CLINICAL STUDY PROTOCOL

TITLE PAGE

Protocol Title:	A Phase 1b/2 Study Investigating the Safety, Tolerability, Pharmacokinetics, and Preliminary Antitumor Activity of Ociperlimab (BGB-A1217) in Combination With Tislelizumab (BGB-A317) or Rituximab in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma
Protocol Number:	AdvanTIG-101
Phase:	1b/2
Investigational Product(s):	Ociperlimab (BGB-A1217), Tislelizumab (BGB-A317), and Rituximab
Proposed Indication(s):	Diffuse Large B-Cell Lymphoma
Sponsor:	BeiGene, Ltd. c/o BeiGene USA, Inc. 1840 Gateway Drive 3rd Floor San Mateo, CA 94404 USA BeiGene (Guangzhou) Biologics Manufacturing Co., Ltd. No. 83 South Kangyao Road Huangpu District Guangzhou, P.R. China
Sponsor Medical Monitor:	[redacted] Telephone: [redacted] Email: [redacted]
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Confidentiality Statement

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FINAL PROTOCOL APPROVAL SHEET

A Phase 1b/2 Study Investigating the Safety, Tolerability, Pharmacokinetics, and Preliminary Antitumor Activity of Ociperlimab (BGB-A1217) in Combination With Tislelizumab (BGB-A317) or Rituximab in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma

BeiGene (Guangzhou) Biologics Manufacturing Co., Ltd., Approval:

See electronic signature	*See electronic signature*
Development Core Team Lead	Date

INVESTIGATOR SIGNATURE PAGE

Protocol Title: A Phase 1b/2 Study Investigating the Safety, Tolerability, Pharmacokinetics, and Preliminary Antitumor Activity of Ociperlimab (BGB-A1217) in Combination With Tislelizumab (BGB-A317) or Rituximab in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Protocol Identifier: AdvanTIG-101

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 Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd., or one of its subsidiaries.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 prior to implementation of this sponsor-approved protocol. 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. BeiGene (Guangzhou) Biologics Manufacturing Co., Ltd.
Investigational Product(s): Ociperlimab (also known as BGB-A1217), Tislelizumab (also known as BGB-A317), and Rituximab
Title of Study: A Phase 1b/2 Study Investigating the Safety, Tolerability, Pharmacokinetics, and Preliminary Antitumor Activity of Ociperlimab (BGB-A1217) in Combination With Tislelizumab (BGB-A317) or Rituximab in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma
Protocol Identifier: AdvanTIG-101
Phase of Development: 1b/2
Number of Patients: Approximately 66 to 80 patients in total Cohort 1 (patients with programmed cell death ligand-1 [PD-L1] positive on the surface of tumor cells for both Dose Confirmation and Dose Expansion Stages): Approximately 43 to 50 patients Cohort 2 (patients with PD-L1 negative on the surface of tumor cells for Dose Confirmation Stage and relapsed or refractory (R/R) diffuse large B cell lymphoma (DLBCL) patients regardless of PD-L1 expression for Dose Expansion Stage): Approximately 23 to 30 patients
Study Centers: Approximately 15 centers in China
Study Objectives **Primary:** • To assess the safety and tolerability of ociperlimab (also known as BGB-A1217) in combination with tislelizumab (also known as BGB-A317) or rituximab in patients with R/R DLBCL • To confirm the recommended Phase 2 dose (RP2D) of ociperlimab when administered in combination with tislelizumab or rituximab in patients with R/R DLBCL **Secondary**: • To assess the preliminary antitumor activity of ociperlimab in combination with tislelizumab or rituximab in patients with R/R DLBCL as measured by investigator-assessed response using the Lugano Classification (2014) (as described in Section 10.2) • To characterize the pharmacokinetics (PK) of ociperlimab in combination with tislelizumab or rituximab • To assess the host immunogenicity to ociperlimab in combination with tislelizumab or rituximab **Exploratory:** • To explore the correlation of PD-L1 expression level and the preliminary antitumor activity of ociperlimab in combination with tislelizumab

- To characterize the exploratory biomarkers and their association with preliminary antitumor activity of ociperlimab in combination with tislelizumab or rituximab

Study Endpoints

Primary:

- Adverse events (AEs) and serious adverse events (SAEs) as characterized by type, frequency, severity (as graded by National Cancer Institute-Common Terminology Criteria for Adverse Events [NCI-CTCAE] Version 5.0), seriousness, and relationship to study drug(s); physical examinations, electrocardiograms (ECGs), laboratory abnormalities, and changes in laboratory assessments as needed; and AEs meeting protocol-defined dose-limiting toxicity (DLT) criteria
- RP2D of ociperlimab when administered in combination with tislelizumab or rituximab

Secondary:

- To evaluate the preliminary antitumor activity of ociperlimab in combination with tislelizumab or rituximab in patients with R/R DLBCL as measured by investigator-assessed response using the Lugano Classification (2014) (as described in Section 10.2) as measured by:
  - Overall response rate (ORR)
  - Complete response (CR) rate
  - Duration of response (DOR)
  - Time to response (TTR)
  - Progression-free survival (PFS)
  - Overall survival (OS)
- Serum concentration and PK parameters (as appropriate) of ociperlimab in combination with tislelizumab or rituximab
- Immunogenic responses to ociperlimab in combination with tislelizumab or rituximab, which will be evaluated through the detection of antidrug antibodies (ADAs)

Exploratory:

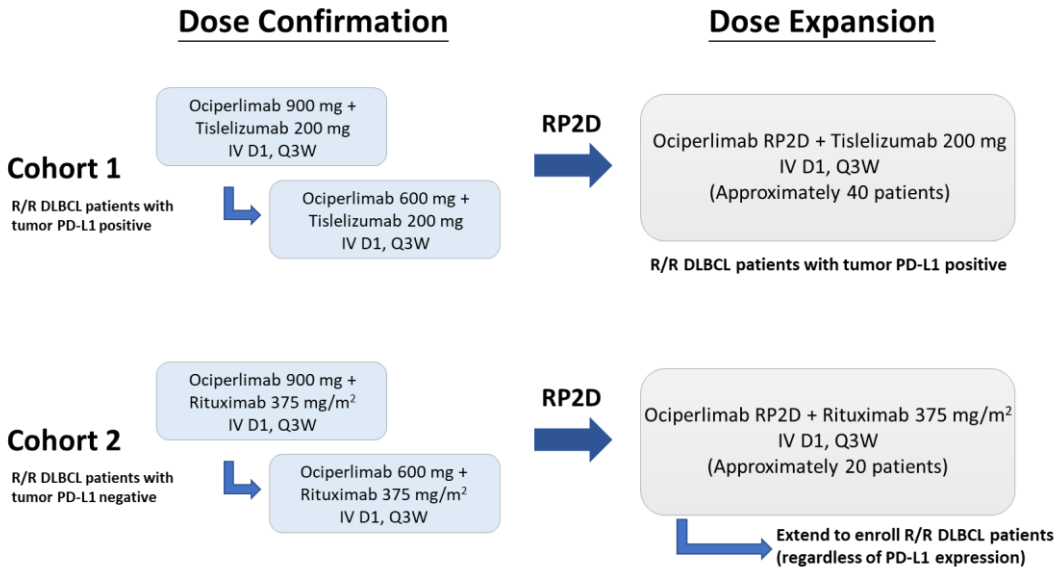
- Evaluate PD-L1 expression in archival or fresh patient-derived tumor tissue samples at screening and its association with the preliminary antitumor activity of ociperlimab in combination with tislelizumab.
- Evaluate biomarkers from patient-derived tumor tissue and/or blood (or blood derivative) samples obtained before, during, and/or after treatment, and their association with preliminary antitumor activity of ociperlimab in combination with tislelizumab or rituximab. Biomarkers may include expression of T cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain (TIGIT), CD226, CD155, and CD112, PD-L1/2 gene alteration, Epstein-Barr virus (EBV) status, tumor microenvironment, immune-related gene expression profile, and gene mutation profile in tumor tissue; immune-cell quantification and phenotypes, cytokine profiling,

immune-related gene expression profiling, and DNA/ circulating tumor DNA (ctDNA) sequencing in peripheral blood
Study Design • This is a Phase 1b/2, open-label, Dose Confirmation, and dose-expansion study to evaluate the safety, tolerability, PK, and preliminary antitumor activity of ociperlimab in combination with tislelizumab or rituximab in patients with R/R DLBCL. • First, each cohort will conduct Dose Confirmation Stage to confirm the RP2D of ociperlimab. Then, the confirmed RP2D will be implemented in Dose Expansion Stage. • Eligible patients will be allocated to 2 cohorts: – Cohort 1: R/R DLBCL patients with positive PD-L1 on the surface of tumor cells (with any expression level identified by local laboratory by immunohistochemistry) will receive ociperlimab in combination with tislelizumab – Cohort 2: R/R DLBCL patients with negative PD-L1 on the surface of tumor cells (for Dose Confirmation Stage) identified by local laboratory by immunohistochemistry and R/R DLBCL patients regardless of PD-L1 expression (for Dose Expansion Stage) will receive ociperlimab in combination with rituximab • Dose Confirmation Stage: Ociperlimab will be tested at the dose level of 900 mg initially. If ociperlimab 900 mg exceeds the maximum tolerated dose, ociperlimab 600 mg will be tested. Other dose levels of ociperlimab (eg, lower than 600 mg) may be explored to confirm the optimal dose level of ociperlimab in combination with tislelizumab or rituximab per the Safety Monitoring Committee's (SMC's) recommendation considering the totality of emerging data. The dose of tislelizumab and rituximab will be fixed at 200 mg and 375 mg/m^2, respectively. Every treatment cycle contains 21 days, and the combination regimen will be administrated intravenously on Day 1 of each cycle. Patients in both Cohort 1 and Cohort 2 will be monitored for DLTs for the first cycle (starting from the first dose of study treatment and ending on C1D21). RP2D confirmation will occur in accordance with the modified 3 + 3 principles. The RP2D of combination therapy will be confirmed from safety, tolerability, and any other relevant and available data (eg, PK and efficacy data). • Dose Expansion Stage: After the RP2D of ociperlimab in combination with tislelizumab or rituximab is confirmed, further enrollment of both cohorts will commerce to their target sample size. For Cohort 1, approximately 40 patients will be enrolled at RP2D. One futility interim analysis will be planned when approximately 20 patients have been enrolled and have ≥ 1 post-baseline disease evaluation. The SMC along with the sponsor will make the decision of proceeding or not. To reflect the natural distribution across PD-L1 expression given a relatively small sample size at interim analysis, the number of eligible patients with PD-L1 expression ≤ 5% on the surface of tumor cells as determined by local laboratory will be capped to ≤ 50% of the first 20 patients enrolled, and the benefit-risk profile may also be evaluated by the SMC and sponsor for these patients. After the interim analysis, the number of these patients with PD-L1 expression ≤ 5% on the surface of tumor cells as determined by local laboratory may be further capped per the SMC's recommendation

considering the totality of emerging data. For Cohort 2, approximately a total of 20 patients regardless of PD-L1 expression will be enrolled at RP2D (refer to Section 1.5.4).

