CLINICAL STUDY PROTOCOL

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
Protocol Number:	AdvanTIG-206
Phase:	2
Investigational Products:	Ociperlimab (BGB-A1217), Tislelizumab (BGB-A317), and BAT1706
Proposed Indication(s):	Advanced Hepatocellular Carcinoma
Sponsor:	BeiGene, Ltd. c/o BeiGene USA, Inc. 2955 Campus Drive, Suite 200 San Mateo, CA 94403 USA
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Original Protocol Version 0.0:	03 March 2021
NCT Number:	NCT04948697

FINAL PROTOCOL APPROVAL SHEET

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

BeiGene, Ltd., Approval:

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Date

INVESTIGATOR SIGNATURE PAGE

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Protocol Identifier: AdvanTIG-206

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 Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd., or one of its subsidiaries.

Instructions for Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name and address of the center in which the study will be conducted.

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

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

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SYNOPSIS

Name of Sponsor/Company: BeiGene, Ltd.
Investigational Product(s): Ociperlimab, tislelizumab and BAT1706
Title of Study: 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
Protocol Identifier: AdvanTIG-206
Phase of Development: 2
Number of Patients: Approximately 90
Study Centers: Approximately 30 centers in Mainland China/Taiwan
Study Objectives: **Primary:** • 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 (HCC) **Secondary**: • 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 **Exploratory**: • To explore potential biomarkers that may correlate with clinical responses/resistance to ociperlimab in combination with tislelizumab plus BAT1706, and to tislelizumab plus BAT1706

Study Endpoints:

Primary:

- 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

Secondary:

- 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 date of first dose of study drug 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 ≥ 24 weeks)
  - PFS, defined as the time from the date of the first dose of study drug to the date of first documentation of disease progression or death, whichever occurs first
- OS, defined as the time from the date of the first dose of study drug 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] Version [v] 5.0, 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 antidrug antibodies (ADAs)

Exploratory:

- Potential biomarkers including programmed cell death protein ligand-1 (PD-L1) expression, T cell immunoreceptor with Ig and ITIM domains (TIGIT) pathway related protein expression (TIGIT, poliovirus receptor/PVR and nectin cell adhesion molecule 2/nectin-2), tumor mutational burden (TMB)/DNA mutation, blood tumor mutational burden (bTMB)/circulating tumor DNA (ctDNA) monitoring/DNA mutation, alpha-fetoprotein (AFP), gene expression profile (GEP), and the association of biomarkers with disease status, and response/resistance to ociperlimab in combination with tislelizumab plus BAT1706, and to tislelizumab plus BAT1706

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 2 treatment arms:

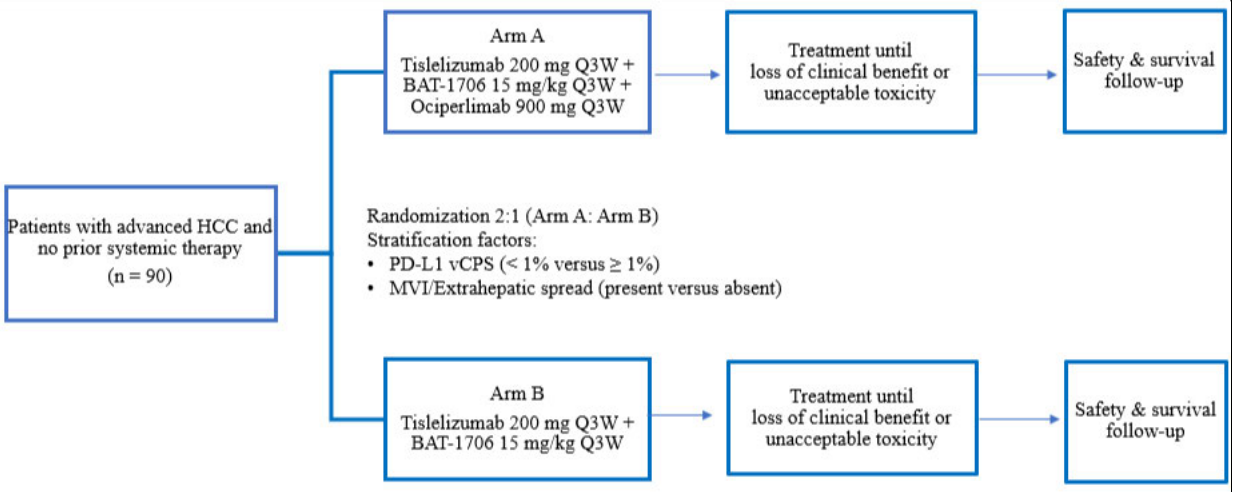
- Arm A (n = 60): tislelizumab 200 mg intravenously once every 3 weeks (dosed in 21-day cycles) + BAT1706 15 mg/kg intravenously once every 3 weeks (dosed in 21-day cycles) + ociperlimab 900 mg intravenously once every 3 weeks (dosed in 21-day cycles)
- Arm B (n = 30): tislelizumab 200 mg intravenously 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%)
- Macrovascular invasion (MVI)/Extrahepatic spread (EHS) (present versus absent)

The study schema is shown in Figure 1.

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.

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.

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.

Study Assessments:

- The baseline tumor imaging will be performed ≤ 28 days before randomization. During the study treatment period, tumor response will be evaluated by the investigator every 6 weeks for the first 48 weeks, and every 12 weeks thereafter, in accordance with RECIST v1.1.
- If, at the investigator's discretion, a patient could continue to benefit from the assigned study drug(s) after progressive disease (PD) per RECIST v1.1 criteria is met, the patient may continue their assigned treatment.

- The following criteria must be met in order to treat patients who may continue to benefit from study drug(s) after PD:
  - Absence of clinical symptoms and signs of PD (including clinically significantly worsening of laboratory values)
  - Stable Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 1
  - Absence of rapid disease progression or of progressive tumor at critical anatomical sites (eg, cord compression) that requires urgent alternative medical intervention
  - Investigators must obtain written informed consent for treatment beyond radiologic PD and inform patients that this practice is not considered standard in the treatment of cancer
  - The decision to continue study drug(s) beyond initial investigator-assessed progression must be agreed with the sponsor medical monitor and documented in the study records.

  Patients who receive study drug(s) beyond disease progression will have tumor assessments performed according to the original schedule until all study drug(s) are discontinued.
- If a patient discontinues study drug(s) due to any reason other than PD (eg. toxicity), tumor assessments will be performed according to the original schedule until disease progression, death, loss to follow-up, withdrawal of consent, or study termination, whichever occurs first.
- Patients will report any AEs and serious adverse events (SAEs), regardless of causality to study drugs, occurring within either 30 days after the last dose of study drug (all severity grades, per NCI-CTCAE v5.0) or initiation of new anticancer therapy, whichever occurs first. Patients must also report all immune-mediated adverse events (imAEs) occurring up to 90 days after the last dose of ociperlimab or tislelizumab, whichever occurs later, 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.
- The occurrence of any of the following toxicities during the first 21 days of study will be considered a dose-limiting toxicity (DLT), if assessed by the investigator as related to the study drug administration:

  <u>Hematologic DLTs:</u>

  1. Grade 4 neutropenia lasting > 7 days
  2. Febrile neutropenia (defined as absolute neutrophil count [ANC] < 1 x 10^9/L with a single temperature of 38.3°C or a sustained temperature of 38°C for > 1 hour)
  3. Grade 3 neutropenia with infection
  4. Grade 3 thrombocytopenia with bleeding indicated for clinical intervention
  5. Grade 4 thrombocytopenia
  6. Grade 4 anemia (life-threatening)

  <u>Non-hematologic DLTs:</u>

  1. Grade 4 or higher toxicity
  2. Grade 3 toxicity lasting for > 7 days despite optimal supportive care

Note: The following AEs will not be considered as DLTs:

- Grade 3 endocrinopathy that is adequately controlled by hormonal replacement
- Grade 3 rash
- Grade 3 infusion-related AE that is transient (resolving within 6 hours of onset)
- Grade 3 to Grade 4 laboratory abnormalities that are not associated with clinical sequelae (eg, lactate dehydrogenase increased)
- ALT/AST from 5x to 10x upper limit of normal (ULN) the return to baseline in ≤ 14 days with optimal management

Clinically important or persistent AEs that are not part of the DLT criteria may also be considered a DLT, after review by the sponsor and in consultation with the investigator.

The Safety Monitoring Committee (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.

- For the first 6 patients enrolled in Arm A, if ≤ 1 in 6 patients experience a DLT, the dosing regimen is tolerable and will be used in subsequent cycles. If ≥ 2 in 6 patients experience a DLT, the starting dose will be considered as exceeding the maximum tolerated dose (MTD), and the sponsor will pause enrollment to allow for further evaluation of the safety data.
- 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 1 out of 3 patients experience a DLT, an additional 3 patients will be enrolled. Otherwise, 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.

- 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 nonevaluable safety assessments within the first 21 days, additional patients may be required to be randomized to replace patients whose safety assessment cannot be performed.
- An established SMC will monitor and review the safety results to evaluate the safety and tolerability of selected study drug dose, and recommend whether a dose adjustment is needed to manage adverse events. The SMC may recommend modifications to the study, including termination due to safety concerns.

Duration of Patient Participation:

- **Screening Period** will be ≤ 28 days before randomization.
- **Treatment Period** will start with the first day of study drug administration and end when the patient is discontinued from the study drug(s), for any reason.
- **End-of-Treatment/Safety Follow-up Period**: The EOT Visit is conducted when the investigator determines that one or more study drugs, ie, ociperlimab and tislelizumab in Arm A, tislelizumab

in Arm B, and BAT1706 in both arms, will no longer be used. If routine laboratory tests (eg, hematology, serum chemistry) were completed within 7 days of the EOT Visit, these tests do not need to be repeated.

Tumor assessment is required at the EOT Visit if the investigator determines that the study drug(s) must be discontinued. However, the tumor assessment may be omitted at the EOT visit provided that ≤ 6 weeks have passed since the last assessment. Patients who discontinue all study drugs prior to disease progression will need to undergo tumor assessment.

Patients who permanently discontinue ociperlimab and tislelizumab in Arm A, or tislelizumab in Arm B, will be asked to return to the clinic for the Safety Follow-up Visit, which is required to be conducted 30 (± 7) days after the last dose of the specific study drug(s), unless otherwise specified, or before the initiation of subsequent anticancer therapy, whichever occurs first.

If the decision to end treatment is taken ≥ 23 days after the last dose of ociperlimab and tislelizumab in Arm A, or tislelizumab in Arm B, the EOT and the Safety follow-up visits should be conducted concurrently within 7 days of the decision to end treatment.

In addition, patients who discontinue ociperlimab or tislelizumab in Arm A, or tislelizumab in Arm B, will be asked to return to the clinic or will be contacted via telephone to assess imAEs and concomitant medications (if appropriate, ie, associated with an imAE) at 60 and 90 (± 14) days after the last dose of ociperlimab or tislelizumab, whichever is later, regardless of whether they started a subsequent anticancer therapy. If patients report a suspected imAE at a follow-up visit or a telephone contact, the investigator should arrange an unscheduled visit if further assessment is indicated.

- **Survival Follow-up**: Patients will be followed up for survival and to obtain information on subsequent anticancer therapy after discontinuation of all study drugs 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.

Study Population: Patients with histologically confirmed advanced HCC who have not received systemic therapy for the advanced disease, and who have not received treatment targeting PD-1/PD-L1, or targeting TIGIT or who have not received bevacizumab (originator or biosimilar) in any prior therapy setting.

Key Eligibility Criteria: Adult patients with histologically confirmed advanced HCC, defined as either BCLC Stage C disease, or BCLC Stage B disease that is not amenable to or has progressed after loco-regional therapy, and is not amenable to a curative treatment approach, and those who have not been previously treated with systemic therapy are eligible. All patients are required to provide archived or fresh tumor samples and have an evaluable PD-L1 expression result (presented as vCPS) assessed by the central laboratory. All patients are required to have a Child-Pugh A classification, assessed within 7 days of randomization, and ≥ 1 measurable lesion per RECIST v1.1.

Patients with active autoimmune disease or an history of autoimmune disease that may relapse, with untreated or incompletely treated esophageal or gastric varices with bleeding or high risk of bleeding are excluded.

Investigational Product, Dose, and Mode of Administration:

Arm A:
Ociperlimab will be administered at a dose of 900 mg intravenously once every 3 weeks.
Tislelizumab will be administered at a dose of 200 mg intravenously once every 3 weeks.
BAT1706 will be administered at a dose of 15 mg/kg intravenously once every 3 weeks.

Arm B:
Tislelizumab will be administered at a dose of 200 mg intravenously once every 3 weeks.
BAT1706 will be administered at a dose of 15 mg/kg intravenously once every 3 weeks.

Reference Therapy, Dose, and Mode of Administration:
Not applicable

Statistical Methods:

Analysis Sets:

- The Safety Analysis Set (SAS) includes all patients of each arm who received ≥ 1 dose of study drugs. This will be the primary analysis set for the safety analysis.
- 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 Efficacy Evaluable Analysis Set (EAS) includes all patients in the ITT Analysis Set without critical protocol deviation who had measurable disease at baseline per RECIST v1.1 by investigator and who had ≥ 1 evaluable post-baseline tumor assessment unless discontinued due to clinical PD or death within 7 weeks after the first dose. This analysis set will be used for the sensitivity 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 the scheduled ociperlimab (if applicable), ≥ 80% of the scheduled tislelizumab, and ≥ 80% of the 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 received ≥ 1 dose of any component of study drug per the protocol, and for whom any postdose PK data are available.
- The Immunogenicity Analysis Set includes all patients who received ≥ 1 dose of any component of study drugs for whom both baseline ADA results and ≥ 1 postbaseline ADA result are available.

Efficacy Analysis:

Primary Efficacy Analysis

The primary efficacy endpoint is ORR as determined by the investigator based on RECIST v 1.1, in Arm A and Arm B. ORR is defined as the proportion of patients achieving confirmed best overall responses of CR or PR. ORR will be summarized in the ITT Analysis Set with a Clopper-Pearson 95% CI constructed to assess the precision of the point estimate.

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

The sensitivity analysis of ORR will be carried out in the Efficacy Evaluable Analysis Set.

Secondary Efficacy Analysis

Other efficacy endpoints based on investigator assessed tumor assessments (ie, DOR, PFS, TTR, DCR and CBR), as well as OS, will be summarized in the ITT Analysis Set for the secondary efficacy analysis.

The DOR will be analyzed among the responders in the ITT Analysis Set. The median and other quartiles of DOR will be estimated using the Kaplan-Meier method. The 2-sided 95% CIs will be constructed with the generalized Brookmeyer and Crowley method. Event-free rates at selected timepoints for DOR will be estimated using the Kaplan-Meier method with the corresponding 95% CI constructed using Greenwood's formula. The DOR censoring rule will follow US Food and Drug Administration (FDA) Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2018).

The PFS and OS will be analyzed in the ITT Analysis Set using methods similar to those described for the DOR, except for censoring rules. The PFS censoring rule will follow the same as the DOR censoring rule. For OS, patients will be censored either at the date that the patient was last known to be alive or the data cutoff date, whichever comes first, in the absence of death.

The TTR will be analyzed in the ITT Analysis Set using sample statistics such as mean, median, and standard deviation for patients who have achieved an objective response.

The DCR and CBR will be summarized similarly as the ORR in the ITT Analysis Set, and also in the Efficacy Evaluable Analysis Set for the sensitivity analysis.

Safety Analyses:

Safety will be assessed by monitoring and recording of AEs and laboratory values (hematology, clinical chemistry, coagulation, and urinalysis). Vital signs, physical examinations, and electrocardiogram (ECG) findings will also be used in determining the safety profile. The severity of AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v5.0). The incidence of DLT events and treatment-emergent adverse events (TEAEs) will be reported as the number (percentage) of patients with TEAEs by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, and maximum for continuous variables; n [%] for categorical variables) and changes from baseline will be determined for laboratory parameters and vital signs.

Extent of exposure to a study drug will be summarized descriptively as the number of cycles received (number and percentage of patients), duration of exposure, cumulative total dose received per patient, dose intensity (mg/day), and relative dose intensity (%).

The number (and percentage) of patients with a dose reduction, treatment interruption, or study drug discontinuation will be summarized with the respective reasons.

The AE verbatim descriptions (as recorded by the investigator on the electronic case report form [eCRF]) will be classified into standardized medical terminology using the MedDRA®.

The DLTs will be summarized for the safety run-in period.

A 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(s) and up to 30 days after the last dose of study drug(s), or initiation of new anticancer therapy, whichever occurs first. The TEAE classification also applies to imAEs that are recorded up to 90 days after the last dose of ociperlimab and tislelizumab , 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 the time since the last dose of study drug. Only those AEs that were treatment-emergent will be included in the summary tables. All AEs, treatment-emergent or otherwise, will be presented in the patient data listings.

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

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

All TEAE, SAEs, deaths, ≥ Grade 3 TEAEs, imAEs, AEs of special interest related to BAT1706, treatment-related TEAEs, and TEAEs that led to treatment discontinuation and dose modification (interruption/delay/reduction, as appropriate) will be summarized.

Safety data will be summarized using the Safety Analysis Set and by arm.

Clinical laboratory data with values outside of the normal ranges will be identified. Selected laboratory data will be summarized by grade and by worst postbaseline change. Changes in vital signs will also be summarized by visit.

Pharmacokinetic Analyses:

The ociperlimab, tislelizumab, and BAT1706 serum concentration data will be tabulated and summarized by visit/cycle at which these samples are collected. Descriptive statistics will include means, medians, ranges, and standard deviations, as appropriate.

Additional PK analyses may be conducted, as appropriate.

Immunogenicity Analyses:

The immunogenicity results will be summarized using descriptive statistics by the number and percentage of patients who develop detectable ADAs. The incidence of positive ADAs and

neutralizing ADAs will be reported for evaluable patients. The effect of immunogenicity on PK, efficacy, and safety may be evaluated if data allows.

Sample Size Consideration:

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

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

These patients will be enrolled to evaluate the preliminary efficacy of ociperlimab in combination with tislelizumab plus BAT1706, and tislelizumab plus BAT1706.

No formal hypothesis testing is planned in the efficacy evaluation.

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
ADAs	antidrug antibodies
AE	adverse event
AFP	alpha-fetoprotein
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration
BCLC	Barcelona Clinic Liver Cancer
BGB-A1217	ociperlimab
BGB-A317	tislelizumab
BOR	best overall response
bTMB	blood tumor mutational burden
CBR	clinical benefit rate
CD	cluster of differentiation
CNS	central nervous system
C_{max}	maximum concentration
CR	complete response
CT	computed tomography
ctDNA	circulating tumor DNA
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
EAS	Efficacy Evaluable Analysis Set
EC	Ethics Committee
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
EDC	electronic data capture (system)
EMA	European Medicines Agency
EOT	End-of-Treatment (Visit)
FDG	fluorine-18 [F-18] fluorodeoxyglucose
GCP	Good Clinical Practice
GEP	gene expression profiling
HBV	hepatitis B virus
HbsAg	hepatitis B surface antigen
HbsAb	hepatitis B surface antibody
HCC	hepatocellular carcinoma

Abbreviation	Definition
HCV	hepatitis C virus
HR	hazard ratio
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
INF	interferon
IgG	immunoglobulin G
imAE	immune-mediated adverse event
IRB	Institutional Review Board
ITIM	immunoreceptor tyrosine-based inhibitory motif
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NK	natural killer (cells)
NMPA	National Medical Products Administration
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PD	progressive disease
PD-1	programmed cell death protein-1
PD-L1	programmed cell death protein-ligand 1
PET	positron-emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PT	Preferred Term
PVR	poliovirus receptor
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SMC	Safety Monitoring Committee
SOC	System Organ Class
TACE	transarterial chemoembolization
Tbil	total bilirubin
TEAE	treatment-emergent adverse event

Abbreviation	Definition
TIGIT	T-cell immunoreceptor with Ig and ITIM domains
TMB	tumor mutational burden
Tregs	regulatory T (cells)
TIL	tumor-infiltrating lymphocyte
TTR	time to response
ULN	upper limit of normal
US FDA	United States Food and Drug Administration
vCPS	visually estimated combined positive score
VEGF	vascular endothelial growth factor

1. INTRODUCTION AND RATIONALES

1.1. Background Information on Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is a major global health problem, accounting for 85-90% of all reported cases of liver cancer (a term with which HCC is often used interchangeably) (El-Serag and Rudolph 2007). According to the World Health Organization's GLOBOCAN 2012 database, liver cancer was the sixth most common type of cancer that year, with 782,000 new cases worldwide; it was also the second most common cause of cancer-related mortality, responsible for an estimated 746,000 deaths (Torre et al 2015).

Most HCC cases (> 80%) occur in Eastern Asia and in sub-Saharan Africa, with typical incidence rates of > 20 per 100,000 individuals. China alone accounts for approximately 50% of both new HCC cases and HCC-related deaths worldwide (Torre et al 2015). Southern European countries, such as Spain, Italy, and Greece, tend to have more moderate incidence rates (approximately10 to 20 per 100,000 individuals), whereas North America, South America, Northern Europe, and Oceania have a relatively low incidence of HCC (< 5 per 100,000 individuals) (El-Serag 2012).

A variety of risk factors are known to be causative for HCC. These include infection with hepatitis viruses, aflatoxin B, tobacco, vinyl chloride, heavy alcohol intake, non-alcoholic fatty liver disease, hemochromatosis, and diabetes. Together, hepatitis B virus (HBV) and hepatitis C virus (HCV) account for 80-90% of all HCC cases worldwide (Bosch 2005). Chronic HBV infection is the dominant risk factor for the disease in most areas of Asia, with the exception of Japan (El-Serag 2012), while chronic infection with HCV is the leading cause of HCC in Western countries and in Japan (Choo 2016).

1.2. Current Treatment of Hepatocellular Carcinoma

Treatment options for HCC are based on the disease stage at diagnosis per the Barcelona Clinic Liver Cancer (BCLC) classification system, which draws from a combination of Eastern Cooperative Oncology Group Performance Status (ECOG PS) (Appendix 3), Child-Pugh classification criteria for liver function (Appendix 9), and extent of disease (Llovet et al 2004) to define disease staging for HCC. Approximately 30% of HCC cases are diagnosed at the early stages (ie, BCLC stages 0 or A) and are amenable to potentially curative treatments, including liver transplantation, resection, or locoregional procedures such as radiofrequency ablation and percutaneous ethanol injection. However, there is a high rate (70%) of HCC recurrence within 5 years (Oikonomopoulos et al 2016).

In intermediate-stage HCC (ie, BCLC Stage B), transarterial chemoembolization (TACE) is the recommended treatment modality (Han and Kim 2015), but the data are difficult to interpret in the context of BCLC staging; the data supporting the recommendation were not categorized according to BCLC classification (Han and Kim 2015). Nonetheless, patients experience disease progression after TACE treatment and become ineligible for further TACE therapy.

The majority (approximately 70%) of patients diagnosed with HCC present with unresectable disease (ie, BCLC Stage C) (Mazzaferro et al 1996). In 2008, sorafenib (NEXAVAR Prescribing Information [PI]), a multi-kinase inhibitor, was approved by the United States (US) Food and Drug Administration (FDA) for use in this patient population. It inhibits multiple

intracellular (CRAF, BRAF) and cell surface kinases (KIT, FLT-3, RET, VEGFR1/2/3, and PDGFRβ), thus impeding tumor growth and angiogenesis.

Clinical data have illustrated a robust sorafenib-derived treatment benefit for HCC patients, irrespective of the underlying cause of their disease (Lee and Han 2010). Currently, sorafenib is recommended in all published guidelines (Keating 2017; Heimbach et al 2017; National Comprehensive Cancer Network [NCCN] 2020) for patients with advanced HCC and relatively preserved liver function who are not candidates for either resection or liver transplantation, and who have disease progression after locoregional therapies (Bruix et al 2012).

However, sorafenib is difficult for patients to tolerate. The most common side effects include hypertension, hemorrhage, hand-foot skin reaction, diarrhea, sensory neuropathy, weight loss, rash, alopecia, anorexia, and pain in the abdomen (NEXAVAR PI). As reported in an observational field study, 54% and 40% of patients treated with sorafenib have required dose reduction and treatment interruption, respectively (Iavarone et al 2011). Given that the median overall survival (OS) in advanced-stage HCC patients treated with sorafenib is < 12 months, and in light of the relatively poor tolerability of the drug, novel therapies are needed for this patient population.

Another multiple tyrosine kinase inhibitor, lenvatinib (LENVIMA Prescribing Information for the Unites States, Europe, and China) was approved for the first-line treatment of patients with unresectable HCC by the US FDA and the European Medicines Agency (EMA) in 2015; and by the National Medical Products Administration (NMPA) in 2018. Lenvatinib was compared to sorafenib in terms of its efficacy in treating advanced-stage HCC in a Phase 3 study, Study REFLECT, conducted in patients with unresectable HCC, and it has established the noninferiority of lenvatinib to sorafenib in a comparison of OS (Eisai 2017). The tolerability and safety profile of oral lenvatinib in the REFLECT trial in patients with unresectable HCC was also generally similar to that of sorafenib (Al-Salama 2019).

Approved first-line treatment options for patients presenting with unresectable HCC had been limited to systemic therapies with multikinase inhibitors, such as sorafenib and lenvatinib and oxaliplatin-based chemotherapy, such as FOLFOX4 (fluorouracil, leucovorin, and oxaliplatin) which was approved for advanced HCC in China (Zhou 2017) until atezolizumab plus bevacizumab was approved by the FDA (atezolizumab prescribing information), the EMA (atezolizumab summary of product characteristics) ,and the NMPA in 2020, based on the interim analysis results of Study IMbrave150 (Finn et al 2020a).

IMbrave150, a Phase 3 study of atezolizumab, an anti-programmed cell death ligand 1 (PD-L1) antibody, plus bevacizumab, an anti-vascular endothelial growth factor (VEGF) inhibitor, showed that treatment with atezolizumab plus bevacizumab was associated with significantly improved OS (hazard ratio [HR] = 0.58, p < 0.001) and progression-free survival (PFS) (HR = 0.59, p < 0.001) than sorafenib in patients with advanced unresectable HCC not previously treated with systemic therapy (Finn et al 2020a). Serious toxic effects were noted in 38% of the patients who received the combination therapy; however, no new or unexpected toxic effects were observed.

Orient-32, an investigational Phase 3 study of sintilimab, an anti-PD-1 inhibitor, plus IBI305, a bevacizumab biosimilar, versus sorafenib in unresectable or metastatic, systemic treatment-naive HCC, demonstrated similar improvement in OS (HR = 0.57, p < 0.0001) and PFS (HR = 0.57, p

< 0.0001) with the combination therapy versus sorafenib (Ren et al 2020). This further supports the potential use of an anti-PD-1 antibody with an anti-VEGF inhibitor in the first-line HCC setting.

Treatments after disease progression on sorafenib or chemotherapy include regorafenib (STIVARGA Prescribing Information) and carbozantinib (CABOMETYXUS Prescribing Information), and ramucirumab in patients with alfa-fetoprotein (AFP) ≥ 400 ng/mL (CYRAMZA Prescribing Information).

Despite these treatments, a high unmet medical need remains for patients with advanced HCC.

1.2.1. Anti-PD-1/Anti-PD L1 or Anti-PD-1/Anti-PD L1-Combination Therapy for Advanced Hepatocellular Carcinoma

The immune checkpoint-inhibitory receptor known as programmed cell death protein-1 (PD-1) is mainly expressed in activated T-cells (Topalian et al 2012, Bersanelli et al 2017). The PD-1 signaling cascade negatively regulates T-cell receptor activities while attenuating T-cell proliferation and function, with the ultimate consequence of T-cell exhaustion.

The expression of PD-1 is markedly upregulated in tumor-infiltrating lymphocytes (TILs), and the expression of PD-L1 is significantly increased in tumor cells and tumor-associated immune cells in the presence of stimulating cytokines (eg, interferon-alpha [IFN-α] and interferon gamma [IFN-γ]) in the tumor microenvironment. Furthermore, increased PD-1 expression in TILs and/or PD-L1 expression in tumor cells and tumor-associated stromal cells has been observed in many types of solid tumors (Jin and Yoon 2016, Patel and Kurzrock2015, Van Der Kraak et al 2016, McDaniel et al 2016, Gong et al 2011).

Based on the data from Phase 2 studies, several anti-PD-1 therapies have been approved in the US and China, eg, nivolumab with or without ipilimumab, pembrolizumab monotherapy (received FDA accelerated approval), and camrelizumab (received NMPA conditional approval) (OPDIVO prescribing information, KEYTRUDA prescribing information, Wang 2020).

Nivolumab monotherapy did not show statistically significant OS improvement compared with sorafenib (HR = 0.84, p = 0.0419) in first-line HCC patients. However, clinical benefit was observed with a median OS (mOS) of 16.4 months for nivolumab and 14.7 months for sorafenib (HR = 0.85 [95% CI: 0.7, 1.02]; p = 0.0752) (Yau et al 2019).

In addition to these observed clinical activities of anti-PD-1 monotherapy, novel combination of anti-PD-1/PD-L1 with anti-VEGF agents have demonstrated improved survival benefit compared with sorafenib in first-line HCC (Finn et al 2020a, Ren et al 2020). In a Phase 1b study of lenvatinib plus pembrolizumab in patients with unresectable HCC with no prior systemic therapy, the confirmed objective response rate (ORR) of 100 patients was 36.0% per RECIST v1.1.by independent imaging review; and the median DOR was 12.6 months (Finn 2020b). These data support combining treatment targeting PD-1/PD-L1 pathway with anti-angiogenic agents as first-line therapy in patients with HCC.

1.3. Background Information on Ociperlimab

Ociperlimab (also known as BGB-A1217) is a humanized immunoglobulin G (IgG) 1 monoclonal antibody binding to T-cell immunoglobulin and immunoreceptor tyrosine-based

inhibitory motif (ITIM) domain (TIGIT) under clinical development for the treatment of human malignancies.

TIGIT (also known as VSIG9, VSTM3, or WUCAM) is a 26-kDa type I transmembrane glycoprotein and an immune checkpoint receptor, and member of the poliovirus receptor (PVR)/nectin family that plays an important role in promoting T-cell exhaustion in both chronic viral infections and tumor escape from immune surveillance (Yu et al 2009; Boles et al 2009; Stanietsky et al 2009; Levin et al 2011; Johnston et al 2014). TIGIT was initially discovered in a genomic search for genes specifically expressed in T cells that had a protein domain that consisted of inhibitory signaling motifs. The genes and circulating DNAs (cDNAs) coding for TIGIT were cloned and characterized in mouse and human cells (Yu et al 2009). Mature human TIGIT contains 223 amino acid residues (National Center for Biotechnology Information 2018). Its extracellular domain consists of amino acid residues 1 to 120, and the transmembrane domain and cytoplasmic C-terminal tail comprises residues 121 to 223.

TIGIT-deficient mice ($TIGIT^{-/-}$) showed increased susceptibility to an experimental autoimmune model (Joller et al 2014). Natural killer (NK) cells that overexpressed TIGIT produced less IFN-γ upon TIGIT/PVR ligation. In contrast, NK cells form TIGIT-deficient mice produced more IFN-γ in the presence of PVR-expressing target cells (Li et al 2014). Agonistic anti-TIGIT antibody could reduce the production of proinflammatory cytokines including IFN-γ and interleukin (IL)-17 by antigen-restimulated splenocytes and decrease antigen-specific proliferation. Consistent with these observations, the blockade of the TIGIT pathway in vivo by TIGIT-blocking antibody alone or in combination with an anti-PD-1 antibody reduced tumor growth in syngeneic mouse models (College of American Pathologist [CAP] guidelines 2018; Argast et al 2018; Dixon et al 2018). These findings strongly suggest that TIGIT is a critical immune checkpoint receptor in the maintenance of immune tolerance.

