized for Ociperlimab, Tislelizumab and BAT1706 (One cycle is defined as 21 days of treatment):

- Duration of exposure (months): will be calculated as (last date of exposure - first dose date + 1)/30.4375, where data cutoff date is used as last date of exposure for ongoing patients, and min(cutoff date, death date, last dose date + 20) is used for discontinued patients (with non-missing EOT date).
- Number of treatment cycles received: defined as the total number of treatment cycles in which at least one dose of the study drug is administered.
- Cumulative dose Administered (mg): defined as the cumulative dose of the study drug during the treatment period of the study. It will be calculated by summing all actual doses per administration at all visits prior to or on the cutoff date.
- Actual dose intensity: for ociperlimab and tislelizumab, actual dose intensity (mg/cycle) is defined as

$$\frac{\sum_1^{\#of\ cycles} actual\ dose \times 21}{last\ dose\ date\ up\ to\ cutoff\ date - first\ dose\ date\ +\ 21}$$

  For BAT1706, actual dose intensity (mg/kg/cycle) is defined as

$$\frac{\sum_1^{\#of\ cycles} \frac{actual\ dose}{weight} \times 21}{last\ dose\ date\ up\ to\ cutoff\ date - first\ dose\ date\ +\ 21}$$

  where weight refers to the weight used in dose calculation, that is, baseline weight unless there is a weight change of > 10%.

- Relative dose intensity (%): defined as the ratio of the actual dose intensity and the planned dose intensity. The value of planned dose intensity is identical to the planned one cycle dose. Planned dose intensities for tislelizumab and ociperlimab (mg/cycle) are 200 mg/cycle and 900 mg/cycle, respectively. The planned dose intensity of BAT1706 is 15 (mg/kg/cycle).

In this study, treatment modification of BAT1706/Tislelizumab/Ociperlimab includes infusion interruption and dose delay. The number of patients with dose delays and dose interruptions will

be summarized by counts and percentages according to study drug. The number of patients with treatment modification due to COVID-19 will also be summarized. In addition, frequency of infusion interruptions will be summarized by categories (1, 2, >2).

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

7.5.2. Adverse Events

AEs will be graded by the investigators using CTCAE version 5.0. The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using MedDRA. Adverse events will be coded to the MedDRA Version 24.0 or higher lowest level term closest to the verbatim term, along with the linked MedDRA preferred term (PT) and primary system organ class (SOC).

7.5.2.1. Treatment-emergent Adverse Event

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

It is noteworthy that the definition of TEAE in the protocol is different from the one in this SAP, while the definition of imAE remains the same. The update of TEAE window streamlines the TEAE derivation so all TEAEs can be identified programmatically without undergoing the identification process of imAE. imAE occurring outside of the above mentioned TEAE window will not be classified as treatment-emergent adverse events. All imAE will be reported separately.

An AE overview table, including the number and percentage of patients with TEAEs, treatment-emergent serious adverse events (SAEs), TEAEs with Grade 3 or above, TEAEs that led to death excluding/including death due to disease under study, TEAEs that led to treatment discontinuation, TEAEs that led to treatment modification, treatment-related version of any of the above categories will be provided. DLT will also be summarized. Treatment-related AEs include those events considered by the investigator to be related to study drug or with a missing assessment of the causal relationship.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by SOC, PT and the worst grade. A patient will be counted only once by the highest severity grade within a SOC and PT, even if the patient experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of patients with TEAEs will also be summarized by relationship to the study drug.

Summaries of the following TEAEs will be provided:

- TEAEs by SOC and PT
- TEAEs >= Grade 3 by SOC, PT, and Worst Grade

- Treatment-related TEAEs by SOC and PT, AND
  - Treatment-related TEAEs of Tislelizumab by SOC and PT
  - Treatment-related TEAEs of Ociperlimab by SOC and PT
  - Treatment-related TEAEs of BAT1706 by SOC and PT
- Treatment-related TEAEs with Grade >=3 by SOC, PT, and Worst Grade
- Serious, TEAEs by SOC and PT
- Serious, Treatment-related TEAEs by SOC and PT, AND
  - Serious, Treatment-related TEAEs of Tislelizumab by SOC and PT
  - Serious, Treatment-related TEAEs of Ociperlimab by SOC and PT
  - Serious, Treatment-related TEAEs of BAT1706 by SOC and PT
- TEAEs Leading to Death Excluding death due to disease under study by SOC and PT
- TEAEs Leading to Death Including death due to disease under study by SOC and PT
- TEAEs Leading to Treatment Discontinuation by SOC and PT, AND
  - TEAEs Leading to Tislelizumab Discontinuation by SOC and PT
  - TEAEs Leading to Ociperlimab Discontinuation by SOC and PT
  - TEAEs Leading to BAT1706 Discontinuation by SOC and PT
- TEAEs Leading to Treatment Modification by SOC and PT, AND
  - TEAEs Leading to Modification of Tislelizumab by SOC and PT
  - TEAEs Leading to Modification of Ociperlimab by SOC and PT
  - TEAEs Leading to Modification of BAT1706 by SOC and PT
- Treatment-related TEAEs Leading to Death Excluding death due to disease under study by SOC and PT
- Treatment-related TEAEs Leading to Treatment Discontinuation by System Organ Class and Preferred Term
- Treatment-related TEAEs Leading to Treatment Modification by System Organ Class and Preferred Term

The TEAEs listed above may also be summarized by PT or by PT and worst grade as appropriate.