- Patients will continue to receive study drug until they meet a study treatment discontinuation criterion (see Section 7.5).

The study schema is as follows:



Abbreviations: D, Day; IV, intravenous; Q3W, once every 3 weeks; RP2D, recommended Phase 2 dose.
Note: Refer to Section 3.1 for dose confirmation details.

Study Assessments

The schedule of study assessments for both Dose Confirmation and Dose Expansion Stages are provided in Appendix 1. Patients will be closely monitored for safety and tolerability throughout the study.

Dose-Limiting Toxicity Definitions

All AEs will be graded according to the NCI-CTCAE Version 5.0.

A DLT is defined as 1 of the following toxicities occurring during the DLT assessment window (the first cycle of the study treatment, starting from the first dose of study treatment and ending on C1D21) and considered by the investigator to be related to ociperlimab and/or tislelizumab or rituximab without a clear alternative cause to study treatment.

Hematologic:

1. Grade 4 neutropenia lasting > 7 days
2. ≥ Grade 3 febrile neutropenia
3. Grade 3 thrombocytopenia with ≥ Grade 2 bleeding (including but not limited to central nervous system bleeding of any grade)
4. Grade 4 thrombocytopenia lasting > 7 days

5. ≥ Grade 4 anemia

Nonhematologic:

1. ≥ Grade 4 toxicity
2. Grade 3 toxicity that is clinically significant and does not resolve to baseline or ≤ Grade 1 within 7 days after optimal supportive care is initiated

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 nausea, vomiting, or diarrhea lasting for ≤ 72 hours with adequate antiemetic and/or other supportive care
- Fatigue lasting for ≤ 7 days
- Electrolyte abnormality that lasts for ≤ 72 hours, is not clinically complicated, and resolves spontaneously or responds to convention medical interventions
- Asymptomatic biochemical laboratory abnormalities resolve to Grade 1 or baseline ≤ 7 days with or without medical interventions

During the DLT assessment window, any other grade of AEs occurred which is assessed to be related to study drug and leads to dose discontinuation or interruption of any study drug (ociperlimab, tislelizumab, or rituximab) for > 7 days will also be considered DLTs after review by the SMC.

Clinically important or persistent AEs that are not part of the DLT criteria (Section 3.2.4) may also be considered a DLT after review by the SMC in consultation with the investigators. Additionally, any clinically significant AEs that occur after the DLT assessment window (eg, late immune-mediated AE [imAE]) for a given dose level may be considered a DLT regarding decisions of subsequent dose level.

Patients who are not DLT-evaluable may be replaced if needed.

Tumor Assessments

Tumor imaging will be performed ≤ 28 days before the first dose of study drug(s). Screening assessments must include both contrast computed tomography (CT) and positron emission tomography-CT (PET-CT) scans of the neck, chest, abdomen, and pelvis. During the study, contrast CT will be performed every 9 weeks (± 7 days), from Day 1 of Cycle 1, for the first 54 weeks; every 18 weeks (± 7 days) for additional 54 weeks; then every 24 weeks thereafter based on the Lugano Classification (2014) (Cheson et al 2014). For patients who are positive for PET-CT scans at screening, PET-CT should be repeated at Week 9 (± 7 days), Week 18 (± 7 days), at time when confirming CR or progressive disease (PD), and as clinically indicated.

If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the study, a magnetic resonance imaging (MRI) should be performed but must be used consistently throughout the study.

For immune therapies such as ociperlimab and tislelizumab, pseudoprogression may occur due to immune-cell infiltration and other mechanisms leading to an apparent increase of existing tumor masses or appearance of new tumor lesions. Also, some patients may benefit from additional immune therapies despite evidence of PD. If radiographic PD is suspected by the investigator to reflect pseudoprogression and the clinical condition is stable, patients may continue treatment of study drugs as long as they meet the criteria below and until PD is confirmed by a repeated imaging ≥ 4 weeks later (but not exceeding 12 weeks from the initial documentation of PD):

- Absence of clinical symptoms and signs of PD (including clinically significantly worsening of laboratory values)
- Stable Eastern Cooperative Oncology Group (ECOG) Performance Status
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, cord compression) that requires urgent alternative medical intervention

Tumor assessment should continue as planned in patients until the patient begins a new antitumor therapy, experiences PD, withdraws consent, is lost to follow-up, dies, or until the study terminates, whichever occurs first. Clinical suspicion of disease progression at any time will require a physical examination and radiological confirmation to be performed promptly, rather than waiting for the next scheduled tumor assessment.

Tumor assessments must be performed on schedule regardless of whether study treatment has been administered or withheld. That is, they should not be adjusted for delays in cycles.

Bone Marrow Examinations

Bone marrow biopsy and aspirate are required to assess bone marrow involvement of patients during the screening period, unless they have been performed within 60 days before the first dose of study drug and there has been no intervening therapy from the time of the biopsy/aspirate until the first dose of study drug. For patients who have evidence of bone marrow disease at screening, repeated bone marrow biopsy may not be needed if PET-CT shows bone marrow clearance at CR.

Duration of Patient Participation:

This study will consist of 5 periods:

1. **Screening Period** will be performed ≤ 28 days before first dose of study drug(s).
2. **Treatment Period** starts with the first study drug administration and ends when the patient is discontinued from study treatment for any reason.
3. **Safety Follow-up Period:** Patients who permanently discontinue study drugs will be asked to return to the clinic for the Safety Follow-up Visit, which is required to be conducted 30 days (± 7 days) after the last dose of study drugs unless otherwise specified or before the initiation of subsequent anticancer therapy, whichever occurs first. Additional Safety Follow-up Visits at 60, 90, 120, 180 days after the last dose of study drugs (the visits at 120-day and 180-day are only required for women of childbearing potential) are required (in clinic or over the phone, as needed based on the assessments required). Patients will be contacted by telephone to assess imAEs and relevant concomitant medications (ie, those associated with an imAE or any new anticancer therapy). These contacts should be conducted at 60 days (± 14 days) and 90 days (± 14 days) after the last dose of study treatment, regardless of whether the patient starts a new

anticancer therapy. For women of childbearing potential, an additional visit to perform a pregnancy test will occur at approximately 120 days after the last dose of tislelizumab and ociperlimab and 180 days after the last dose of rituximab (see Appendix 5). If a patient reports a suspected imAE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated.

4. **Efficacy Follow-up Period:** Patients who discontinue study drug(s) for reasons other than PD (eg, toxicity) will continue to undergo tumor assessments following the original tumor assessment schedule until the patient experiences PD, withdraws consent, dies, or starts a subsequent anticancer therapy, or for any other reason listed in Section 7.5.2, whichever occurs first.
5. **Survival Follow-up:** Patients will be followed for survival and to obtain information on subsequent anticancer therapy after discontinuation of study treatment via telephone calls, patient medical records, and/or clinic visits approximately every 12 weeks (± 14 days) after the Safety Follow-up Visit or as directed by the sponsor until death, withdrawal of consent, loss to follow-up, or study termination by sponsor.

Study Population:

Patients with histologically confirmed R/R DLBCL who have previously received ≥ 1 line of adequate systemic anti-DLBCL therapy (defined as an anti-CD20 antibody-based chemoimmunotherapy for ≥ 2 consecutive cycles, unless patients had PD before Cycle 2)

Key Eligibility Criteria:

Adult patients (≥ 18 years of age, at the time of voluntarily signing of informed consent) with histologically confirmed DLBCL NOS (Not Otherwise Specified), or EBV+ DLBCL NOS or high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology (double/triple-hit lymphoma [DHL/THL]) with R/R disease before study entry. All patients should be ineligible for high dose therapy/hematopoietic stem cell transplantation. All patients are also required to demonstrate an ECOG Performance Status score of ≤ 2 and adequate organ function.

Patients who have current or history of central nervous system lymphoma or histologically transformed lymphoma will be excluded from the study.

Investigational Product, Dose, and Mode of Administration:

Dose Confirmation: Tislelizumab (200 mg, for Cohort 1) or rituximab (375 mg/m^2, for Cohort 2) will be intravenously administered first followed by ociperlimab (900 mg or 600 mg) on Day 1 of each 21-day cycle (once every 3 weeks). Lower dose levels of ociperlimab may be evaluated while the dosing regimen of tislelizumab and rituximab will remain fixed.

Dose Expansion: Tislelizumab (200 mg, for Cohort 1) or rituximab (375 mg/m^2, for Cohort 2) will be intravenously administered first followed by ociperlimab (RP2D) on Day 1 of each 21-day cycle (once every 3 weeks).

Statistical Methods:

Analysis Sets:

- The Safety Analysis Set includes all patients who received any dose of any study drug(s). This will be the analysis set for the safety analyses.
- The Efficacy Analysis Set includes all patients who received any dose of any study drug(s), have evaluable disease at baseline, and have ≥ 1 evaluable postbaseline tumor

response assessment unless any clinical PD or death occurred before the first postbaseline tumor assessment.

- The DLT-Evaluable Analysis Set includes patients who 1) experienced a DLT event or 2) received ≥ 80% each of the assigned dose of ociperlimab in combination with tislelizumab or rituximab and remained on study during the DLT assessment window.
- The PK Analysis Set includes all patients who received any dose of any study drug(s) per the protocol, for whom any quantifiable postdose PK concentrations are available.
- The Immunogenicity Analysis Set includes all patients who received any dose of any study drug(s), for whom both baseline ADA and ≥ 1 postbaseline ADA results are available.

Efficacy Analysis:

Efficacy analyses in both dose confirmation and dose expansion will be conducted based upon the investigators' tumor assessments in the Efficacy Analysis Set using the Lugano Classification (2014) (Cheson et al 2014), performed by cohort and dose if necessary, and summarized with below endpoints to evaluate the preliminary antitumor activities of ociperlimab in combination with tislelizumab or rituximab:

- ORR is defined as the proportion of patients who have best response is CR or PR
- CR rate is defined as the proportion of patients whose best response is CR
- DOR is defined as the time from the first documentation of an overall response until the first documentation of progression or death, whichever comes first
- TTR is defined as time from the starting date of the therapy to the date of the first documentation of an overall response
- PFS is defined as the time from the date of the first dose of study drug(s) to the date of the first documentation of PD or death, whichever occurs first
- OS is defined as the time from the starting date of the therapy to the date of death due to any causes

ORR and CR rate will be summarized along with their 95% CI using the Clopper-Pearson method.

Kaplan-Meier methodology will be used to estimate DOR/PFS/OS medians or other quartiles, and their 95% CI will be constructed using the Brookmeyer and Crowley method. Kaplan-Meier curves will also be provided. DOR will be analyzed only in responders.

TTR will be summarized only in responders using sample statistics, such as sample mean, median, and standard deviation.

For patients in the Efficacy Analysis Set but with clinical PD or death occurring before the first postbaseline tumor assessment, their best overall response will be considered as PD or Not Assessable, respectively. Their documented date of PD or death will be used in the PFS/OS analyses accordingly as event time.