TIGIT is primarily expressed on immune cells, such as T cells, and NK cells (Manieri et al 2017). When expressed on effector T cells (cluster of differentiation [CD] 4^+ [CD4+] and $CD8^+$), activation of TIGIT has been shown to reduce cytokine production and T-cell proliferation, both of which could be rescued by TIGIT-blocking antibodies or TIGIT expression knockdown (Lozano et al 2012; Joller et al 2014; Chauvin et al 2015). A similar phenomenon was also observed for NK cells (Stanietsky et al 2009; Zheng et al 2017).

TIGIT is also expressed on $FoxP3^+$ regulatory T (Treg) cells, especially in tumor tissues (Joller et al 2014; Kurtulus et al 2015). TIGIT-positive Treg cells demonstrated greater suppressive functions when compared to TIGIT-negative Treg cells, with higher expression of effector molecules, such as IL-10, granzymes, and Fgl2 (Joller et al 2014). A high TIGIT/CD226 ratio in Treg cells is associated with increased Treg frequencies in tumors and poor clinical outcome upon immune checkpoint blockade (Fourcade et al 2018). Some studies have also shown that TIGIT suppresses immune responses mediated by dendritic cells by binding with PVR, especially in enhancement of IL-10 production and the inhibition of IL-12 production (Yu et al 2009).

As an immune "checkpoint" molecule, TIGIT initiates inhibitory signaling in immune cells when engaged by its ligands, PVR (CD155) and PVR–related 2 (PVR-L2) (CD112, or nectin-2). These ligands are primarily expressed on antigen-presenting cells and tumor cells (Casado et al 2009; Stanietsky et al 2009; Yu et al 2009; Levin et al 2011). The binding affinity of TIGIT to

PVR (equilibrium dissociation constant [K_D]: approximately 1 nM) is much higher than to PVR-L2 and whether the TIGIT: PVR-L2 interaction is functionally relevant in mediating inhibitory signals remains to be determined. The co-stimulatory receptor, CD226, binds to the same ligands with lower affinity (K_D: approximately 100 nM) but delivers a positive signal and enhances cytotoxicity of T cells and NK cells (Bottino et al 2003; Stanietsky et al 2009). High-affinity binding of TIGIT to PVR could compete off CD226-PVR interaction, therefore reducing T cells or NK cells activation (Stanietsky et al 2009).

The cytoplasmic tail of TIGIT has an inhibitory ITIM and an immunoreceptor tail tyrosine-like motif. In NK cells, TIGIT engagement induces the phosphorylation of tyrosine residues in its ITIM and immunoreceptor tail tyrosine-like motifs through the Src kinases Fyn and Lck. The phosphorylation of TIGIT then leads to binding of Grb2 and β-arrestin 2 and the subsequent recruitment of SHIP-1 and SHP-2 to terminate PI3K and NK-κB signaling in the NK cells (Stanietsky et al 2009; Liu et al 2013). Engagement of agonistic TIGIT antibody induced T-cell receptor complex disruption (Stanietsky et al 2009). In addition, interaction between TIGIT and PVR on dendritic cells could lead to phosphorylation of PVR and modulation of ERK activation in dendritic cells (Yu et al 2009).

Up-regulation of TIGIT expression in TILs has been reported in many types of cancers, such as lung (Tassi et al 2017), stomach (He et al 2017), breast (Gil Del Alcazar et al 2017), esophageal (Xie et al 2016), HCC (Chiu et al 2020), brain (Hung et al 2018), acute myeloid leukemia (Kong et al 2016), and melanoma (Mahnke and Enk 2016). Interestingly, TIGIT expression appears to be minimally expressed by peripheral effector cells while being significantly up-regulated by tumor localized effector cells, which strongly suggests that the tumor microenvironment utilizes TIGIT signaling to further suppress/evade immune-mediated tumor cytotoxicity (Johnston et al 2014). Further, up-regulation of TIGIT signaling plays an important role in immune tolerance to cancer, similar to its function in the presence of chronic viral infections (Chauvin et al 2015; Yin et al 2018). The blockade of the TIGIT receptor alone or in combination with PD-1/PD-L1 blockade has been shown both in vitro and in vivo to rescue functionally "exhausted" T cells (Johnston et al 2014; Chauvin et al 2015). In mouse models, TIGIT blockade in combination with anti–PD-1/PD-L1 antibodies demonstrated significantly better antitumor efficacy than either monotherapy (Johnston et al 2014; Dixon et al 2018).

In mouse models, Fc with effector functions is critical for TIGIT antibody-mediated antitumor activity (College of American Pathologist [CAP] guidelines 2018; Argast et al 2018; Leroy et al 2018). In the CT26.WT mouse colon cancer model, anti-mouse TIGIT antibody of mIgG2a isotype (antibody-dependent cellular cytotoxicity [ADCC] enabling) demonstrated potent antitumor activity as monotherapy and in combination with anti-PD-1 antibody. In contrast, anti-TIGIT antibody with Fc devoid of effector functions did not show any of the antitumor efficacies in the same model, indicating that Fc-mediated effector functions are required for TIGIT antibody-mediated antitumor effects. In addition, the observed efficacy was associated with an increased activity of effector T cells ($CD8^+$ and $CD4^+$) and also with Treg depletion within the tumor microenvironment. Argast and colleagues' (College of American Pathologist [CAP] guidelines 2018; Argast et al 2018) also observed that effector functions were critical for TIGIT antibody-induced in vivo efficacy. Waight and colleagues (Waight et al 2018) reported that the interaction of anti-TIGIT with gamma fragment crystallizable region (Fc) receptor

(FcγR) on antigen-presenting cells enhanced antigen-specific T cell responses and antitumor activity.

Moreover, exhausted T cells demonstrate that upregulation of the inhibitory immune receptor TIGIT represents a hallmark in the process of T cell exhaustion in liver cancer. In combination with PD-1 inhibition, targeting TIGIT with antagonistic antibodies resulted in synergistic inhibition of liver cancer growth in immunocompetent mice (Ostroumov et al 2020) .

Taken as a whole, targeting TIGIT provides a potential mechanism to rescue immune cells (eg, T cells, NK cells, and dendritic cells) from the immunosuppressive tumor microenvironment, thereby inducing an efficient antitumor immune response. The strategy of blocking antibodies that target the PD-1/PD-L1 pathway has achieved remarkable results in the treatment of many different tumor types. However, based upon the rate of primary and secondary resistance to PD-1 blockade, it is apparent that additional immuno-regulatory mechanism(s) underlie tumor immune escape. Indeed, research shows that the TIGIT pathway cooperates with PD-1 to maximize the suppression of effector TILs and promote resistance to anti-PD-1 therapy. Therefore, TIGIT represents an ideal target with the potential to significantly improve and/or extend the therapeutic benefit of anti-PD-1 therapy, which could offer a synergistic inhibition of cancer growth in patients with HCC.

1.3.1. Nonclinical Experience

1.3.1.1. Pharmacology

Ociperlimab binds to the extracellular domain of human TIGIT with high specificity and affinity (K_D = 0.135 nM), as demonstrated by target-binding assays and surface plasmon resonance characterization. It competitively blocks the binding of TIGIT to PVR. Ociperlimab has shown antitumor activity in both the GL261 mouse glioma tumor model and the CT26.WT mouse colon cancer model in humanized TIGIT knock-in mice. Additionally, in the MC-38 mouse colon cancer model in humanized TIGIT knock-in mice, ociperlimab in combination with anti–mouse PD-1 significantly inhibited tumor growth compared with either therapy alone.

Ociperlimab has the constant region of a wild-type human IgG1 to enable the Fc-mediated effector functions. Ociperlimab has demonstrated competent binding to complement 1q (C1q) and all FcγRs, including FcγRI, FcγRIIA, FcγRIIB, and FcγRIIIA, in in vitro binding assays, and induces ADCC against TIGIT-overexpressing cell line, but no ADCC or complement-dependent cytotoxicity against primary T cells in the cell-based assays.

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

1.3.1.2. Toxicology

Humanized TIGIT knock-in mice containing human TIGIT gene and cynomolgus monkeys were selected for nonclinical safety evaluation of ociperlimab based on the homology of TIGIT amino acid sequence, binding affinity, and efficacy studies.

Cynomolgus monkeys was the most relevant species based on the homology sequence of TIGIT, although it demonstrates a relatively lower ociperlimab-binding affinity compared with human TIGIT (with the concentration for 50% of maximal effect [EC_{50}] 756-fold weaker).

Ociperlimab does not bind to mouse TIGIT due to the significant sequence divergence between human and mouse TIGIT; however, ociperlimab demonstrates a comparable binding affinity in TIGIT receptor occupancy assays with CD3+ splenocytes from humanized TIGIT knock-in mice compared to CD3+ human peripheral blood mononuclear cells (PBMCs) (with EC_{50} of 48.8 ng/mL versus 63.2 ng/mL, respectively). In addition, ociperlimab shows significant inhibition of GL261 tumor growth in humanized TIGIT knock-in mice at a dose of 0.4 mg/kg and above via weekly intraperitoneal dosing.

The toxicity and safety profile of ociperlimab was characterized in a 4-week repeated-dose toxicity study in humanized TIGIT knock-in mice and a 13-week repeat dose toxicology study in cynomolgus monkeys. These toxicity studies were conducted in accordance with Good Laboratory Practice (GLP) regulations. Furthermore, ociperlimab was evaluated in a 4-week repeated-dose study in humanized TIGIT knock-in mice with subcutaneous MC-38 tumors. The dose levels spanned from the intended human therapeutic doses to 10-fold higher in the 4-week mouse studies and 20-fold higher in the 13-week monkey study. The cynomolgus monkey was considered the relevant species for toxicity studies based on the target sequence homology and cross-species TIGIT-binding activities of ociperlimab. Tissue cross-reactivity was evaluated in normal frozen tissues from humans. Cytokine release response was also evaluated using fresh human PBMCs.

No apparent toxicity was noted in humanized mice after repeated dosing of ociperlimab at either 5 or 50 mg/kg weekly for 4 weeks, nor in monkeys after repeated dosing at 10, 30, or 100 mg/kg once every 2 weeks for 13 weeks. The toxicokinetic profile was characterized in both the mouse and monkey studies and the systemic exposure appeared to be dose proportional with no sex difference in either study. A trend of accumulation was noted after repeated doses in mice; however, no accumulation was observed over the 13-week dosing period in monkeys. No immunotoxicity was apparent, as no changes in clinical pathology or histopathology were observed in these studies. Immunogenicity with positive antidrug antibodies (ADAs) against ociperlimab was noted in several mice dosed at 5 and 50 mg/kg over the 4 weeks; however, with the exception of 1 animal that had a strong ADA response at 5 mg/kg dose, most of these animals showed weak ADA signals or the signals were proved to be false positives. In monkeys, positive ADAs against ociperlimab were observed in 6 of 10, 3 of 10, and 4 of 10 animals during the dosing period and 3 of 4, 2 of 4, and 2 of 4 during the recovery period, at dose levels of 10, 30, and 100 mg/kg, respectively. The anti-ociperlimab antibodies showed a rapid clearance of ociperlimab in serum in a few individual animals but did not appear to have an effect on the overall systemic exposure (area under the concentration-time curve[AUC]) or toxicity assessment.

Tissue cross-reactivity of ociperlimab was evaluated in normal human frozen tissues using an immunohistochemistry method and appropriate positive and negative controls. No specific binding of ociperlimab was noted with normal human tissues. A variety of factors might contribute to the negative results, including negligible target expression in normal tissues (Yang 2016; Human Protein Atlas 2019) and sensitivity of the immunohistochemistry method.

No significant increase in cytokine release was observed from an in vitro cytokine release assay after treatment of non-activated PBMCs with ociperlimab when compared to human IgG. The results suggested that ociperlimab has potentially low risks of causing acute cytokine release syndrome.

Overall, no apparent toxicity was noted in the monkey or transgenic mouse toxicity studies. No unexpected tissue cross-reactivity was found in human or monkey tissues. The toxicokinetic profile was well characterized with dose-proportional increases in systemic exposure without apparent accumulation or sex difference. Immunogenicity was observed without apparent immunotoxicity or effect on the systemic exposure. The no-observed-adverse-effect level (NOAEL) of ociperlimab was 50 mg/kg in the 4-week mouse study and 100 mg/kg in the 13-week monkey toxicity study. The safety profile of ociperlimab is considered adequate to support first-in-human dosing.

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

1.3.2. Clinical Experience

1.3.2.1. Clinical Pharmacology

As of the data cutoff date of 16 June 2020, preliminary pharmacokinetic (PK) data of ociperlimab are available from a total of 11 patients treated with ociperlimab at 50 mg (n = 1), 150 mg (n = 3), 450 mg (n = 4), and 900 mg (n = 3) dose levels in combination with tislelizumab 200 mg in the dose-escalation portion of Study BGB-900-105. Ociperlimab serum concentrations declined in a biexponential manner after intravenous infusion and the ociperlimab exposures (C_{max} and AUC) increased approximately dose-proportionally from 50 mg to 900 mg.

Peripheral TIGIT receptor occupancy data were available for 11 enrolled patients treated with ociperlimab at 50 mg (n = 1), 150 mg (n = 3), 450 mg (n = 4), and 900 mg (n = 3) dose levels in Study BGB-900-105. Complete TIGIT receptor occupancy (100%) was observed on CD8, CD4, NK and Treg cells in peripheral blood at all the tested dose levels.

1.3.2.2. Preliminary Safety Profile

The first-in-human BGB-900-105 study evaluating the safety and tolerability of ociperlimab in combination with tislelizumab in advanced solid tumors is still ongoing.

As of 16 June 2020, 11 dose-limiting toxicity (DLT)-evaluable patients received ≥ 1 dose of ociperlimab combined with tislelizumab 200 mg once every 3 weeks in the dose escalation stage. The dosage of ociperlimab ranged from 50 mg to 900 mg once every 3 weeks: 1 patient at 50 mg once every 3 weeks, 3 patients at 150 mg once every 3 weeks, 4 patients at 450 mg once every 3 weeks, and 3 patients at 900 mg once every 3 weeks. The maximum administered dose was ociperlimab 900 mg combined with tislelizumab 200 mg once every 3 weeks as of the data cutoff date. The maximum tolerated dose (MTD) was not reached. Ociperlimab was safe and well-tolerated up to the dose level of 900 mg once every 3 weeks. No DLTs, treatment-related serious adverse events (SAEs), or Grade 4 or Grade 5 treatment-emergent adverse events (TEAEs) occurred during the treatment period at any dose level. The clinical activity documented as stable disease can be observed in 1 patient at each of the following ociperlimab doses of 150 mg, 450 mg, and 900 mg.

After the data cutoff date of 16 June 2020, 6 additional patients have been enrolled and dosed at the maximum administered dose of ociperlimab 900 mg combined with tislelizumab 200 mg once every 3 weeks. Exploration of more dose levels is ongoing.

As of the data cutoff date of 16 June 2020, 8 (72.7%) of the 11 patients had ≥ 1 TEAE. Most TEAEs were Grade 1 or Grade 2. Three TEAEs (atrial flutter, pericardial effusion malignant, and dyspnea), which occurred in 1 patient each, were Grade 3. Treatment-related TEAEs, and serious TEAEs occurred in 3 (27.3%) patients each. Treatment-related TEAEs included influenza, aspartate aminotransferase increased, and dry skin in 1 patient; abdominal pain, dry eye, and diarrhea in 1 patient; and fatigue in 1 patient. All treatment-related TEAEs were Grade 1.

Serious TEAEs included atrial flutter in 1 patient, dyspnea in 1 patient, and pericardial effusion malignant in 1 patient. All serious TEAEs were Grade 3. These 3 serious TEAEs were considered not related to study drug treatment by the investigator

No patients had Grade 4 or Grade 5 TEAEs, serious treatment-related TEAEs, TEAEs leading to treatment discontinuation, or TEAEs leading to death (Table 1). No TEAE met the criteria of DLT.

The most commonly reported TEAEs were fatigue (3 [27.3%]) and diarrhea and aspartate aminotransferase (AST) increased (2 [18.2%] each). All other TEAEs occurred in 1 (9.1%) patient each (Table 2).

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

Table 1: Overview of Treatment-Emergent Adverse Events (Safety Analysis Set)

	Ociperlimab 50 mg + tislelizumab 200 mg (N = 1) n (%)	Ociperlimab 150 mg + tislelizumab 200 mg (N = 3) n (%)	Ociperlimab 450 mg + tislelizumab 200 mg (N = 4) n (%)	Ociperlimab 900 mg + tislelizumab 200 mg (N = 5) n (%)	Total (N = 11) n (%)
Any TEAE	1 (100.0)	3 (100.0)	3 (75.0)	1 (33.3)	8 (72.7)
Any treatment-related TEAE	1 (100.0)	0 (0.0)	2 (50.0)	0 (0.0)	3 (27.3)
≥ Grade 3 TEAE	1 (100.0)	1 (33.3)	1 (25.0)	0 (0.0)	3 (27.3)
≥ Grade 3 treatment-related TEAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious TEAE	1 (100.0)	1 (33.3)	1 (25.0)	0 (0.0)	3 (27.3)
Serious treatment-related TEAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAE leading to treatment discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment-related TEAE leading to treatment discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAE leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: N, total number of patients treated; TEAE, treatment-emergent adverse event.
Notes: A patient with multiple occurrences of an AE is counted only once in the AE category. Treatment-related TEAE includes patients who had a tislelizumab- or ociperlimab-related TEAE.
Data cutoff date: 16 June 2020

Table 2: Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term	Ociperlimab 50 mg + tislelizumab 200 mg (N = 1) n (%)	Ociperlimab 150 mg + tislelizumab 200 mg (N = 3) n (%)	Ociperlimab 450 mg + tislelizumab 200 mg (N = 4) n (%)	Ociperlimab 900 mg + tislelizumab 200 mg (N = 3) n (%)	Total (N = 11) n (%)
Patients with ≥ 1 TEAE	**1 (100.0)**	**3 (100.0)**	**3 (75.0)**	**1 (33.3)**	**8 (72.7)**
Gastrointestinal disorders	**1 (100.0)**	**1 (33.3)**	**2 (50.0)**	**0 (0.0)**	**4 (36.4)**
Diarrhoea	0 (0.0)	1 (33.3)	1 (25.0)	0 (0.0)	2 (18.2)
Abdominal pain	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (9.1)
Constipation	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (9.1)
Dry mouth	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)
General disorders and administration site conditions	**1 (100.0)**	**0 (0.0)**	**1 (25.0)**	**1 (33.3)**	**3 (27.3)**
Fatigue	1 (100.0)	0 (0.0)	1 (25.0)	1 (33.3)	3 (27.3)
Musculoskeletal and connective tissue disorders	**0 (0.0)**	**1 (33.3)**	**1 (25.0)**	**1 (33.3)**	**3 (27.3)**
Back pain	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	1 (9.1)
Flank pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	1 (9.1)
Groin pain	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (9.1)
Infections and infestations	**1 (100.0)**	**0 (0.0)**	**1 (25.0)**	**0 (0.0)**	**2 (18.2)**
Influenza	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)
Otitis externa	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (9.1)
Investigations	**1 (100.0)**	**1 (33.3)**	**0 (0.0)**	**0 (0.0)**	**2 (18.2)**

System Organ Class Preferred Term	Ociperlimab 50 mg + tislelizumab 200 mg (N = 1) n (%)	Ociperlimab 150 mg + tislelizumab 200 mg (N = 3) n (%)	Ociperlimab 450 mg + tislelizumab 200 mg (N = 4) n (%)	Ociperlimab 900 mg + tislelizumab 200 mg (N = 3) n (%)	Total (N = 11) n (%)
Aspartate aminotransferase increased	1 (100.0)	1 (33.3)	0 (0.0)	0 (0.0)	2 (18.2)
Nervous system disorders	**1 (100.0)**	**0 (0.0)**	**1 (25.0)**	**0 (0.0)**	**2 (18.2)**
Neuralgia	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)
Somnolence	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (9.1)
Respiratory, thoracic, and mediastinal disorders	**0 (0.0)**	**1 (33.3)**	**1 (25.0)**	**0 (0.0)**	**2 (18.2)**
Cough	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (9.1)
Dyspnoea	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	1 (9.1)
Skin and subcutaneous tissue disorders	**1 (100.0)**	**0 (0.0)**	**0 (0.0)**	**1 (33.3)**	**2 (18.2)**
Drug eruption	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	1 (9.1)
Dry skin	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)
Blood and lymphatic system disorders	**0 (0.0)**	**0 (0.0)**	**1 (25.0)**	**0 (0.0)**	**1 (9.1)**
Anaemia	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (9.1)
Cardiac disorders	**1 (100.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (9.1)**
Atrial flutter	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)
Ear and labyrinth disorders	**0 (0.0)**	**1 (33.3)**	**0 (0.0)**	**0 (0.0)**	**1 (9.1)**
Ear discomfort	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	1 (9.1)
Eye disorders	**0 (0.0)**	**0 (0.0)**	**1 (25.0)**	**0 (0.0)**	**1 (9.1)**

System Organ Class Preferred Term	Ociperlimab 50 mg + tislelizumab 200 mg (N = 1) n (%)	Ociperlimab 150 mg + tislelizumab 200 mg (N = 3) n (%)	Ociperlimab 450 mg + tislelizumab 200 mg (N = 4) n (%)	Ociperlimab 900 mg + tislelizumab 200 mg (N = 3) n (%)	Total (N = 11) n (%)
Dry eye	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (9.1)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	**0 (0.0)**	**0 (0.0)**	**1 (25.0)**	**0 (0.0)**	**1 (9.1)**
Cancer pain	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (9.1)
Pericardial effusion malignant	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (9.1)
Psychiatric disorders	**0 (0.0)**	**1 (33.3)**	**0 (0.0)**	**0 (0.0)**	**1 (9.1)**
Confusional state	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	1 (9.1)

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; N, total number of patients treated; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PT, Preferred Term; SOC, System Organ Class; TEAE, treatment-emergent adverse event.
Notes: A patient with multiple occurrences of an AE is counted only once in the AE category. MedDRA version 22.0 was used to code adverse events. Adverse events were graded using NCI-CTCAE version 5.0 per protocol. Events are sorted in descending order of the number of patients for SOC and PT in the Total column.
Data cutoff date: 16 June 2020

1.3.2.3. Preliminary Efficacy Profile

The first-in-human study BGB-900-105 evaluating the efficacy of ociperlimab in combination with tislelizumab in advanced solid tumors is still ongoing. As of 16 June 2020, the clinical activity documented as stable disease can be observed in 1 patient each at ociperlimab doses of 150 mg, 450 mg, and 900 mg.

1.3.2.4. Clinical Experience With Other TIGIT Inhibitors

To date, first-in-human Phase 1 and Phase 2 clinical studies have been initiated for 6 anti-TIGIT antibodies: MTIG7192A from Genentech/Roche (NCT02794571 and NCT03563716), BMS-986207 from Bristol-Myers Squibb (NCT02913313), MK-7684 from Merck Sharp & Dohme (NCT02964013), OMP-313M32 from OncoMed (NCT03119428), ASP8374 from Astellas/Potenza (NCT03260322), and AB-154 from Arcus (NCT03628677). The goals for these clinical studies are to evaluate the safety and efficacy of anti-TIGIT antibodies alone and/or in combination with anti-PD-1 or anti-PD-L1 antibodies.

To date, clinical data have been released for OncoMed's OMP-313M32 (Sharma et al 2018), Merck's MK-7684 (Golan et al 2018), and Genentech/Roche's tiragolumab (Bendell et al 2020; Rodriguez-Abreu et al 2020). A total of 68 patients have been treated with MK-7684 alone or MK-7684 in combination with pembrolizumab (an anti–PD-1 antibody) in a Phase 1 study sponsored by Merck Sharp & Dohme, with doses of MK-7684 ranging from 2.1 mg to 700 mg. The preliminary results showed that MK-7684 was well tolerated in the dose escalation phase of the study, with no DLT. Adverse events (AEs) that occurred in > 15% of patients were fatigue (n = 5, 15%) for MK-7684 monotherapy and pruritus (n = 10, 21%) for MK-7684 and pembrolizumab combination therapy. Furthermore, only 2 treatment-related AEs ≥ Grade 3 were reported (Grade 3 anemia and Grade 3 diarrhea) for monotherapy and 5 treatment-related AEs ≥ Grade 3 were reported for combination with pembrolizumab (5 Grade 3: alanine aminotransferase [ALT] increased, colitis, Gamma-glutamyl transferase [γGT] increased, hypersensitivity, and rash maculopapular). Of the 34 evaluable patients treated with MK-7684 alone, one partial response (PR) (1/34 [3.0%]) and a 35% disease control rate (DCR) were observed. For combination of MK-7684 and pembrolizumab, 6 PRs (6/34 [18%]) and a 48% DCR were observed. In addition, PK findings were linear above 200 mg.

Eighteen patients have been treated with OMP-313M32 alone in a Phase 1 study sponsored by OncoMed, with doses ranging from 0.3 mg/kg to 20 mg/kg. The preliminary results showed that OMP-313M32 was well tolerated in the dose escalation phase of the study, with no DLT. Treatment-related AEs that occurred in > 15% of patients were rash (n = 5; 27.8%), fatigue (n = 3, 16.7%), nausea (n = 3, 16.7%), and pruritus (n = 3, 16.7%) for OMP-313M32 monotherapy. Grade 3 or higher treatment-related AEs included rash (n = 3, 16.7%), fatigue (n = 1, 5.6%), hypophosphatemia (n = 1, 5.6%), and autoimmune hepatitis (n = 1, 5.6%). Based upon the safety profile of OMP-313M32 monotherapy, OncoMed has initiated the dose expansion with the combination of OMP-313M32 and nivolumab (an anti–PD-1 antibody) in patients with non-small cell lung, head and neck, esophageal, gastric, cervical, triple negative breast, anal, and hepatocellular cancers or with microsatellite instability-high tumors (NCT03119428).

The Phase 1 data for tiragolumab was released at the 2020 American Association of Cancer Research meeting (Bendell et al 2020). No objective responses occurred in 24 patients treated with tiragolumab monotherapy in Phase 1a. However, in Phase 1b, 5 of 44 patients (11.4%) treated with tiragolumab combined with atezolizumab had achieved PR (Bendell et al 2020). In the Phase 1a (tiragolumab monotherapy) cohort, there were no Grade 3-5 immune-mediated AEs (imAEs). Grade 1-2 imAEs included infusion-related reaction (n = 2, 8%), rash (n = 2, 8%), hepatitis (n = 1, 4%), and pancreatitis (n = 1, 4%). In the Phase 1b (tiragolumab combined with atezolizumab) cohort, 4% of patients experienced Grade 3-5 imAEs; no Grade 5 imAEs were associated with tiragolumab and/or atezolizumab. These imAEs included infusion-related reaction (n = 4, 8%), rash (n = 14, 29%), hepatitis (n = 10, 20%), pancreatitis (n = 1, 2%), hyperthyroidism (n = 4, 8%), hypothyroidism (n = 3, 6%), and anemia (n = 1, 2%).

A total of 135 patients with previously untreated PD-L1-selected non-small cell lung cancer (NSCLC) were treated with tiragolumab 600 mg by intravenous infusion once every 3 weeks plus atezolizumab 1200 mg by intravenous infusion once every 3 weeks (n = 67) or atezolizumab 1200 mg by intravenous infusion once every 3 weeks plus placebo by intravenous infusion once every 3 weeks (n = 68) in a Phase 2 study (CITYSCAPE) sponsored by Genentech/Roche. Patients were randomly assigned to 1 of these treatment groups and were stratified by tumor proportion score (TPS) (1% to 49% or ≥ 50%), histology (squamous versus nonsquamous), and tobacco use (yes or no). Preliminary efficacy results showed a clinically meaningful improvement in ORR and PFS in patients treated with tiragolumab plus atezolizumab (ORR, 31%; PFS, 5.42 months) compared with those treated with atezolizumab plus placebo (ORR, 16%; PFS, 3.58 months). This improvement was still observed 6 months later: tiragolumab plus atezolizumab (ORR, 37%; PFS, 5.55 months) compared with atezolizumab plus placebo (ORR, 21%; PFS, 3.88 months). In addition, analysis at this 6-month follow-up timepoint showed a greater improvement in ORR in patients in the PD-L1 TPS ≥ 50% subgroup who received tiragolumab plus atezolizumab (ORR, 66%) compared with atezolizumab plus placebo (ORR, 24%). Preliminary safety results showed that treatment with tiragolumab plus atezolizumab was well tolerated; results were generally similar between the 2 treatment groups. More patients in the tiragolumab plus atezolizumab group experienced imAEs compared with those in the atezolizumab plus placebo group (46 [69%] versus 32 [47%]); most imAEs were Grade 1 or Grade 2 events of infusion-related reaction and rash and were manageable. Based on these observed efficacy and safety results, Genentech/Roche is conducting an ongoing Phase 3 study (SKYSCRAPER-01) in first-line PD-L1 TPS ≥ 50% NSCLC (NCT04294810).

Overall, tiragolumab in combination with atezolizumab has been well tolerated, adverse events were manageable, and the safety profile seems to be consistent as reported across different solid tumor indications.

All of these findings support further development of anti-TIGIT antibody in combination with existing therapeutic modalities.

1.4. Background Information on Tislelizumab as a PD-1 Inhibitor

1.4.1. Pharmacology

Tislelizumab (also known as BGB-A317) is a humanized, immunoglobulin G4 (IgG4)-variant monoclonal antibody against PD-1 under clinical development for the treatment of several human malignancies.

Tislelizumab acts by binding to the extracellular domain of human PD-1 with high specificity and affinity (dissociation constant [K_D] = 0.15 nM). It competitively blocks binding efforts by both PD-L1 and programmed cell death protein ligand-2 (PD-L2), thus inhibiting PD-1-mediated negative signaling in T cells. In in vitro cell-based assays, tislelizumab was observed to consistently, and in a dose-dependent manner, enhance the functional activity of human T cells and pre-activated, primary PBMC. Tislelizumab has demonstrated in-vivo antitumor activity in several allogeneic xenograft models, in which PBMC were co-injected with human cancer cells (A431 [epidermoid carcinoma]) or tumor fragments (BCCO-028 [colon cancer]) into immunocompromised mice.

Tislelizumab is an IgG4-variant antibody to FcγR such as FcγRI and FcγRIIIA, and it has very low binding affinity to C1q, a subunit of complement 1. In vitro assays with tislelizumab suggest either low or no ADCC, antibody-dependent cellular phagocytosis, or complement-dependent cytotoxicity effects in humans (Labrijn et al 2009). Tislelizumab was specifically engineered to abrogate these potential mechanisms of T-cell clearance and potential resistance to anti-PD-1 therapy.

Please refer to the Tislelizumab Investigator's Brochure for additional details regarding nonclinical studies of tislelizumab.

1.4.2. Toxicology

The toxicity and safety profile of tislelizumab was characterized in single-dose toxicology studies in mice and cynomolgus monkeys and in a 13-week, repeat-dose toxicology study in cynomolgus monkeys.

Overall, no apparent toxicity was noted in mouse or monkey toxicity studies. No tissue cross-reactivity was found in either human or monkey tissues, nor was any effect on cytokine release observed in the human whole-blood assay. The toxicokinetic profile was well characterized, with dose-proportional increases in systemic exposure without apparent accumulation or sex difference. Immunogenicity was observed without apparent immunotoxicity or effect on the systemic exposure. The NOAEL of tislelizumab in the 13-week monkey toxicity study was considered to be 30 mg/kg.

Please refer to the Tislelizumab Investigator's Brochure for more detailed information on the toxicology of tislelizumab.