DLT will only be assessed in safety run-in period. All DLTs will be flagged for patients in DLT evaluable analysis set in the listing of AE.

7.5.2.2. Immune-mediated Adverse Event

Immune-mediated adverse events (serious or nonserious) were reported until 90 days after the last dose of all study drugs regardless of initiation of a new anti-cancer therapy.

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

An overview table will be provided. In addition, summaries of the following incidences of immune-mediated adverse events will be provided:

- imAEs by Category
- imAEs by Category and PT

- imAEs leading to Death Excluding Death Due to Disease Under Study by Category and PT
- imAEs leading to Tislelizumab Discontinuation by Category and PT
- imAEs leading to Ociperlimab Discontinuation by Category and PT
- imAEs leading to BAT1706 Discontinuation by Category and PT
- imAEs Outcome, Time to Onset, and Duration by Category
- Summary of imAEs Treated with Systemic Corticosteroids by Category

7.5.2.3. Infusion-related Adverse Event

The symptoms of infusion-related reactions may include, but are not limited to, fever, chills/rigor, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness, or hypertension. Severe reactions may include acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, or cardiogenic shock. The following process was used for the final determination of IRRs:

a. The investigator/site must have checked the IRR box on the AE pages in the CRF.

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, an overview table will be provided. Summary of incidence by SOC & PT and by PT will be provided.

7.5.2.4. Deaths

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. 'Related to COVID-19' will be shown under the reasons that are related to COVID-19. A patient listing of death will be provided.

To determine whether the death occurred within or post 30 days after last dose, death with missing month and/or day will be imputed as follows: impute max (last available date showing patients alive + 1, first day of year/month of death date) only if it is partially missing. Then the decision would be made based on the imputed death date(s).

7.5.3. Laboratory Values

Local laboratory assessments of clinical chemistry, hematology, coagulation, and urinalysis will be conducted, of which certain elements will be collected as specified in Table 2. Parameters selected from Table 2 will be summarized as appropriate.

Laboratory parameters that are graded in NCI CTCAE Version 5.0 will be summarized by shifts from baseline CTCAE grades to maximum post-baseline grades, as appropriate. In the summary of laboratory parameters by CTCAE grade, parameters with CTCAE grading in both high and low directions will be summarized separately.

Summary of liver laboratory abnormalities and thyroid laboratory test will also be provided. The criteria for identifying potential Hy's Law cases may be adjusted as deemed necessary, considering that the inclusion/exclusion criteria for this study allow patients with more severe hepatic conditions to be enrolled.

Box-whisker plots will be generated for parameters of interest.

Patient data listings will be provided as appropriate.

Table 2: Clinical Laboratory Assessments

Serum Chemistry	Hematology	Coagulation	Urinalysis	Thyroid Function
Alkaline phosphatase	Hemoglobin	Prothrombin time	pH	Thyroid stimulating hormone
Alanine aminotransferase	Hematocrit	Partial thromboplastin time or activated partial thromboplastin time	Specific gravity	Free triiodothyronine
Aspartate aminotransferase	Platelet counts	International normalized ratio	Glucose	Free thyroxine
Albumin	White blood cell count		Protein	
Total bilirubin	Lymphocyte count		Ketones	
Direct bilirubin	Neutrophil count		Blood	
Blood Urea Nitrogen or urea			24-hour protein	
Chloride				
Creatinine				
Calcium				
Phosphorus				
Glucose				
Lactate dehydrogenase				
Total Protein				
Potassium				
Sodium				
Magnesium				

Serum Chemistry	Hematology	Coagulation	Urinalysis	Thyroid Function
Creatine kinase/CK-MB*				

* CK-MB: creatine kinase-muscle/brain.

7.5.4. Vital Signs

The change from baseline might be summarized for all vital sign parameters except for height. Vital signs will be listed by patient and visit. Box-whisker plot will be generated for parameters of interest, as appropriate.

7.5.5. Physical Examination

Physical examination will be assessed during screening and study visits. Physical examination findings prior to first dose of study treatment will be collected in medical history, clinically significant abnormalities found in physical examination will be reported in adverse events. No separate physical examination data will be collected and reported in this study.