All PD-L1-related subgroups analyses, where deemed necessary, will be conducted using the same method as above and based on centrally tested PD-L1 expression level.

Safety Analyses:

Safety data will be summarized using the Safety Analysis Set and DLT-Evaluable Analysis Set and by cohort and dose if necessary.

Safety will be determined by the spontaneous reporting of AEs and by 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 Version 5.0. The incidence of DLT events and treatment-emergent adverse events (TEAEs) will be reported as the number (percentage) of patients with TEAEs by the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class, Preferred Term, and worst grade. 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 provided for laboratory parameters and vital signs.

Pharmacokinetic Analyses:

Serum concentration data and PK parameters (as appropriate) of ociperlimab and tislelizumab will be tabulated and summarized by visit/cycle for each treatment. Additional PK analyses may be conducted as appropriate.

Sample Size Consideration:

The study plans to enroll approximately 66 to 80 patients:

- Cohort 1: Approximately 43 to 50 patients
- Cohort 2: Approximately 23 to 30 patients

For Cohort 1, the sample size of approximately 40 patients at RP2D is based on the precision of the estimate of ORR, a consideration that a relatively sufficient number of patients is needed to justify performing further analysis (eg, the subgroup analysis based on the cutoff value of tumor PD-L1 expression), and a probability that is high enough to observe certain AEs of interest (eg, rash). With 40 patients, if the observed ORR is 60%, the corresponding Clopper-Pearson 95% CI will be 43.3% to 75.1%. One futility interim analysis for ORR is planned to be conducted when approximately 20 patients have been enrolled with a futility boundary of 35% (equivalent to observe ≤ 7 responders). For an AE with a rate of 10%, there is 98.5%of probability to observe ≥ 1 event of such an AE among all 40 patients (multiple same AE on one patient will be counted only once). To reflect the natural distribution across PD-L1 expression given a relatively small sample size at interim analysis, the number of eligible patients with PD-L1 expression ≤ 5% on the surface of tumor cells as determined by local laboratory will be capped to ≤ 50% of the first 20 patients enrolled, and the benefit-risk profile may also be evaluated by the SMC and sponsor for these patients. After the interim analysis, the number of these patients with PD-L1 expression ≤ 5% on the surface of tumor cells as determined by local laboratory may be further capped per the SMC's recommendation considering the totality of emerging data. Considering the patients in the Dose Confirmation Stage that are not dosed at RP2D dose level (approximately 3 to 10 patients), approximately 43 to 50 patients in total will be enrolled in Cohort 1.

For Cohort 2, the sample size of approximately 20 patients at RP2D is based on the precision of the estimate of ORR. With 20 patients, if the observed ORR is 60%, the corresponding Clopper-Pearson 95% CI will be 36.1% to 80.9%. Considering the patients in the Dose Confirmation Stage that are not dosed at RP2D dose level (approximately 3 to 10 patients), approximately 23 to 30 patients in total will be enrolled in Cohort 2.

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
ADA	antidrug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
auto-HCT	autologous hematopoietic cell transplantation
BGB-A1217	ociperlimab
BGB-A317	tislelizumab
CL	clearance
CR	complete response
CT	computed tomography
ctDNA	circulating tumor DNA
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EBV	Epstein-Barr virus
GCB	germinal center B-cell-like
GCP	Good Clinical Practice
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
ICF	informed consent form
IEC	Independent Ethics Committee
Ig	immunoglobulin
IHC	immunohistochemistry
imAE	immune-mediated adverse event
IRB	Institutional Review Board
IRR	infusion-related reaction

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin lymphomas
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein-1
PD-L1	programmed cell death ligand-1
PD-L1 TC	PD-L1 expression by tumor cells
PET	positron-emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
R-CHOP	rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisone
R/R	relapsed or refractory
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SMC	Safety Monitoring Committee
TEAE	treatment-emergent adverse event
TIGIT	T-cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif (ITIM) domain
ULN	upper limit of normal

1. INTRODUCTION AND RATIONALES

1.1. Introduction

1.1.1. Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is an aggressive and heterogeneous disease with a variable clinical outcome (Susanibar-Adaniya and Barta 2021) and is the most common subtype of aggressive non-Hodgkin lymphomas (NHL) in the Western Countries, accounting for around 31% of NHL cases in adults (Thandra et al 2021). There were 544,352 new cases of NHL and 259,793 deaths resulting from this disease worldwide in 2020 (Sung et al 2021). The incidence rate for DLBCL is approximately 6.9 cases per 100,000 person-years (Teras et al 2016). Based on the study report of National Central Cancer Registry of China, an estimated of 88,200 new lymphoma cases and 52,100 lymphoma deaths occurred in China in 2015, ranked in the 12th and 11th place among all cancer cases, respectively (Chen et al 2016). Two locally retrospective studies for NHL distributions in China showed that DLBCL made up about 29.1% and 40.9% of NHL, respectively (Liu et al 2011; Gross et al 2008). According to the current Surveillance Epidemiology and End Results (SEER) data, the median age at diagnosis is 66 years (SEER 2020).

Accordingly, there are 3 subtypes of DLBCL: the germinal center B-cell-like (GCB) subtype with expression of normal germinal center B cells, the activated B-cell-like subtype with expression of post-germinal or activated B cells, and the unclassified subtype. The GCB and activated B-cell-like subtypes are essentially different entities and are characterized by differences in survival, disease biology, and gene expression (Wilson et al 2015). Patients in the GCB subtype have a higher 5-year survival rate compared with those in the activated B-cell-like subtype (60% versus 35%, respectively) (Rosenwald et al 2002; Alizadeh et al 2000).

Originally proposed in 1993, the International Prognostic Index still remains as the primary clinical tool to predict clinical outcome for patients with DLBCL (International NHL Prognostic Factors Project 1993). The specific factors are age > 60 years, stage III or IV disease (per the Ann Arbor classification [Carbone et al 1971]), Eastern Cooperative Oncology Group (ECOG) Performance Status ≥ 2, elevated lactate dehydrogenase (LDH) levels, and extranodal involvement > 1 site. These factors are combined in the International Prognostic Index into 4 categories, with a 5-year progression-free survival (PFS) ranging from 40% to 70% and a 5-year overall survival (OS) ranging from 26% to 73% among patients treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) (Ziepert 2010).

1.1.2. Current Treatment of DLBCL

Historically, the addition of rituximab to a chemotherapy regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) has significantly improved the clinical outcome (Coiffier et al 2002; Sehn et al 2005). Recently, the Phase III POLARIX study comparing polatuzumab vedotin in combination with chemotherapy regimen R-CHP versus the standard of care R-CHOP in treatment of first-line DLBCL met its primary endpoint by demonstrating significantly improved and clinically meaningful PFS (Roche Group 2021). However, 30% to 40% of patients with DLBCL eventually relapse and 10% of them are primary refractory, which remains as a consistent clinical problem (Flowers et al 2010).

The standard approach has been proceeded toward salvage therapy and consolidation with autologous hematopoietic stem cell transplantation (auto-HCT) for patients with relapsed/refractory (R/R) DLBCL (Philip et al 1995). Approximately 20% to 30% of patients who received auto-HCT can get long-term remission, but at the cost of high toxicity and treatment-related mortality (Gisselbrecht et al 2010). Generally, relapse and refractory cases still pose highly unmet medical needs, especially in patients who are not eligible for intensive therapeutic strategies based on hematopoietic stem cell transplantation. Both the US National Comprehensive Cancer Network (NCCN) (NCCN 2023) and the European Society for Medical Oncology (ESMO) recommend inclusion in a clinical study whenever possible (Tilly et al 2015).

1.1.3. Anti-PD-1 Inhibitors in DLBCL

Immune surveillance plays a critical role in preventing tumor progression and metastasis. However, tumors have developed resistance mechanisms to suppress and/or escape the host immune system, thereby enabling tumorigenesis to proceed unchecked (Schreiber et al 2011; Swann and Smyth 2007). One such resistance mechanism involves upregulation of immune checkpoint receptors expressed on immune cells (eg, effector T cells), such as programmed cell death protein-1 (PD-1). It is known that programmed cell death ligand-1 (PD-L1) is often upregulated in various types of solid tumors associated with poor prognosis (Wu et al 2019) and anti-PD-1/anti-PD-L1 monoclonal antibodies are demonstrated to have obvious antitumor effects (Armand et al 2013; Brahmer et al 2012).

One retrospective study assessed the expression of PD-L1 in 1253 DLBCL samples and analyzed the clinicopathological features of DLBCL with PD-L1 positive (PD-L1$^+$). The prevalence rates of PD-L1$^+$ (with a 30% threshold) and microenvironment PD-L1$^+$ (mPD-L1$^+$with a 20% threshold) DLBCL was 11% and 15.3%, respectively. Regarding OS, patients with PD-L1$^+$ DLBCL had inferior OS compared with that in patients with PD-L1$^-$ DLBCL, while the expression of mPD-L1$^+$ showed limited influence on OS. Thus, blockade of the PD-1/PD-L1 pathway may have the potential to exert antitumor effects in certain subsets of DLBCL (Kiyasu et al 2015).

A Phase II study evaluated the efficacy and safety of nivolumab in patients with R/R DLBCL who were ineligible for auto-HCT or who had experienced failure with auto-HCT. Among the 121 treated patients, 87 patients in the auto-HCT-failed cohort and 34 patients in the auto-HCT-ineligible cohorts reached the overall response rates (ORR) of 10% and 3%, and median duration of response (DOR) of 11 and 8 months, respectively. There were 3 patients in the auto-HCT-failed cohort with a durable response of > 11 months. The median PFS and OS were 1.9 and 12.2 months in the auto-HCT-failed cohort and 1.4 and 5.8 months in the auto-HCT-ineligible cohort, respectively (Ansell et al 2019).

ORR to anti-PD-1 therapy in unselected patients with R/R DLBCL is modest. These mixed outcomes likely reflect the heterogeneous nature of DLBCL. Studies suggest that if anti-PD-1 therapy is to impact the management of DLBCL, then future efforts should be focused on developing predictive biomarkers that accurately identify subsets of patients likely to benefit.

In a prospective KEYNOTE-013 study, among 29 R/R DLBCL patients, pembrolizumab has shown ORR of 13.8%. Interestingly, 2 of 3 patients with PD-L1 gene-altered DLBCLs achieved a clinical response to pembrolizumab. In contrast, only 2 of 26 patients with PD-L1-unaltered

DLBCLs responded. Thus, the presence of PD-L1 alterations significantly enriched for response to pembrolizumab (P = 0.005). Positive PD-L1 protein expression (PD-L1 H score ≥ 30) also enriched for response (2 of 5 patients), although this did not reach statistical significance (P = 0.062) (Godfrey et al 2019).