1.4.3. Clinical Pharmacology

Population PK analysis was conducted using data from 798 patients with solid tumors or classical Hodgkin lymphoma who received doses of 0.5, 2.0, 5.0, and 10 mg/kg once every 2 weeks, 2.0 and 5.0 mg/kg once every 3 weeks, and 200 mg once every 3 weeks.

Population PK analysis demonstrated that baseline age, race, alanine aminotransferase, AST, bilirubin, lactate dehydrogenase, estimated glomerular filtration rate, ECOG PS, immunogenicity, and sum of products of perpendicular diameters in classical Hodgkin lymphoma patients did not show statistically significant impact on the PK of tislelizumab. Although tumor size, albumin, and tumor type were significant covariates on CL, while body weight, sex, and tumor type were significant covariates on V_c, these covariates are not expected to have a clinically relevant impact on tislelizumab exposure. Exposure-response analysis indicated that there was a lack of clinically significant exposure-response relationships for ORR and safety endpoints across a variety of advanced solid tumors and classical Hodgkin lymphoma for tislelizumab. Population PK analysis supports fixed-dosing across different ethnic groups.

1.4.4. Prior Clinical Experience of Tislelizumab

As of 20 May 2020, 1181 patients with solid tumors had been treated with tislelizumab monotherapy in 5 clinical studies.

A pooled monotherapy analysis was conducted to provide a comprehensive review of the tislelizumab safety profile. Patients included in this analysis (N=1181) had a median age of 60.0 years with 67.1% of them being male. Median treatment exposure duration was 3.7 months (range: 0.1 to 55.3) and median study follow-up duration was 9.9 months (range: 0.1 to 58.9).

Refer to the Tislelizumab Investigator's Brochure for more detailed information on tislelizumab safety and efficacy data when given as monotherapy or in combination with chemotherapy.

1.4.4.1. Treatment-Emergent Adverse Events Assessed as Related to Tislelizumab

Of the 1181 patients with solid tumors treated with tislelizumab monotherapy, 788 (66.7%) experienced ≥ 1 treatment-related TEAE. The most commonly occurring TEAEs (≥ 5% of patients) assessed as related to tislelizumab irrespective of grade were AST increased (136 patients, 11.5%), alanine aminotransferase (ALT) increased (125 patients, 10.6%), hypothyroidism (106 patients, 9.0%), rash (97 patients, 8.2%), and pruritus and fatigue (95 patients each, 8.0%), anaemia (89 patients, 7.5%), blood bilirubin increased (77 patients, 6.5%), diarrhoea (71 patients, 6.0%), decreased appetite (65 patients, 5.5%), proteinuria (60 patients, 5.1%), nausea (59 patients, 5.0%).

One hundred sixty-seven patients (14.1%) experienced at least 1 ≥ Grade 3 TEAE assessed as related to tislelizumab. The most frequent ≥ Grade 3 TEAEs that occurred in ≥ 1% of the patients were AST increased (21 patients, 1.8%), ALT increased (17 patients, 1.4%), and anaemia (13 patients, 1.1%).

1.4.4.1.1. Treatment-Emergent Serious Adverse Events

Of the 1181 patients with solid tumors treated with tislelizumab monotherapy, 415 (35.1%) experienced ≥ 1 treatment-emergent SAE. The most commonly occurring treatment-emergent SAEs (≥ 1% of patients) (irrespective of relationship to study drug) were pneumonia (41 patients, 3.5%), and pyrexia and ascites (15 patients each, 1.3%), upper gastrointestinal haemorrhage (13 patients, 1.1%), abdominal pain and pneumonitis (12 patients each, 1.0%).

One hundred seven patients (9.1%) experienced ≥ 1 tislelizumab-related treatment-emergent SAE. The most common treatment-emergent SAEs (≥ 5 patients) deemed related to tislelizumab

were pneumonitis (11 patients, 0.9%), AST increased (6 patients, 0.5%), and colitis, ALT increased, and pyrexia (5 patients each, 0.4%). All other tislelizumab-related treatment emergent SAEs occurred in < 5 patients.

1.4.4.1.2. Immune-Mediated Adverse Events

Anti-PD-1 therapies are known to cause imAEs in some patients and therefore have been defined as adverse events (AEs) of special interest (AESI) in tislelizumab clinical studies and as such are being monitored closely.

Of the 1113 patients with solid tumors included in the pooled analysis of imAEs, 233 (20.9%) experienced ≥ 1 imAE of any grade. The most commonly occurring imAEs of any grade (≥ 3% of patients) were hypothyroidism (69 patients, 6.2%), hyperthyroidism (37 patients, 3.3%), and rash (34 patients, 3.1%). Analysis of the patients with ≥ 1 imAE that was also ≥ Grade 3 in severity showed that 52 patients (4.7%) experienced such events. The most commonly occurring imAEs (≥ 0.5% of patients) that were ≥ Grade 3 in severity were ALT increased (9 patients, 0.8%), and AST increased and pneumonitis (7 patients each, 0.6%).

1.4.4.1.3. Infusion-Related Reactions

Infusion-related reactions, including high-grade hypersensitivity reactions, after administration of tislelizumab are uncommon.

Of the 1181 patients treated with tislelizumab monotherapy , 45 (3.8%) experienced ≥ 1 infusion-related reaction of any grade. The most commonly occurring infusion-related reactions of any grade were infusion-related reactions (28 patients, 2.4%), pyrexia (10 patients, 0.8%), and nausea (4 patients, 0.3%). There were 2 patients (0.2%) with ≥ Grade 3 infusion-related reactions and all other events occurred in single instances; these included rash, flushing, hypotension, and spinal pain.

1.4.4.1.4. Liver Laboratory Abnormalities

Of the 932 patients with solid tumors included in the analysis of drug-induced liver injury, 33.0% of patients experienced ALT or AST > 1x upper limit of normal (ULN) but ≤ 3x ULN and 3.6% of patients had ALT or AST > 5x the ULN but ≤ to 10x the ULN. ALT or AST were > 3x the ULN with total bilirubin> 2x the ULN in 25 patients (2.7%).

Of the 249 patients with HCC in the adjudicated analysis of drug-induced liver injury in BGB-A317-208, an open-label, single-arm, multicenter Phase 2 study of tislelizumab monotherapy in patients with previously treated unresectable HCC, 56.2% of patients experienced ALT or AST > 1x ULN but ≤ to 3x ULN and 9.6% of patients had ALT or AST > 5x ULN but ≤ to 10x ULN. ALT or AST were > 3x ULN with total bilirubin > 2x ULN in 18 patients (7.2%).

1.4.4.1.5. Fatal Adverse Events

Out of 1181 patients treated with tislelizumab monotherapy who were included in the analysis, 18 patients (1.5%) experienced a fatal AE ≤ 30 days after the last study drug dose. A total of 9 patients (0.8%) experienced fatal AEs that were deemed related to tislelizumab, including hepatic failure (2 patients, 0.2%); and large intestinal obstruction, pneumonitis, respiratory arrest, respiratory failure, hepatitis acute, brain oedema, and death (1 patient each, 0.1%).

1.4.4.2. Efficacy Assessment of Tislelizumab

Efficacy data of tislelizumab monotherapy in HCC are available from 2 ongoing monotherapy studies, BGB-A317_Study_001 (data cutoff: 26 August 2020) and BGB-A317-102 (data cutoff: 31 May 2020), which are summarized below.

1.4.4.2.1. Study BGB-A317_Study_001

Study BGB-A317_Study_001 is a 2-stage study consisting of a Phase 1a dose-escalation (0.5 to 10 mg/kg) and dose-finding component with 3 parts (2 and 5 mg/kg given either once every 2 or 3 weeks, and a fixed dose of 200 mg given once every 3 weeks) to establish MTD, if any, and a recommended Phase 2 dose (RP2D). Phase 1a was followed by a Phase 1b component to investigate efficacy in select tumor types at the RP2D to further evaluate safety and tolerability of tislelizumab. Indication-specific cohorts included esophageal cancer (EC), gastric cancer, HCC, and NSCLC cohorts.

Responses were assessed by the investigator per the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) criteria.

There were 451 patients treated in the study and 441 patients were included in the Efficacy Evaluable Analysis Set (EAS). The EAS includes all treated patients who had at least 1 measurable baseline target lesion and had at least 1 evaluable postbaseline tumor assessment. This set included 49 patients in the HCC cohort.

The RP2D and schedule for tislelizumab was determined to be 200 mg administered once every 3 weeks. At the data cutoff date of 26 August 2020, of the 49 patients in the HCC cohort, no patients (0%) had a CR and 6 patients (12.2%) had a confirmed PR. Additionally, 17 patients (34.7%) had a best overall response (BOR) of stable disease. A total of 24 patients (48.9%) had a best response of progressive disease (PD) in this cohort.

1.4.4.2.2. Study BGB-A317-102

Study BGB-A317-102 is a non-randomized, Phase 1/2 study of tislelizumab monotherapy in Chinese patients with advanced solid tumors. Phase 1 includes a dose verification substudy and a substudy of PK evaluation of the products derived from 2 manufacturing processes and scales. Phase 2 evaluates the activity and safety of tislelizumab at its RP2D of 200 mg given once every 3 weeks in indication-specific expansion cohorts.

Responses were assessed by the investigator per the RECIST v1.1 criteria.

Of the 300 patients treated in Study BGB-A317-102, a total of 249 patients were included in the EAS. The EAS includes all treated patients who had at least 1 measurable baseline target lesion and had at least 1 evaluable postbaseline tumor assessment. The EAS included 18 patients in the HCC cohort.

At the data cutoff date of 31 May 2020, of the 18 patients in the HCC cohort, no patients (0%) had a CR and 3 patients (16.7%) had a confirmed PR. Additionally, there were 7 patients (38.9%) with a BOR of stable disease. A total of 8 patients (44.4%) had a best response of PD in this cohort.

1.5. Background Information on BAT1706, a Bevacizumab Biosimilar

BAT1706 is a similar biological product to the bevacizumab injection (Bevacizumab Injection, brand name Avastin® [hereafter referred to as "Avastin"]). Bevacizumab contains a type of recombinant humanized immunoglobulin G1 (IgG1) monoclonal antibody as the active ingredient and binds with high affinity to human VEGF.

The expression of VEGF receptors (VEGFRs) is markedly elevated in the blood vessels of many tumors. Through its mechanism of action of neutralizing, bevacizumab VEGF is able to specifically inhibit tumor angiogenesis and block the growth and metastasis of tumors.

Bevacizumab can selectively bind with high affinity to all human VEGF A isoforms and blocks the binding of VEGF to VEGFR-1 and VEGFR- 2, thereby neutralizing the bioactivity of VEGF.

To date, more than a million patients globally have undergone treatment with bevacizumab, the world's first anti-VEGF antibody that has been proven to significantly extend the OS and PFS in multiple cancers. BAT1706 is a recombinant humanized anti-VEGF monoclonal antibody injection, which is a proposed biosimilar of Avastin. BAT1706 has been compared against US- and European Union (EU)-sourced Avastin in a comprehensive comparative analytical and nonclinical study program, which is summarized in the BAT1706 Investigator's Brochure. The results from these investigations provide evidence of the structural and functional similarity of BAT1706 to Avastin.

1.5.1. Nonclinical Experience

1.5.1.1. Pharmacology

The results of comparative in vitro pharmacodynamic research showed that BAT1706 and Avastin both exhibited specific binding with VEGF- A121 and VEGF- A165, which was consistent with literature reports. The biological activity of BAT1706 was also found to be comparable to that of Avastin within the predetermined range of $(1.0 \pm 0.2) \times 10^4$ U/mg.

The anti-tumorigenic effect of BAT1706 and Avastin in several models of human cancer (NSCLC, ovarian cancer, and rhabdomyosarcoma) was also investigated. These results showed that treatment with BAT1706 and Avastin at higher doses (5 mg/kg in NSCLC and rhabdomyosarcoma and 10 mg/kg in ovarian cancer) was effective in all 3 tumor models, and none was effective at lower doses (0.5 mg/kg in NSCLC and rhabdomyosarcoma and 1 mg/kg in ovarian cancer). Except for the 0.5 mg/kg dose in the rhabdomyosarcoma model, all other doses showed similar pharmacodynamic effects for BAT1706 and Avastin, and the tumor growth curves showed a high degree of coincidence.

The results of a PK study conducted suggested equivalency in in vivo metabolic processes of BAT1706 and Avastin. The concentration of the drug in blood plasma revealed extremely slow elimination, consistent with literature reports.

Please refer to the BAT1706 Investigator Brochure for more detailed information on the pharmacology of BAT1706.

1.5.1.2. Toxicology

Toxicokinetic parameters assessed showed no significant gender-based difference in the drug exposure and that the plasma drug concentration, mean area under the plasma concentration-time curve from 0 hours to time t (AUC_{0-t}), and maximum concentration (C_{max}) were dose-related. The values of AUC_{0-t}, elimination half-life ($t_{1/2}$), clearance (CL_z), and C_{max} for the same dose (4 mg/kg) of BAT1706 and Avastin were not notably different.

Results of the nonclinical toxicology studies demonstrated that BAT1706 has good local tolerance for intravenous administration, with no impact on the central nervous system (CNS), or cardiovascular or respiratory systems, no immunogenicity or severe immunotoxicity, and no specific binding to non-target tissues in the body when compared with Avastin.

A study conducted to observe the irritant effects on the administration sites as well as the surrounding tissues for BAT1706 did not reveal any irritation reactions at the vascular injection sites during or after drug administration.

An evaluation of the effects of BAT1706 injection on in vitro hemolysis and red blood cell (RBC) agglutination in rabbits showed that BAT1706 had no in vitro hemolytic or RBC agglutination-causing effects in rabbits.

Please refer to the BAT1706 Investigator Brochure for more detailed information on the toxicology of BAT1706.

1.5.2. Clinical Experience

The pharmacokinetics of BAT1706 has been studied in 2 Phase 1 studies:

- BAT1706-001-CR, a randomized, double-blind, single-dose, 3-arm parallel design comparative pharmacokinetic and safety Phase 1 study of BAT1706 versus EU-sourced Avastin and US-sourced Avastin administered in healthy subjects
- BAT1706-002-CR, a Randomized, double-blind, single-dose, 2 parallel groups study to compare the pharmacokinetics and safety of BAT1706 injection with bevacizumab (European Product) in healthy subjects

The 2 Phase 1 studies BAT1706-001-CR and BAT1706-002-CR revealed that a single intravenous infusion of BAT1706 (1 mg/kg) is safe and well tolerated in healthy subjects. There were no deaths reported during either study, and only 1 serious TEAE which was unrelated to BAT1706 as determined by the investigator. The key PK parameters of both Phase 1 studies also revealed that BAT1706 is a bioequivalent of Avastin (bevacizumab). No ADA positive result was reported for any subject included in either study.

A Phase 3 study of BAT1706, BAT1706-003-CR, a multicenter, randomized, double-blind, study of BAT1706 versus EU- sourced Avastin plus chemotherapy in patients with advanced non-squamous NSCLC is ongoing.

1.5.2.1. Clinical Pharmacology

The Phase 1 study BAT1706-001-CR compared the PK of BAT1706 with that of EU-sourced Avastin and US-sourced Avastin in healthy subjects after a single intravenous infusion (1 mg/kg). The results showed that PK parameters were similar between the 3 drug products. The

mean concentration profiles for BAT1706, EU- and US- sourced Avastin were similar over the entire sampling time interval.

The PK results of another Phase 1 study BAT1706-002-CR are consistent with results observed in the Phase 1 study BAT1706-001-CR. The BAT1706-002-CR study compared the PK of BAT1706 with bevacizumab (Avastin) and showed that the change of concentration-time curve over time was similar between the BAT1706 injection group and the bevacizumab group. The geometric mean ratio and 90% CI of the major PK parameters ($AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and C_{max}) were in the acceptable equivalent range (0.8 to 1.25), indicating that PK of BAT1706 injection is equivalent to bevacizumab.

Please refer to the BAT1706 Investigator Brochure for more detailed information on the clinical pharmacology of BAT1706.

1.5.2.2. Clinical Safety

Study BAT1706-001-CR

The Phase 1 study BAT1706-001-CR assessed the safety of BAT1706 and compared that to the safety of EU-sourced Avastin and US-sourced Avastin in healthy subjects. A total of 125 healthy subjects received a single, 1 mg/kg administration of 1 of 3 study drugs: BAT1706, EU-sourced Avastin, or US-sourced Avastin, as a 90-minute intravenous infusion. The results revealed that a single intravenous infusion of BAT1706 is safe and well tolerated, associated with mild injection site reactions.

There were no deaths or TEAEs leading to premature withdrawal reported during the study. One subject in the BAT1706 group reported a serious TEAE of fibula fracture, which was unrelated to study drug (as assessed by the investigator) and resolved during the study.

Overall, 107 subjects (85.6%) experienced ≥ 1 TEAE during the study. The incidence of subjects experiencing ≥ 1 TEAE was slightly higher in the BAT1706 group (37 subjects, 92.5%) than in the EU-sourced Avastin group (34 subjects, 79.1%), and the US-sourced Avastin group (36 subjects, 85.7%).

The majority of TEAEs reported (≥ 7.5%) in the BAT1706 group were: upper respiratory tract infection (13 subjects, 32.5%), headache (10 subjects, 25.0%), contusion (6 subjects, 15.0%), nasopharyngitis (5 subjects, 12.5%), skin abrasion (4 subjects, 10.0%), and ligament sprain (3 subjects, 7.5%). Upper respiratory tract infection and headache were the most common TEAEs reported in all the 3 treatment groups.

A majority of the TEAEs reported during the study were mild in intensity. Only 2 subjects (1 subject [2.5%] in the BAT1706 group and 1 subject [2.4%] in the US-sourced Avastin group) experienced a TEAE of severe intensity (fibula fracture and muscle enzyme increased, respectively), both of which were unrelated to the study drug as assessed by the investigator.

A total of 62 subjects (49.6%) reported at least 1 TEAE considered to be related to the study drug: 22 (55.0%) subjects in the BAT1706 group, 21 subjects (48.8%) in the EU-sourced Avastin group, and 19 subjects (45.2%) in the US-sourced Avastin group. The majority of reported TEAEs assessed as related to BAT1706 (≥5%) were headache (7 subjects, 17.5%), upper respiratory tract infection (5 subjects, 12.5%), and nausea (2 subjects, 5%). In the EU-sourced Avastin group, the incidence of reported TEAEs was also similar: headache (7

subjects, 16.3%) and upper respiratory tract infection (5 subjects, 11.6%). In the US-sourced Avastin group the reported TEAEs were similar: headache (4 subjects, 9.5%) and upper respiratory tract infection (3 subjects, 7.1%).

Study BAT1706-002-CR

The Phase 1 study BAT1706-002-CR assessed the safety of BAT1706 and compared it with that of bevacizumab (European product) in healthy subjects. A total of 80 healthy subjects received a single, 1 mg/kg administration of study drug (39 subjects in the BAT1706 injection group and 41 subjects in the bevacizumab group [European product]). The study results showed that both drugs were safe and well tolerated. No death or SAE was reported throughout the study.

The overall incidences of AEs and AEs in each category were comparable between the 2 groups. The overall incidence of TEAEs in the BAT1706 injection group was 59.0%. The most common TEAEs reported in ≥ 10.0% of subjects by Preferred Term (PT) included ALT increase (9 subjects, 23.1%), AST increase (6 subjects, 15.4%), and white blood cell count decrease (4 subjects, 10.3%). The overall incidence of TEAE in the bevacizumab group was 46.3%. The most common TEAE reported in ≥ 10.0% by PT included hypertriglyceridemia (6 subjects, 14.6%) and ALT increase (5 subjects, 12.2%).

None of the subjects reported injection site reactions during the study.

The incidence and severity of TEAEs were similar between the BAT1706 injection group and the bevacizumab (European product) group. Most of the TEAEs that occurred in the BAT1706 and the bevacizumab group were of Grade 1 or 2 (CTCAE, version 4.03). In the BAT1706 and bevacizumab group, 1 subject (2.6%) and 7 subjects (17.1%) respectively, had ≥ Grade 3 TEAEs. In the BAT1706 group, 1 subject (2.6%) developed Grade 3 hypertriglyceridemia. No subject developed a Grade 4 or 5 TEAE. In the bevacizumab group, 1subject (2.4%) had Grade 3 and Grade 4 hypokalemia, 5 subjects (12.2%) had Grade 3 hypertriglyceridemia, and 1 subject (2.4%) had Grade 4 hypertriglyceridemia. In the bevacizumab group no subject developed Grade 5 TEAE.

The incidence of study drug-related TEAEs in the BAT1706 group was 38.5%. The study drug-related TEAEs reported in ≥ 5.0% of patients by PT included ALT increase (15.4%), AST increase (7.7%), white blood cell count decrease (5.1%), blood albumin decrease (5.1%), hyperglycemia (5.1%) and hematuria (5.1%). The incidence of study drug-related TEAEs in the bevacizumab group was 24.4%. The study drug-related TEAEs reported in ≥ 5.0% of patients by PT included ALT increase (7.3%).

Please refer to the BAT1706 Investigator Brochure for more detailed information on the safety of BAT1706.

1.6. Study Rationale

As described in previous sections, anti-PD-1/PD-L1 treatment in combination with anti-angiogenic agents has demonstrated significant improvement in patient survival compared with sorafenib. This combination is becoming the new worldwide standard-of-care in the first-line HCC setting, with the approval of atezolizumab plus bevacizumab. Tislelizumab monotherapy has shown clinical activity in previously treated HCC, comparable with that of other agents of the same molecule class, with a tolerable and manageable safety profile. Therefore, tislelizumab

in combination with BAT1706 is expected to provide clinical benefit comparable to that of other combination of anti-PD-1/PD-L1 plus anti-angiogenesis treatments.

Despite the wealth of evidence supporting the role of TIGIT in promoting tumor immune tolerance, TIGIT blockade alone (ie, ociperlimab monotherapy) is unlikely to result in an effective antitumor response according to existing anti-TIGIT clinical data (see Section 1.3). However, TIGIT represents a hallmark in the process of T-cell exhaustion in liver cancer. Compared to PD-1, TIGIT expression more reliably identified exhausted CD8 T cells at different stages of their differentiation. In combination with PD-1 inhibition, targeting of TIGIT with antagonistic antibodies resulted in synergistic inhibition of liver cancer growth in immunocompetent mice (Ostroumov et al 2020).

Taking these data into account, the combinations of tislelizumab plus BAT1706, with or without ociperlimab, are designed to prove the concept of synergistic benefit of adding TIGIT blockade to an anti-PD-1-based regimen by evaluating the effect of adding ociperlimab to the tislelizumab plus BAT1706 regimen. This approach is intended to maximize the patient's potential therapeutic benefit while simultaneously achieving the clinical objective of characterizing the safety and efficacy of the combination of ociperlimab with tislelizumab and BAT1706.

1.6.1. Rationale for Dose Selection

1.6.1.1. Rationale for the Selection of Ociperlimab Dose in Combination with Tislelizumab and BAT1706

Ociperlimab doses ranging from 50 mg to 900 mg once every 3 weeks, in combination with 200 mg of tislelizumab once every 3 weeks were explored in the ongoing Ph1/1b Study BGB-900-105. All the tested ociperlimab dose levels cleared the DLT window without any significant safety or tolerability events. The ociperlimab exposures increased in an approximately dose-proportional manner (Ociperlimab Investigator's Brochure). As of 07 August 2020, the maximum administered ociperlimab dose of 900 mg, was selected as RP2D.

Complete TIGIT receptor occupancy was observed on circulating T cells and NK cells in peripheral blood at all the tested doses in the Phase 1 study. However, since the correlation between TIGIT receptor occupancy in periphery and receptor occupancy in tumor tissues is unknown, quantitative systems pharmacology (QSP) modeling was performed and preliminary results predict near complete TIGIT receptor occupancy in tumor tissues at doses of 450 mg and above. Due to the lack of information on the impact of immunogenicity on ociperlimab PK, a conservative estimate of 900 mg dose, which was deemed to be safe and tolerable in patients, was selected. This dose level increases the likelihood of efficacious concentrations and saturation of TIGIT receptors in tumor tissues completely over the entire dosing interval. Absence of any dose-dependent safety events in the ongoing Phase 1 study additionally supports selecting this dose for further evaluation. The preliminary ociperlimab PK data from the ongoing BGB-900-105 study indicates lack of significant relationship between the ociperlimab exposures and patients' body weight, thus supporting the selection of a fixed dose for ociperlimab.

As discussed in Section 1.6.1.3, the potential for drug-drug interaction with therapeutic antibodies is low, and these monoclonal antibodies are unlikely to influence drug-metabolizing enzymes or transporters. Considering the different therapeutic targets of immune-checkpoint

inhibitors and VEGF, the RP2D of ociperlimab 900 mg administered intravenously once every 3 weeks with tislelizumab 200 mg will also be applicable to the combination of ociperlimab plus tislelizumab and BAT1706 regimen.

1.6.1.2. Rationale for the Selection of Tislelizumab Dose

The PK, safety, and efficacy data obtained from the first-in-human study BGB-A317_Study_001, as well as other clinical study data, were analyzed in aggregate to determine the recommended dose for studies of tislelizumab. The dose of 200 mg intravenously once every 3 weeks was selected for further evaluation.

Rates of treatment-related AEs and SAEs observed in patients receiving 2 mg/kg and 5 mg/kg once every 2 weeks and once every 3 weeks were comparable, suggesting no clear dose-dependence across these regimens. Similarly, confirmed ORRs in patients treated with tislelizumab 2 mg/kg and 5 mg/kg once every 2 weeks ranged between 10% and 15%, compared to a range of 15% to 38% for patients treated at 2 mg/kg and 5 mg/kg once every 3 weeks.

According to PK data from BGB A317_Study_001, Phase 1a, the clearance of tislelizumab was found to be independent of body weight, ethnicity, and sex, and the observed serum exposure of a 200-mg dose fell between the serum exposure observed after 2 mg/kg and 5 mg/kg doses (dose range with comparable safety and efficacy rates).

Additionally, no unexpected treatment-related AEs occurred in the 200-mg fixed dose cohort (BGB-A317_Study_001, Phase 1a, Part 3) when compared with body-weight-based cohorts. Of the evaluable patients treated (n = 13), 3 patients (23%) had a BOR of PR, 4 patients (31%) had a BOR of stable disease, and 6 patients (46%) had a BOR of PR. Therefore, clinical activity with a manageable and tolerable safety profile is expected to be maintained in patients receiving tislelizumab 200 mg every 3 weeks.

Tislelizumab 200 mg administered intravenously every 3 weeks is the approved dosage for tislelizumab (BaiZeAn® Product information) in China. This dosage has been demonstrated to be tolerable with clinical manageable safety profile in previously treated HCC patients.

Therefore, the recommended dosage of 200 mg once every 3 weeks will be utilized for the tislelizumab combination studies with BAT1706 and ociperlimab; however, alternate doses or dose schedules may be evaluated based on emerging clinical data.

1.6.1.3. Rationale for the Selection of BAT1706 Dose in Combination with Tislelizumab

The Phase 1b study GO30140 showed durable antitumor responses and significantly improved PFS outcomes with atezolizumab plus bevacizumab than with atezolizumab monotherapy, which suggests that both atezolizumab and bevacizumab contribute to the overall treatment benefit of the combination in patients with HCC (Lee et al 2020).

Atezolizumab selectively targets PD-L1 to prevent interaction with receptors PD-1 and B7-1, thus reversing T-cell suppression (Herbst et al 2014). Modest single-agent activity in HCC has been observed with bevacizumab (Boige et al 2012, Siegal et al 2008). Bevacizumab is a monoclonal antibody that targets VEGF, inhibits angiogenesis and tumor growth, and showed response rates of 13% to 14% in single-agent Phase 2 studies in patients with advanced liver cancer (Siegel et al 2008, Finn et al 2009). As a monotherapy and in combination with PD-L1

inhibitors, bevacizumab has shown immunomodulatory effects in other tumor types, with promising clinical benefit and a good safety profile (Wallin et al 2016, McDermott et al 2018).

BAT1706 is a proposed biosimilar to Avastin (bevacizumab). Several analytical assays and stress degradation studies have been conducted to compare multiple lots of BAT1706 and Avastin. Specifically, the data indicate that BAT1706 is at least as pure as Avastin and relevant biological functional assays also showed similar results. BAT1706 showed similar reactions during the incubating conditions and similar degradation rates as Avastin. Therefore, the data have demonstrated that BAT1706 is similar to the reference product US-Avastin, and the comparator EU-Avastin (BAT1706 Investigator's Brochure).

BAT1706 will be administered intravenously at a dosage of 15 mg/kg once every 3 weeks which is the approved dosage for bevacizumab (Avastin local labels). The potential for drug-drug interaction between tislelizumab and BAT1706 is very low because BAT1706 and tislelizumab are therapeutic monoclonal antibodies. Both are expected to be degraded into amino acids and recycled into other proteins and are unlikely to influence drug-metabolizing enzymes or transporters. The different therapeutic targets of immune checkpoint and VEGF may suggest different safety profiles and different spectrums of related AEs. The combination isn't expected to exacerbate the known safety risk of either study drug.

Moreover, the same dosage of Avastin and its biosimilar was administered in combination with other anti-PD-1/PD-L1 inhibitors (Finn et al 2020a; Ren et al 2020), and was tolerable and clinical manageable. Therefore, BAT1706 at a dosage of 15 mg/kg once every 3 weeks will be used for the combination with tislelizumab.

1.6.2. Rationale for Combination of Ociperlimab With Tislelizumab and BAT1706 in the First-Line Treatment of Advanced Hepatocellular Carcinoma

As described earlier, anti-PD-1/PD-L1 inhibitor monotherapy has shown clinical benefit in previously treated HCC (OPDIVO prescribing information, KEYTRUDA prescribing information, Qin et al 2020). However, it does not show significant improvement compared with sorafenib in first-line HCC patients (Yau et al 2019). Given the promising anti-tumor activity of anti-PD-1 antibodies reported in HCC and given that TIGIT may improve the therapeutic benefit of anti-PD-1 therapy, the combination of ociperlimab and tislelizumab may bring significant clinical benefit in this indication and support further clinical development.

Modest single-agent activity has been observed with bevacizumab in HCC patients (Boige et al 2012, Siegal et al 2008). In combination with PD-L1 inhibitors, bevacizumab has shown immunomodulatory effects in other tumor types, with promising clinical benefits and a good safety profile (Wallin et al 2016). The positive results of the IMbrave150 study and Orient32 study demonstrate the synergistic benefit of combining anti-PD-1/PD-L1 inhibitors with anti-angiogenic agents.

Targeting TIGIT provides a potential mechanism to rescue immune cells from the immunosuppressive tumor microenvironment, thereby inducing an efficient antitumor immune response. Research shows that the TIGIT pathway cooperates with PD-1 to maximize the suppression of effector TILs as well as promote resistance to anti-PD-1 therapy. Antibodies targeting the PD-1/PD-L1 pathway have achieved remarkable results in the treatment of HCC.

Therefore, TIGIT represents an ideal target with the potential to significantly improve and/or extend the therapeutic benefit of anti-PD-1 therapy in HCC.

Given the promising antitumor activity of anti-PD-1 antibodies in combination with anti-angiogenic agents reported in patients with HCC and given the scientific rationale that TIGIT may improve the therapeutic benefit of anti-PD-1 therapy, the combination of ociperlimab, tislelizumab and BAT1706 may bring significant clinical benefit in this indication and support further clinical development.

1.6.3. Biomarker Strategy Rationale

A number of biomarkers have been identified that correspond with response to immunotherapy for patients with HCC.