7.5.6. Ophthalmologic Examination

A data listing of ophthalmologic examination results will be provided, as appropriate.

7.5.7. Electrocardiograms (ECG)

QT intervals corrected with Fridericia's formula (QTcF) will be summarized by arm using descriptive statistics, where QTcF = QT interval / ((60/heart rate)^0.33).

The number and percentage of patients satisfying the following QT and QTcF conditions at any time post-baseline will be summarized:

- >450, > 480, or > 500 msec
- > 30 or > 60 msec maximum increase from baseline

Patient listing of ECG will be provided for all ECG recordings.

7.5.8. Eastern Cooperative Oncology Group Performance Status (ECOG PS)

A shift table from baseline to worst post-baseline in ECOG performance status will be summarized. ECOG status will be summarized by visit and arm, as appropriate.

7.6. Pharmacokinetic Analyses

PK samples will be collected in this study as outlined in Appendix 1 of original protocol.

The following analysis plan provides the framework for the summarization of the PK data from study AdvanTIG-206. The objective is to summarize available ociperlimab, tislelizumab, and BAT1706 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, tislelizumab and BAT1706 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, tislelizumab, and BAT1706, 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 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 or follow-up observation period, 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. CHANGES IN THE PLANNED ANALYSIS

Not applicable.

9. REFERENCES

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics. 1982; 38:29-41.

Greenwood M. The Natural Duration of Cancer. Reports on Public health and medical subjects. 1926; 33:1-26.

Kaplan E, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958; 53:457-81.

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

Robins, J. M., Breslow, N., and Greenland, S. Estimators of the Mantel-Haenszel Variance Consistent in Both Sparse Data and Large-Strata Limiting Models. Biometrics. 1986;42: 311–323.

Sato T. On the Variance Estimator of the Mantel-Haenszel Risk Difference. Biometrics. 1989; 45:1323–1324.

APPENDIX 1. IMPUTATION OF MISSING OR PARTIALLY MISSING DATES

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

1 Impute partial dates for concomitant medication (excluding anticancer therapy)

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 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, 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.

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 > min(death date, end of study date), then set to min (death date, end of study 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 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

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

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

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

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

In addition, according to exclusion criteria 4 and 28 of this study, the following rules should also be followed:

- Regarding Prior Systemic Therapy for cancer, Prior Anti-cancer Radiotherapy [except liver], if imputed end date >= randomization date – 14, then set to randomization date – 15. (Exclusion criteria 28)
- Regarding Liver Local Regional Therapy, if imputed end date >= randomization date – 28, then set to randomization date – 29. (Exclusion criteria 4)

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 day of the month
- If the imputed start date > end date, then set to the end date

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

4. Impute partial dates for subsequent anti-cancer therapy as collected in the post-treatment page (same rule applies to safety and efficacy flag)

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

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

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

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

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

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

Note: if the imputed subsequent anti-cancer therapy date collected from CRF "post-treatment discontinuation anti-cancer systemic therapy" or "post-treatment discontinuation anti-cancer procedure" page is before the last dosing date, send data query.

5. Impute partial dates for anti-cancer therapy collected in the prior and concomitant medication page (same rule applies to safety and efficacy flag)

If start date of 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 (last dose date, death date, study discontinuation date, data cutoff date), then set to min (last dose date, death date, study discontinuation date, data cutoff date)

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

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

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

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

APPENDIX 2. MISSING TWO TUMOR ASSESSMENTS

Identifying two missing tumor assessments

1) Input scheduled TA visit list for each study
   a. 6wk-12wk-18wk-24wk-30wk-36wk-42wk-48wk-60wk-72wk- 84wk… TA occurs every 6 weeks for the first 48 weeks, then every 12 weeks thereafter.
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. 6wk or 12wk) as –LPTADT_WK. It can be achieved programmatically by following the classification rule (e.g. defining thresholds) depicted in Table 3 below. (The team can consider to map all tumor visits if the scheduled visits code are uncleaned or questionable)
   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
   b. Otherwise, PFS event at the earliest of PD/death date

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 2 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 61, PFS will be censored at LPTADT (Week 44); had the PD occurred prior to or on Week 61, it would be counted as an PFS event.

Table 3 Scheduled tumor assessments with time window for AdavnTIG-206

Weeks	Scheduled week-1	Scheduled week	Scheduled week+1	Threshold
Randomization date		Baseline		
Every 6 weeks for the first 48 weeks	Week 5	Week6	Week 7	Week 9
	Week 11	Week 12	Week 13	Week 15
	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 54
Every 12 weeks afterwards	Week 59	Week 60	Week 61	Week 66
	Week 71	Week 72	Week 73	Week 78
	Week 83	Week 84	Week 85	…