Among the 45 patients with R/R DLBCL, nivolumab in combination with ibrutinib showed an ORR of 36%. Measurable PD-L1 expression was seen in 13 (50%) of 26 samples from the DLBCL cohort, eight of which had elevated (≥ 5%) PD-L1 expression. In post-hoc analyses, 5 (63%) of 8 patients with elevated (≥ 5%) PD-L1 expression achieved an ORR compared with 3 (19%) of 16 without elevated expression of PD-L1, although this finding was not significant (P = 0.065) (Younes et al 2019).

A combination therapy of pembrolizumab and R-CHOP was designed to explore the safety and preliminary efficacy in previously untreated patients with DLBCL. Among the 30 patients treated, the overall and complete response (CR) rates were 90% and 77%, respectively, and the 2-year PFS was 83%. Furthermore, correlative analysis suggested that PD-L1 expression was associated with non-GCB subtype and improved PFS and OS, supporting PD-L1 as a biomarker to identify patients with DLBCL who may benefit from this anti-PD-1 inhibitor contained regimen (Smith et al 2020).

1.2. Ociperlimab as a TIGIT Inhibitor

1.2.1. Nonclinical Summary

1.2.1.1. Pharmacology

Ociperlimab (also known as BGB-A1217) is a humanized IgG1 monoclonal antibody against T cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif (ITIM) domain (TIGIT) under clinical development for the treatment of human malignancies.

Ociperlimab binds to the extracellular domain of human TIGIT with high specificity and affinity (equilibrium dissociation constant [KD] = 0.135 nM), as demonstrated by target binding assays and surface plasmon resonance (SPR) characterization. Ociperlimab has shown antitumor activity in both the GL261 mouse glioma tumor model and the CT26WT mouse colon cancer model in humanized *TIGIT* knock-in mice. In the MC38 mouse colon cancer model in humanized *TIGIT* knock-in mice, ociperlimab in combination with antimouse PD-1 significantly inhibited tumor growth compared with either therapy alone.

Ociperlimab has the constant region of a wild-type human immunoglobulin G1 (IgG1) to enable the Fc-mediated effector functions. Ociperlimab has demonstrated competent binding to C1q and all gamma Fc receptors (FcγRs) and induces antibody-dependent cellular cytotoxicity (ADCC) against a TIGIT overexpressing cell line, but no antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity against primary T effector cells in the cell-based assays.

Cynomolgus monkeys and humanized *TIGIT* knock-in mice (ie, mice expressing the human *TIGIT* gene) were selected for nonclinical safety evaluation based on the homology of the TIGIT amino acid sequence, binding affinity, and efficacy studies. Ociperlimab inhibits GL261 tumor growth significantly in humanized *TIGIT* knock-in mice at doses ≥ 0.4 mg/kg administered once weekly.

Refer to the Ociperlimab (BGB-A1217) Investigator's Brochure for detailed information regarding pharmacology studies.

1.2.1.2. Toxicology

The toxicity and safety profile of ociperlimab was characterized in 4- and 13-week repeated-dose toxicity studies in humanized *TIGIT* knock-in mice and in a 13-week repeated-dose toxicity study in cynomolgus monkeys.

No apparent toxicity was observed in the 4- or 13-week humanized *TIGIT* knock-in mouse studies or in the13-week cynomolgus monkey study. A dose-proportional increase in systemic exposure (area under the concentration-time curve [AUC] and maximum observed serum concentration [C_{max}]) was noted in both species, without apparent sex difference, while excluding the impact of positive antidrug antibodies (ADAs) in individual animals with lower systemic exposure and/or faster clearance. No accumulation was observed in monkeys following once-every-2-weeks dosing for 13 weeks. A trend of accumulation was shown in mice following once-weekly dosing for 4 and 13 weeks. The no-observed-adverse-effect level (NOAEL) of ociperlimab was 50 mg/kg in mice and 100 mg/kg in monkeys, which were the highest doses tested in each species.

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 (IHC) method.

In an in vitro cytokine release assay using human peripheral blood mononuclear cells (PBMCs), ociperlimab did not induce significant increases in interferon gamma (IFN-γ), interleukin (IL)-2, IL-6, tumor necrosis factor-alpha (TNF-α), IL-1β, or granulocyte-macrophage colony-stimulating factor (GM-CSF) as commonly seen in the "cytokine storm." Selective induction of monocyte chemoattractant protein-1 (MCP-1) and IFN-γ-inducible protein 10 (IP-10) in PBMCs by ociperlimab were observed and were not considered to be a risk in causing acute cytokine release syndrome.

The safety profile of ociperlimab was considered adequate to support human studies.

Refer to the Ociperlimab (BGB-A1217) Investigator's Brochure for detailed information regarding toxicology studies.

1.2.2. Prior Clinical Experience With Ociperlimab

1.2.2.1. Clinical Pharmacology

Preliminary pharmacokinetic (PK) data are available from a total of 52 patients in Phase 1 (dose escalation and dose verification in China) portion of Study AdvanTIG-105. In the dose escalation part, 32 patients were treated with ociperlimab at 50 mg, 150 mg, 450 mg, 900 mg, or 1800 mg dose levels on Day 1, and on Day 8 tislelizumab 200 mg once every 3 weeks was added for the first cycle. Cycle 2 was initiated on Day 28, and the dose regimen of once every 3 weeks was followed thereafter for the combination.

In the China dose verification part, 20 patients were treated with 900 mg ociperlimab, either as monotherapy (n = 9) or in combination with tislelizumab 200 mg (n = 11).

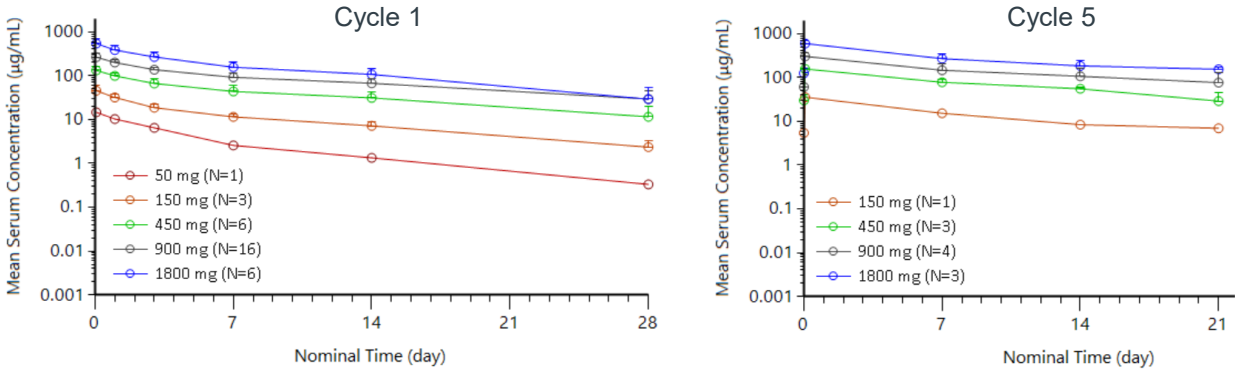
Ociperlimab exposures increased approximately dose proportionally from the 50 mg dose to 1800 mg dose for C_{max} and AUC. There was minimal accumulation observed in Cycle 5 following multiple doses. Across dose groups, serum concentrations of ociperlimab decreased in a biexponential manner after administration. The geometric mean terminal half-life estimate following the first dose ranged from approximately 7 days to 11 days. Postdose PK sampling duration may not be sufficient for robust characterization of elimination half-life using noncompartmental analysis (NCA); hence, the reported half-life values should be interpreted with caution. The mean serum concentration-time profiles of ociperlimab from dose escalation are shown in (Figure 1).

As of 13 August 2023, treatment-emergent ADAs for ociperlimab at doses of 50 to 1800 mg once every 3 weeks have been observed for 0.3% (1 of 324) of ADA-evaluable patients.

Peripheral TIGIT receptor occupancy data were available for 32 enrolled patients treated with ociperlimab at 50 mg, 150 mg, 450 mg, 900 mg, and 1800 mg dose levels in Study AdvanTIG-105. Complete TIGIT receptor occupancy (100%) at all tested dose levels was observed on $CD8^+$, $CD4^+$, and regulatory T cells in peripheral blood.

Refer to the Ociperlimab (BGB-A1217) Investigator's Brochure for detailed information on ociperlimab clinical PK and pharmacodynamics.

Figure 1: Cycle 1 and 5 Mean (+ SD) Serum Concentration-Time Profiles of Ociperlimab in Study AdvanTIG-105



Note: For the 1800 mg dose, only 3 concentrations were available on Day 28.

1.2.2.2. Safety Assessment of Ociperlimab

As of the data cutoff date of 28 July 2023, 729 patients had received at least one dose of ociperlimab, either as monotherapy (n = 9 patients), in combination with tislelizumab only (n = 370 patients), in combination with tislelizumab plus chemotherapy (n = 214 patients), in combination with tislelizumab plus concurrent chemoradiotherapy (n = 63 patients), in combination with tislelizumab plus BAT1706 (n = 62 patients), or in combination with rituximab (n = 11 patients) across a variety of tumor types. Refer to the Ociperlimab (BGB-A1217) Investigator's Brochure for detailed information.

1.2.2.2.1. Treatment-Emergent Adverse Events Assessed as Related to Ociperlimab

A total of 534 patients (73.3%) experienced adverse events assessed by the investigator as related to ociperlimab treatment, with 152 patients (20.9%) having experienced an event ≥ Grade 3 in severity.

The most frequently reported (≥ 10%) ociperlimab-related adverse events were rash (17.7%), pruritus (12.9%), aspartate aminotransferase (AST) increased (12.3%), alanine aminotransferase (ALT) increased (11.2%), and hypothyroidism (10.7%). The most frequently reported (≥ 3%) ociperlimab-related adverse event of ≥ Grade 3 was rash (3.0%).

1.2.2.2.2. Treatment-Emergent Serious Adverse Events as Related to Ociperlimab

Serious adverse events assessed by the investigator as related to ociperlimab treatment were experienced by 103 of 729 patients (14.1%). The most frequently reported (≥ 1%) ociperlimab-related serious adverse events were immune-mediated lung disease (1.6%) and pneumonitis (1.1%).

1.2.2.2.3. Treatment-Emergent Adverse Events Leading to Death as Related to Ociperlimab

A total of 7 patients experienced adverse events leading to death that were assessed by the investigator as related to ociperlimab. Ociperlimab-related adverse event leading to death was experienced by a single patient each (1 of 729 patients; 0.1%). These were: blood creatine phosphokinase increased, cardiac failure, immune-mediated lung disease, multiple organ dysfunction syndrome, pneumonitis, septic shock, and upper gastrointestinal perforation.

1.2.2.2.4. Immune-Mediated Adverse Events

A total of 312 patients (42.8%) experienced immune-mediated adverse events, with 79 patients (10.8%) having experienced an event of ≥ Grade 3 in severity. The most frequently reported (≥ 10%) immune-mediated adverse events were rash (18.7%) and hypothyroidism (12.5%). The most frequently reported (≥ 3%) immune-mediated adverse event of ≥ Grade 3 was rash (3.3%).