PD-L1 expression has been demonstrated to be positively correlated with response to anti-PD-1 therapy across tumor types (Cristescu et al 2018). Although PD-L1 expression has not been widely approved to be a predictive factor for anti-PD(L)-1 treatment in patients with HCC, higher PD-L1 expression was shown to be associated with better response and survival benefit (Studies A317-001, CHECKMATE-040, CHECKMATE-459, Keynote-224, NCT02989922), indicating the potential role of PD-L1 in predicting response to anti-PD(L)-1 therapies. Internal HCC data (A317-001/102) and TCGA database analysis demonstrated that PD-L1 expression positively correlates with TIGIT expression, implying that PD-L1 expression may work as the surrogate marker for TIGIT expression. High expression of PD-L1 (TPS $\geq$ 50%) is also correlated with a better response in patients with NCSLC treated with atezolizumab plus tiragolumab (CITYSCAPE study), but its role in predicting the efficacy of the anti-TIGIT therapy in patients with HCC has not been reported so far. In summary, these data support further exploration of the correlation of PD-L1 expression with response to tislelizumab plus BAT1706 and ociperlimab.

Tumor mutational burden (TMB) works as the surrogate marker for neo-antigen prediction and has been reported to positively correlate with the response to anti-PD(L)-1, and serves as an independent biomarker from PD-L1, indicating that its combination with PD-L1 may lead to predictive synergy (Fumet et al 2020; Cristescu et al 2018). In patients with HCC, the correlation between TMB and anti-PD(L)-1 therapy has not been extensively reported, and needs further exploration in future studies. Blood TMB (bTMB) demonstrated good correlation with TMB when assessed with large panels, which has been explored due to its non-invasiveness, and has been reported to predict clinical benefit with anti-PD(L)-1 therapy in several clinical studies (Studies POPLAR, OAK, MYSTIC) (Gandara et al 2018). Circulating tumor DNA (ctDNA) monitoring can be derived from a bTMB panel. The GO30140 study in patients with HCC has reported the role of baseline ctDNA in predicting response to atezolizumab plus bevacizumab. These data indicate the potential role of bTMB/ctDNA monitoring in predicting response to anti-PD(L)-1 therapies in HCC. Apart from TMB, DNA mutation can also be explored from the (b)TMB detection panel to identify genes/pathways associated with response/resistance to immunotherapies. In summary, the role of (b)TMB in predicting response/resistance to tislelizumab plus BAT1706 and ociperlimab can be explored.

Gene expression profile (GEP) panels have been designed to investigate immune features (tumor immunogenicity, interferon gamma signature, immune cell population abundance, etc) and tumor features (epithelial-mesenchymal transition, angiogenesis, hypoxia, cell adhesion, etc). IFNγ

signature has been shown to be positively correlated with response to anti- PD(L)-1 monotherapy across tumor types (Cristescu et al 2018). Publications or presentations for HCC (Lee et al 2020, Sangro et al 2020), have reported the association of GEP panels (selected genes) with response to anti-PD(L)-1 immunotherapies. Apart from their potential predictive value, GEP panels can be designed to explore underlying resistance mechanisms such as immunosuppressive cytokines and cells to guide potential therapeutic strategies (Fumet et al 2020; Cristescu et al 2018). In summary, the role of GEP in predicting response/resistance to tislelizumab plus BAT1706 and ociperlimab can be further explored.

The correlation between the expression of the TIGIT pathway molecules (TIGIT, PVR and nectin-2) and the response to anti-TIGIT related therapies is unclear. $TIGIT^{high}$ immune cells are mainly composed of exhausted T and Treg cells (Zheng et al 2017), although $TIGIT^{high}$ immune cells may not optimally represent more responsive immune cells in the tumor microenvironment. As one of the molecules mediating the antitumor role of ociperlimab, TIGIT may play a critical role in the Fcγ receptor mediated activation of myeloid and NK cells through crosslinking, which depends on TIGIT expression. Consequently, the correlation of TIGIT expression with response to tislelizumab plus BAT1706 and ociperlimab can be further explored. As the ligands for TIGIT, PVR and nectin-2 are differently expressed across tumor types and even within a single tumor type (SITC-2019-COM902), whether their expression correlates with response to ociperlimab and tislelizumab plus BAT1706 as well as the regulation of their expression await further exploration.

Alpha-fetoprotein (AFP) has been reported to be a prognostic/diagnostic biomarker for HCC (Wang 2018). Whether AFP plays a potential role in predicting the response to ociperlimab in combination with tislelizumab plus BAT1706 will be further explored in this study.

Consequently, PD-L1, TMB/DNA mutation, bTMB/ctDNA monitoring/DNA mutation, AFP, GEP and TIGIT/PVR/nectin-2 can be explored in tumor or blood samples to identify their potential predictive value, as well as resistance mechanisms in patients who receive ociperlimab in combination with tislelizumab plus BAT1706, and tislelizumab plus BAT1706.

1.7. Benefit-Risk Assessment

Patients with advanced HCC represent a population with an unmet medical need, although significant improvements in survival have been reported with anti-PD-1/PD-L1 inhibitor combined with anti-angiogenic agents when compared with sorafenib as first-line therapy.

The safety profile of tislelizumab monotherapy is considered as acceptable based on previous nonclinical and clinical data. Ociperlimab combined with tislelizumab 200 mg once every 3 weeks is safe and well-tolerated, with no DLTs, no treatment-related SAEs, or treatment-related high-grade AEs occurring during the treatment period for each dose level in the ongoing BGB-900-105 Phase 1/1b study as of 16 June 2020.

Bevacizumab has been used in clinical practice for more than 15 years. Its well-established clinical efficacy and safety profiles support further development for combination therapy approaches. (Garcia 2020). Combining BAT1706, a biosimilar of bevacizumab, with checkpoint inhibitors isn't expected to exacerbate the known AEs related to immune checkpoint inhibitors, considering the different therapeutic targets.

Given the unmet medical need and limited treatment options for this indication, the benefit/risk assessment, based on the available safety and efficacy data of anti-TIGIT monoclonal antibodies with or without anti-PD-1/PD-L1 antibodies and the available efficacy data from the PD-1 antibodies and their combination with bevacizumab in this indication, the benefit/risk of the combination of tislelizumab and BAT1706 with or without ociperlimab is considered favorable. This Phase 2 study will be conducted in order to evaluate the potential benefit and safety of ociperlimab with tislelizumab plus BAT1706 and tislelizumab plus BAT1706.

A Safety Monitoring Committee (SMC) will be established to regularly monitor the safety of ociperlimab, tislelizumab, and BAT1706.

1.8. Study Conduct

This study will be conducted in compliance with the protocol approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and in accordance with Good Clinical Practice (GCP) standards.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objectives

- 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

2.1.2. Secondary Objectives

- 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

2.1.3. Exploratory Objectives

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

2.2. Study Endpoints

2.2.1. Primary Endpoints

- 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

2.2.2. 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 date of first dose of study drug 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 ≥ 24 weeks)
  - PFS, defined as the time from the date of the first dose of study drug to the date of first documentation of disease progression or death, whichever occurs first
- OS, defined as the time from the date of the first dose of study drug 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

2.2.3. Exploratory Endpoints

- Potential biomarkers including programmed cell death protein ligand-1 (PD-L1) expression, T cell immunoreceptor with Ig and ITIM domains (TIGIT) pathway-related protein expression (TIGIT, poliovirus receptor/PVR and nectin cell adhesion molecule 2/nectin-2), tumor mutational burden (TMB)/DNA mutation, blood tumor mutational burden (bTMB)/ctDNA monitoring/DNA mutation, alpha-fetoprotein (AFP), gene expression profile (GEP), and the association of biomarkers with disease status, and response/resistance to ociperlimab in combination with tislelizumab plus BAT1706, and to tislelizumab plus BAT1706

3. STUDY DESIGN

3.1. Summary of 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 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:

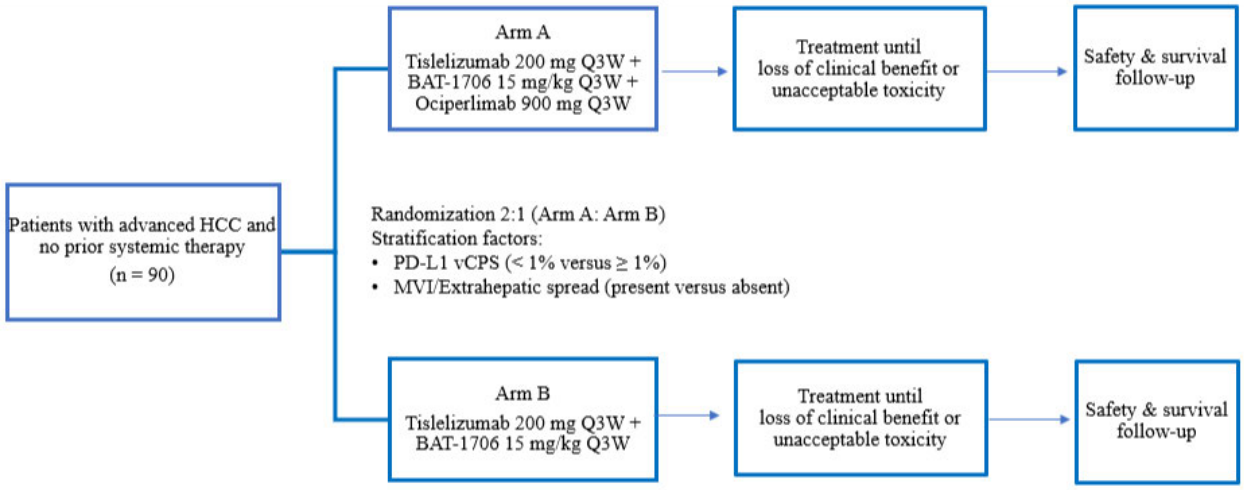
- PD-L1 expression (visually estimated combined positive score [vCPS] <1% versus ≥1%) by SP263. The vCPS score is the total percentage of the tumor area covered by tumor cells with PD-L1 membrane staining at any intensity and tumor-associated immune cells with PD-L1 staining at any intensity.
- Macrovascular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

The study schema is shown in Figure 2.

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.

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 2: 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.

3.2. Screening Period

Screening evaluations will be performed ≤ 28 days before randomization.

Patients who agree to participate in this study will sign the informed consent form (ICF) before undergoing any screening procedure. Screening evaluations may be repeated as needed within the screening period; the investigator is to assess preliminary patient eligibility according to the latest screening assessment results.

Tumor imaging (computed tomography [CT] with or without contrast, or magnetic resonance imaging [MRI]) must be performed ≤ 28 days before randomization.

3.3. Treatment Period

The treatment period will start on the first day of study drug administration and end when the patient is discontinued from the study drug(s) for any reason.

After completing all screening activities, eligible patients will be randomized in a 2:1 (Arm A: Arm B) ratio to receive ociperlimab + tislelizumab + BAT1706 (Arm A), or tislelizumab + BAT1706 (Arm B).

Study drug(s) will be administered as follows:

- Arm A: tislelizumab 200 mg intravenously once every 3 weeks followed by BAT1706 15 mg/kg intravenously once every 3 weeks followed by ociperlimab 900 mg intravenously once every 3 weeks
- Arm B: tislelizumab 200 mg intravenously once every 3 weeks followed by BAT1706 15 mg/kg intravenously once every 3 weeks

No crossover between Arm A and Arm B will be allowed.

Eligible patients will be stratified by the following factors:

- PD-L1 expression (vCPS < 1% versus ≥ 1%) by SP263
- MVI/EHS (present versus absent)

During the study treatment period, tumor response will be evaluated by the investigator every 6 weeks in the first 48 weeks, and every 12 weeks thereafter, in accordance with RECIST v1.1.

If, at the investigator's discretion, a patient could continue to benefit from the assigned study drug(s) after PD per RECIST v1.1 criteria is met, the patient may continue their assigned treatment.

The following criteria must be met in order to treat patients who may continue to benefit from study drug(s) after PD:

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

Patients who receive study drug(s) beyond disease progression will have tumor assessments performed according to the original schedule until all study drug(s) are discontinued.

If a patient discontinues study drug(s) due to any reason other than PD (eg. toxicity), tumor assessments will be performed according to the original schedule until disease progression, death, loss to follow-up, withdrawal of consent, or until the study terminates, whichever occurs first.

Patients will report any AEs and SAEs, regardless of causality to study drugs, occurring within either 30 days after the last dose of study drug (all severity grades, per NCI CTCAE v5.0) or initiation of new anticancer therapy, whichever occurs first. Patients must also report all imAEs occurring up to 90 days after the last dose of ociperlimab or tislelizumab, whichever occurs later, 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.

To determine the PK properties of ociperlimab, tislelizumab, and BAT1706 and host immunogenic response to ociperlimab, tislelizumab, and BAT1706, blood samples will be collected at various timepoints as outlined in Appendix 1.

Vital signs, physical examinations, ECOG PS change, electrocardiogram (ECG) results, and other examinations will also be used for safety assessment.

Dose-limiting toxicities: The occurrence of any of the following toxicities during the first 21 days of study will be considered a DLT, if assessed by the investigator as related to the study drug administration:

Hematologic DLTs:

1. Grade 4 neutropenia lasting > 7 days
2. Febrile neutropenia (defined as absolute neutrophil count [ANC] < 1 x 10^9/L with a single temperature of 38.3°C or a sustained temperature of 38°C for > 1 hour)
3. Grade 3 neutropenia with infection
4. Grade 3 thrombocytopenia with bleeding indicated for clinical interventions
5. Grade 4 thrombocytopenia
6. Grade 4 anemia (life-threatening)

Non-hematologic DLTs:

1. Grade 4 or higher toxicity
2. Grade 3 toxicity lasting for > 7 days despite optimal supportive care

Note: The following AEs will not be considered DLTs:

- Grade 3 endocrinopathy that is adequately controlled by hormonal replacement
- Grade 3 rash
- Grade 3 infusion-related AE that is transient (resolving within 6 hours of onset)
- Grade 3 or Grade 4 laboratory abnormalities that are not associated with clinical sequelae (eg, lactate dehydrogenase increased)
- ALT/AST from 5x to 10x ULN that return to baseline in ≤ 14 days with optimal management

Clinically important or persistent AEs that are not part of the DLT criteria may also be considered a DLT, after review by the sponsor and in consultation with the investigator.

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 ≤ 1 in 6 patients experience a DLT, the dosing regimen is tolerable and will be used in subsequent cycles. If ≥ 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 1 out of 3 patients experiences a DLT, an additional 3 patients will be enrolled. Otherwise, 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 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.

Safety assessments are further detailed in Section 7.4 and the Schedule of Assessments (Appendix 1).

3.4. End-of-Treatment/Safety Follow-up

The End-of -Treatment (EOT) Visit is conducted when the investigator determines that one or more study drugs, ie, tislelizumab and ociperlimab in Arm A, tislelizumab in Arm B, or BAT1706 in both arms, will no longer be used. If routine laboratory tests (eg, hematology, serum chemistry) were completed within 7 days of the EOT Visit, these tests do not need to be repeated.

Tumor assessment is required at the EOT Visit if the investigator determines that the study drug(s) must be discontinued. However, the tumor assessment may be omitted at the EOT visit provided that < 6 weeks have passed since the last assessment. Patients who discontinue all study drugs prior to disease progression will need to undergo tumor assessment.

3.4.1. Safety Follow-up for Tislelizumab and/or Ociperlimab

Patients who permanently discontinue ociperlimab and tislelizumab in Arm A, or tislelizumab in Arm B, will be asked to return to the clinic for the Safety Follow-up Visit, which is required to be conducted 30 (± 7) days after the last dose of the specific study drug(s), unless otherwise specified, or before the initiation of subsequent anticancer therapy, whichever occurs first.

If the decision to end treatment is taken ≥ 23 days after the last dose of ociperlimab and tislelizumab in Arm A or tislelizumab in Arm B, the EOT and Safety follow-up visits should be conducted concurrently within 7 days of the decision to end treatment.

In addition, patients who discontinue ociperlimab or tislelizumab in Arm A, or tislelizumab in Arm B, will be asked to return to the clinic or will be contacted via telephone to assess imAEs and concomitant medications (if appropriate, ie, associated with an imAE) at 60 and 90 (± 14) days after the last dose of ociperlimab or tislelizumab, whichever is later, regardless of whether they started a subsequent anticancer therapy. If patients report a suspected imAE at a follow-up visit or a telephone contact, the investigator should arrange an unscheduled visit if further assessment is indicated.

All AEs, including SAEs, will be collected as described in Section 8.6. Patients will be asked for any subsequent anticancer therapy information at the EOT/Safety Follow-up visits or telephone contacts.

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

3.5. Survival Follow-up

Patients will be followed-up for survival and to obtain information on subsequent anticancer therapy after discontinuation of all study drugs 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, loss to follow-up, withdrawal of consent, or study completion by the sponsor.

3.6. Discontinuation From Study Drug(s) or From the Study

3.6.1. Patient Discontinuation From Study Drug(s)

Patients have the right to discontinue study drug(s) at any time for any reason. In addition, the investigator has the right to discontinue a patient from study drug(s) at any time. Patients who discontinue the study drug(s) for reasons other than PD should be followed for an assessment of antitumor activity (Section 7.5), safety (Section 7.4) and survival (Section 3.5), if possible.

If the decision to discontinue the study drug(s) is made, all study drugs should be discontinued.

The primary reason for study drug discontinuation should be documented on the appropriate electronic case report form (eCRF). Patients may discontinue study drug(s) for reasons that include, but are not limited to, the following:

- Radiographic PD per RECIST v1.1
- AE
- Patient decision
- Pregnancy
- Any medical condition that the investigator or sponsor determines may jeopardize the patient's safety, if he or she were to continue the study drug(s)
- Use of any concurrent anticancer therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents [including Chinese (or other country) herbal medicine and Chinese (or other country) patent medicines] for the treatment of cancer) (Section 6.3)
- Patient noncompliance
  Investigative site staff should first counsel patients who are significantly noncompliant (eg, missing 2 treatment cycles) on the importance of study drug compliance and drug accountability. The investigator may, in consultation with the medical monitor, discontinue patients from treatment if they are consistently noncompliant.

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

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

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

3.7. End of Study

The end of study is defined as the timepoint when the final data point is collected from the last patient in the study. This is when the last patient dies, withdraws consent, completes all study assessments, or is lost to follow up, whichever occurs first. Alternatively, the end of study is when the sponsor decides to terminate the study.

The sponsor has the right to terminate this study at any time. Reasons for terminating the study early may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients
- Overall patient enrollment is unsatisfactory

The sponsor will notify each investigator if a decision is made to terminate the study. Should this be necessary, prematurely discontinued patients should be seen as soon as possible for an EOT Visit.

The investigators may be informed of additional procedures to be followed to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs/ IECs of the early termination of the study.

At the end of study, any patients who, in the opinion of the investigator, continue to benefit from study drugs at study termination, may be offered the option to continue the study drug(s) in a company-sponsored clinical trial until it is commercially available in the country of the patient's residence.

The sponsor has the right to close a site at any time. The decision will be communicated to the site in advance. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- GCP noncompliance
- Completion of study activity (ie, all patients have completed the study, and all obligations have been fulfilled)

4. STUDY POPULATION

The specific eligibility criteria for selection of patients are provided in Section 4.1 and Section 4.2. The sponsor will not grant any eligibility waivers.

4.1. Inclusion Criteria

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

1. Able to provide written informed consent and can understand and agree to comply with the requirements of the study and the schedule of assessments
2. Aged ≥ 18 years on the day of signing the ICF (or the legal age of consent in the jurisdiction in which the study is taking place)
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 loco-regional therapy, and is not amenable to a curative treatment approach
4. Tumor tissue (archival tumor tissues as formalin-fixed paraffin-embedded blocks or approximately 15 [≥ 6] freshly cut unstained slides) is required for an evaluable PD-L1 expression result presented as vCPS by SP263 and for retrospective analysis of other exploratory biomarkers.

   A fresh biopsy is mandatory in the absence of archival tumor tissues.
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.
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.
7. ECOG PS ≤ 1
8. Patients with a history of treated and, at the time of screening, stable central nervous system (CNS) metastases are eligible, provided they meet all the following:
   a. Brain imaging at Screening shows no evidence of interim progression, clinically stable for ≥ 2 weeks and no evidence of new brain metastases
   b. Have measurable and/or evaluable disease outside the CNS
   c. No ongoing requirement for corticosteroids as therapy for CNS disease; off steroids 3 days prior to randomization; anticonvulsants at a stable dose are allowed
   d. No stereotactic radiation or whole-brain radiation within 14 days of randomization
9. Adequate organ function, as indicated by the following laboratory values, during screening and before randomization:

a. Patients must not have required blood transfusion or growth factor support ≤ 14 days before sample collection at screening for the following:
   - ANC ≥ 1.5 x 10^9/L
   - Platelets ≥ 75 x 10^9/L
   - Hemoglobin ≥ 90 g/L

b. Estimated glomerular filtration rate ≥ 30 mL/min/1.73 m^2 by Chronic Kidney Disease Epidemiology Collaboration equation
c. Child-Pugh A classification for liver function assessed within 7 days of randomization.
   - Serum albumin ≥ 29 g/L
   - Serum total bilirubin ≤ 3 mg/dl

d. AST and ALT ≤ 5 x ULN
e. For patients not receiving therapeutic anticoagulation: International normalized ratio (INR) or activated partial thromboplastin time (aPTT) ≤ 2 x ULN
f. Proteinuria < 2+ (within 7 days of randomization). Patients discovered to have ≥ 2+ proteinuria at baseline should undergo a 24-hour urine collection and must demonstrate < 1 g of protein in 24 hours.

10. Women of childbearing potential must be willing to use a highly effective method of birth control for the duration of the study, and for ≥ 120 days after the last dose of tislelizumab, and have a negative urine or serum pregnancy test ≤ 7 days before randomization.
11. Nonsterile men must be willing to use a highly effective method of birth control for the duration of the study and for ≥ 120 days after the last dose of tislelizumab
    - A sterile man is defined as one for whom azoospermia has been previously demonstrated in a semen sample examination as definitive evidence of infertility.
    - Males with known "low sperm counts" (consistent with "sub-fertility") are not to be considered sterile for the purposes of this study.

4.2. Exclusion Criteria

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

1. known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC histology
2. Tumor thrombus involving main trunk of portal vein (ie, VP4) or inferior vena cava
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
4. Any major surgical procedure or any liver loco-regional therapy (ie, TACE, transcatheter embolization, hepatic arterial infusion, radiation, radioembolization, or ablation) ≤ 28

days before randomization. Patients must have recovered adequately from the toxicity and/or complications from the intervention prior to randomization.

5. Any prior history of ≥ Grade 2 hepatic encephalopathy
6. Active leptomeningeal disease or uncontrolled, untreated brain metastasis.
7. Active autoimmune diseases or history of autoimmune diseases that may relapse.

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

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

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

   a. Adrenal replacement steroid (dose ≤ 10 mg daily of prednisone or equivalent)
   b. Topical, ocular, intra-articular, intranasal, or inhaled corticosteroid with minimal systemic absorption
   c. Short course (≤ 7 days) of corticosteroid prescribed prophylactically (eg, for contrast dye allergy) or for the treatment of a non-autoimmune condition (eg, delayed-type hypersensitivity reaction caused by contact allergen)
10. With uncontrolled diabetes or > Grade 1 laboratory test abnormalities in potassium, sodium, or corrected calcium despite standard medical management or ≥ Grade 3 hypoalbuminemia ≤ 14 days before randomization
11. Uncontrollable pleural effusion, pericardial effusion, or ascites requiring frequent drainage (recurrence within 2 weeks of intervention)
12. History of interstitial lung disease, non-infectious pneumonitis or uncontrolled lung diseases including pulmonary fibrosis, acute lung diseases, etc. Patients with significantly impaired pulmonary function or who require supplemental oxygen at baseline must undergo an assessment of pulmonary function at screening
13. Infection (including tuberculosis) requiring systemic antibacterial, antifungal, or antiviral therapy within 14 days of randomization

Note: Antiviral therapy is permitted for chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection.

14. Untreated chronic hepatitis B or chronic HBV carriers with HBV DNA > 500 IU/mL (or > 2500 copies/mL) at Screening

    Note: Inactive hepatitis B surface antigen (HBsAg) carriers and treated and stable hepatitis B patients (HBV DNA < 500 IU/mL or < 2500 copies/mL) can be enrolled. Patients with detectable HBsAg or detectable HBV DNA should be managed per treatment guidelines. Patients receiving antivirals at Screening should have been treated for > 2 weeks before randomization.

15. Known history of HIV infection
16. Prior allogeneic stem cell transplantation or organ transplantation
17. Any of the following cardiovascular risk factors:
    a. Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living, ≤ 28 days before randomization
    b. Pulmonary embolism ≤ 28 days before randomization
    c. Any history of acute myocardial infarction ≤ 6 months before randomization
    d. Any history of heart failure meeting New York Heart Association (NYHA) (Appendix 5) Classification ≥ II within 6 months before randomization
    e. Any event of ventricular arrhythmia ≥ Grade 2 in severity ≤ 6 months before randomization
    f. Any history of cerebrovascular accident ≤ 6 months before randomization
    g. Inadequately controlled hypertension (defined as systolic blood pressure [BP] ≥ 150 mmHg and/or diastolic blood pressure > 100 mmHg), based on an average of ≥ 3 BP readings on ≥ 2 sessions) that cannot be managed by standard anti-hypertension medications ≤ 28 days before randomization
    h. Any episode of syncope or seizure ≤ 28 days before randomization
18. Untreated or incompletely treated esophageal or gastric varices with bleeding or high risk of bleeding.

    Note: Patients must undergo an esophagogastroduodenoscopy (EGD), and all size of varices (small to large) must be assessed and treated per local standard of care prior to enrollment. Patients who have undergone an EGD within 6 months before randomization do not need to repeat the procedure.

19. A history of hemoptysis (≥ 2.5 mL of bright red blood per episode) within 28 days of randomization
20. Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation)
21. Current or recent (within 10 days of randomization) use of aspirin (≥ 325 mg/day) or treatment with dipyramidole, ticlopidine, clopidogrel, and cilostazol
22. Current or recent (within 10 days of randomization) use of full-dose oral or parenteral anticoagulants or thrombolytic agents for therapeutic (as opposed to prophylactic) purpose

Note: Prophylactic anticoagulation for the patency of venous access devices is allowed provided the activity of the agent results in an INR < 1.5 x ULN and aPTT is within normal limits within 14 days of randomization. For prophylactic use of anticoagulants or thrombolytic therapies, local label-approved dose levels may be used.

23. A history of abdominal or tracheoesophageal fistula, gastrointestinal (GI) perforation, or intra-abdominal abscess within 6 months of randomization
24. History of intestinal obstruction and/or clinical signs or symptoms of GI obstruction including sub-occlusive disease related to the underlying disease or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding within 6 months of randomization

    Note: Patients with signs/symptoms of sub-/occlusive syndrome/intestinal obstruction at the time of initial diagnosis may be enrolled if they had received definitive (surgical) treatment for symptom resolution.
25. Evidence of abdominal free air that is not explained by paracentesis or recent surgical procedure
26. Serious, non-healing or dehiscing wound, active ulcer, or untreated bone fracture
27. History of severe hypersensitivity reactions to other monoclonal antibodies
28. Has received any chemotherapy, immunotherapy (eg, interleukin, interferon, thymosin) or any investigational therapies within 14 days or 5 half-lives (whichever is longer) before randomization, or has received palliative radiation treatment or other local regional therapies within 14 days of randomization.
29. Toxicities (as a result of prior anticancer therapy) that have not recovered to baseline or stabilized, except for AEs not considered a likely safety risk (eg, alopecia, neuropathy, and specific laboratory abnormalities)
30. Was administered a live vaccine ≤ 28 days before randomization, through 60 days after the last dose of tislelizumab or ociperlimab, whichever is later

    Note: Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines that are live vaccines are not allowed.
31. Underlying medical conditions (including laboratory abnormalities) or alcohol or drug abuse or dependence that will be unfavorable for the administration of study drug, or affect the explanation of drug toxicity or AEs, or result in insufficient or impaired compliance with study conduct
32. Women who are pregnant or are breastfeeding
33. Concurrent participation in another therapeutic clinical study

    Note: Concurrent participation in observational or non-interventional studies is allowed. In addition, patients who have completed active treatment in a clinical study and are in the follow-up period can be enrolled in this study.

5. STUDY DRUGS

5.1. Formulation, Packaging, and Handling

5.1.1. Tislelizumab

Tislelizumab is a monoclonal antibody formulated for intravenous injection in a single-use vial (20R glass, USP type I), containing a total of 100 mg of antibody in 10 mL of isotonic solution. Tislelizumab has been aseptically filled in single-use vials with a Flurotec-coated butyl rubber stopper and an aluminum cap. Each vial is packaged into a single-carton box.

The contents of the label will be in accordance with all applicable local regulatory requirements.

The study drug must be kept at the temperature and conditions specified on the label. Shaking should be avoided.

Refer to the Pharmacy Manual for details regarding intravenous administration, accountability, and disposal. Refer to the Tislelizumab Investigator's Brochure for other details regarding tislelizumab.

5.1.2. Ociperlimab

Ociperlimab is a monoclonal antibody formulated for intravenous injection in a single-use vial (20 mL glass vial, USP type I) containing a total of 300 mg antibody in 15 mL of buffered isotonic solution. ociperlimab has been aseptically filled in single-use vials with a Flurotec-coated butyl rubber stopper and an aluminum cap. Each vial is packaged into a single-carton box.

The contents of the label will be in accordance with all applicable local regulatory requirements.

The study drug must be kept at the temperature and conditions specified on the label. Shaking should be avoided.

Refer to the Pharmacy Manual for details regarding intravenous administration, accountability, and disposal. Refer to the Ociperlimab Investigator's Brochure for other details regarding ociperlimab.

5.1.3. BAT1706

BAT1706 is a similar biological product of the bevacizumab injection (Bevacizumab Injection, brand name Avastin®). BAT1706 contains a recombinant humanized immunoglobulin G1 (IgG1) monoclonal antibody as the active ingredient and binds with high affinity to human VEGF.

BAT1706 is formulated for intravenous injection in a single-use vial containing a total of 25 mg/mL of antibody (100 mg diluted in a 4 mL volume or 400 mg diluted in 16 mL). BAT1706 vials should be protected from light, and never frozen or shaken.

The contents of the label will be in accordance with all applicable local regulatory requirements.

The study drug must be kept at the temperature and conditions specified on the label.

Refer to the Pharmacy Manual for details regarding intravenous administration, accountability, and disposal. Refer to the BAT1706 Investigator's Brochure for other details regarding BAT1706.

5.2. Dosage, Administration, and Compliance

The first dose of study drugs is to be administered within 2 business days of randomization.

Dosing schedules for all arms, broken out by individual treatment arm, are provided in Table 3. Dosing administration and monitoring times, broken out by individual treatment arm, are provided in Table 4.

Table 3: Planned Dose, Frequency of Administration, and Route of Administration for Study Drugs

Study drugs	Dose	Timing of Administration	Route of Administration	Duration of Treatment
Tislelizumab	200 mg	Day 1 of each 21-day cycle	Intravenous	Refer to Section 3.3
BAT1706	15 mg/kg	Day 1 of each 21-day cycle	Intravenous	Refer to Section 3.3
Ociperlimab	900 mg	Day 1 of each 21-day cycle	Intravenous	Refer to Section 3.3

Table 4: Administration of Study Drugs and Monitoring Time

Cycle	Tislelizumab Plus BAT1706 With Ociperlimab/Tislelizumab Plus BAT1706
Day 1, Cycle 1	Tislelizumab infusion over 60 (± 5) minutes, followed by BAT1706 infusion over 90 (± 15) minutes, followed by ociperlimab infusion over 60 (± 5) minutes (Arm A) or Tislelizumab infusion over 60 (± 5) minutes followed by BAT1706 infusion over 90 (± 15) minutes (Arm B) Patient monitoring for ≥ 120 minutes
Day 1, Cycle 2, if tolerated	Tislelizumab infusion over 30 (± 5) minutes, followed by BAT1706 infusion over 60 (± 10) minutes, followed by ociperlimab infusion over 30 (± 5) minutes (Arm A) or Tislelizumab infusion over 30 (± 5) minutes followed by BAT1706 infusion over 60 (± 10) minutes (Arm B) Patient monitoring for ≥ 60 minutes
Day 1, Cycle 3 onwards, if tolerated	Tislelizumab infusion over 30 (± 5) minutes, followed by BAT1706 infusion over 30 (± 10) minutes, followed by ociperlimab infusion over 30 (± 5) minutes (Arm A) or Tislelizumab infusion over 30 (± 5) minutes followed by BAT1706 infusion 30 (± 10) minutes (Arm B) Patient monitoring for ≥ 60 minutes

Treatment Administration

In Arm A, tislelizumab 200 mg will be administered followed by BAT1706 15 mg/kg, followed by ociperlimab 900 mg on Day 1 of each 21-day cycle (once every 3 weeks).

In Arm B, tislelizumab 200 mg will be administered followed by BAT1706 15 mg/kg on Day 1 of each 21-day cycle (once every 3 weeks).

The dose of BAT1706 will be based on the baseline weight, defined as the weight of the patient (in kilograms) measured ≤ 14 days before the initiation of study drug, and will remain the same throughout the study unless there is a weight change of > 10%. If re-assessment of baseline weight is needed, the latest baseline weight should always be used to calculate percent change in weight for all subsequent doses.

The initial infusion (Day 1, Cycle 1) will be delivered over 60 minutes for tislelizumab, over 90 minutes for BAT1706, and over 60 minutes for ociperlimab. If this infusion regimen is well tolerated, then the subsequent infusion (Day 1 Cycle 2) may be administered over 30 minutes for tislelizumab and ociperlimab, and over 60 minutes for BAT1706.

If well tolerated, the subsequent infusions (Day 1 Cycle 3 onwards) of each study drug may be administered over 30 minutes, which is the shortest period permissible for infusion (see Table 4).

The study drugs must be administered by intravenous infusion through an intravenous line containing a sterile, nonpyrogenic, low-protein-binding 0.2- or 0.22-micron in-line or add-on filter. Specific instructions for product preparation and administration are provided in the Pharmacy Manual.

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

At the end of the infusion period, the line should be flushed with enough normal saline to make sure that all of the study drugs are administered to the patient.

As a routine precaution, after infusion of the study drugs on Day 1 of Cycle 1, patients must be monitored for ≥ 120 minutes. If the infusion completion time was shortened, on Day 1 Cycle 2 patients must be monitored for ≥ 60 minutes, and from Cycle 3 onward, a ≥ 60-minute monitoring period is required. Regardless of the infusion completion time, patients must be monitored in an area with resuscitation equipment and emergency agents.

The study drugs must not be concurrently administered with any other drug (Section 6).

All patients will be monitored continuously for AEs. Treatment modifications (eg, dose delay, interruption, or discontinuation) will be based on specific laboratory and AE criteria, as described in Section 5.5. Guidelines for dose modification, treatment interruption, or discontinuation and for managing imAEs and infusion-related reactions are provided in Section 8.7 and Appendix 6.

5.3. Incorrect Administration or Overdose

Any incorrect administration of ociperlimab or BAT1706, or overdose of tislelizumab (defined as ≥ 600 mg in a 24-hour period) should be noted in the patient's chart and on the appropriate eCRF.

An incorrect administration or overdose of study drug(s) is not itself an AE, but it may result in an AE. AEs associated with an incorrect administration or overdose of study drugs will be recorded on the AE eCRF. Any SAEs associated with an incorrect administration or overdose must be reported within 24 hours of awareness via the SAE reporting process as described in Section 8.6.2. Supportive-care measures should be administered as appropriate.

5.4. Study Drug Accountability

The study drugs required for completion of this study (ociperlimab, tislelizumab, and BAT1706) will be provided by the sponsor. The investigational site will acknowledge receipt of the study drugs. Any damaged shipments will be replaced.

Accurate records of all study drug received, dispensed, returned, and disposed of should be recorded on the site's Drug Inventory Log. Refer to the Pharmacy Manual for details on managing study drugs.

5.5. Dose Delay or Modification

Every effort should be made to administer the study drugs in a synchronized manner according to the planned dose and schedule as described in Section 5.2. In the event of significant toxicities, dosing of one or more study drugs may be delayed and/or interrupted based on the guidelines provided below. Reasons for dose interruptions or delays, the supportive measures taken, and the outcome will be documented in the patient's chart and recorded in the eCRF.

If the administration of ociperlimab plus tislelizumab (in Arm A) or tislelizumab (in Arm B) is delayed for ≤ 10 days, or BAT1706 (in both arms) is delayed ≤ 3 days during a planned dosing cycle (eg, Cycle 3 Day 1), the drug(s) should be administered in the current cycle, at the end of the delay. If the study drugs need to be withheld for > 10 days, they should be omitted from the current cycle and administration should restart on Day 1 of the next planned cycle (eg, Cycle 4 Day 1) to remain synchronized with the administration of other study drug(s).

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.

If treatment is delayed due to TEAEs, treatment may resume only after the AEs have returned to baseline or ≤ Grade 1 severity, excluding alopecia or any AE that, in the opinion of the investigator, is not considered a safety risk to the patient. If a treatment delay is due to worsening of hematologic or biochemical parameters, the frequency of relevant blood tests should be increased as clinically indicated. In general, dose delays for reasons other than management of AEs are prohibited.

The tumor assessment schedule will not be altered even if the administration of study drugs is delayed.

Management guidelines for infusion-related reactions and imAEs and AEs related to BAT1706 in patients are presented in Section 8.7 and Appendix 6 and Appendix 7 respectively.

5.5.1. Dose Modifications for Ociperlimab and Tislelizumab

No dose reduction or increase is allowed for ociperlimab and tislelizumab. However, dose interruption or dose delay is allowed. A dose interruption is an interruption of an infusion that has begun. A dose delay is a deviation from prescribed dosing schedule (ie, the drug is withheld after the visit window). For patients in Arm A, both ociperlimab and tislelizumab should be withheld or permanently discontinued simultaneously, if necessary.

If a dose delay is required due to AEs related to ociperlimab and/or tislelizumab in Arm A, both ociperlimab and tislelizumab should be held and restarted at the same time, if applicable.

If an AE leading to discontinuation is considered related to ociperlimab and/or tislelizumab, both ociperlimab and tislelizumab should be discontinued. Exceptions may be considered after consultation between the investigator and the medical monitor.

A dose delay of ≤ 12 weeks for ociperlimab and tislelizumab in Arm A and tislelizumab in Arm B is allowed under the above guidance and at the discretion of the investigator after consultation with the medical monitor or designee. If the delay is > 12 weeks, the patient should be permanently discontinued from ociperlimab and tislelizumab in Arm A and tislelizumab in Arm B, unless the patient is likely to derive clinical benefit at the discretion of the investigator after consultation with the medical monitor or designee.

5.5.2. Dose Modifications for BAT1706

No dose reduction is allowed for BAT1706 after the safety run-in period. Dose interruption and dose delay is allowed for BAT1706.

A dose delay of ≤ 42 days for BAT1706 in Arm A and Arm B due to AEs related to BAT1706 is allowed. If BAT1706 is delayed for > 42 days, the patient should be permanently discontinued from BAT1706, unless the patient is likely to derive clinical benefit at the discretion of the investigator after consultation with the medical monitor or designee.

6. PRIOR AND CONCOMITANT THERAPY

6.1. Prior Therapy

The exclusion criteria (Section 4.2) specify that patients should not have received prior therapies targeting PD-1, PD-L1, PD-L2, TIGIT, or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways or any prior treatment with bevacizumab or its biosimilar before randomization.

6.2. Permitted Concomitant Medications/Procedures

Unless noted otherwise, most concomitant medications and therapies are allowed at the discretion of the investigator if they are deemed necessary and are in keeping with local standards of medical care for supportive care (eg, antiemetics, antidiarrheals, hematopoietic growth factors, red blood cell/platelet transfusions) and in a patient's interest. Opiates and other medication required for palliative management of patients are allowed. Patients must notify the investigator of all concurrent medications used during the study.

All concomitant medications will be recorded on the eCRF, including all prescription and over-the-counter medicines, herbal supplements, and intravenous medications and fluids.

6.2.1. Systemic Corticosteroids

Systemic corticosteroids administered for the control of imAEs must be tapered gradually (see Appendix 6) and must be administered at nonimmunosuppressive doses (≤ 10 mg/day of prednisone or equivalent) before the next administration of tislelizumab with or without ociperlimab. The short-term use of steroids as prophylactic treatments (eg, patients with contrast allergies to diagnostic imaging contrast dyes) is permitted.

6.2.2. Hepatitis B Treatment

Management of prophylactic antiviral therapy for patients with inactive, treated, and stable hepatitis B (HBV DNA < 500 IU/mL) is at the discretion of the investigator as aligned with local guidance. Such medications must be documented in the patient's chart and recorded in the eCRF. Patients receiving antivirals at screening should be treated for > 2 weeks before randomization and continue treatment during the study and for 6 months after study drug discontinuation.

6.2.3. Hepatitis C Treatment

The sponsor does not require patients with active hepatitis C to receive treatment with antiviral therapy. Patients with detectable HCV RNA who are receiving treatment at screening should remain on continuous, effective antiviral therapy during the study. Investigators can consider treatment with antiviral agents, in accordance with international or local guidelines. However, interferon-based therapy for HCV is not permitted during the study. Patients who are given antiviral therapy must initiate treatment > 2 weeks before randomization and continue treatment during the study and for 6 months after study drug treatment discontinuation.

6.2.4. Radiation Therapy

Palliative (limited-field) radiation therapy is permitted, but only for pain control or prophylaxis of bone fracture to sites of bone disease present at baseline if the following criteria are met:

- Repeat imaging shows no new sites of bone metastases;
- The lesion being considered for palliative radiation is not a target lesion per RECIST v1.1;
- The case is discussed with the medical monitor and he/she agrees that the conditions required to receive palliative radiation are met.

Additionally, palliative radiation or other focally ablative therapy for other nontarget sites of the disease is permitted if clinically indicated per the investigator's discretion and after consultation with the medical monitor. Whenever possible, these patients should have a tumor assessment of the lesion(s) before receiving the radiation therapy to rule out PD. It is not required to withhold study drugs during palliative radiotherapy.

6.3. Prohibited Concomitant Medications/Procedures

The following medications/therapies are prohibited:

- Any concurrent anticancer therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents including Chinese [or other country] herbal medicine and Chinese [or other country] patent medicines for the treatment of cancer [with anticancer activity included in the label, regardless of cancer type]) for ≤ 14 days (or ≤ 5 half-lives, whichever is longer) before randomization and during the study.
- Any concurrent anticancer surgeries or locoregional therapies (eg, TACE, transcatheter embolization, hepatic arterial infusion, radiation, radioembolization, ablation) ≤ 28 days of randomization and during the study.
- Live vaccines administered ≤ 28 days before randomization through the 60 days after the last dose of ociperlimab or tislelizumab, whichever is later.
- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) are prohibited within 28 days or 5 half-lives (whichever is longer) of randomization and during the study.
- Herbal remedies with immunostimulatory properties (eg, mistletoe extract) or that are known to potentially interfere with liver or other major organ functions (eg, hypericin) within 14 days (or within 5 half-lives, whichever is longer) before randomization and during the study. Patients must notify the investigator of all herbal remedies used during the study.
- Use of warfarin or Coumadin-like products (including for prophylactic use) is prohibited
  - Prophylactic use of low-dose anticoagulants, unfractionated heparin or low-molecular-weight heparin is permitted.

- Current use of full-dose anticoagulants, thrombolytic therapy at therapeutic doses, or anti-platelet therapy are prohibited. However, if a patient experiences a venous thromboembolism (VTE) event while still receiving the study drug, it may still be possible for the patient to remain on study medication despite anticoagulation treatment (See Section 4.2)
- Concomitant chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs) while receiving study drugs is prohibited. However, for the symptomatic relief of medical conditions (eg, headache, fever), sporadic or short-term intake of oral NSAIDs is allowed, when co-administered with proton-pump inhibitors to reduce potential GI damage.

6.4. Restricted Concomitant Medications/Procedures

The following medications are restricted during the study:

- Immunosuppressive agents (except to treat a drug-related AE)
- Systemic corticosteroids > 10 mg daily (prednisone or equivalent), except to treat or control an AE (per protocol) or for short-term use as prophylactic treatment
- Patients should not abuse alcohol or other drugs during the study.
- Use of potentially hepatotoxic drugs in patients with impaired hepatic function should be carefully monitored.
- Radiation therapy is not allowed, except for palliative radiation therapy, as described in Section 6.2.4.

6.5. Potential Interactions Between the Study Drugs and Concomitant Medications

Information regarding clinical drug interactions with ociperlimab is not available and no dedicated drug-drug interaction studies are planned. However, the potential for drug-drug interaction between the study drugs (ociperlimab and tislelizumab) and other drug products is very low because ociperlimab and tislelizumab are therapeutic monoclonal antibodies. Because ociperlimab and tislelizumab are expected to be degraded into amino acids and recycled into other proteins, they are unlikely to influence drug-metabolizing enzymes or transporters.

7. STUDY ASSESSMENT AND PROCEDURES

A table of scheduled study assessments is provided in Appendix 1. Patients will be closely monitored for safety and tolerability throughout the study. All assessments must be performed and documented in the medical record for each patient.

Dosing will occur only if the clinical assessment and local laboratory test values (that must be available before any dosing) have been reviewed and found to be acceptable per protocol guidelines.

7.1. Screening Period

Screening evaluations will be performed ≤ 28 days of randomization. A patient who agrees to participate in this study will sign the ICF before undergoing any screening assessment. The screening period begins on the first day that a screening assessment is conducted. Screening evaluations may be repeated as needed within the screening period. The investigator is to assess patient eligibility according to the latest screening assessment results.

Results of standard-of-care tests or examinations performed before informed consent has been obtained and within 28 days of randomization may be used for the purposes of screening rather than repeating the standard-of-care tests, unless otherwise indicated.

Rescreening under limited conditions may be allowed after consultation with the sponsor (eg, when a patient's laboratory result narrowly misses laboratory criterion and it is correctable and not due to rapidly deteriorating condition or progression of disease). Rescreening is allowed only once.

Procedures conducted only during the Screening Visit are described in this section. For the description of other assessments that are conducted during screening as well as throughout the study, refer to the safety assessments (Section 7.4), tumor and response evaluations (Section 7.5), PK and ADA assessments (Section 7.6), and tumor tissue and biomarker assessment procedures (Section 7.7) sections.

7.1.1. Informed Consent and Screening Log

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

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

7.1.2. Patient Numbering

After obtaining informed consent, study site personnel will access the Interactive Response Technology (IRT) system to assign a unique patient number to a potential study participant.

7.1.3. Demographic Data and Medical History

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

Medical history includes any history of clinically significant disease, surgery, or cancer history; reproductive status (ie, of childbearing potential or no childbearing potential); history of alcohol and tobacco consumption (ie, never, previous, and current); and all medications (eg, prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 30 days before randomization.

Cancer history will include an assessment of prior anticancer surgery, prior locoregional therapy to liver, prior radiotherapy, and prior drug therapy including start and stop dates, best response, and reason for discontinuation. Radiographic studies performed before study entry may be collected for review by the investigator. Pre-existing AEs at baseline should be recorded as medical history.

7.1.4. Women of Childbearing Potential and Contraception

Urine or serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented with a negative result within 7 days of randomization. Urine pregnancy tests will be performed at each visit prior to dosing, and at the EOT/Safety Follow-up Visit. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.

Childbearing potential is defined as the physiological ability to become pregnant. Refer to Appendix 4 for contraception guidelines and definitions of "women of childbearing potential" and "women of no childbearing potential."

7.1.5. Pulmonary Function Tests

Patients who are suspected of having or known to have serious and/or severe respiratory conditions, or who exhibit significant respiratory symptoms unrelated to the underlying cancer, or who have a history of thoracic radiotherapy will undergo pulmonary function testing that may include, but is not limited to, spirometry and assessment of diffusion capacity done during the screening period to assist the determination of suitability for the study.

The test may be repeated as clinically indicated while on study (refer to Appendix 1 for details).

7.1.6. Esophagogastroduodenoscopy

All patients must undergo an EGD and all size of varices (small to large) must be assessed and treated per local standard of care prior to enrollment.

7.2. Enrollment

7.2.1. Confirmation of Eligibility

The investigator will assess and confirm the eligibility of each patient. The results of all screening procedure and relevant medical history must be available before eligibility can be determined. All inclusion criteria must be met and none of the exclusion criteria may apply. No eligibility waivers will be granted.

After a patient is screened and the investigator determines that the patient is eligible for randomization, study site personnel will complete an Eligibility Confirmation Packet and email it to the medical monitor or designee to confirm the enrollment in writing. Study site personnel

should ensure that a medical monitor's confirmation has been received before proceeding with study procedures.

7.2.2. Randomization

Site personnel will access the IRT system to randomize the patient and assign study drugs by permuted block stratified randomization.

All patients are required to receive the study drug(s) within 2 business days of randomization and treatment assignment.

7.3. Study Drug Dispensation

Ociperlimab, tislelizumab, and BAT1706 will be dispensed and administered as described in Section 5.2.

7.4. Safety Assessment

7.4.1. Vital Signs

Vital signs will include measurements of body temperature (˚C), pulse rate, respiratory rate, and blood pressure (systolic and diastolic). Pulse rate and blood pressure will be measured while the patient is in a seated position after resting for 10 minutes.

If coinciding with administration of study drugs, the patient's vital signs should be recorded within 60 minutes of study drug administration. For patients treated with BAT1706, vital signs will be measured at the end of BAT1706 infusion and 2 (± 1) hours after the end of the infusion, and during the study if clinically indicated.

Height should only be measured and recorded during screening. Weight will be measured before study drug administration in every cycle.

7.4.2. Physical Examinations

During the Screening Visit, a complete physical examination will be conducted, including evaluations of the head, eyes, ears, nose, and throat and of the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Any abnormality identified during screening will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v5.0) and recorded on the eCRF with appropriate disease/condition terms.

At subsequent visits (and as clinically indicated), limited, symptom-directed physical examinations will be performed. New or worsened clinically significant abnormalities are to be recorded as AEs on the eCRF.

Refer to Section 8.3 regarding AE definitions and reporting and follow-up requirements.

7.4.3. Eastern Cooperative Oncology Group Performance Status

ECOG PS (Appendix 3) will be assessed during the study. Each patient's ECOG PS will be assessed at the Screening Visit, pretreatment on Day 1 of each treatment cycle, and at the EOT/Safety Follow-up visits.

7.4.4. Laboratory Safety Tests

Local laboratory assessments of clinical chemistry, hematology, coagulation, and urinalysis will be conducted, of which certain elements will be collected as specified in Appendix 2.

If laboratory tests at screening are not performed ≤ 7 days of randomization on Day 1 of Cycle 1, these tests should be repeated and reviewed before randomization. After Cycle 1, laboratory tests are to be conducted and results are to be reviewed within 48 hours before study drug administration.

Thyroid assessments will be performed as specified in Appendix 1.

Details about sample collection and shipment will be provided in a separate instruction manual. Investigators should use results from the same local laboratories for assessing eligibility, safety monitoring, and dosing decision for each patient.

7.4.4.1. Cardiac Enzyme Monitoring

Although immune-mediated myocarditis is a rare complication of immune checkpoint inhibitors, serum creatine kinase (CK) and CK-MB are monitored in all tislelizumab studies to protect study patients and to quantify the risk of muscle inflammation (see Appendix 1 for the blood collection schedule and Appendix 6 for guidelines for management of suspected immune-mediated myocarditis, respectively).

CK and CK-MB testing will be implemented for all patients at Screening, repeated at all scheduled visits during the first 3 treatment cycles, all predose assessments from Cycle 4 onwards, and the EOT/Safety Follow-up Visit (30 days after the last dose). If CK-MB fractionation is not available, serum troponins (troponin I and/or T) may be tested instead.

7.4.5. Electrocardiograms

ECG recordings will be obtained during Screening, at the EOT/Safety Follow-up Visit, and as clinically indicated.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper or electronic copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

All ECGs are to be obtained before other assessments scheduled at that same time (eg, vital sign measurements, blood draws). The patient should rest in a semirecumbent supine position for ≥ 10 minutes in the absence of environmental distractions that may induce changes in heart rate (eg, television, radio, conversation) before each ECG collection.

7.4.6. Adverse Events

AEs will be graded and recorded throughout the study according to NCI-CTCAE v5.0. Characterization of toxicities will include severity, duration, and time to onset.

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

7.4.7. Hepatitis B and C Testing

Testing will be performed at Screening (and as clinically indicated) and will include HBV/HCV serology (HBsAg, hepatitis B surface antibody [HBsAb], hepatitis B core antibody [HBcAb], and HCV antibody) and viral load assessment (HBV DNA and HCV RNA).

For patients who have detectable HBV DNA or HCV RNA at Screening, a respective viral load test will be performed every 4 cycles (ie, Day 1 of Cycle 5, 9, 13, etc) starting from Cycle 5.

Blood samples will be collected on Day 1 of Cycle 1 before dosing of study drug, stored and may be analyzed if patients develop hepatic AEs.

7.4.8. Ophthalmologic Examination

Ophthalmologic examination, as described below, will be performed on all patients during Screening, and subsequently throughout the study.

Eye exam, visual acuity test, and optical coherence tomography (or equivalent diagnostic test) will be assessed by an ophthalmologist at Screening. Eye exam, visual acuity test, and optical coherence tomography (or equivalent diagnostic test for retinal examination) captured as standard of care prior to obtaining written informed consent and within 28 days of randomization may be used for the Screening evaluation. Patients will undergo repeat assessments by an ophthalmologist approximately every 15 weeks (± 7 days) during study treatment and a final assessment during the EOT Visit for ociperlimab and/or tislelizumab.

In addition, investigators should solicit patients regarding changes in vision, visual disturbance, or ocular inflammation at each scheduled study visit during study treatment. For any change in vision, referral to an ophthalmologist will be made for further management guidance.

7.5. Tumor and Response Evaluations

Tumor imaging will be performed ≤ 28 days before 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.

During the study, tumor imaging will be performed approximately 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 assessments must be performed on schedule regardless of whether the study drug(s) have been administered or withheld, ie, they should not be adjusted for delays in cycles.

Screening assessments and each subsequent assessment must include CT scans (with oral/intravenous contrast) of the chest, abdomen, and pelvis. If a contraindication exists, other modalities can be allowed after consultation with the medical monitor (eg, MRI, CT without contrast); bone scan or positron-emission tomography (PET) is required if clinically indicated. Other known or suspected sites of disease must be included in the imaging assessments (neck, brain, etc). For patients who are suspected to have CNS metastases, CT/MRI of the head is required at baseline. MRI may be used when it is the standard of care at a site, regardless of whether or not CT is contraindicated.

The liver should be imaged using tri-phasic scans (ie, late arterial phase, portal venous phase, and delayed/equilibrium phase are required). Every effort should be made to keep the methodology consistent across visits for a subject (ie, phases acquired, timing for each phase, etc).

All measurable and evaluable lesions should be assessed and documented at the Screening Visit and reassessed at each subsequent tumor evaluation. The same radiographic procedure used to assess disease sites at screening must be used throughout the study (eg, the same contrast protocol for CT scans).

- If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the study, a noncontrast CT of the chest plus a contrast-enhanced MRI (if possible) of the abdomen and pelvis should be performed.
- If a CT scan for tumor assessment is performed on a PET/CT scanner, the CT acquisition must be consistent with the standards of a diagnostic CT scan.
- Bone scans (Technetium-99m [TC-99m]) or PET should be performed at screening if clinically indicated. If bone metastases are present at screening and cannot be seen on CT or MRI scans, TC-99m or PET bone scans should be repeated when a CR is suspected in a target lesion or when progression in bone is suspected.
- CT scans of the head, neck, or extremities should be performed at screening only if clinically indicated and should be repeated throughout the study if there is evidence of metastatic disease in these regions at screening.
- At the investigator's discretion, other methods of assessment of target lesion and non-target lesions per RECIST v1.1 may be used.

Response will be assessed by the investigator using RECIST v1.1 (see Appendix 8). The same evaluator should perform assessments, if possible, to ensure internal consistency across visits.

After first documentation of response (CR or PR), confirmation of tumor response should occur at 4 weeks or later after the first response or at the next scheduled assessment timepoint.

If, at the investigator's discretion, a patient could continue to benefit from study drugs after PD per RECIST v1.1 criteria, the patient may continue to receive study drug(s). The following criteria must be met in order to treat patients who may continue to benefit from study drug(s) after PD:

- Absence of clinical symptoms and signs of PD (including clinically significantly worsening of laboratory values)
- Stable ECOG PS $\leq$ 1
- Absence of rapid PD or of progressive tumor at critical anatomical sites (eg, cord compression) that requires urgent alternative medical intervention
- Investigators must obtain written informed consent for treatment beyond radiologic PD and inform patients that this practice is not considered standard in the treatment of cancer.

- The decision to continue study drug(s) beyond initial investigator-assessed progression must be agreed with by the sponsor medical monitor and documented in the study records.

Tumor assessment should continue as planned in patients receiving study drug(s) after initial investigator-assessed 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, withdrawal of consent, loss to follow-up, death, or until study termination, whichever occurs first.

7.6. Pharmacokinetic and Antidrug Antibody Assessments

Ociperlimab, tislelizumab, and BAT1706 may elicit an immune response. Patients with signs of any potential immune response will be closely monitored. Validated screening and confirmatory assays will be employed to detect ADAs at multiple timepoints throughout the study. In addition, blood samples will be collected for characterization of ociperlimab, tislelizumab and BAT1706 PK at the timepoints specified in the Appendix 1.

PK and ADA assays of ociperlimab, tislelizumab, and BAT1706 will be managed through a central laboratory. Serum samples will be assayed for ociperlimab, tislelizumab and BAT1706 concentrations using validated immunoassays.

- ADA assays: Serum samples will be tested for the presence of ADAs to ociperlimab, tislelizumab and BAT1706 using a validated immunoassay.
- PK assays: Serum samples will be assayed for ociperlimab, tislelizumab and BAT1706 concentrations using a validated immunoassay.

Refer to the laboratory manual for instructions regarding sample collection, handling, labeling, storage, and shipping of laboratory samples.

7.7. Tumor Tissue and Biomarker Assessment Procedures

Instructions for the processing, storage, and shipping of samples will be provided in the study laboratory manual. Refer to the Schedule of Assessments (Appendix 1) for sample collection timepoints.

Archival tumor tissues (formalin-fixed paraffin-embedded [FFPE] blocks or approximately 15 freshly cut unstained FFPE slides [≥ 6]) need to be sent for central laboratory assessment of PD-L1 status during the screening period (an evaluable PD-L1 result presented as vCPS by SP263 is required, with vCPS score being defined as the total percentage of the tumor area covered by tumor cells with PD-L1 membrane staining and tumor-associated immune cells with PD-L1 staining at any intensity) and for retrospective analysis of other exploratory biomarkers related to response and resistance for all patients in a sponsor-designated central/local laboratory. These exploratory biomarkers include TMB/DNA mutation, TIGIT/PVR/nectin-2 and GEP. Submission of < 15 unstained slides is not a protocol deviation.

A fresh tumor biopsy at a tumor lesion is mandatory if there are no available archival tumor samples during the screening period. Optional fresh biopsies in patients who have confirmed PD

will also be collected in the two cohorts during the study from accessible tumor sites. If feasible, any follow-up biopsy should ideally be taken from the same tumor lesion as the baseline biopsy. Written patient consent is required for fresh tumor biopsies.

For fresh biopsies, acceptable samples include core needle biopsies for nonsuperficial tumor tissue or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. Tumor tissue should be of good quality based on total and viable tumor content. Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable.

Blood samples will be obtained for the evaluation of exploratory biomarkers including bTMB/ctDNA monitoring/DNA mutation, which will be collected at baseline (predose on Cycle 1 Day 1, required), at the time of first tumor response (predose on Day 1 of the following cycle, optional), and at the time of PD (optional) (approximately 10 mL for each timepoint). In addition, local laboratory assessments of AFP are required at baseline (predose on Cycle 1 Day 1). Written patient consent is required for blood sample collections.

7.8. Visit Windows

All visits must occur within ± 3 days from the scheduled date, unless otherwise noted (see Appendix 1). All assessments will be performed on the day of the specified visit unless an acceptable time window is specified. Assessments scheduled on the day of study drug administration (Day 1) of each cycle should be performed before any study drug is given unless otherwise noted. Laboratory results must be reviewed before dosing.

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other events, the visit should be scheduled for the nearest feasible date (the visit window is provided in Appendix 1), with subsequent visits conducted according to the planned schedule every 3 weeks from Day 1 of Cycle 1.

7.9. Unscheduled Visits

Unscheduled visits may be performed at any time at the patient's or the investigator's request and may include vital signs/physical examination, ECOG PS, AE review, concomitant medications and procedure reviews, radiographic assessments, physical examination of the liver, spleen, and lymph nodes, disease-related constitutional symptoms, and hematology and clinical chemistry laboratory assessments. The date and reason for the unscheduled visit must be recorded in the source documentation.

If an unscheduled visit is necessary to assess toxicity or for suspected PD, then diagnostic tests may be performed based on the investigator's assessment as appropriate, and the results of these tests should be entered on the unscheduled visit eCRF.

8. SAFETY MONITORING AND REPORTING

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

8.1. Risks Associated With Study Drugs

8.1.1. Risks Associated With Ociperlimab and Tislelizumab

Ociperlimab and tislelizumab are investigational agents that are currently in clinical development. Limited safety data are available in patients, and the full safety profile has not been characterized. The following recommendation is based on results from nonclinical and clinical studies with tislelizumab and ociperlimab and published data on other molecules within the same biologic class.

The PD-L1/PD-1 pathway is involved in peripheral immune tolerance; therefore, such therapy may increase the risk of imAEs, specifically the induction or enhancement of autoimmune conditions. AEs observed with anti-PD-1 therapy are presented in Section 8.7.3. Ociperlimab-mediated TIGIT inhibition may further increase the risk of imAEs. However, no apparent immunotoxicity, or toxicity in general, has been observed in animal models treated with ociperlimab. Furthermore, in the absence of activation, peripheral effector T-cells do not typically express TIGIT, thereby minimizing any potential negative additive effect as it relates to peripheral immune tolerance.

Although most imAEs observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Suggested workup procedures for suspected imAEs are provided in Appendix 6.

8.1.2. Risks Associated With BAT1706

In Study BAT1706-001-CR, the most commonly reported TEAEs in heathy subjects administered a single dose (1 mg/kg) of BAT1706 were upper respiratory tract infection, headache, contusion, nasopharyngitis, skin abrasion, nausea, and ligament sprain.

In Study BAT1706-002-CR, the most commonly reported TEAEs in heathy subjects administered with a single dose (1 mg/kg) of BAT1706 were ALT increase, AST increase, white blood cell count decrease, white blood cell count increase, neutrophil count increase, positive urine blood, γ -glutamyl transpeptidase increase, blood albumin decrease, neutrophil count decrease, hyperglycemia, and hematuria.

The most common adverse reactions observed in Avastin patients at a rate > 10% and at least twice the control arm rate, are epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain, and exfoliative dermatitis.