1.2.2.2.5. Infusion-Related Reactions

A total of 79 patients (10.8%) experienced infusion-related reactions (IRRs), with 8 patients (1.1%) having experienced an event of ≥ Grade 3 in severity. The most frequently reported (≥ 1%) infusion-related reactions were chills (5.1%), pyrexia (4.7%), and dyspnoea (1.0%). Other important, but less common, IRRs experienced by patients included flushing (0.3%), palpitations (0.3%), urticaria (0.3%), anaphylactic reaction (0.1%), dizziness (0.1%), and infusion-related reaction (0.1%). The most frequently reported (≥ 0.5%) event of ≥ Grade 3 infusion-related reactions was dyspnoea (0.5%).

1.2.2.3. Preliminary Efficacy Profile

As of the data cutoff date of 29 September 2022, a total of 30 evaluable patients had received ociperlimab in combination with tislelizumab 200 mg intravenously once every 3 weeks (Frentzas et al 2023). Ociperlimab doses consisted of 50 mg (1 patient), 150 mg (3 patients), 450 mg (5 patients), 900 mg (16 patients), and 1800 mg (5 patients). Unconfirmed partial

responses were observed in 3 patients (10.0% of the 30 efficacy-evaluable patients). Each patient had received a different dose of ociperlimab: 450 mg, 900 mg, or 1800 mg. The overall response rate was 10.0% (95% CI: 2.11% to 26.53%). The median duration of response was 3.6 months (95% CI: 2.8 months to not evaluable). Stable disease was observed in 12 patients (40.0%) (2 patients receiving ociperlimab 150 mg, 2 receiving 450 mg, 7 receiving 900 mg, and 1 receiving 1800 mg). The disease control rate was 50.0% (95% CI: 31.30% to 68.70%).

As of the data cutoff date of 05 April 2022, efficacy data from Study AdvanTIG-105 Dose Expansion Cohort 3 (a total of 39 evaluable patients with PD-L1 expression by tumor cells (PD-L1 TC) ≥ 1%, untreated metastatic squamous or non-squamous non-small cell lung cancer (NSCLC) received ociperlimab 900 mg plus tislelizumab 200 mg) were presented at the 2022 meeting of the World Conference of Lung Cancer (Rajiv et al 2022). The unconfirmed objective response rate was 53.8% (95% CI: 37.2, 69.9); in patients with PD-L1 TC 1% to 49% and PD-L1 TC ≥ 50%, the unconfirmed ORR was 44.0% and 71.4%, respectively. The overall disease control rate (DCR) was 89.7%; in patients with PD-L1 TC 1% to 49% and PD-L1 TC ≥ 50%, the DCR was 88.0% and 92.9%, respectively. The median DOR was not evaluable (NE), and the median PFS was 5.4 months (95% CI: 4.2, NE), with 5.2 months and 5.6 months in the PD-L1 TC 1% to 49% and PD-L1 TC ≥ 50% subgroups, respectively.

1.3. Tislelizumab as a PD-1 Inhibitor

1.3.1. Nonclinical Summary

1.3.1.1. Pharmacology

Tislelizumab 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 [KD] = 0.15 nM). It competitively blocks binding of both PD-L1 and PD-L2, thus inhibiting PD-1-mediated negative signaling in T cells.

In vitro assays with tislelizumab suggest either low or no antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, or complement-dependent cytotoxicity effects in humans (Labrijn et al 2009; Zhang et al 2018a). 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 (BGB-A317) Investigator's Brochure for additional details regarding nonclinical studies of tislelizumab.

1.3.1.2. Toxicology

The nonclinical toxicity and toxicokinetic profile of tislelizumab was characterized in single-dose toxicology studies in mice and cynomolgus monkeys and in a 13-week, repeated-dose toxicology study in cynomolgus monkeys dosed once every 2 weeks for 13 weeks. Tissue cross-reactivity in normal human and cynomolgus monkey frozen tissues was also evaluated. In addition, the potential off-target binding of tislelizumab was screened using the Retrogenix microarray assay. The single-dose regimens spanned from the intended human dose to 10-fold

higher than the maximum of the intended human dose, and the repeated-dose regimens spanned to 3-fold higher than the maximum of the intended human dose. Cynomolgus monkey was the only relevant species based on the target sequence homology and binding activity.

Overall, no apparent toxicity was noted in mice 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. Based on the Retrogenix cell microarray screening of more than 6400 different proteins, tislelizumab clearly exhibited relatively high selective binding to the intended target, PD-1 protein, and had weak binding to only one off target protein. 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 of tislelizumab in the 13-week monkey toxicity study was considered to be 30 mg/kg. The toxicity profile of tislelizumab is considered adequate to support the current study of BGB-A317-A1217-101.

Please refer to the Tislelizumab (BGB-A317) Investigator's Brochure for more detailed information on the toxicology of tislelizumab.

1.3.2. Prior Clinical Experience With Tislelizumab

1.3.2.1. Clinical Pharmacology

Based on pooled data from 2596 patients across 12 clinical studies, the PK of tislelizumab was best characterized using a 3-compartmental linear population PK model with linear clearance mechanisms. No time-varying clearance was observed in tislelizumab PK. The C_{max} and AUC increased in a nearly dose-proportional manner from 0.5 mg/kg to 10 mg/kg. The terminal half-life was estimated to be approximately 23.8 days, and the steady state is expected to be reached after 12 weeks.

Please refer to the Tislelizumab (BGB-A317) Investigator's Brochure for more detailed information on the clinical pharmacology of tislelizumab.

1.3.2.2. Pooled Safety Assessment of Tislelizumab Monotherapy in Solid Tumors

As of 27 October 2023, 2377 patients with solid tumors had been treated with tislelizumab monotherapy in 9 clinical studies. The patients in the pooled solid tumor monotherapy studies had a median treatment exposure duration of 4.0 months (range: 0 to 64 months) and median study follow-up duration of 11.9 months (range: 0 to 64 months).

Please refer to the Tislelizumab (BGB-A317) Investigator's Brochure for more detailed information on the clinical safety of tislelizumab.

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

A total of 1690 (71.1%) patients experienced ≥ 1 treatment-related TEAE. The most commonly occurring (≥ 10%) treatment-related TEAEs were AST increased (14.5%) and ALT increased (13.0%).

Three hundred and fifty-one patients (14.8%) experienced a tislelizumab-related TEAE of ≥ Grade 3. The most commonly occurring (≥ 1%) ≥ Grade 3 TEAEs were AST increased (1.6%) and ALT increased (1.1%).

1.3.2.2.2. Treatment-Emergent Serious Adverse Events as Related to Tislelizumab

As of 27 October 2023, 245 (10.3%) patients experienced tislelizumab-related treatment-emergent SAE. The most commonly occurring treatment-related SAE was pneumonitis (1.1%). All other events occurred in less than 1% of patients.

1.3.2.2.3. Treatment-Emergent Adverse Events Leading to Death as Related to Tislelizumab

A total of 22 (0.9%) patients experienced tislelizumab-related TEAE leading to death. The most commonly occurring tislelizumab-related TEAEs leading to death were hepatic failure (0.2%), and pneumonitis, death, multiple organ dysfunction syndrome, and pneumonia (0.1% each). All other events occurred in single patients.

1.3.2.2.4. Immune-Mediated Adverse Events

A total of 768 (32.3%) patients experienced immune-mediated adverse event (imAE), with 115 (4.8%) patients having experienced an imAE of ≥ Grade 3 in severity. The most commonly occurring (≥ 1%) imAEs of any grade were hypothyroidism (10.9%), rash (8.8%), hyperthyroidism (4.4%), pneumonitis (3.2%), and rash maculo-papular (1.6%). The most commonly occurring (≥ 0.5%) ≥ Grade 3 imAEs were pneumonitis (0.8%) and rash (0.5%).

1.3.2.2.5. Infusion-Related Reactions

A total of 109 (4.6%) patients experienced IRR, with 4 (0.2%) patients having experienced IRR of ≥ Grade 3 in severity. The most commonly occurring (≥ 1%) IRRs were rash (2.3%) and infusion-related reaction (1.2%).

1.3.2.3. Pooled Safety Assessment of Tislelizumab Monotherapy in Hematological Malignancies

As of 27 October 2023, 192 patients with hematologic malignancies had been treated with tislelizumab monotherapy in 3 clinical studies. The patients in the pooled hematologic malignancies monotherapy studies had a median treatment exposure duration of 7.0 months (range: 1 to 39 months) and a median study follow-up duration of 20.7 months (range: 1 to 39 months).

Please refer to the Tislelizumab (BGB-A317) Investigator's Brochure for more detailed information on the clinical safety of tislelizumab.

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

A total of 153 (79.7%) patients experienced ≥ 1 treatment-related TEAE, with 38 (19.8%) patients having experienced TEAE of ≥ Grade 3. The most commonly occurring (≥ 10%) treatment-related TEAEs were pyrexia (26.6%), hypothyroidism (19.3%), and pruritus (11.5%).

The most commonly occurring (≥ 2%) ≥ Grade 3 treatment-related TEAEs were anaemia (2.6%) as well as neutropenia, neutrophil count decreased, and pneumonia (2.1% each).

1.3.2.3.2. Treatment-Emergent Serious Adverse Events as Related to Tislelizumab

Thirty-six (18.8%) patients experienced tislelizumab-related treatment-emergent SAE. The most commonly occurring (≥ 1%) treatment-related SAEs were pneumonia and pyrexia (2.1%), and interstitial lung disease and pneumonitis (1.0% each).

1.3.2.3.3. Immune-Mediated Adverse Events

Seventy-four (38.5%) patients experienced imAE, with 8 (4.2%) patients having experienced imAE of ≥ Grade 3. The most commonly occurring imAEs were hypothyroidism (20.3%), rash (6.8%), hyperthyroidism (3.6%), rash maculo-papular (3.1%), and pneumonitis (2.1%). All other imAEs occurred in ≤ 2 patients. The most commonly occurring ≥ Grade 3 imAE was pneumonitis (1.0%). All other ≥ Grade 3 imAEs occurred in a single patient each.

1.3.2.3.4. Infusion-Related Reactions

Twenty-two (11.5%) patients experienced IRR, with none of them having experienced an IRR of ≥ Grade 3. The most commonly occurring IRRs were rash (3.6%), chills (2.6%), and infusion-related reaction, cytokine release syndrome, and eyelid oedema (1.0% each). All other IRRs occurred in a single patient each.

1.3.2.3.5. Treatment-Emergent Adverse Events Leading to Death as Related to Tislelizumab

Of the 192 patients in the hematologic malignancy group of pooled tislelizumab monotherapy studies, no patient experienced tislelizumab-related TEAE leading to death.

1.3.3. Regulatory Status

As of the data cutoff date of 27 October 2023, tislelizumab has been approved and is currently marketed in Europe, South Korea, China, and Macao, China, for various indications, including for solid tumor and hematologic malignancies.