8.2. General Plan to Manage Safety Concerns

8.2.1. Eligibility Criteria

Eligibility criteria were selected to guard the safety of patients in this study. Results from the nonclinical toxicology studies and clinical data with ociperlimab and tislelizumab, as well as the nonclinical/clinical data from other PD-L1/PD-1 inhibitors, were considered. Specifically, patients who are at risk for treatment-emergent active autoimmune diseases or who have a history of autoimmune diseases that may relapse, patients who have undergone allogeneic stem cell or organ transplantation, and patients who have received a live viral vaccine ≤ 28 days before randomization are excluded from the study.

Refer to Section 4.2 for the full list of exclusion criteria.

8.2.2. Safety Monitoring Plan

Safety will be evaluated in this study through the monitoring of all AEs, defined and graded according to NCI-CTCAE v5.0. Patients will be assessed for safety (including laboratory values) according to the schedule in Appendix 1.

All enrolled patients will be evaluated clinically and with standard laboratory tests at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of AEs (see Table 5), physical examinations, laboratory measurements (hematology, clinical chemistry, etc), and other assessments including those listed in Appendix 1. In addition, patients will be closely monitored for the development of any signs or symptoms of autoimmune conditions or infection.

At the start of each cycle, study drug(s) will be administered only after clinical laboratory results have been reviewed. Administration of study drugs will be performed in a setting where emergency medical equipment and staff who are trained to respond to medical emergencies are available (for additional information, see Section 5.2).

Serum samples will be drawn for determination of ADAs to ociperlimab, tislelizumab, and BAT1706 in all randomized patients.

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

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

8.3. Adverse Events

8.3.1. Definitions and Reporting

An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study drugs, whether considered related to study drugs or not.

Examples of AEs include:

- Worsening of a chronic or intermittent pre-existing condition, including an increase in severity, frequency, duration, and/or an association with a significantly worse outcome
- New conditions detected or diagnosed after study drug administration even though the condition might have been present before the start of the study
- Signs, symptoms, or clinical sequelae of a suspected interaction
- Signs, symptoms, or clinical sequelae of a suspected overdose of any of the study drugs or a concurrent medication (overdose per se should not be reported as an AE or SAE)

When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory results, and diagnostics reports) related to the AE or SAE. The investigator will then record all relevant information regarding an AE or SAE in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by the sponsor. In this instance, all patient identifiers will be obscured on the copies of the medical records before submission to the sponsor.

8.3.2. Assessment of Severity

The investigator will assess the severity of each AE and SAE reported during the study. AEs and SAEs should be assessed and graded per NCI-CTCAE v5.0.

Toxicities that are not specified in NCI-CTCAE will be defined as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care, activities of daily living
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

Note: The terms “severe” and “serious” are not synonymous. Severity is a measure of intensity (eg, grade of a specific AE, mild [Grade 1], moderate [Grade 2], severe [Grade 3], or life-threatening [Grade 4]), whereas, seriousness is classified by the criteria based on the regulatory definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the sponsor to applicable regulatory authorities as described in Section 8.6.2.

8.3.3. Assessment of Causality

The investigator is obligated to assess the relationship between the study drugs and the occurrence of each AE or SAE using their best clinical judgement. Alternative causes, such as

natural history of the underlying diseases, concomitant therapy, and other risk factors, and the temporal relationship of the AE or SAE to the study drugs should be considered and investigated. The investigator should consult the, Ociperlimab Investigator's Brochure, Tislelizumab Investigator's Brochure, and BAT1706 Investigator's Brochure in the determination of his/her assessment.

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always assesses causality for every SAE before transmission of the SAE report to the sponsor because the causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator may change his/her opinion of causality after considering follow-up information, amending the SAE report accordingly.

The causality of each AE should be assessed and classified by the investigator as "related" or "not related." An AE is considered related if there is "a reasonable possibility" that the AE may have been caused by the study drugs (ie, there are facts, evidence, or arguments to suggest possible causation). A number of factors should be considered in making this assessment including:

- Temporal relationship of the AE to the administration of study drug(s)/study procedure
- Whether an alternative etiology has been identified
- Mechanism of action of the study drugs
- Biological plausibility

An AE should be considered "related" to study drugs if any of the following are met; otherwise, the event should be assessed as "not related" if:

- There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
- There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
- There is some evidence to suggest a causal relationship (eg, the AE occurred within a reasonable time after administration of the study drug[s]). However, the influence of other factors may have contributed to the AE (eg, the patient's clinical condition or other concomitant AEs).

8.3.4. Follow-up of Adverse Events

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

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

All AEs and SAEs will be followed up until resolution, the condition stabilizes or is considered chronic, the AE or SAE is otherwise explained, the patient is lost to follow-up, or the patient withdraws consent. The investigator will ensure that follow-up includes any supplemental

investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, radiographic imaging, or consultation with other health care professionals.

The sponsor may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obligated to assist. If a patient dies during participation in the study or during a recognized follow-up period, the sponsor will be provided with a copy of any postmortem findings, including histopathology.

New or updated information should be reported to the sponsor according to the SAE instructions provided by the sponsor within the time frames outlined in Section 8.6.2.

8.3.5. Laboratory Test Abnormalities

Abnormal laboratory findings (eg, clinical chemistry, complete blood count, coagulation, or urinalysis) or other abnormal assessments (eg, ECGs, x-rays, or vital signs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs. This includes clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and that worsen significantly during the study. The definition of clinically significant is based on the judgement of the investigator. In general, these are the laboratory test abnormalities or other abnormal assessments that:

- are associated with clinical signs or symptoms, or
- require active medical intervention, or
- lead to dose interruption or discontinuation, or
- require close observation, more frequent follow-up assessments, or further diagnostic investigation.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (eg, alkaline phosphatase and bilirubin 5x ULN associated with cholestasis), only the diagnosis (ie, cholestasis) should be recorded on the Adverse Event eCRF.

If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L (or mmol/L) should be recorded as “hyperkalemia.”

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

8.4. Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening

  Note: The term "life-threatening" in the definition of "serious" refers to an AE in which the patient was at risk of death at the time of the AE. It does not refer to an AE that hypothetically might have caused death if it were more severe.

- Requires hospitalization or prolongation of existing hospitalization

  Note: In general, hospitalization signifies that the patient was admitted (usually involving at least an overnight stay) to the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.

- Results in disability/incapacity

  Note: The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect
- Is considered a significant medical AE by the investigator based on medical judgement (eg, may jeopardize the patient or may require medical/surgical intervention to prevent the outcomes listed above)

The following are NOT considered SAEs:

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

8.5. Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is a serious adverse reaction that is both unexpected (ie, not present in the study drug's reference safety information [RSI]) and meets the definition of an serious adverse drug reaction (SADR), the specificity or severity of which is not consistent with those noted in the Ociperlimab Investigator's Brochure, Tislelizumab Investigator's Brochure, and BAT1706 Investigator's Brochure.

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

8.6.1. Adverse Event Reporting Period

After the ICF has been signed, but before the administration of the study drugs, only SAEs should be reported to the sponsor.

After initiation of study drugs, all AEs and SAEs, regardless of relationship to study drugs, will be reported until either 30 days after last dose of study drugs or initiation of subsequent anticancer therapy, whichever occurs first. Serious or nonserious imAEs should be reported until 90 days after the last dose of study drugs, regardless of whether the patient starts a subsequent 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 treatment.

AEs and SAEs should be recorded as described in Table 5. For the follow-up period for AEs, see Section 8.3.4. For the definition of TEAEs, see Section 9.3.2.

Table 5: Guidance for Duration of Recording New or Worsening Adverse Events in Both Arms

Event type	Record new or worsening events that occur during this period	
	Begin	**End**
SAEs[a]	Signing of informed consent	Up to 30 days after last dose, initiation of a new anticancer therapy, death, withdrawal of consent, or loss to follow-up, whichever occurs first
Nonserious AEs due to PD	Do not record (see Section 8.6.4)	
All nonserious AEs, except those due to PD	First dose of study drug	Up to 30 days after last dose, initiation of a new anticancer therapy, death, withdrawal of consent, or loss to follow-up, whichever occurs first
Immune-mediated AEs (serious or nonserious)	First dose of study drug	Up to 90 days after last dose (regardless of initiation of new anticancer therapy), death, withdrawal of consent, or loss to follow-up, whichever occurs first

Abbreviations: AE, adverse event; PD, progressive disease; SAE, serious adverse event.
[a] 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 treatment.

8.6.2. Reporting Serious Adverse Events

8.6.2.1. Prompt Reporting of Serious Adverse Events

As soon as the investigator determines that an AE meets the protocol definition of an SAE, the event must be reported promptly (within 24 hours) to the sponsor or designee as described in Table 6.

Table 6: Time Frames and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

	Time frame for making initial/follow-up report[a]	Documentation method	Reporting method
All SAEs	Within 24 hours after first knowledge of the SAE	SAE report	Electronic submission of SAE Form to safety portal[b]

Abbreviations: AE, adverse events; EDC, electronic data capture; SAE, serious adverse event.
[a] Report follow-up information that is clinically relevant and pertaining to the SAE which includes but is not limited to the following: Update to the SAE, new additional SAE, outcome, seriousness criteria, investigator causality, event start date/date of onset, date of death, relationship to each study drug. Follow-up information will also be reported as per the discretion of the investigator if the new or updated information changes the medical assessment of the case.
[b] SAE reports should be submitted to the sponsor safety database electronically from within the EDC. If the electronic submission is not available for any reason, a paper SAE form should be submitted by email or fax.

8.6.2.2. Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a patient, he/she is to report the information to the sponsor within 24 hours, as outlined above in Section 8.6.2.1. The SAE report should always be completed as thoroughly as possible, including all available details of the event, and forwarded to the sponsor or designee within the designated time frames.

If the investigator does not have all information regarding an SAE, he/she is not to wait to receive additional information before notifying the sponsor or designee of the SAE and completing the form. The form will be updated when additional information is received.

The investigator must always provide an assessment of causality for each SAE as described in Section 8.3.3.

The sponsor will provide contact information for SAE receipt.

8.6.2.3. Regulatory Reporting Requirements for Serious Adverse Events

The investigator will promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 8.6.2.1. The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a drug under clinical investigation.

The investigator, or other responsible person according to local requirements will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the IRB/IEC.

All SUSARs (as defined in Section 8.5) will be submitted to all applicable regulatory authorities and investigators for ociperlimab and tislelizumab studies.

When a study center receives an initial or follow-up safety report or other safety information (eg, revised Investigator's Brochure) from the sponsor, the investigator or designated responsible person is required to promptly notify his/her IRB or IEC. The investigator should place copies of safety reports from the sponsor in the investigator site file.

8.6.3. Eliciting Adverse Events

The investigator or designee will ask patients about AEs by asking the following standard questions:

- How are you feeling?
- Have you had any medical problems since your last visit?
- Have you taken any new medicines since your last visit?

8.6.4. Disease Progression

PD, which is expected in this study population and measured as an efficacy endpoint, should not be recorded as an AE term. Similarly, nonserious AEs that are clearly consistent with the pattern of progression of the underlying disease and are considered unequivocally due to PD should not be recorded. However, if there is any uncertainty as to whether a nonserious AE is due to PD, it should be recorded as an AE. All SAEs and deaths regardless of relatedness to PD should be recorded and reported (see Section 8.6.2).

8.6.5. Deaths

Death is an outcome and not usually considered an AE. If the only information available is death and the cause of death is unknown, then the death is reported as an event (eg, "death," "death of unknown cause," or "death unexplained").

8.6.6. Pregnancies

If a female patient or the partner of a male patient becomes pregnant while receiving study drugs or within 120 days after the last dose of study drugs, a pregnancy report form must be completed and expeditiously submitted to the sponsor to facilitate outcome follow-up. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow-up will be no longer than 6 to 8 weeks after the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE.

An abortion, whether accidental, therapeutic, or spontaneous, should always be reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a patient exposed to the study drugs should be recorded and reported as an SAE.

8.6.7. Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Independent Ethics Committees

The sponsor will promptly assess all SAEs against cumulative study drug experience to identify and expeditiously communicate new safety findings to regulatory authorities, investigators, IRBs, and IECs based on applicable legislation.

To determine the reporting requirements for individual SAEs, the sponsor will assess the expectedness of the SAEs using the following reference safety information documents:

- Ociperlimab Investigator's Brochure
- Tislelizumab Investigator's Brochure
- BAT1706 Investigator's Brochure

8.6.8. Assessing and Recording Immune-Mediated Adverse Events

Because treatment with anti-PD-1 or immune checkpoint inhibitors can cause autoimmune disorders, AEs considered by the investigator to be immune-mediated (see Section 8.7.3) should be classified as imAEs and identified as such on the eCRF AE page until Day 90 after treatment discontinuation.

Investigators should consult the guidance on diagnostic evaluation and management of imAEs, that are commonly seen with immune checkpoint inhibitors, in Appendix 6.

An extensive list of potential imAEs appears in Section 8.7.3, Table 8. All conditions like those listed should be evaluated to determine whether they are imAEs based on a similar diagnostic process to those reactions that are presented in more detail in Appendix 6.

8.6.9. Recording Infusion-Related Reactions

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. Each individual sign and symptom of an infusion reaction should be recorded each as a separate AE in the eCRF and identified as an infusion-related reaction.

Refer to the eCRF completion guidelines for details.

8.7. Management of Adverse Events of Special Interest

As a routine precaution, after infusion of the study drugs on Day 1 of Cycle 1, patients must be monitored for ≥ 120 minutes. If the infusion completion time was shortened, patients must be monitored for ≥ 60 minutes on Day 1 Cycle 2, and from Cycle 3 onward, a ≥ 30-minute monitoring period is required. Regardless of the infusion completion time, patients must be monitored in an area with resuscitation equipment and emergency agents.

The management guidelines for infusion-related reactions, severe hypersensitivity reactions, and imAEs according to the NCI-CTCAE criteria are outlined in the following subsections.

8.7.1. Infusion-Related Reactions

Patients should be closely monitored for infusion-related reactions. Immediate access to an Intensive Care Unit or equivalent environment and appropriate medical therapy (including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen) must be available to treat infusion-related reactions.

Treatment modifications for symptoms of infusion-related reactions due to study drugs is provided in Table 7.

Table 7: Treatment Modification for Symptoms of Infusion-Related Reactions Due to Study Drugs

NCI-CTCAE grade	Treatment modification for study drugs
Grade 1 - mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease infusion rate by 50%. Any worsening is closely monitored. Medical management as needed.
Grade 2 - moderate Therapy or infusion interruption indicated but the patient responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, intravenous fluids); prophylactic medications indicated for ≤ 24 hours.	Stop infusion. Infusion may be resumed at 50% of previous rate after infusion-related reactions have resolved or decreased to Grade 1 in severity. Any worsening is closely monitored. Proper medical management should be instituted as described in the text that follows this table.
Grade 3 - severe Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms after initial improvement; hospitalization indicated for clinical sequelae.	Immediately stop the infusion. Proper medical management should be instituted as described in the text that follows this table. The patient should be withdrawn from the study drug(s) associated with the infusion-related reaction.
Grade 4 - life-threatening Life-threatening consequences; urgent intervention indicated.	Immediately stop the infusion. Proper medical management should be instituted as described in the text that follows this table. The patient should be withdrawn from the study drug(s) associated with the infusion-related reaction. Hospitalization is recommended.

Abbreviations: NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events. (NCI-CTCAE)

After the infusion rate has been decreased by 50% or suspended due to an infusion-related reaction, it must remain decreased for all subsequent infusions. If the patient has a second infusion-related reaction (≥ Grade 2) on the slower infusion rate, the infusion should be discontinued and the patient should be withdrawn from the assigned study drugs.

NCI-CTCAE Grade 1 or 2 infusion reactions: Proper medical management should be instituted, as indicated per the type of reaction. This includes but is not limited to an antihistamine (eg, diphenhydramine or equivalent), antipyretic (eg, paracetamol or equivalent), and, if considered indicated, oral or intravenous glucocorticoids, epinephrine, bronchodilators, and oxygen. In the next cycle, the patient should receive oral premedication with an antihistamine (eg, diphenhydramine or equivalent) and an antipyretic (eg, paracetamol or equivalent), and the patient should be closely monitored for clinical signs and symptoms of an infusion reaction.

NCI-CTCAE Grade 3 or 4 infusion reactions: Proper medical management should be instituted immediately, as indicated per type and severity of the reaction. This includes but is not limited to oral or intravenous antihistamine, antipyretic, glucocorticoids, epinephrine, bronchodilators, and oxygen.

8.7.2. Severe Hypersensitivity Reactions and Flu-like Symptoms

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

If a systemic anaphylactic/anaphylactoid reaction occurs, the infusion must be stopped immediately and the patient discontinued from the study treatment. Systemic anaphylactic/anaphylactoid reactions typically manifest within minutes after the administration of the drug/antigen, are characterized by respiratory distress, laryngeal edema, and/or intense bronchospasm, and are often followed by vascular collapse or shock without antecedent respiratory difficulty; cutaneous manifestations such as pruritus and urticaria with/without edema; and gastrointestinal manifestations such as nausea, vomiting, crampy abdominal pain, and diarrhea.

Epinephrine injection and dexamethasone infusion will be administered to patients if a hypersensitivity reaction is observed, and then the patient should be placed on monitor immediately and an Intensive Care Unit should be alerted for possible transfer if needed.

For prophylaxis of flu-like symptoms, a dose of 25 mg indomethacin or a comparable dose of a nonsteroidal anti-inflammatory drug (ie, 600 mg ibuprofen, 500 mg naproxen sodium) may be administered 2 hours before and 8 hours after the start of each dose of study drug infusion. Alternative treatments for fever (ie, paracetamol) may be administered to the patient at the discretion of the investigator.

8.7.3. Immune-Mediated Adverse Events

Immune-mediated AEs are of special interest in this study. If the events listed below or similar events occur, the investigator should exclude alternative explanations (eg, combination drugs, infectious disease, metabolic, toxin, PD, or other neoplastic causes) with appropriate diagnostic tests that may include but are not limited to serologic, immunologic, and histologic (biopsy) data. If alternative causes have been ruled out, the AE required the use of systemic steroids, other immunosuppressants, or endocrine therapy and is consistent with an immune-mediated mechanism of action, the imAE indicator on the eCRF AE page should be checked.

A list of potential imAEs is shown below in Table 8. All conditions similar to those listed should be evaluated in patients to determine whether they are immune-mediated.

Recommendation for diagnostic evaluation and management of imAEs is based on European Society for Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) guidelines (Haanen et al 2017; Brahmer et al 2018) and common immune-mediated toxicities are detailed in Appendix 6. For any AEs not included in Appendix 6, refer to the ASCO Clinical

Practice Guideline (Brahmer et al 2018) for further guidance on diagnostic evaluation and management of immune-mediated toxicities.

Table 8: Immune-Mediated Adverse Events

Body System Affected	Events
Skin (mild-common)	pruritus or maculopapular rash; vitiligo
Skin (moderate)	follicular or urticarial dermatitis; erythematous/lichenoid rash; Sweet syndrome
Skin (severe-rare)	full-thickness necrolysis/Stevens-Johnson syndrome
Gastrointestinal	colitis (includes diarrhea with abdominal pain or endoscopic/radiographic evidence of inflammation); pancreatitis; hepatitis; aminotransferase (ALT/AST) elevation; bowel perforation
Endocrine	thyroiditis, hypothyroidism, hyperthyroidism; hypophysitis with features of hypopituitarism (eg, fatigue, weakness, weight gain); insulin-dependent diabetes mellitus; diabetic ketoacidosis; adrenal insufficiency
Respiratory	pneumonitis/diffuse alveolitis
Eye	episcleritis; conjunctivitis; iritis/uveitis
Neuromuscular	arthritis; arthralgia; myalgia; neuropathy; Guillain-Barre syndrome; aseptic meningitis; myasthenic syndrome/myasthenia gravis; myositis
Blood	anemia; leukopenia; thrombocytopenia
Renal	interstitial nephritis; glomerulonephritis; acute renal failure
Cardiac	pericarditis; myocarditis; heart failure
Neurologic	encephalitis, meningitis, meningoradiculitis, meningoencephalitis

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Recommendations for managing imAEs are detailed in Appendix 6.

If a toxicity does not resolve to ≤ Grade 1 within 12 weeks, study drugs should be discontinued after consultation with the sponsor. Patients who experience a recurrence of any event at the same or higher severity grade with rechallenge should permanently discontinue treatment.

8.7.4. Adverse Events of Special Interest Related to BAT1706

Adverse events of special interest for BAT1706 are as follows:

- Grade ≥ 2 cardiac disorders (eg, atrial fibrillation, myocarditis, pericarditis)
- Severe cutaneous reactions (eg, Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- Grade ≥ 3 hypertension
- Grade ≥ 3 proteinuria
- Any grade GI perforation, abscesses, or GI fistulae

- Grade ≥ 2 non-GI fistula or abscess
- Tracheoesophageal fistula
- Grade ≥ 3 wound-healing complication
- Hemorrhage
  - Any grade CNS bleeding
  - Grade ≥ 2 hemoptysis
  - Other Grade ≥ 3 hemorrhagic event
- Any arterial thromboembolic event
- Grade ≥ 3 venous thromboembolic event
- Any grade posterior reversible encephalopathy syndrome
- Grade ≥ 3 congestive heart failure.

For diagnosis and management of patients with AEs related to BAT1706, please refer to Appendix 7.

8.7.5. Hepatic Function Abnormalities

Patients with advanced HCC generally have underlying cirrhosis with decreased hepatic function. Special attention is needed because they may also have a concomitant chronic viral infection. Therefore, when a hepatic event, such as liver function laboratory abnormalities, is observed, the investigator must evaluate for re-activation of viral hepatitis, consider other drug-related toxicities, and exclude PD involving the liver. For diagnosis and management of patients with AST or ALT values ≤ Grade 1 at baseline, please see Section 8.7.3 and refer to Appendix 6.

In patients with Grade 2 AST/ALT abnormalities at baseline, therapeutic interventions with a steroid treatment may be required with rising AST and ALT laboratory abnormalities while considering the total bilirubin (TBil) changes, when the AST or ALT elevation is suspected with immune-mediated nature. The following algorithm is proposed for the use of steroid treatment and actions with immune checkpoint inhibitors:

- If AST or ALT increases but is still within Grade 2, continue the study treatment and monitor AST/ALT within 1-2 weeks. In case total bilirubin > 1.5x ULN, the monitoring should be more frequent.
- If AST or ALT increases to 5-8x ULN and TBil ≤ 3x ULN, temporarily hold the immune checkpoint inhibitors and monitor AST/ALT within 1 week. In case of TBil >1.5xULN, the monitoring should be more frequent. If AST/ALT improves, continue, or resume the immune checkpoint inhibitors. If AST/ALT doesn't improve, initiate oral prednisone at 0.2-0.5 mg/kg/day or equivalent. If AST/ALT improves, taper the corticosteroid over 4 weeks and resume the immune checkpoint inhibitors when AST/ALT elevation returns to Grade 1 or baseline. Otherwise, it should be managed as AST or ALT with 8-20x ULN. Note: in case of TBil > 3x ULN, consider permanent discontinuation of immune checkpoint inhibitors.

- If AST or ALT increases to 8-20 x ULN, initiate prednisone immediately at 0.5-1 mg/kg/day via oral or intravenous route depending on general condition, presence of liver decompensation and expected patient compliance. If no further improvement within 4-7 days is observed, consider prednisolone pulses or mycophenolate mofetil. Monitor every 2-3 days, particularly if TBil is > 1.5x ULN. If AST/ALT improves, taper the corticosteroid over 4 weeks and resume the immune checkpoint inhibitors when AST/ALT returns to Grade 1 or baseline, after discussion with the medical monitor. In case of TBil > 2x ULN, AST/ALT > 10x ULN for > 2 weeks or AST/ALT > 15x ULN, consider permanent discontinuation of immune checkpoint inhibitors.
- If any ALT or AST increases meet Grade 4 criteria, initiate steroid or immunosuppressant therapy promptly per Appendix 6. Study drug(s) will be discontinued permanently.

9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

The statistical analyses will be performed by the sponsor or designee after the data collection is completed and the database is locked and released. Details of the statistical analyses will be included in a separate Statistical Analysis Plan (SAP).

9.1. Statistical Analysis

The following descriptive statistics will be used to summarize the trial data on the basis of their nature unless otherwise specified:

- Continuous variables: number of non-missing observations, mean, standard deviation, median, minimum, and maximum
- Categorical variables: frequencies and percentages
- Time-to-event variables: number of non-missing observations (N), median, minimum, and maximum. Kaplan-Meier event-free rates may also be provided if applicable for specific time-to-event variables

9.1.1. Analysis Sets

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 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 Efficacy Evaluable Analysis Set (EAS) includes all patients in the ITT Analysis Set without critical protocol deviations 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 the first dose date. This analysis set will be used for sensitivity 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 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 and for whom both baseline ADA and ≥1 postbaseline ADA result are available.

9.1.2. Patient Disposition

The number of patients randomized, treated, and discontinued from study drugs and/or study and those with critical protocol deviations will be counted. The primary reason for study drug and/or study discontinuation will be summarized according to the categories in the eCRF. The end-of-study status (alive, dead, withdrew consent or lost to follow-up) at the data cutoff date will be summarized using the data from the eCRF.

Critical protocol deviations will be summarized and listed by each category.

9.1.3. 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, vital signs, time since initial cancer diagnosis, time since advanced/metastatic disease diagnosis, etc.

Categorical variables include gender, ECOG PS, geographical region, country, race, histological subtype, disease stage, metastatic site, tobacco use, etc.

9.1.4. Prior and Concomitant Medications

Prior medications will be defined as medications that stopped before randomization.

Concomitant medications will be defined as medications that 1) started before randomization and were continuing at the time of randomization, or 2) started on or after the date of randomization up to 30 days after the patient's last dose (as of the on-site Safety Follow-up Visit).

Concomitant medications will be coded using the World Health Organization Drug Dictionary drug codes and further coded to the appropriate Anatomical Therapeutic Chemical code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class in the Clinical Study Report (CSR) for this protocol.

9.2. Efficacy Analyses

9.2.1. Primary Efficacy Analysis

The primary efficacy endpoint is ORR as determined by investigator based on RECIST v1.1, in Arm A and Arm B.

ORR is defined as the proportion of patients achieving confirmed BOR of CR or PR. BORs is defined as the best response recorded from the first dose of study drug until data cutoff or the initiation of new anticancer treatment, whichever occurs earlier. Patients with no postbaseline response assessment (due to any reason) will be considered as nonresponders for BOR. The proportion of patients in each response category will be presented.

ORR will be summarized in the ITT Analysis Set with a Clopper-Pearson 95% CI constructed to assess the precision of the point estimate.

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.

The sensitivity analysis of ORR will be carried out in the Efficacy Evaluable Analysis Set.

9.2.2. Secondary Efficacy Analysis

Other efficacy endpoints with necessary tumor assessments (ie, DOR, PFS, TTR, DCR and CBR), as well as OS, will be summarized for the secondary efficacy analysis. The secondary efficacy analysis will be conducted in the ITT Analysis Set assessed by investigator (if applicable) in Arm A and Arm B.

Disease Control Rate (DCR)

The DCR is defined as the proportion of patients who achieve CR, PR, or stable disease.

The DCR will be summarized similarly as ORR in the ITT Analysis Set and also in Efficacy Evaluable Analysis Set for sensitivity analysis.

Clinical Benefit Rate (CBR)

The CBR is defined as the proportion of patients who achieve CR, PR, or durable stable disease (stable disease ≥ 24 weeks).

The CBR will be summarized similarly as ORR in the ITT Analysis Set and also in the Efficacy Evaluable Analysis Set for sensitivity analysis.

Duration of Response (DOR)

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

The DOR will be analyzed among the responders in the ITT Analysis Set. The median and other quartiles of DOR will be estimated using the Kaplan-Meier method. The 2-sided 95% CIs will be constructed with the generalized Brookmeyer and Crowley method (Brookmeyer and Crowley 1982). Event-free rates at selected timepoints for DOR will be estimated using the Kaplan-Meier method with the corresponding 95% CI constructed using Greenwood's formula (Greenwood 1926). The DOR censoring rule will follow the US Food and Drug Administration (FDA) Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (US FDA 2018).

More details, including the censoring rules, will be provided in the SAP.

Progression-Free Survival (PFS)

The PFS is defined as the time from treatment initiation to disease progression or death due to any cause, whichever occurs first.

The PFS will be analyzed in the ITT Analysis Set using methods similar to those described for the DOR. The PFS censoring rule will follow the same as that followed for the DOR. The PFS rates at 3 months, 6 months, 9 months, and 12 months will be calculated based on the Kaplan-Meier method.

Overall Survival (OS)

The OS is defined as the time from treatment initiation to death due to any cause.

The OS will be analyzed in the ITT Analysis Set using similar methods to those described for the DOR, except for censoring rules. For OS, patients will be censored either at the date that the patient was last known to be alive or the date of data cutoff, whichever comes earlier, in the absence of death. The OS rates at 3 months, 6 months, 9 months, and 12 months will be calculated based on the Kaplan-Meier method.

Time to Response (TTR)

The TTR is defined as the time from treatment initiation to the first documented response.

The TTR will be analyzed in the ITT Analysis Set using sample statistics such as mean, median, and standard deviation for patients who have achieved an objective response.

Waterfall plots of maximum tumor shrinkage per patient will be presented.

9.2.3. Subgroup Analysis

Subgroup analysis on key efficacy endpoints (ORR, OS, etc.) will be conducted to explore the consistency of efficacy across a variety of subgroups, as appropriate. Subgroup variables may include but are not limited to age, gender, ECOG PS, hepatitis viral status, BCLC stage at study entry, prior loco-regional therapy, baseline AFP level, MVI and/or EHS, and PD-L1 expression.

9.3. Safety Analyses

Safety will be assessed by monitoring and recording of AEs and laboratory values (hematology, clinical chemistry, coagulation, and urinalysis). Vital signs, physical examinations, and ECG findings will also be used in determining the safety profile. The severity of AEs will be graded according to NCI-CTCAE v 5.0. The incidence of DLT events and TEAEs will be reported as the number (percentage) of patients with TEAEs by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and PT. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, and maximum for continuous variables; n [%] for categorical variables) and changes from baseline will be determined for laboratory parameters and vital signs.

Safety data will be summarized using the Safety Analysis Set and by arm.

9.3.1. Extent of Exposure

Extent of exposure to a study drug will be summarized descriptively as the number of cycles received (number and percentage of patients), duration of exposure, cumulative total dose received per patient (mg), dose intensity (mg/day) and relative dose intensity (%).

The number (and percentage) of patients with a dose reduction, dose delay, treatment interruption, or study drug discontinuation will be summarized with the respective reasons.

Patient data listings will be provided for all dosing.

9.3.2. Adverse Events

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

DLTs will be summarized for the safety run-in period.

A 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(s) and up to 30 days after last dose of study drug(s), or initiation of new anticancer therapy, whichever occurs first. The TEAE classification also applies to imAEs that are recorded 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 the time since the last dose of study drug. 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.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by SOC and PT A patient will be counted only once by the highest severity grade per NCI-CTCAE v 5.0 within a SOC and PT, even if the patient experienced > 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(s). Treatment-related TEAEs include those events considered by the investigator to be related to study drug or with missing assessment of the causal relationship.

All TEAEs, SAEs, deaths, ≥ Grade 3 TEAEs, imAEs, AEs of special interest related to BAT1706 (see Section 8.7.4), treatment-related TEAEs, and TEAEs that led to treatment discontinuation and dose modification (interruption/delay/reduction, as appropriate) will be summarized.