Tislelizumab is approved for the following indication in Europe:

- for use in adult patients with unresectable locally advanced or metastatic esophageal squamous cell carcinoma (ESCC) after prior platinum-based chemotherapy

Tislelizumab is approved for the following indication in South Korea:

- for use in adult patients with unresectable, recurrent, locally advanced or metastatic ESCC who are unable to continue prior platinum-based chemotherapy or relapsed or progressed after administration

Tislelizumab is approved for the following indications in China as well as in Macao, China, except for the first-line gastric/gastroesophageal junction adenocarcinoma and first-line ESCC indications:

- for use in combination with paclitaxel plus carboplatin or paclitaxel for injection (albumin bound) plus carboplatin as first-line treatment in patients with unresectable, locally advanced, or metastatic squamous NSCLC (both China and Macao, China)
- for use in combination with pemetrexed and platinum chemotherapy as first-line treatment in patients with unresectable, locally advanced, or metastatic nonsquamous NSCLC with *EGFR* genomic tumor aberrations negative or *ALK* genomic tumor negative status (both China and Macao, China)
- for use in adult patients with locally advanced or metastatic nonsquamous NSCLC, with *EGFR* genomic tumor aberrations negative and *ALK* genomic tumor negative status, that has progressed after or did not tolerate prior platinum-based chemotherapy and in adult patients with locally advanced or metastatic squamous NSCLC, with *EGFR* and *ALK* negative or unknown status, that has progressed after or did not tolerate prior platinum-based chemotherapy (both China and Macao, China)
- for use in patients with locally advanced or metastatic ESCC who have disease progression or are intolerant to first-line standard chemotherapy (both China and Macao, China)
- for use in combination with gemcitabine and cisplatin as first-line treatment in patients with recurrent or metastatic nasopharyngeal cancer (both China and Macao, China)
- for use in combination with fluoropyrimidine and platinum chemotherapy as first-line treatment of patients with locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma with PD-L1-high expression (China only)
- for use in combination with paclitaxel and platinum- or fluoropyrimidine- and platinum-based chemotherapy as first-line treatment in patients with unresectable locally advanced, recurrent or metastatic ESCC (China only)

In addition, the following indications are conditionally approved in China and Macao, China, based on data from single-arm pivotal clinical studies (1 study for each indication). Full approval of these indications depends on demonstration of a significant clinical benefit of tislelizumab over the standard of care in ongoing randomized confirmatory clinical studies:

- treatment of patients with relapsed or refractory classical Hodgkin lymphoma who received ≥ 2 lines of systemic chemotherapy regimens
- treatment of patients with locally advanced or metastatic urothelial carcinoma with PD-L1-high expression whose disease progressed during or after platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
- treatment of patients with hepatocellular carcinoma who have been previously treated with ≥ 1 systemic therapy
- treatment of adult patients with advanced unresectable or metastatic microsatellite instability-high or mismatch-repair-deficient solid tumors, including patients with advanced colorectal cancer who had been treated with fluoropyrimidine, oxaliplatin,

and irinotecan and patients with other advanced solid tumors who develop disease progression after prior treatment and have no satisfactory alternative treatment options.

1.4. Rituximab as a CD20 Inhibitor

Rituximab is a genetically engineered, chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen expressed on the surface of pre-B and mature B-lymphocytes. Upon binding to CD20, rituximab mediates B cell lysis, with possible mechanisms of lysis including complement-dependent cytotoxicity (CDC) and ADCC. Most common AEs associated with rituximab (≥ 25%) in clinical trials for NHL were infusion reaction, fever, lymphopenia, chills, infection, and asthenia. Tumor lysis syndrome (TLS) can be associated with rituximab treatment in patients with NHL, with a high number of circulating malignant cells (≥ 25,000/mm^3) or high tumor burden conferring a greater risk of TLS (Rituximab prescribing information 2021).

Rituximab is currently approved in China for the treatment of $CD20^+$ NHL, including the $CD20^+$ DLBCL.

1.5. Study Rationale

1.5.1. Rationale for the Selection of Ociperlimab Dose

The ociperlimab dose of 900 mg once every 3 weeks combined with tislelizumab 200 mg once every 3 weeks was selected as the RP2D for further investigation based on clinical safety, tolerability, PK, and pharmacodynamic data from the ongoing Phase 1/1b Study AdvanTIG-105.

Complete TIGIT receptor occupancy was observed in circulating T cells in peripheral blood at all the tested doses of ociperlimab in Study AdvanTIG-105. However, the correlation between TIGIT receptor occupancy in the periphery and in tumor tissues is unknown. In a previous Phase 1 study of tiragolumab, another anti-TIGIT antibody, complete peripheral receptor occupancy was reached at the 30 mg dose level, but the clinical dose of 600 mg was determined as the RP2D, which was 20 times the 30 mg dose (Bendell et al 2020). Similarly, although complete peripheral receptor occupancy was observed at the 50 mg dose level of ociperlimab, the RP2D of 900 mg is approximately 20 times the dose of 50 mg, to ensure sufficient TIGIT receptor occupancy in the tumor tissue.

As of 12 May 2021, a total of 3 patients were assessed to have a confirmed PR, including 1 patient each in the 450 mg, 900 mg, and 1800 mg cohorts. Ociperlimab exposure in all 3 patients with a PR is consistent with that expected at the 900 mg dose level. The confirmed DCRs observed in the 450 mg, 900 mg, and 1800 mg cohorts were 60% (3 of 5 patients), 64.3% (9 of 14 patients), and 60% (3 of 5 patients), respectively.

Although the best overall response rate and DCR were numerically comparable at the 450 mg and 900 mg dose levels, the 900 mg dose was chosen as the RP2D for the following reasons:

- 900 mg was well tolerated in patients enrolled in Study AdvanTIG-105
- Exposure in all 3 patients with a PR was consistent with that expected at the 900 mg dose

- Lack of sufficient information on the impact of immunogenicity on ociperlimab PK
- An overall intent to minimize exposure overlap with doses < 450 mg.

1.5.2. Rationale for Selection of Tislelizumab Dose

The dosage of 200 mg intravenously once every 3 weeks was selected based on safety, efficacy, and PK assessments in the first-in-human Study BGB-A317_Study_001. A wide range of dosages were investigated in this study, including 2 mg/kg or 5 mg/kg on schedules of once every 2 weeks or once every 3 weeks. For the once-every-3-week schedule, a fixed dose of 200 mg was also investigated, and was ultimately selected for the following reasons:

- All dosages tested, including 200 mg once every 3 weeks, were tolerated. The MTD was not reached with dosages up to 10 mg/kg once every 2 weeks. The observed serum concentration after 200 mg dosing was within the range seen after the 2 mg/kg and 5 mg/kg dosing.
- Preliminary clinical activity was observed at this dosage.
- Exposure-response relationships were flat for ORR and safety endpoints across a variety of tumor types (data from studies BGB-A317_Study_001 and BGB-A317-102 in solid tumors, and BGB-A317-203 in classical Hodgkin lymphomas). In addition, no clinically significant covariates were identified in population PK analysis.
- Compared with doses based on patient's body weight, a fixed dose simplifies dose administration and reduces the chance of medical errors.
- Compared with a once every 2 weeks schedule, a once every 3 weeks schedule allows for more convenient integration with common chemotherapeutic regimens and increases patient convenience.

1.5.3. Rationale for the Combination of Ociperlimab and Tislelizumab in the Treatment of DLBCL With PD-L1 Positive

TIGIT and PD-1 function as immune checkpoint receptors in the overlapping regulation of immune tolerance. 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). Clinically, treatment with anti-TIGIT antibody in combination with anti-PD-1/PD-L1 therapy has the potential to be more effective than anti-PD-1/PD-L1 alone in metastatic NSCLC without prior checkpoint inhibitor therapy. The combination of tiragolumab plus atezolizumab reported an ORR of 31% and a PFS of 5.42 months versus placebo plus atezolizumab with an ORR of 16% and a PFS of 3.58 months in first-line Stage IV NSCLC patients with PD-L1 Tumor Proportion Score ≥ 1% (Rodriguez-Abreu et al 2020). Similarly, the vibostolimab plus pembrolizumab combination reported an unconfirmed and confirmed ORR of 29% and 24%, respectively, in patients with NSCLC who were untreated or had been treated with at least 1 line of platinum-containing chemotherapy and had not previously received anti-PD-1/PD-L1 therapy (Niu et al 2020).

Gene expression analysis has previously verified upregulation of TIGIT and PD-L1 in DLBCL compared with normal controls (Laurent et al 2015). Characterization of coinhibitory receptor expression in intratumoral T cells from DLBCL revealed that both TIGIT and PD-1 were expressed at higher frequency than all other receptors (eg, T cell immunoglobulin domain and mucin domain-3 [TIM-3] and lymphocyte-activation-gene-3 [LAG-3]). The co-expression pattern of TIGIT and PD-1 not only contributes to impaired T cell effector function as tested by cytokine production, but also inhibits the antitumor activity of T cell through interaction with ligand-expressing tumor cells in DLBCL (CD155 and CD122 expression). All these indicate the value of combinatorial blockade of TIGIT and PD-1 in DLBCL and exploration for mechanisms of immune escape by characterizing the tumor microenvironment (Josefsson et al 2019).

However, the limitation of single agent of anti-PD-1 is also observed in patients with R/R DLBCL, with the ORR of approximately 10%. A trend of increasing ORR and CR rate was observed in patients with high PD-L1 expression on the surface of tumor cells in a combination therapy of nivolumab and ibrutinib (Section 1.1.3). Given the tolerable and manageable safety profile of tislelizumab in DLBCL (Section 1.1.1) and the scientific rationale of synergistic antitumor effects between anti-TIGIT and anti-PD-1 therapies, the combination of ociperlimab and tislelizumab may bring significant clinical benefit in R/R DLBCL with PD-L1 positive and support further clinical development.

1.5.4. Rationale for Ociperlimab and Rituximab in the Treatment of DLBCL

As a monoclonal antibody with intact Fc effector function, rituximab can be responsible for rapidly killing tumor targets via FcγR-mediated ADCC or antibody-dependent cellular phagocytosis (ADCP), a short-term process mediated by natural killer cells and myeloid effector cells from innate immune system (Taylor and Lindorfer 2008, Minard-Colin et al 2008). Studies also reveal that the therapeutic function and long-term immune memory of rituximab require active crosstalk with adaptive immunity. Evidence in lymphoma patients suggests that rituximab can induce a strong antitumor vaccinal effect by priming antitumor T cell responses, resulting in durable response (Cartron et al 2004). Using a murine lymphoma model to express huma^{n} CD20, CD4+ and CD8+ T cells are demonstrated to be required for anti-CD20 mAb-mediated long-term memory immune response (Abès et al 2010), and the mechanism of rituximab is proved to engage the macrophage for immediate ADCC and dendritic cells for long-term antitumor cellular immune response (DiLillo et al 2015). Furthermore, adaptive resistance is gradually developed through Treg accumulation in larger lymphomas; and blockade of CTLA-4 can synergize with anti-CD20 treatment to overcome the resistance associated with adaptive immune response in advanced B cell lymphoma (Ren et al 2017).