9.3.3. Laboratory Analyses

Clinical laboratory (eg, hematology, clinical chemistry, coagulation, and urinalysis) values will be evaluated for each laboratory parameter, as appropriate. Abnormal laboratory values will be flagged and identified as those outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be included in the CSR for this protocol. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, and maximum for continuous variables; n [%] for categorical variables) for laboratory parameters and their changes from baseline will be calculated. Laboratory values will be summarized by visit and by worst postbaseline change.

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

9.3.4. Vital Signs

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

9.3.5. Physical examination

Physical examination parameters will be listed by visit, as appropriate.

9.3.6. Electrocardiograms

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

9.3.7. Eastern Cooperative Oncology Group Performance Status

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

9.3.8. Ophthalmologic examination

Ophthalmologic examination results will be listed by patient, if necessary.

9.4. Pharmacokinetic Analyses

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

The ociperlimab, tislelizumab, and BAT1706 serum concentration data will be tabulated and summarized by visit/cycle at which these concentrations are collected. Descriptive statistics will include means, medians, ranges, and standard deviations, as appropriate.

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

9.5. Immunogenicity Analyses

Samples to assess anti-ociperlimab, anti-BAT1706, and anti-tislelizumab antibodies will be collected only in patients who receive study drugs and at sites that are able to adequately perform sampling, handling, and processing as outlined in the laboratory manual.

The immunogenicity results will be summarized using descriptive statistics by the number and percentage of patients who develop detectable ADAs. The incidence of positive ADAs and neutralizing ADAs will be reported for evaluable patients. The effect of immunogenicity on PK, efficacy, and safety may be evaluated if data allows.

9.6. Other Exploratory Analyses

Summary statistics might be provided for exploratory biomarkers including expression of PD-L1 and TIGIT pathway-related proteins (TIGIT, poliovirus receptor/PVR and nectin cell adhesion molecule 2/nectin-2), TMB/DNA mutation, bTMB/ctDNA monitoring/DNA mutation, AFP and GEP.

The association of biomarkers with disease status, response/resistance to tislelizumab plus BAT1706 with or without ociperlimab will be explored, when appropriate.

9.7. Sample Size Consideration

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.

10. STUDY COMMITTEES AND COMMUNICATION

10.1. Safety Monitoring Committee

A SMC will be established and include both the sponsor (including the medical monitor and study team members from Pharmacovigilance/Drug Safety, Clinical Pharmacology, and Biostatistics with other members as appropriate) and investigators. The SMC will review all available safety, PK, and exploratory data and make recommendations on dose modification, and dose selection to ensure that the study treatment is tolerable and that patients are adequately monitored.

The SMC will evaluate the safety and tolerability of the 2 combination therapies and will review the safety data including, but not limited, to DLTs, all TEAEs, and laboratory abnormalities when all patients enrolled in the safety run-in stage have completed 21 days of treatment or when ≥ 2 DLTs occur.

The SMC will make recommendations on safety management (including resumption of enrollment, or de-escalation of BAT1706, or termination of enrollment, etc) and will assess whether it is suitable to expand the cohorts.

The SMC may also be called upon by the sponsor on an ad hoc basis where applicable to the conduct of the study. The details of SMC membership, responsibilities, and meeting schedule are outlined in a separate SMC Charter.

10.2. Communication

When the CSR is completed, the sponsor will provide the major findings of the study to the investigator.

The sponsor will not routinely inform the investigator or patient of the test results, because the information generated from this study will be preliminary in nature, and the significance and scientific validity of the results will be undetermined at such an early stage of research.

11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

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

11.1. Access to Information for Monitoring

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

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

11.2. Access to Information for Auditing or Inspections

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

12. QUALITY ASSURANCE AND QUALITY CONTROL

12.1. Regulatory Authority Approval

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

12.2. Quality Assurance

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

12.3. Study Site Inspections

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

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

12.4. Drug Accountability

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

At study initiation, the monitor will evaluate the site's standard operating procedure for study drug disposal/destruction to ensure that it complies with the requirements of the sponsor specified in the Pharmacy Manual. At appropriate timepoints during the conduct of the study or at the end of the study after the final drug inventory reconciliation by the medical monitor, the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures. If the site cannot meet the sponsor's requirements specified in the Pharmacy Manual for disposal, arrangements will be made between the site and the sponsor or its representative for destruction or return of unused study drug supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

13. ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1. Ethical Standard

This study will be conducted by the principal investigator and the study center in full conformance with the ICH E6 guideline for GCP and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will also comply with the requirements of the ICH E2A guideline (ICH E2A 1994).

13.2. Institutional Review Board/Independent Ethics Committee

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

The principal investigator is responsible for providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC. Investigators are also responsible for promptly informing the IRB/IEC of any protocol amendments. In addition to the requirements for reporting all AEs to the sponsor, investigators must comply with requirements for reporting SAEs to the local health authority and IRB/IEC. Investigators may receive written Investigational New Drug Safety Reports or other safety-related communications from the sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/IEC and archived in the site's study file.

13.2.1. Protocol Amendments

Any protocol amendments will be prepared by the sponsor. All protocol modifications must be submitted to competent authorities according to local requirements and to the IRB/IEC together with, if applicable, a revised model ICF in accordance with local requirements. Written documentation from competent authorities (according to local requirements) and from the IRB/IEC and required site approval must be obtained by the sponsor before changes can be implemented, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (eg, change in medical monitor or contact information).

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

13.3. Informed Consent

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

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

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

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

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

13.4. Patient and Data Confidentiality

The principal investigator and sponsor will maintain confidentiality and privacy standards by following applicable data privacy laws covering the collection, storage, transmission, and processing of patients' personal and medical information.

The principal investigator shall code the medical information obtained during the study with a unique patient identification number assigned to each patient enrolled in the study. This approach ensures that patients' names are not included in any data set transmitted to any sponsor location.

Patient medical information obtained during this study is confidential and may be disclosed to third parties only as permitted by the signed ICF (or a separate authorization for the use and disclosure of personal health information that has been signed by the patient), unless permitted or required by law.

In the event of a breach of the confidentiality of a patient's personal and medical information, the principal investigator and sponsor, as appropriate, shall fulfill all mediation steps and reporting obligations under applicable data privacy laws.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare for treatment purposes.

Data generated during this study must be available for inspection upon request by representatives of the China National Medical Products Administration and all other national and local health authorities; by sponsor monitors, representatives, and collaborators; and by the IRBs/IECs for each study site, as appropriate.

The investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. The investigator agrees that all information received from the sponsor, including but not limited to the Ociperlimab Investigator's Brochure,

Tislelizumab Investigator's Brochure, BAT1706 Investigator's Brochure, this protocol, eCRFs, the information on the investigational new drugs, and any other study information, remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

If a written contract for the conduct of the study that includes confidentiality provisions inconsistent with this section is executed, that contract's provisions shall apply to the extent they are inconsistent with this section.

13.5. Financial Disclosure

Investigators are required to provide the sponsor with sufficient accurate financial information in accordance with regulations to allow the sponsor to submit complete disclosure or certification to the absence of certain financial interest of clinical investigators and/or disclose those financial interests, as required, to the appropriate health authorities. This is intended to ensure that financial interests and arrangements of clinical investigators with the sponsor that could affect reliability of data submitted to health authorities are identified and disclosed by the sponsor. Investigators are responsible for providing information about their financial interests before participation in the study and to update this information if any relevant changes occur during the study and for 1 year after completion of the study (ie, last patient, last visit).

14. DATA HANDLING AND RECORD KEEPING

14.1. Data Collection and Management Responsibilities

14.1.1. Data Entry in the Electronic Case Report Form

All study-related data collected or received by the investigator or study team shall be promptly entered into the eCRFs. In no event should the entry of the study data into the eCRF be later than what is stipulated in the site contract after the data is collected or received by the investigator or study team without prior communication with and approval by the sponsor.

14.1.2. Data Collection

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

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

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

14.1.3. Data Management/Coding

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

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

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

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

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

14.2. Data Integrity and In-house Blinding

Due to the open-label design of the study, access to the unblinded patient level clinical data in the EDC system will only be assigned to predefined study personnel. Functions/persons with access to the EDC system shall be prohibited from using the EDC system to generate unnecessary listings/summaries that may introduce unwanted bias, or share such outputs or the unblinded data from the EDC system with other functions/persons who do not have access to the EDC. Although the study is open-label, analyses or summaries generated by treatment assignment and actual treatment received will be limited and documented.

14.3. Study Records Retention

The investigator must maintain adequate and accurate records so that the conduct of the study can be fully documented and the study data can be subsequently verified. These documents should be classified into at least 1 of the following 2 categories: the investigator's study file or the patient clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRF and query forms, IRB/IEC, and governmental approval with correspondence, ICFs, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Patient clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the eCRFs) would include, but not be limited to, documents such as the following: patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, electroencephalogram, x-ray, pathology and special assessment reports, consultant letters, and screening and enrollment log, etc.

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

The sponsor will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that study center for the study, as dictated by any institutional requirements or local laws or regulations, or the sponsor's standards/procedures; otherwise, the retention period will default to 15 years.

The investigator must notify the sponsor of any changes in the archival arrangements including, but not limited to, the following: archival at an off-site facility or transfer of ownership of or responsibility for the records in the event the investigator leaves the study center.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and the sponsor to store these in sealed containers at a separate location so that they can be sealed and returned to the investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the site.

At the conclusion of this study, biological samples may be retained as outlined in the agreement with the contract research organization managing the biological samples, for a period of up to 10 years or as allowed by the IRB/IEC, whichever is shorter.

14.4. Protocol Deviations

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

The investigator is to document and explain any deviations from the approved protocol. In accordance with established IRB/IEC policies and procedures, the investigator must promptly report any important deviations that might impact patient safety and/or data integrity to the sponsor and to the IRB/IEC.

14.5. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency(ies). The sponsor will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). An abbreviated report may be prepared in certain cases.

The results of this study will be published or presented at scientific meetings in a timely, objective, and clinically meaningful manner that is consistent with good science, industry and regulatory guidance, and the need to protect the intellectual property of the sponsor, regardless of the outcome of the study. The data generated in this clinical study are the exclusive property of the sponsor and are confidential. For a multicenter study, the first publication or disclosure of study results shall be a complete, joint multicenter publication, or disclosure coordinated by the sponsor. Thereafter, any secondary publications will reference the original publication(s). Authorship will be determined by mutual agreement and all authors must meet the criteria for authorship established by the International Committee of Medical Journal Editors or stricter local criteria (International Committee of Medical Journal Editors 2018).

Each investigator agrees to submit all manuscripts, abstracts, posters, publications, and presentations (both oral and written) to the sponsor for review before submission or presentation in accordance with the clinical study agreement. This allows the sponsors to protect proprietary information, provide comments based on information from other studies that may not yet be available to the investigator, and ensure scientific and clinical accuracy. Each investigator agrees that, in accordance with the terms of the clinical study agreement, a further delay of the publication/presentation may be requested by the sponsor to allow for patent filings and/or protection in advance of the publication/presentation.

14.6. Study and Study Center Closure

Upon completion of the study, the monitor will conduct the following activities in conjunction with the investigator or study center personnel, as appropriate:

- Return/provide all study data to the sponsor
- Resolution and closure of all data queries
- Accountability, reconciliation, and arrangements for unused study drugs
- Review of study records for completeness
- Collection of all study documents for the trial master file filing according to GCP and local regulation
- Shipment of samples (including but not limited to those for PK, ADA, and biomarkers) to the assay laboratory for central laboratory analysis according to protocol and laboratory manual requirements

In addition, the sponsor reserves the right to suspend the enrollment or prematurely discontinue this study either at a single study center or at all study centers at any time for any reasons. Potential reasons for suspension or discontinuation include but are not limited to safety or ethical issues or noncompliance with this protocol, GCP, the sponsor's written instructions, the clinical study agreement, or applicable laws and regulations. If the sponsor determines such action is needed, the sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. When feasible, the sponsor will provide advance notification to the investigator of the impending action before it takes effect.

The sponsor will promptly inform all other investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IRB/IEC promptly and provide the reason for the suspension or termination.

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

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

14.7. Information Disclosure and Inventions

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

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

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

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

These restrictions do not apply to:

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

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

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16. APPENDICES

APPENDIX 1. SCHEDULE OF ASSESSMENTS

Assessment	Screening[a]	Treatment cycles				End-of-treatment visit Safety follow-up [b]	Survival follow-up [c]
		Cycles 1 to 3 (every 21 days)			Cycle 4 and subsequent cycles (every 21 days)		
Days (window)	**-28 to -1**	**1 (± 3)**	**8 (± 2)**	**15 (± 2)**	**1 (± 3)**	**30 ± 7 Days after last dose**	**Every 3 months**
Informed consent	x						
Inclusion/exclusion criteria	x						
Randomization	x [d]						
Demographics/medical history/prior medications [e]	x						
Vital signs/ height and weight [f]	x	x			x	x	
Physical examination [g]	x	x			x	x	
ECOG Performance Status	x	x			x	x	
12-lead ECG [i]	x	As clinically indicated				x	
EGD [h]	x						
Optical coherence tomography (or equivalent diagnostic test) and visual acuity test [j]	x				x	x	
Adverse events [k]	x	x	x[l]	x [l]	x	x	x
Concomitant medications	x	x	x[l]	x [l]	x	x	
Hematology [m]	x [a]	x	x	x	x	x	
Serum chemistry [m]	x [a]	x	x	x	x	x	
CK and CK-MB [m,n]	x[a]	x	x	x	x	x	

Assessment	Screening[a]	Treatment cycles				End-of-treatment visit Safety follow-up [b]	Survival follow-up [c]
		Cycles 1 to 3 (every 21 days)			Cycle 4 and subsequent cycles (every 21 days)		
Days (window)	**-28 to -1**	**1 (± 3)**	**8 (± 2)**	**15 (± 2)**	**1 (± 3)**	**30 ± 7 Days after last dose**	**Every 3 months**
Coagulation parameters [m]	x	x			x	x	
Urinalysis [m]	x	x			x	x	
Pregnancy test [o]	x	x			x	x	
Thyroid function [p]	x[a]				x	x	
HBV/HCV tests [q]	x	As clinically indicated					
Pulmonary function tests [r]	x						
Pharmacokinetics [s]		Predose: Day 1 of Cycles 1, 2, 5, 9, and 17 Postdose: Day 1 of Cycles 1 and 5				x	
Anti-drug antibodies [t]		Day 1 of Cycles 1, 2, 5, 9, and 17				x	
Blood biomarkers [u]		Predose: Day 1 of Cycle 1	Optional: At time of response and at time of confirmed PD				
Tumor assessment [v]	x	Every 6 weeks (± 7 days) from Cycle 1 Day 1, for the first 48 weeks, and every 12 weeks (± 7 days) thereafter					x
Archival tumor tissue or fresh tumor tissue [w]	x	At time of confirmed PD					
Tislelizumab administration [x]		x			x		
Ociperlimab administration [y]		x			x		
BAT-1706 administration [z]		x			x		
Survival status							x

Abbreviations: ADA, anti-drug antibodies; AE, adverse event; CK, creatine kinase; CK-MB, creatine kinase cardiac muscle isoenzyme; CT, computed tomography; EC, Ethics Committee; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EGD, esophagogastroduodenoscopy; EOT, end-of-treatment; FT3, free triiodothyronine; FT4, free thyroxine; HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HBsAb, hepatitis B surface antibody; imAE, immune-mediated adverse event; IRB, institutional review board; IRT, interactive response technology; MRI, magnetic resonance imaging; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PD, progressive disease; PET, positron emission tomography; PK, pharmacokinetic; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; TSH, thyroid stimulating hormone; v, version.

[a] Written informed consent is required before performing any study-specific tests or procedures. Results of standard-of-care tests or examinations performed before obtaining informed consent and within 28 days of randomization may be used for Screening assessments rather than repeating such tests.

[b] The EOT Visit is conducted when the investigator determines that one or more of the study drugs, ie, ociperlimab and tislelizumab in Arm A, tislelizumab in Arm B, or BAT1706 in both arms will no longer be used. Optical coherence tomography, visual acuity test, CK and CK-MB, and thyroid function assessments are not required at the EOT Visit for BAT1706. If routine laboratory tests (eg, hematology, serum chemistry) were completed within 7 days before the EOT Visit, the tests do not need to be repeated. Tumor assessment is required at the EOT Visit if the investigator determines that the study drug(s) must be discontinued. However, the tumor assessment may be omitted at the EOT visit provided that ≤ 6 weeks have passed since the last assessment. Patients who discontinue all study drugs prior to disease progression will need to undergo tumor assessment.

Patients who permanently discontinue tislelizumab and ociperlimab in Arm A, or tislelizumab in Arm B, will be asked to return to the clinic for the Safety Follow-up Visit, which is required to be conducted 30 (± 7) days after the last dose of the specific study drug(s), unless otherwise specified, or before the initiation of subsequent anticancer therapy, whichever occurs first.

If the decision to end treatment is taken ≥ 23 days after the last dose of ociperlimab/tislelizumab in Arm A, or tislelizumab in Arm B, the EOT and the Safety follow-up visits should be conducted concurrently within 7 days of the end of treatment decision.

Patients who discontinue ociperlimab/tislelizumab in Arm A or tislelizumab in Arm B will be asked to return to the clinic or will be contacted via telephone to assess imAEs and concomitant medications (if appropriate, ie, associated with an imAE) at 60 and 90 (± 14) days after the last dose of ociperlimab or tislelizumab, whichever is later, regardless of whether they started a subsequent anticancer therapy. If patients report a suspected imAE at a follow-up visit or a telephone contact, the investigator should arrange an unscheduled visit if further assessment is indicated.

[c] Survival follow-up information will be collected 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, loss to follow-up, withdrawal of consent, or study termination by the sponsor. All patients will be followed up for survival and subsequent anticancer therapy information unless a patient requests to be withdrawn from follow-up.

[d] Patients will be randomized into either the ociperlimab + tislelizumab + BAT1706 arm (Arm A) or tislelizumab + BAT1706 arms (Arm B) via IRT. All patients are required to receive the study drug(s) within 2 business days of randomization.

[e] Includes age or date of birth, gender, and self-reported race/ethnicity; history of treatment for the primary diagnosis, including prior medication, loco-regional treatment(s), and surgical treatment(s). Information on radiographic studies performed prior to study entry may be collected for review by the investigator. Pre-existing AEs at baseline should be recorded as medical history.

[f] Vital signs collected on study include temperature, pulse rate, respiratory rate and blood pressure (systolic and diastolic) while the patient is in a seated position after resting for 10 minutes. The patient's vital signs should be examined up to 60 minutes before all study drug infusions. For patients treated with BAT1706, vital signs will be measured at the end of BAT1706 infusion and 2 (± 1) hours after end of the infusion and during the study if clinically indicated.
The dose of BAT1706 will be based on the baseline weight, defined as the weight of the patient (in kilograms) measured ≤ 14 days before the initiation of study drug, and will remain the same throughout the study unless there is a weight change of > 10%. If re-assessment of baseline weight is needed the latest baseline weight should always be used to calculate percent change in weight for all subsequent doses.

[g] A complete physical examination is required at Screening while subsequent visits entail limited, symptom-directed physical examinations. Investigators should solicit patients regarding changes in vision, visual disturbance, or ocular inflammation at each scheduled study visit during tislelizumab treatment. For any change in vision, referral to an appropriate specialist will be made for further management guidance.

[h] All patients must undergo an EGD and all size of varices (small to large) must be assessed and treated per local standard of care prior to enrollment.

[i] The ECG recordings will be obtained during Screening, the EOT/Safety Follow-up visits, and as clinically indicated at other time points. Patients should be resting in a semi-recumbent supine position for ≥ 10 minutes prior to each ECG collection.

[j] Eye exam, including visual acuity test and optical coherence tomography (or equivalent diagnostic test), will be assessed by an appropriate specialist at the Screening Visit. Patients will undergo repeat assessments by an ophthalmologist approximately every 15 weeks (± 7 days) during study treatment and a final assessment during the EOT Visit for ociperlimab and/or tislelizumab.

[k] The AEs and laboratory abnormalities will be graded per NCI-CTCAE v5.0. All AEs will also be evaluated for seriousness. After the informed consent form has been signed, but prior to the first administration of study drug, only SAEs should be recorded. After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until either 30 days after last dose of study drug(s) or initiation of new anticancer therapy, whichever occurs first. The imAEs (serious or non-serious) should be reported until 90 days after the last dose of study drugs, regardless of whether 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 treatment.

[l] Review of AEs and concomitant medications may be conducted by telephone on Days 8 and 15.

[m] Local laboratory assessments on serum chemistry, hematology, coagulation, and urinalysis will be conducted, of which certain elements will be collected. If laboratory tests at Screening are not performed within 7 days of randomization, these tests should be repeated and reviewed before randomization. Hematology and serum chemistry (including liver function tests) will be performed weekly for the first 3 cycles and then at the

beginning of each subsequent cycle. After Cycle 1, the tests are to be performed and the results are to be reviewed within 48 hours before study drug administration. Proteinuria must be < 2+ within 7 days of randomization. Patients that have ≥ 2+ proteinuria on urinalysis at baseline should undergo a 24-hour urine collection and must demonstrate < 1 g of protein in 24 hours. Urinalysis is to be conducted for predose assessment at the beginning of each cycle.

[n] All patients will have CK and CK-MB testing at Screening, and repeated at all scheduled visits during the first 3 treatment cycles, all predose assessments from Cycle 4 onwards, and at the EOT and Safety Follow-up visits. If CK-MB fractionation is not available, troponin I and/or troponin T may be tested instead.

[o] Urine or serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented with a negative result within 7 days of randomization. Urine pregnancy tests will be performed at each visit prior to dosing, and at the EOT/Safety Follow-up visit. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.

[p] Analysis of FT3, FT4, and TSH will be performed by a central laboratory or the local study site laboratory. Thyroid function tests will be performed at Screening and every 3 cycles (ie, Day 1 of Cycles 4, 7, 10, et cetera), and at the EOT/Safety Follow-up Visit.

[q] Testing will be performed by a central laboratory and/or the local laboratory at Screening and will include HBV/HCV serology (HBsAg, HBsAb, HBcAb, and HCV antibody) and viral load assessment (HBV DNA and HCV RNA), which will be performed only when HBsAg or HCV antibody is positive, respectively. Patients who have detectable HBV DNA or HCV RNA at Screening will undergo the respective viral load test every 4 cycles (ie, Day 1 of Cycle 5, 9, 13, etc). Blood samples will be collected on Day 1 of Cycle 1 before dosing of study drug, and stored and may be analyzed if patients develop hepatic AEs.

[r] Patients who are suspected of having or known to have serious and/or severe respiratory conditions, exhibit significant respiratory symptoms unrelated to the underlying cancer, or have with a history of thoracic radiotherapy will undergo pulmonary function testing which may include, but is not limited to, spirometry and assessment of diffusion capacity done during the Screening period to assist the determination of suitability for the study.

[s] Procedures for collection of PK samples are described in the Laboratory Manual. Predose (within 60 minutes before starting infusion) samples are required to be collected on Day 1 of Cycles 1, 2, 5, 9 and 17. A postdose (within 30 minutes after completing infusion) sample is required to be collected on Day 1 of Cycles 1 and 5. For ociperlimab/tislelizumab, an additional PK sample is required to be collected at the Safety Follow-up Visit. For BAT1706, an additional PK sample is required to be collected at the EOT Visit. Should a patient present with any ≥ Grade 3 imAE, an additional blood PK sample may be taken to determine the serum concentration of tislelizumab/ociperlimab/BAT1706. These tests are required when allowed by local regulations/IRBs/ECs.

[t] Blood samples used to test for ADAs should be collected within 60 minutes before beginning the Day 1 infusion of Cycles 1, 2, 5, 9, and 17; ADAs for ociperlimab/tislelizumab are required to be tested at the Safety Follow-up Visit. For BAT1706, an additional ADA sample is required to be collected at the EOT Visit. All samples should be drawn at the same time as blood collection for predose PK analysis. These tests are required when allowed by local regulations/IRBs/ECs.

[u] Blood samples will be collected for all patients at baseline (predose on Cycle 1 Day 1, required), at the time of first tumor response (predose on Day 1 of the following cycle, optional), and at the time of PD (optional) [approximately 10 mL for each timepoint]. In addition, local laboratory assessment of alpha-fetoprotein is required at baseline (predose on Cycle 1 Day 1). Written patient consent is required for blood sample collections.

[v] Radiological images captured as standard-of-care before obtaining written informed consent and ≤ 28 days before randomization may be used rather than repeating tests. All measurable and evaluable lesions are required to be assessed and documented at the Screening Visit and reassessed at each subsequent tumor evaluation. The same radiographic procedure used to assess disease sites at Screening is required to be used throughout the study (eg, the same imaging protocol for CT or MRI). Bone scan or PET is required if clinically indicated. During the study, tumor imaging will be performed 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 assessments are required to be performed on schedule regardless of whether study drug(s) have been administered or held. That is, they should not be adjusted for possible delays in cycles. Tumor assessment should continue until study drug discontinuation. Patients who discontinue study drugs early for reasons other than disease progression (eg, toxicity) will continue to undergo tumor assessments following the original plan until the patient begins a subsequent anticancer treatment, experiences disease progression, withdraws consent, is lost to follow-up, or dies, or until the study terminates, whichever occurs first.

[w] Archival tumor tissues (if available) must be sent to the central laboratory for PD-L1 detection during the screening period and for retrospective analysis of exploratory biomarkers. If archival tumor tissues are not available during the screening period, a fresh tumor biopsy is mandatory. Optional fresh biopsies in patients who have confirmed PD will be collected during the study from accessible tumor sites. Written patient consent is required for fresh tumor biopsies.

For fresh biopsy, acceptable samples include core needle biopsies for nonsuperficial tumor tissue or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. Tumor tissue should be of good quality based on total and viable tumor content. Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable.

[x] Tislelizumab will be given intravenously on Day 1 of each 21-day cycle (once every 3 weeks). Note: Tislelizumab must not be concurrently infused with any other drug.

[y] For patients randomized to Arm A, ociperlimab will be given intravenously on Day 1 of each 21-day cycle (once every 3 weeks). Note: Ociperlimab must always be prepared and administered separately from any other systemic medication including tislelizumab and BAT1706. Ociperlimab infusion must always occur after infusion of tislelizumab has been completed.

[z] BAT1706 will be given intravenously on Day 1 of each 21-day cycle (once every 3 weeks).

APPENDIX 2. CLINICAL LABORATORY ASSESSMENTS

Clinical Chemistry	Hematology	Coagulation	Urinalysis
Alkaline phosphatase	Hematocrit	Prothrombin time	pH
ALT	Hemoglobin	Partial thromboplastin time or activated partial thromboplastin time	Specific gravity
AST	Platelet counts	International normalized ratio	Glucose
Albumin	White blood cell count		Protein
Total bilirubin	Neutrophil count		Ketones
Direct bilirubin	Lymphocyte count		Blood
Blood urea nitrogen or urea			24-hour protein[a]
Potassium			
Sodium			
Calcium			
Phosphorus			
Magnesium			
Chloride			
Creatinine			
Glucose			
Lactate dehydrogenase			
Total protein			
Creatine kinase/CK-MB [b]			

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK-MB, creatine kinase-muscle/brain.

[a] On routine urinalysis, if urine protein is ≥ 2+ then obtain a 24-hour urine sample for total protein or a random urine sample for total protein and creatinine to determine a protein-to-creatinine ratio.

[b] Cardiac enzyme testing has been added to monitor for potential event of immune-mediated myocarditis. If CK-MB fractionation is not available, assess troponin I and/or troponin T instead. Investigators should make every effort to perform either CK-MB, troponin I and/or troponin T consistently at screening and at follow-up visits.

APPENDIX 3. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

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

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

APPENDIX 4. CONTRACEPTION GUIDELINES AND DEFINITIONS OF "WOMEN OF CHILDBEARING POTENTIAL," "NO CHILDBEARING POTENTIAL"

Contraception Guidelines

The Clinical Trials Facilitation Group's recommendations related to contraception and pregnancy testing in clinical trials include the use of highly effective forms of birth control. These methods include the following:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with the inhibition of ovulation (oral, intravaginal, or transdermal).
- Progestogen-only hormonal contraception associated with the inhibition of ovulation:
  - oral
  - injectable
  - implantable
- Intrauterine device.
- Intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Vasectomized male partner, provided that the vasectomized partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of surgical success.
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of exposure associated with the study drug(s)).

  NOTE: Total sexual abstinence should only be used as a contraceptive method if it is in line with the patient's usual and preferred lifestyle.

  Periodic abstinence (eg, calendar, ovulation, symptothermal, or postovulation methods), declaration of abstinence for the duration of exposure to study drugs, and withdrawal are not acceptable methods of contraception.

Of note, barrier contraception (including male and female condoms with or without spermicide) is not considered a highly effective method of contraception and if used, this method must be combined with another acceptable method listed above.

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

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

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

- Surgically sterile (ie, through bilateral salpingectomy, bilateral oophorectomy, or hysterectomy)

- Postmenopausal, defined as:
  - ≥ 55 years of age with no spontaneous menses for ≥ 12 months OR
  - < 55 years of age with no spontaneous menses for ≥ 12 months AND with a postmenopausal follicle-stimulating hormone concentration > 30 IU/mL

Adapted from: Recommendations related to contraception and pregnancy testing in clinical trials

APPENDIX 5. NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

Class	Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Adapted from Dolgin et al 1994.
Original source: Criteria Committee, New York Heart Association, Inc. Diseases of the Heart and Blood Vessels. Nomenclature and Criteria for diagnosis, 6th edition Boston, Little, Brown and Co. 1964, p 114.

APPENDIX 6. IMMUNE-MEDIATED ADVERSE EVENT EVALUATION AND MANAGEMENT

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

Criteria used to diagnose imAEs include blood tests, diagnostic imaging, histopathology, and microbiology assessments to exclude alternative causes such as infection, PD, and adverse effects of concomitant drugs. In addition to the results of these tests, the following factors should be considered when making an imAE diagnosis:

- What was the temporal relationship between initiation of study drugs and the AE?
- How did the patient respond to withdrawal of study drugs?
- Did the event recur when study drugs was/were reintroduced?
- Was there a clinical response to corticosteroids?
- Is the event an autoimmune endocrinopathy?
- Is PD or an alternative diagnosis a more likely explanation?

When alternative explanations to autoimmune toxicity have been excluded, the imAE field associated with the AE in the electronic case report form should be checked.

Recommended Diagnostic Tests in the Management of Possible Immune-Mediated Adverse Events	
Immune-Mediated Toxicity	**Diagnostic Evaluation Guideline**
Thyroid disorders	Scheduled and repeat thyroid function tests (TSH and T4).
Hypophysitis	Check visual fields and consider pituitary endocrine axis blood profile. Perform pituitary and whole brain MRI in patients with headache, visual disturbance, unexplained fatigue, asthenia, weight loss, and unexplained constitutional symptoms. Consider consultation with an endocrinologist if an abnormality is detected.
Pneumonitis	All patients presenting with new or worsened pulmonary symptoms or signs, such as an upper respiratory infection, new cough, shortness of breath or hypoxia should be assessed by high-resolution CT. Consider pulmonary function test including *D*LCO. Radiographic appearance is often nonspecific. Depending on the location of the abnormality, bronchoscopy and bronchoalveolar lavage or lung biopsy may be considered. Consult with a respiratory medicine physician for cases of uncertain cause.
Neurological toxicity	Perform a comprehensive neurological examination and brain MRI for all CNS symptoms; review alcohol history and other medications. Conduct a diabetic screen, and assess blood B12/folate, HIV status, TFTs, and consider autoimmune serology. Consider the need for brain/spine MRI/MRA and nerve conduction study for peripheral neuropathy. Consult with a neurologist if there are abnormal findings.