TIGIT is an immune checkpoint receptor primarily expressed on immune cells, such as T cells and natural killer (NK) cells. TIGIT plays a key role in promoting T cell exhaustion and maintaining immune tolerance, in both chronic viral infections and the tumor microenvironment (Johnston et al 2014). NK cells from TIGIT-deficient mice produce more IFNγ in the presence of poliovirus receptor (PVR)-expressing target cells (Li et al 2014). TIGIT blockade also prevents NK cell exhaustion and elicits potent antitumor immunity (Zhang et al 2018b). Therefore, TIGIT blockade may have potential to promote NK-cell activation against poliovirus receptor^{+} (PVR^{+}) tumor cells and to synergize the therapeutic monoclonal antibody (such as rituximab) mediated ADCC activity.

TIGIT is also highly expressed on tumor infiltrated Treg cells (Joller et al 2014; Kurtulus et al 2015). TIGIT-positive Treg cells demonstrated greater suppressive functions when compared to TIGIT-negative Tregs, with higher expression of effector molecules, such as IL-10, granzymes, and Fgl2 (Joller et al 2014). A high TIGIT/CD226 ratio in Tregs is associated with increased Treg frequencies in tumors and poor clinical outcome upon immune checkpoint blockade (Fourcade et al 2018). Moreover, as a therapeutic monoclonal antibody with human IgG1, TIGIT blockade antibody is proved to be able to deplete suppressive $TIGIT^{hi}$ Treg cells while spare $TIGIT^{low/mid}$ effector T cells in tumor microenvironment (Preillon et al 2021 and data on file). Thus, targeting TIGIT provides a potential strategy to rescue the immunosuppressive microenvironment, thereby inducing an efficient antitumor immune response.

Rituximab is recommended as the backbone of R/R DLBCL treatment per treatment guidelines (NCCN 2023; Tilly et al 2015), ociperlimab may synergize with rituximab by enhancing T-cell/NK-cell activation and Treg depletion/inhibition to promote both immediate tumor killing and long-term memory immune response. Hence, ociperlimab is designed to be used in combination with rituximab in this study.

At the Dose Confirmation Stage of Cohort 2 (in R/R DLBCL with PD-L1 negative), ociperlimab of 900 mg was confirmed by SMC as being safe and RP2D to be used in combination with rituximab, similar safety profile is expected in R/R DLBCL with PD-L1 positive population under this combination treatment.

Based on the observed preliminary anticancer activity from the Dose Confirmation Stage of Cohort 2, in order to explore more potential treatment regimen and to potentially maximize clinical benefit for all R/R DLBCL patients, the target population in Cohort 2 is considered to extend to all R/R DLBCL patients regardless of PD-L1 expression at the Dose Expansion Stage.

1.5.5. Rationale for Biomarker Strategy

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 DLBCL. Higher PD-L1 expression was shown to be associated with better response and survival benefit (Section 1.1.3), indicating the potential role of PD-L1 in predicting response to anti-PD(L)-1 therapies. In summary, these data support further exploration of the correlation of PD-L1 expression with response to tislelizumab and ociperlimab.

Meanwhile, mechanisms of resistance to immunotherapies are also not well understood and need more exploration. Identification of tumor and immune-related features associated with disease progression or acquired resistance to ociperlimab in combination with tislelizumab or rituximab may increase the understanding of disease pathobiology and provide biological evidence for the combination strategy.

Thus, for Cohort 1, archival or fresh tumor samples at screening will be collected for PD-L1 expression analysis to explore its association with the preliminary efficacy of ociperlimab in combination with tislelizumab. Other biomarker analyses in tumor tissues will include the expression of TIGIT, CD226, CD155, and CD112, PD-L1/2 gene alteration, Epstein-Barr virus (EBV) status, tumor microenvironment, immune-related gene expression profile, and gene mutation profile to explore potential predictive and prognostic biomarkers and mechanisms of action and resistance.

In addition, blood-based biomarkers will be analyzed, including immune-cell quantification and phenotypes, cytokine profiling, immune-related gene expression profiling, and DNA/circulating tumor DNA (ctDNA) sequencing. The association of these biomarkers with clinical response to ociperlimab in combination with tislelizumab or rituximab will be further explored.

1.6. Benefit-Risk Assessment

Patients with R/R DLBCL represent a population with high unmet medical needs: although R-CHOP in first-line treatment and auto-HCT in second-line treatment have significantly improved the survival and the recently released positive result of Phase III POLARIX study may impact the treatment landscape, patients who relapse after auto-HCT or are ineligible for auto-HCT have poor outcomes with limited treatment options. As discussed earlier (Section 1.1.3), although the clinical benefits of anti-PD-1 antibodies are limited in R/R DLBCL, patients with tumor PD-L1 positive may achieve improved survival after being treated with anti-PD-1 antibody as first-line treatment, supporting to identify PD-L1 as a biomarker for clinical benefit. The coexpressed PD-L1 and TIGIT in DLBCL lymphocytes are observed to correlate with inhibiting the antitumor activity of T cell, suggesting the potential value of combined blockade of TIGIT and PD-1 for R/R DLBCL (Section 1.1.3 and Josefsson et al 2019).

The safety profile of tislelizumab monotherapy is similar across tumor types. There is no pattern in the incidence, severity, or causality of AEs to tislelizumab dose level. The safety profile for single-agent tislelizumab is similar to those observed with other PD-1 inhibitors.

Based on the safety profile in 9 patients with ociperlimab monotherapy and 268 patients with ociperlimab in combination with tislelizumab as of 20 July 2022, ociperlimab in combination with tislelizumab was well tolerated and the toxicities were manageable, with no DLTs reported, most TEAEs were Grade 1 or Grade 2, and most ≥ Grade 3 TEAEs and all serious TEAEs were recovered. In addition, the RP2D of combination regimen has been determined to be 900 mg ociperlimab in combination with 200 mg tislelizumab once every 3 weeks.

As has been shown for other anti-PD-1-based immune-oncology combinations, the risk of observing augmented safety signals remains. Therefore, a monitoring plan derived from the European Society for Medical Oncology and American Society for Clinical Oncology has been established to monitor, diagnose, and manage imAEs (Appendix 9).

Rituximab has been used in clinical practice for more than 20 years. The well-established clinical efficacy and safety profiles drive its backbone role on DLBCL treatment. To maximize the clinical benefit in patients with PD-L1 negative, rituximab in combination with anti-TIGIT antibodies are expected to exert synergetic effect on relieving the immunosuppressive microenvironment (Section 1.5.4).

In summary, there is a strong scientific rationale that the combined blockade of TIGIT and PD-1 or CD20 may result in enhanced antitumor activity without a major increase in the risk of immune-mediated toxicities. The benefit/risk of the combination of ociperlimab and tislelizumab or rituximab is considered favorable.

A SMC will be established to regularly monitor the safety of ociperlimab in combination of tislelizumab or rituximab. Refer to Section 8.2 and Section 9 for information regarding safety monitoring and considerations related to potential risk.

Based on the historical data of prevalence of PD-L1 expression in patients with DLBCL through the literature research (Younes et al 2019; Smith et al 2020; Ansell et al 2019; Xing et al 2016; Sun et al 2019; Dong et al 2016; Hu et al 2017), the enrollment strategy of capping patients with PD-L1 expression ≤ 5% on the surface of tumor cells in Cohort 1 is adopted to secure that the small sample size of patients enrolled at interim analysis could reflect the natural distribution of patients with DLBCL across PD-L1 expression level as much as possible. The benefit-risk profile may also be evaluated by the SMC and sponsor for these patients.

1.7. 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

Objectives	Endpoints
Primary	
To assess the safety and tolerability of ociperlimab in combination with tislelizumab or rituximab in patients with relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL)	AEs and serious adverse events (SAEs) as characterized by type, frequency, severity (as graded by National Cancer Institute-Common Terminology Criteria for Adverse Events [NCI-CTCAE] Version 5.0), seriousness, and relationship to study drug(s); physical examinations, electrocardiograms (ECGs), laboratory abnormalities, and changes in laboratory assessments as needed; and AEs meeting protocol-defined DLT criteria
To confirm the RP2D of ociperlimab when administered in combination with tislelizumab or rituximab in patients with R/R DLBCL	RP2D of ociperlimab when administered in combination with tislelizumab or rituximab
Secondary	
To assess the preliminary antitumor activity of ociperlimab in combination with tislelizumab or rituximab in patients with R/R DLBCL as measured by investigator-assessed response using the Lugano Classification (2014) (as described in Section 10.2)	To evaluate the preliminary antitumor activity of ociperlimab in combination with tislelizumab or rituximab in patients with R/R DLBCL as measured by investigator-assessed response using the Lugano Classification (2014) as measured by: – Overall response rate (ORR) – Complete response (CR) rate – Duration of response (DOR) – Time to response (TTR) – Progression-free survival (PFS) – Overall survival (OS)
To characterize the PK of ociperlimab in combination with tislelizumab or rituximab	Serum concentration and PK parameters (as appropriate) of ociperlimab in combination with tislelizumab or rituximab
To assess the host immunogenicity to ociperlimab in combination with tislelizumab or rituximab	Immunogenic responses to ociperlimab in combination with tislelizumab or rituximab, which will be evaluated through the detection of ADAs
Exploratory	
To explore the correlation of PD-L1 expression level and the preliminary antitumor activity of ociperlimab in combination with tislelizumab	Evaluate PD-L1 expression in archival or fresh patient-derived tumor tissue(s) samples at screening and its association with the preliminary antitumor activity of ociperlimab in combination with tislelizumab

Objectives	Endpoints
To characterize the exploratory biomarkers and their association with preliminary antitumor activity of ociperlimab in combination with tislelizumab or rituximab	Evaluate biomarkers from patient-derived tumor tissue(s) and/or blood (or blood derivative) samples obtained before, during, and/or after treatment, and their association with preliminary antitumor activity of ociperlimab in combination with tislelizumab or rituximab. Biomarkers may include expression of TIGIT, CD226, CD155, and CD112, PD-L1/2 gene alteration, EBV status, tumor microenvironment, immune-related gene expression profile, and gene mutation profile in tumor tissue; immune-cell quantification and phenotypes, cytokine profiling, immune-related gene expression profiling, and DNA/ctDNA sequencing in peripheral blood

3. STUDY DESIGN

3.1. Summary of Study Design

This is a Phase 1b/2, open-label, dose-confirmation, and dose-expansion study to evaluate the safety, tolerability, PK, and preliminary antitumor activity of ociperlimab in combination with tislelizumab or rituximab in patients with R/R DLBCL (Figure 2).

Eligible patients will be allocated to 2 cohorts. First, each cohort will conduct Dose Confirmation Stage to confirm the RP2D of ociperlimab. Then, the confirmed RP2D will be implemented in Dose Expansion Stage.

- Cohort 1: R/R DLBCL patients with positive PD-L1 on the surface of tumor cells (with any expression level) will receive ociperlimab in combination with tislelizumab
- Cohort 2:
  - Dose Confirmation Stage: R/R DLBCL patients with negative PD-L1 on the surface of tumor cells.
  - Dose Expansion Stage: R/R DLBCL patients regardless of PD-L1 expression. Patients will receive ociperlimab in combination with rituximab.