Recommended Diagnostic Tests in the Management of Possible Immune-Mediated Adverse Events	
Immune-Mediated Toxicity	**Diagnostic Evaluation Guideline**
Colitis	Review dietary intake and exclude steatorrhea. Consider comprehensive testing, including the following: FBC, UEC, LFTs, CRP, TFTs, stool microscopy and culture, viral PCR, *Clostridium difficile* toxin, and cryptosporidia (drug-resistant organism). In case of abdominal discomfort, consider imaging, eg, X-ray, CT scan. If a patient experiences bleeding, pain or distension, consider colonoscopy with biopsy and surgical intervention, as appropriate.
Eye disorders	If a patient experiences acute, new onset, or worsening of eye inflammation, blurred vision, or other visual disturbances, refer the patient urgently to an ophthalmologist for evaluation and management.
Hepatitis	Check ALT/AST/total bilirubin, INR/albumin; the frequency will depend on severity of the AE (eg, daily if ≥ 3-4; every 2-3 days if Grade 2, until recovering). Review medications (eg, statins, antibiotics) and alcohol history. Perform liver screen including hepatitis A/B/C serology, hepatitis E PCR and assess anti-ANA/SMA/LKM/SLA/LP/LCI, iron studies. Consider imaging (eg, ultrasound scan for metastases or thromboembolism). Consult with a hepatologist and consider liver biopsy.
Renal toxicity	Review hydration status and medication history. Test and culture urine. Consider renal ultrasound scan, protein assessment (dipstick/24-hour urine collection), or phase-contrast microscopy. Refer to nephrology for further management assistance.
Dermatology	Consider other causes by conducting a physical examination; consider dermatology referral for skin biopsy.
Joint or muscle inflammation	Conduct musculoskeletal history and perform complete musculoskeletal examination. Consider joint X-ray and other imaging as required to exclude metastatic disease. Perform autoimmune serology and refer to rheumatology for further management assistance. For suspected myositis/rhabdomyolysis/myasthenia include: CK, ESR, CRP, troponin I and consider a muscle biopsy.
Myocarditis	Perform ECG, echocardiogram, troponin I, and refer to a cardiologist.

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

Treatment of Immune-mediated Adverse Events

- Immune-mediated AEs can escalate quickly; study drug(s) interruption, close monitoring, timely diagnostic work-up, and treatment intervention, as appropriate, with patients is required

- Immune-mediated AEs should improve promptly after introduction of immunosuppressive therapy. If this does not occur, review the diagnosis, seek further specialist advice, and contact the medical monitor
- For some Grade 3 toxicities that resolve quickly, rechallenge with study drugs may be considered if there is evidence of a clinical response to study drug(s) after consultation with the medical monitor
- Steroid dosages in the table below are for oral or intravenous (methyl)prednisolone. Equivalent dosages of other corticosteroids can be substituted. For steroid-refractory imAEs, consider use of steroid-sparing agents (eg, mycophenolate mofetil [MMF])
- Consider prophylactic antibiotics for opportunistic infections if the patient is receiving long-term immunosuppressive therapy

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Thyroid disorders	**1-2** Asymptomatic TFT abnormality or mild symptoms	Replace thyroxine if hypothyroid, until TSH/T4 levels return to normal range. Thyrotoxic patients should be referred to an endocrinologist. In cases with systemic symptoms: withhold study treatment, treat with a beta blocker and consider oral prednisolone 0.5 mg/kg/day for thyroid pain. Taper corticosteroids over 2-4 weeks. Monitor thyroid function regarding the need for hormone replacement.	Continue study treatment or withhold treatment in cases with systemic symptoms.
	3-4 Severe symptoms, hospitalization required	Refer patient to an endocrinologist. If hypothyroid, replace with thyroxine 0.5-1.6 µg/kg/day (for the elderly or those with co-morbidities, the suggested starting dose is 0.5 µg/kg/day). Add oral prednisolone 0.5 mg/kg/day for thyroid pain. Thyrotoxic patients require treatment with a beta blocker and may require carbimazole until thyroiditis resolves.	Hold study treatment; resume when resolved/improved to Grade 0-1.
Hypophysitis	**1-2** Mild symptoms	Refer patient to an endocrinologist for hormone replacement. Add oral prednisolone 0.5-1 mg/kg/day for patients with pituitary inflammation. Taper corticosteroids over at least 1 month. If there is no improvement in 48 hours, treat as Grade 3-4. Taper corticosteroids over at least 1 month.	Continue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3-4 Moderate-severe symptoms	Refer patient to an endocrinologist for assessment and treatment. Initiate pulse IV methylprednisolone 1 mg/kg for patients with headache/visual disturbance due to pituitary inflammation. Convert to oral prednisolone and taper over at least 1 month. Maintain hormone replacement according to endocrinology advice. Maintain hormone replacement according to endocrinology advice.	Hold study treatment for patients with headache/visual disturbance due to pituitary inflammation until resolved/improved to Grade 2 or less. Discontinuation is usually not necessary.
Pneumonitis	**1** Radiographic changes only	Monitor symptoms every 2-3 days. If appearance worsens, treat as Grade 2.	Consider holding study treatment until appearance improves and cause is determined.
	2 Symptomatic: exertional breathlessness	Commence antibiotics if infection suspected. Add oral prednisolone 1 mg/kg/day if symptoms/appearance persist for 48 hours or worsen. Consider *Pneumocystis* infection prophylaxis. Taper corticosteroids over ≥ 6 weeks. Consider prophylaxis for adverse steroid effects: eg, blood glucose monitoring, vitamin D/calcium supplement.	Hold study treatment. Retreatment is acceptable if symptoms resolve completely or are controlled on prednisolone ≤ 10 mg/day. Discontinue study treatment if symptoms persist with corticosteroid treatment.
	3-4 Severe or life-threatening symptoms Breathless at rest	Admit to a hospital and initiate treatment with IV methylprednisolone 2-4 mg/kg/day. If there is no improvement, or worsening after 48 hours, add infliximab 5 mg/kg (if no hepatic involvement). Convert to oral prednisolone and taper over at least 2 months. Cover with empiric antibiotics and consider prophylaxis for *Pneumocystis* infection and other adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement.	Discontinue study treatment.
Neurological toxicity	**1** Mild symptoms	–	Continue study treatment.
	2 Moderate symptoms	Treat with oral prednisolone 0.5-1 mg/kg/day. Taper over at least 4 weeks. Obtain neurology consultation.	Hold study treatment; resume when resolved/improved to Grade 0-1.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3-4 Severe/life-threatening	Initiate treatment with oral prednisolone or IV methylprednisolone 1-2 mg/kg/day, depending on symptoms. Taper corticosteroids over at least 4 weeks. Consider azathioprine, MMF, cyclosporine if no response within 72-96 hours.	Discontinue study treatment.
Colitis/diarrhea	**1** Mild symptoms: < 3 liquid stools per day over baseline and feeling well	Symptomatic management: fluids, loperamide, avoid high fiber/lactose diet. If Grade 1 persists for > 14 days manage as a Grade 2 event.	Continue study treatment.
	2 Moderate symptoms: 4-6 liquid stools per day over baseline, or abdominal pain, or blood in stool, or nausea, or nocturnal episodes	Oral prednisolone 0.5 mg/kg/day (non-enteric coated). Do not wait for any diagnostic tests to start treatment. Taper steroids over 2-4 weeks, consider endoscopy if symptoms are recurring.	Hold study treatment; resume when resolved/improved to baseline grade.
	3 Severe symptoms: > 6 liquid stools per day over baseline, or if episodic within 1 hour of eating	Initiate IV methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Consider prophylaxis for adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement. If no improvement in 72 hours or symptoms worsen, consider infliximab 5 mg/kg; if no perforation, sepsis, TB, hepatitis, NYHA Grade III/IV CHF or other immunosuppressive treatment: MMF or tacrolimus. Consult gastroenterologist to conduct colonoscopy/sigmoidoscopy.	Hold study treatment; retreatment may be considered when resolved/improved to baseline grade and after discussion with the study medical monitor.
	4 Life-threatening symptoms		Discontinue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Skin reactions	**1** Skin rash, with or without symptoms, < 10% BSA	Avoid skin irritants and sun exposure; topical emollients recommended.	Continue study treatment.
	2 Rash covers 10%-30% of BSA	Avoid skin irritants and sun exposure; topical emollients recommended. Topical steroids (moderate strength cream once a day or potent cream twice a day) ± oral or topical antihistamines for itch. Consider a short course of oral steroids.	Continue study treatment.
	3 Rash covers > 30% BSA or Grade 2 with substantial symptoms	Avoid skin irritants and sun exposure; topical emollients recommended. Initiate steroids as follows based on clinical judgement: For moderate symptoms: oral prednisolone 0.5-1 mg/kg/day for 3 days then taper over 2-4 weeks. For severe symptoms: IV methylprednisolone 0.5-1 mg/kg/day; convert to oral prednisolone and taper over at least 4 weeks.	Hold study treatment. Re-treat when AE is resolved or improved to mild rash (Grade 1-2) after discussion with the study medical monitor.
	4 Skin sloughing > 30% BSA with associated symptoms (eg, erythema, purpura, epidermal detachment)	Initiate IV methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Admit to a hospital and seek urgent dermatology consultation.	Discontinue study treatment.
Hepatitis	**1** ALT or AST > ULN to 3X ULN	Check LFTs within 1 week and before the next dose check LFTs to verify that there has been no worsening. If LFTs are worsening, recheck every 48-72 hours until improvement is seen.	Continue study treatment if LFTs are unchanged or improving. Hold study treatment if LFTs are worsening until improvement is seen.
	2 ALT or AST 3-5X ULN	Recheck LFTs every 48-72 hours: For persistent ALT/AST elevation: consider oral prednisolone 0.5-1 mg/kg/day for 3 days then taper over 2-4 weeks. For rising ALT/AST: start oral prednisolone 1 mg/kg/day and taper over 2-4 weeks; re-escalate dose if LFTs worsen, depending on clinical judgement.	Hold study treatment; treatment may be resumed when resolved/improved to baseline grade and prednisolone tapered to ≤ 10 mg.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3 ALT or AST 5-20X ULN	ALT/AST < 400 IU/L and normal bilirubin/INR/albumin: Initiate oral prednisolone 1 mg/kg and taper over at least 4 weeks. ALT/AST > 400 IU/L or raised bilirubin/INR/low albumin: Initiate IV (methyl)prednisolone 2 mg/kg/day. When LFTs improve to Grade 2 or lower, convert to oral prednisolone and taper over at least 4 weeks.	Hold study treatment until improved to baseline grade; reintroduce only after discussion with the study medical monitor.
	4 ALT or AST > 20X ULN	Initiate IV methylprednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over ≥ 6 weeks.	Discontinue study treatment.
	Worsening LFTs despite steroids: If on oral prednisolone, change to pulsed IV methylprednisolone If on IV, add MMF 500-1000 mg twice a day If worsens on MMF, consider addition of tacrolimus Duration and dose of steroid required will depend on severity of event		
Nephritis	**1** Creatinine 1.5X baseline or > ULN to 1.5X ULN	Repeat creatinine weekly. If symptoms worsen, manage as per criteria below.	Continue study treatment.
	2 Creatinine > 1.5X-3X baseline or > 1.5X-3X ULN	Ensure hydration and review creatinine in 48-72 hours; if not improving, consider creatinine clearance measurement by 24-hour urine collection. Discuss with nephrologist the need for kidney biopsy. If attributed to study drug, initiate oral prednisolone 0.5-1 mg/kg and taper over at least 2 weeks. Repeat creatinine/U&E every 48-72 hours.	Hold study treatment. If not attributed to drug toxicity, restart treatment. If attributed to study drug and resolved/improved to baseline grade: Restart study drug if tapered to < 10 mg prednisolone.
	3 Creatinine > 3X baseline or > 3X-6X ULN	Hospitalize patient for monitoring and fluid balance; repeat creatinine every 24 hours; refer to a nephrologist and discuss need for biopsy. If worsening, initiate IV (methyl)prednisolone 1-2 mg/kg. Taper corticosteroids over at least 4 weeks.	Hold study treatment until the cause is investigated. If study drug suspected: Discontinue study treatment.
	4 Creatinine > 6X ULN	As per Grade 3, patient should be managed in a hospital where renal replacement therapy is available.	Discontinue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Diabetes/ hyperglycemia	**1** Fasting glucose value ULN to 160 mg/dL; ULN to 8.9 mmol/L	Monitor closely and treat according to local guideline. Check for C-peptide and antibodies against glutamic acid decarboxylase and islet cells are recommended.	Continue study treatment.
	2 Fasting glucose value 160-250 mg/dL; 8.9-13.9 mmol/L	Obtain a repeat blood glucose level at least every week. Manage according to local guideline.	Continue study treatment or hold treatment if hyperglycemia is worsening. Resume treatment when blood glucose is stabilized at baseline or Grade 0-1.
	3 Fasting glucose value 250-500 mg/dL; 13.9-27.8 mmol/L	Admit patient to hospital and refer to a diabetologist for hyperglycemia management. Corticosteroids may exacerbate hyperglycemia and should be avoided.	Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1.
	4 Fasting glucose value > 500 mg/dL; > 27.8 mmol/L	Admit patient to hospital and institute local emergency diabetes management. Refer the patient to a diabetologist for insulin maintenance and monitoring.	
Ocular toxicity	**1** Asymptomatic eye exam/test abnormality	Consider alternative causes and prescribe topical treatment as required.	Continue study treatment.
	2 Anterior uveitis or mild symptoms	Refer patient to an ophthalmologist for assessment and topical corticosteroid treatment. Consider a course of oral steroids.	Continue study treatment or hold treatment if symptoms worsen or if there are symptoms of visual disturbance.
	3 Posterior uveitis/panuveitis or significant symptoms	Refer patient urgently to an ophthalmologist. Initiate oral prednisolone 1-2 mg/kg and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1; reintroduce only after discussion with the study medical monitor.
	4 Blindness (at least 20/200) in the affected eyes	Initiate IV (methyl)prednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks.	Discontinue study treatment.
Pancreatitis	**2** Asymptomatic, blood test abnormalities	Monitor pancreatic enzymes.	Continue study treatment.
	3 Abdominal pain, nausea and vomiting	Admit to hospital for urgent management. Initiate IV (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when amylase/lipase improved to Grade 2, and taper over at least 4 weeks.	Hold study treatment; reintroduce only after discussion with the study medical monitor.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	4 Acute abdominal pain, surgical emergency	Admit to hospital for emergency management and appropriate referral.	Discontinue study treatment.
Arthritis	**1** Mild pain with inflammation, swelling	Management per local guideline.	Continue study treatment.
	2 Moderate pain with inflammation, swelling, limited instrumental (fine motor) activities	Management as per local guideline. Consider referring patient to a rheumatologist. If symptoms worsen on treatment manage as a Grade 3 event.	Continue treatment or, if symptoms continue worsens, hold study treatment until symptoms improve to baseline or Grade 0-1.
	3 Severe pain with inflammation or permanent joint damage, daily living activity limited	Refer patient urgently to a rheumatologist for assessment and management. Initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks.	Hold study treatment unless improved to Grade 0-1; reintroduce only after discussion with the study medical monitor.
Mucositis/ stomatitis	**1** Test findings only or minimal symptoms	Consider topical treatment or analgesia as per local guideline.	Continue study treatment.
	2 Moderate pain, reduced oral intake, limited instrumental activities	As per local guidelines, treat with analgesics, topical treatments, and oral hygiene care. Ensure adequate hydration. If symptoms worsen or there is sepsis or bleeding, manage as a Grade 3 event.	Continue study treatment.
	3 Severe pain, limited food and fluid intake, daily living activity limited	Admit to hospital for appropriate management. Initiate IV (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when symptoms improved to Grade 2 and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1.
	4 Life-threatening complications or dehydration	Admit to hospital for emergency care. Consider IV corticosteroids if not contraindicated by infection.	Discontinue study treatment.
Myositis/ rhabdomyolysis	**1** Mild weakness with/without pain	Prescribe analgesics. If CK is significantly elevated and patient has symptoms, consider oral steroids and treat as Grade 2.	Continue study treatment.
	2 Moderate weakness with/without pain	If CK is 3 X ULN or worse initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1.
	3-4 Severe weakness, limiting self-care	Admit to hospital and initiate oral prednisolone 1 mg/kg. Consider bolus IV (methyl)prednisolone and 1-2 mg/kg/day maintenance for severe activity restriction or dysphagia. If symptoms do not improve add immunosuppressant therapy. Taper oral steroids over at least 4 weeks.	Hold study treatment until improved to Grade 0-1. Discontinue if any evidence of myocardial involvement.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Myocarditis	**< 2** Asymptomatic but significantly increased CK-MB or increased troponin OR clinically significant intraventricular conduction delay	Admit to hospital and refer to a cardiologist. Transfer all patients with moderate/severe cardiac symptoms or any increase in cardiac serum markers to the coronary care unit. Initiate oral prednisolone or IV (methyl)prednisolone at 1-2 mg/kg/day. Manage symptoms of cardiac failure according to local guidelines. If no immediate response change to pulsed doses of (methyl)prednisolone 1 g/day and add MMF, infliximab or anti-thymocyte globulin.	Hold study treatment until completely resolved or myocarditis has been ruled out.
	2 Symptoms on mild-moderate exertion		Discontinue study treatment unless cardiac involvement has been excluded and symptoms have completely resolved.
	3 Severe symptoms with mild exertion		
	4 Life-threatening		

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; CK, creatine kinase; CK-MB, creatine kinase-muscle-brain; CHF, congestive heart failure; INR, international normalized ratio; IV, intravenous; LFT, liver function test; MMF, mycophenolate mofetil; NYHA, New York Heart Association; T4, thyroxine; TB, tuberculosis; TFT, thyroid function test; TSH, thyroid-stimulating hormone; U&E, urea and electrolytes; ULN, upper limit of normal.

APPENDIX 7. MANAGEMENT GUIDELINES FOR ADVERSE EVENTS RELATED TO BAT1706

The management guidelines for adverse events related to BAT1706 are listed in the table below. For cases which is not covered in the management guideline below or in BAT1706 Investigator's Brochures, patients should be managed as deemed appropriate by the investigator according to investigators' best medical judgment.

If corticosteroids are used for treating adverse events related to BAT1706, they must be tapered to ≤ 10 mg/day oral prednisone or equivalent per institutional guidelines before tislelizumab or tislelizumab plus ociperlimab can be resumed.

Tislelizumab or tislelizumab plus ociperlimab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the sponsor medical monitor.

Management Guidelines for Adverse Events Related to BAT1706

Events	Grade	Action to Be taken
Gastrointestinal events		
Gastrointestinal perforation	Any grade	• Discontinue BAT1706. • Initiate treatment per institutional guidelines.
Bowel obstruction	Grade 2	• Hold BAT1706 for partial obstruction requiring medical intervention. • BAT1706 may be restarted upon complete resolution of event.
	Grade 3 - 4	• Hold BAT1706 for complete obstruction. • If surgery is necessary, patient may restart BAT1706 after full recovery from surgery and at investigator's discretion.
Hypertension		
Hypertension	General	• Grade 2 or above, start antihypertensive therapy.
	Grade 2	• Hold BAT1706. • Once blood pressure < 150/100 mmHg, patient may continue BAT1706 therapy.

Events	Grade	Action to Be taken
	Grade 3	• If blood pressure is not controlled to 150/100 mmHg with medication, discontinue BAT1706.
	Grade 4 (includes hypertensive encephalopathy)	• Discontinue BAT1706.
Congestive heart failure		
Congestive heart failure	Grade 3- 4	• Discontinue BAT1706.
Hemorrhage		
Hemorrhage	Grade 1-2	• Patients who are also receiving full-dose anticoagulation will be discontinued from receiving BAT1706. • Hold BAT1706 for the other patients until the following criteria are met: the bleeding has resolved and hemoglobin is stable; no bleeding diathesis would increase the risk of therapy; and no anatomic or pathologic condition significantly increases the risk of hemorrhage recurrence. • After resumption of BAT1706, if the patient experiences another Grade 1 pulmonary or intracranial hemorrhagic event, BAT 1706 should be discontinued.
	Grade 3-4	• Discontinue BAT1706.
	Any grade cerebral hemorrhage	• Discontinue BAT1706.
Venous Thromboembolic Events		
Venous thromboembolic event	Grade ≥ 3	• For Grade 3 thromboembolic events, hold BAT1706 for > 3 weeks. BAT1706 treatment may be resumed during the period of therapeutic-dose anticoagulant therapy

Events	Grade	Action to Be taken
		once the level of anticoagulation therapy is stabilized. • Anticoagulant treatment should be administered per institutional guidelines. • After administration of BAT1706 is restarted, if the patient experiences another Grade ≥ 3 venous thromboembolic event, BAT1706 should be discontinued. • For Grade 4 thromboembolic events, discontinue BAT1706.
Arterial Thromboembolic Events		
Arterial thromboembolic event	Any grade	• Discontinue BAT1706.
Proteinuria		
Proteinuria first occurrence, no diagnosis of nephrosis	proteinuria < 2+	• No BAT1706 dose interruptions.
	Proteinuria ≥ 2+	• Administer BAT1706 as planned and collect 24-hour urine for determination of total protein within 3 days before next scheduled BAT1706 administration. • If 24-hour proteinuria ≤ 2 g, the next BAT1706 dose can be administered as scheduled. • If 24-hour proteinuria > 2 g, hold BAT1706 treatment. Continue to do 24-hour urine collections for determination of total protein within 3 days of each scheduled BAT1706 dose and continue to hold scheduled BAT1706 until proteinuria has decreased to ≤ 2 g/24 hours. • When proteinuria has decreased to ≤ 2 g/24 hours, scheduled BAT1706 may be administered as planned. However, continue to do 24-hour urine collections for determination of total protein within 3 days of each scheduled BAT1706 dose until proteinuria has improved to ≤ 1 g/24 hours.

Events	Grade	Action to Be taken
Proteinuria second and subsequent occurrences, no diagnosis of nephrosis	proteinuria < 3+	• No BAT1706 dose interruptions.
	Proteinuria ≥ 3+	• Administer BAT1706 as planned and collect 24-hour urine for determination of total protein within 3 days before next scheduled BAT1706 administration. • If 24-hour proteinuria ≤ 2 g, the next BAT1706 dose can be administered as scheduled. • If 24-hour proteinuria > 2 g, hold BAT1706 treatment. Continue to do 24-hour urine collections for determination of total protein within 3 days of each scheduled BAT1706 dose and continue to hold scheduled BAT1706 until proteinuria has decreased to ≤ 2 g/24 hours. • When proteinuria has decreased to ≤ 2 g/24 hours, scheduled BAT1706 may be administered as planned. However, continue to do 24-hour urine collections for determination of total protein within 3 days of each scheduled BAT1706 dose until proteinuria has improved to ≤ 1 g/24 hours.
Proteinuria with diagnosis of nephrosis	Any grade	• Discontinue BAT1706.
Fistula		
Tracheoesophageal fistula	Any grade	• Discontinue BAT1706.
Fistula (non-tracheoesophageal)	Grade 4	• Discontinue BAT1706.
Wound healing complications		
Wound dehiscence	Any grade requiring medical or surgical therapy	• Discontinue BAT1706.

Events	Grade	Action to Be taken
Posterior Reversible Encephalopathy Syndrome (PRES)/Reversible Posterior Leukoencephalopathy Syndrome (RPLS)		
PRES/RPLS	Any grade confirmed by MRI	• Discontinue BAT1706.

Abbreviations: MRI, magnetic resonance imaging; PRES, Posterior Reversible Encephalopathy Syndrome; RPLS, Reversible Posterior Leukoencephalopathy Syndrome.

APPENDIX 8. THE RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) GUIDELINES, VERSION 1.1

The text below was obtained from the following reference: Eisenhauer et al 2009.

DEFINITIONS

Response and progression will be evaluated in this trial using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (version 1.1). Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

Measurable Disease

Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm).
- 10 mm caliper measurement by clinical examination (when superficial).
- 20 mm by chest x-ray (if clearly defined and surrounded by aerated lung).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT or MRI scan (CT/MRI scan slice thickness recommended to be ≥ 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter ≥ 10 to < 15 mm with conventional techniques or < 10 mm using spiral CT scan), are considered non-measurable disease. Leptomeningeal disease, ascites, pleural, or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques are all non-measurable.

Bone lesions:

- Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Trial protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organ, but in addition should be those that lend themselves to reproducible repeated measurements.

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

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

Non-target Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression" (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, "multiple enlarged pelvic lymph node" or "multiple liver metastases").

GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are accessible by clinical examination.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and P10 mm diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the trial.

- Chest x-ray: Chest CT is preferred over chest x-ray, particularly when progression is an important endpoint, because CT is more sensitive than x-ray, particularly in identifying new lesions. However, lesions on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scans).
- Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

- Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following CR or surgical resection is an endpoint.
- Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in CR. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and prostate-specific antigen response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.
- Cytology, histology: These techniques can be used to differentiate between partial response (PR) and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease to differentiate between response (or stable disease) and PD.

RESPONSE CRITERIA

Evaluation of Target Lesions

- CR: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- PD: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of 1 or more new lesions is also considered progression).
- Stable disease: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
- Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report recorded in a separate section where, to qualify for CR, each node must achieve a short axis < 10 mm. For PR, stable disease,

and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

- Target lesions that become "too small to measure." While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure."
- When this occurs, it is important that a value be recorded on the electronic case report form (eCRF). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.
- Lesions that split or coalesce on treatment: When non-nodal lesions "fragment," the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion."

Evaluation of Non-target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the protocol.

- CR: Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
- PD: Unequivocal progression (as detailed below) of existing non-target lesions. (Note: the appearance of 1 or more new lesions is also considered progression.)
- Non-CR/Non-PD: Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- When the patient also has measurable disease: In this setting, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of stable

disease or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of 1 or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of stable disease or PR of target disease will therefore be extremely rare.

- When the patient has only non-measurable disease: This circumstance arises in some Phase 3 trials when it is not a criterion of trial entry to have measurable disease. The same general concept applies here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase diameter in a measurable lesion).
- Examples include an increase in a pleural effusion from "trace" to "large," an increase in lymphangitic disease from localized to widespread, or may be described in protocols as "sufficient to require a change in therapy." If "unequivocal progression" is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

New Lesions

The appearance of new malignant lesions denotes PD; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified on a follow-up trial in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate PD. An example of this is the patient who has visceral disease at baseline and while on trial has a CT or MRI brain scan ordered that reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While fluorine-18 [F-18] fluorodeoxyglucose (FDG)-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible "new" disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up, is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Evaluation of Best Overall Response

The BOR is the best response recorded from the start of the study drug treatment until the end of treatment considering any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of BOR. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's BOR assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the trial and the protocol requirements, it may also require confirmatory measurement. Specifically, in nonrandomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "BOR."

The BOR is determined once all the data for the patient is known. Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all timepoints (for example, a patient who has stable disease at first assessment, PR at second assessment, and PD on last assessment has a BOR of PR). When stable disease is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when stable disease is otherwise the best timepoint response, the patient's best response depends on the subsequent assessments. For example, a patient who has stable disease at first assessment, PD at second and does not meet minimum duration for stable disease, will have a best response of PD. The same patient lost to follow-up after the first stable disease assessment would be considered inevaluable.

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
Stable disease	Non-PD or not all evaluated	No	Stable disease
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response.

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the eCRF.

In trials where confirmation of response is required, repeated 'NE' timepoint assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with timepoint responses of PR-not evaluable-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of PD at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping trial therapy.

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

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of CR. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes, or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

Confirmation

In nonrandomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, ie, in randomized trials (Phase 2 or 3) or trials where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in trials which are not blinded.

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

Duration of Overall Response

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

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

Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between 2 measurements for determination of stable disease.

Note: The DOR and stable disease as well as the PFS are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should consider many parameters including disease types and stages, treatment periodicity, and standard practice. However, these limitations of the precision of the measured endpoint should be considered if comparisons between trials are to be made.

APPENDIX 9. CHILD-PUGH CLASSIFICATION SCORING SYSTEM

The information presented here has been obtained from the Washington University Medical Center, with sources as follows:

- Lucey MR, Brown KA, Everson GT, et al. Minimal criteria for placement of adults on the liver transplant waiting list: a report of a national conference organized by the American Society of Transplant Physicians and the American Association for the Study of Liver Diseases. Liver Transpl Surg. 1997;3(6):628-37.
- Pugh RN, Murray-Lyon IN, Dawson DL, et al. Transection of the oesophagus for bleeding oesophageal varices. Br J Surgery. 1973;60:646-9.
- Trey C, Burns DG, Saunders SJ. Treatment of hepatic coma by exchange blood transfusion. N Engl J Med. 1966;274(9):473-81.

Child-Pugh classification is either Grade A (mild: score 5 to 6 points), B (moderate: from 7 to 9 points), or C (severe: from 10 to 15 points) and is determined by both clinical and biochemical parameters (as shown below).

Clinical/Biochemical Parameter	**Score (Anomaly Severity)**		
	1	**2**	**3**
Hepatic encephalopathy (NCI-CTCAE Grade)[a]	0[b]	1[c] or 2[d]	3[e] or 4[f]
Ascites (presence and severity)	None	Mild	Moderate
Total bilirubin (mg/dL)	< 2.0	2.0 to 3.0	> 3.0
Serum albumin (g/dL)	> 3.5	2.8 to 3.5	< 2.8
Prothrombin time (seconds prolonged) or (INR[g])	< 4 or < 1.7	4 to 6 or 1.7 to 2.3	> 6 or > 2.3

Abbreviations: INR, international normalized ratio; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

a. Trey C, Burns DG, Saunders SJ. Treatment of hepatic coma by exchange blood transfusion. N Engl J Med. 1966;274(9):473-81.
b. Grade 0: Consciousness, personality, neurological examination, and electrocardiogram are all normal.
c. Grade 1: Restlessness, sleep disorders, irritability/anxiety, hand tremor, writing disorders, 5CPS waves.
d. Grade 2: Lethargy, time barrier, discomfort, asterixis, ataxia, three-phase slow wave.
e. Grade 3: Drowsiness, coma, orientation disorder, over-reflection, stiff/slow wave.
f. Grade 4: Cannot wake up from coma, no independent personality/behavior, irrational, slow 2-3CPS Delta activity.
g. Lucey MR, Brown KA, Everson GT, et al. Minimal criteria for placement of adults on the liver transplant waiting list: a report of a national conference organized by the American Society of Transplant Physicians and the American Association for the Study of Liver Diseases. Liver Transpl Surg. 1997;3(6):628-37.

APPENDIX 10. BARCELONA CLINIC LIVER CANCER (BCLC) STAGING CLASSIFICATION

The Barcelona Clinic Liver Cancer (BCLC) system has been widely validated and is the most commonly used staging system for HCC. It determines cancer stage and patient prognosis based on tumor burden, severity of liver disease, and the patient's ECOG Performance Status.

The staging according to the BCLC classification assigns prognoses based on clinical and tumor parameters and is summarized as follows:

BCLC Stage[a, b]				
Very early stage (0)	Early stage (A)	Intermediate stage (B)	Advanced stage (C)	Terminal stage (D)
Single nodule < 2 cm Carcinoma in situ Child–Pugh A, ECOG PS 0	Single or 3 nodules < 3 cm Child–Pugh A-B, ECOG PS 0	Multinodular, Child–Pugh A-B, ECOG PS 0	Portal invasion, Extrahepatic spread, Child–Pugh A-B, ECOG PS 1-2	Child–Pugh C ECOG PS 3-4

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

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APPENDIX 11. CHRONIC KIDNEY DISEASE EPIDEMIOLOGY COLLABORATION (CKD-EPI) EQUATION

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

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

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

where:

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

κ is 0.7 for women and 0.9 for men,

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

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

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

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

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

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