Approximately 43 to 50 patients in Cohort 1 and approximately 23 to 30 patients in Cohort 2 will be enrolled in the entire study. Every treatment cycle contains 21 days. The combination of ociperlimab with tislelizumab in Cohort 1 and ociperlimab with rituximab in Cohort 2 will be administrated intravenously on Day 1 of each 21-day cycle continuously until confirmed PD, death, withdrawal of consent, loss of follow-up, or study termination by sponsor, whichever occurs first.

As of 30 November 2023, the study recruitment was complete; a total of 53 patients have been enrolled in 19 activated study sites, with 24 patients in Cohort 1 and 29 patients in Cohort 2.

Dose Confirmation Stage: Because ociperlimab 900 mg in combination with tislelizumab 200 mg administered on Day 1 of each 3-week cycle has been determined as the RP2D in multiple malignancies from the AdvanTIG-105 study, 2 dose levels (900 mg and 600 mg) of ociperlimab are selected as candidates for Dose Confirmation Stage.

Ociperlimab will be tested at the dose level of 900 mg initially. If ociperlimab 900 mg exceeds the MTD, ociperlimab 600 mg will be tested. Other dose levels of ociperlimab (eg, lower than 600 mg) may be explored to confirm the optimal dose level of ociperlimab in combination with tislelizumab or rituximab per the SMC's recommendation considering the totality of emerging data. The dose of tislelizumab or rituximab will be fixed at 200 mg or 375 mg/m^2, respectively. Patients in both Cohort 1 and Cohort 2 will be monitored for DLTs for the first cycle (starting from the first dose of study treatment and ending on C1D21).

RP2D confirmation will occur in accordance with the following modified 3 + 3 principles (Section 3.2.2).

RP2D will be confirmed after discussion with SMC before the initiation of dose expansion. Refer to Section 3.2.5 for the result of RP2D confirmation.

Dose Expansion Stage: After the RP2D of ociperlimab in combination with tislelizumab or rituximab are confirmed, further enrollment of both cohorts will commerce to their target sample size. Based on the safety profile and observed preliminary anticancer activity from the Dose Confirmation Stage of Cohort 2, the target population in Cohort 2 is considered to extend to R/R DLBCL patients regardless of PD-L1 expression at the Dose Expansion Stage.

Refer to Section 3.3 for details of Dose Expansion Stage.

All AEs will be graded according to the NCI-CTCAE Version 5.0. Refer to Section 9 for additional and specific information regarding AE monitoring and reporting. Patients who, at time of confirmed disease progression, have an ongoing AE that leads to treatment discontinuation and has completed the scheduled Safety Follow-up Visit will be followed until the event resolves, the investigator assesses the event as stable, the patient is lost to follow-up, or the patient starts a new antitumor therapy, whichever occurs first.

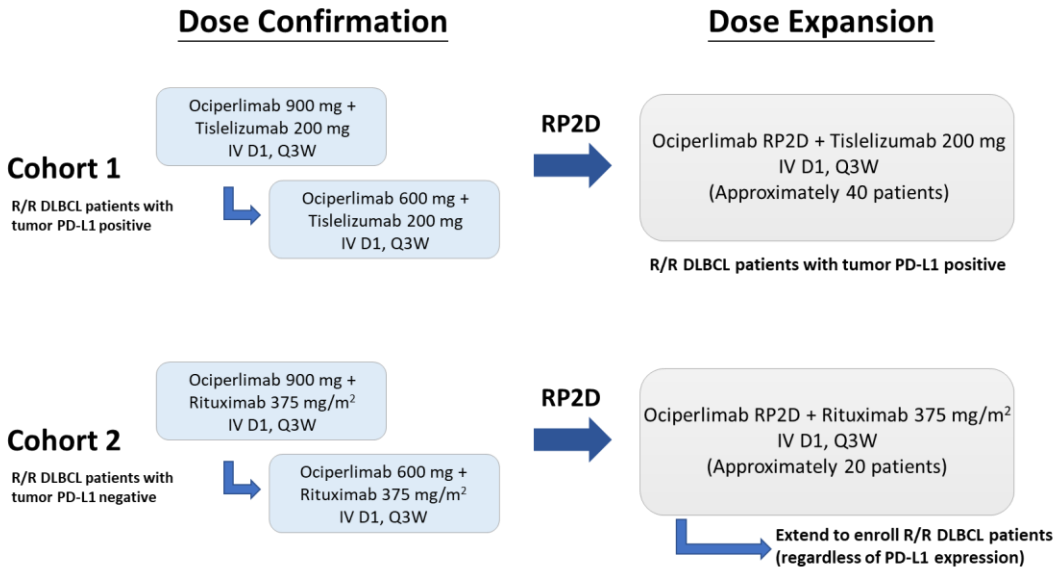
Preliminary antitumor activity will be evaluated by the investigator using the Lugano Classification (Cheson et al 2014 and Appendix 8). If a patient discontinues study drug(s) due to reasons other than PD or death, tumor assessments should continue to be performed following the assessment schedule until the start of new antitumor therapy, PD, death, lost to follow-up, or withdrawal of consent for efficacy follow-up, whichever occurs first (Section 7.4.2).

Samples for PK and ADA assessment will be collected for ociperlimab and tislelizumab (Section 8.6). Biomarker analysis will include expression of TIGIT, CD226, CD155, PD-L1, and CD112, PD-L1/2 gene alteration, EBV status, tumor microenvironment, immune-related gene expression profile, and gene mutation profile in tumor tissues; immune-cell quantification and phenotype, cytokine profiling, immune-related gene expression profiling, and DNA/ctDNA sequencing in peripheral blood (Section 8.7).

Patients will have scheduled follow-up visits for safety and, if applicable, for efficacy per the Schedule of Assessments (Appendix 1).

Study procedures and assessments are further detailed in Section 7 and Section 8, respectively, and the Schedule of Assessments can be found in Appendix 1. Specific details regarding dose confirmation and dose expansion are described in the following sections.

Figure 2: Study Schema



Abbreviations: D, Day; IV, intravenous; Q3W, once every 3 weeks; RP2D, recommended Phase 2 dose.
Note: Refer to Section 3.1 for dose confirmation details.

3.2. Details of Dose Confirmation

3.2.1. Starting Dose and Dose Confirmation Approach

Approximately 2 dose levels of ociperlimab (with a starting dose of 900 mg) (Figure 2) are selected as candidates for Dose Confirmation Stage to confirm the RP2D for ociperlimab in combination with tislelizumab or rituximab. All dose levels of ociperlimab in combination of tislelizumab or rituximab will be administered intravenously on Day 1 of Cycle 1 and every 21 days thereafter (ie, every 3 weeks) as outlined in Section 5.2 and Appendix 1. Each cycle will be 21 days in length, which may be modified based upon emerging data.

Based upon emerging clinical data, if ociperlimab 900 mg exceeds the MTD, dose level of ociperlimab 600 mg may be evaluated while the dosing regimen of tislelizumab and rituximab will remain fixed. However, other dose levels of ociperlimab (eg. lower than 600 mg) may be explored to confirm the optimal dose level of ociperlimab in combination with tislelizumab or rituximab per the SMC's recommendation considering the totality of emerging data.

The SMC will review the accumulated safety data and other available data after the last patient of current cohort has completed the 21-day DLT observation period and will recommend the RP2D for ociperlimab in combination with tislelizumab or rituximab (Section 3.2.5). All patients will continue with their originally assigned dosing regimen until they meet 1 of the discontinuation criteria (Section 7.5).

3.2.2. Rules for Dose Confirmation

Dose confirmation and RP2D determination will occur in accordance with the following modified 3 + 3 principles.

Three to 6 patients will be initially enrolled per dose level.

- If none of the initial 3 patients enrolled at a given dose level experiences a DLT (0/3), this dose level of ociperlimab in combination of tislelizumab or rituximab will be confirmed as RP2D.
- If 1 of the initial 3 patients enrolled at a given dose level experiences a DLT (1/3), at least 3 additional patients will be enrolled at this dose level (for a total of at least 6 evaluable patients).
  - If less than one-third of patients enrolled at a given dose level experiences a DLT (eg, < 2/6), this dose level of ociperlimab in combination of tislelizumab or rituximab will be confirmed as RP2D.
  - If ≥ 2 of the initial 6 patients enrolled at a given dose level experience a DLT, the MTD will be considered as having been exceeded and a next lower dose level will be assessed for toxicity in the same manner as described above. If ≥ 2 of the initial 6 patients enrolled at dose level of ociperlimab 600 mg experience DLT, other dose levels of ociperlimab (eg. lower than 600 mg) may be explored per the SMC's recommendation considering the totality of emerging data.

All available safety data, including AEs, laboratory assessments, PK, and preliminary efficacy analyses (as available), will be reviewed by the medical monitor and study team members from

Pharmacovigilance/Drug Safety, Clinical Pharmacology, and Biostatistics with input from other members as appropriate.

On the basis of a sponsor review of real-time safety data and after consultation with the investigators and SMC, the decision to proceed to other dose levels during the study may be made as deemed appropriate.

3.2.3. Assessment of Dose-Limiting Toxicity

For initial Dose Confirmation recommendations, AEs will be assessed per the DLT criteria below (Section 3.2.4) during the 21-day DLT assessment window, which starts with the first day of study drug administration and ends on C1D21.

Patients will be considered evaluable for DLTs if they 1) experienced a DLT or 2) received ≥ 80% of each scheduled study drug administration and remained on study during the DLT assessment window.

Any patient who experiences a DLT may be withdrawn from treatment or may continue to receive tislelizumab or rituximab alone or the combination therapy with a lower dose level for ociperlimab after discussion with and approval by the medical monitor.

3.2.4. Dose-Limiting Toxicity Definition

All toxicities or AEs will be graded according to the NCI-CTCAE Version 5.0. A DLT is defined as 1 of the following toxicities occurring during the DLT assessment window (starting from the first dose of study treatment and ending on C1D21) and considered by the investigator to be related to ociperlimab and/or tislelizumab or rituximab without a clear alternative cause to study treatment.

Hematologic:

1. Grade 4 neutropenia lasting > 7 days
2. ≥ Grade 3 febrile neutropenia
3. Grade 3 thrombocytopenia with ≥ Grade 2 bleeding (including but not limited to central nervous system bleeding of any grade)
4. Grade 4 thrombocytopenia lasting > 7 days
5. ≥ Grade 4 anemia

Nonhematologic:

1. ≥ Grade 4 toxicity
2. Grade 3 toxicity that is clinically significant and does not resolve to baseline or ≤ Grade 1 within 7 days after optimal supportive care is initiated

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 nausea, vomiting, or diarrhea lasting for ≤ 72 hours with adequate antiemetic and/or other supportive care
- Fatigue lasting for ≤ 7 days
- Electrolyte abnormality that lasts for ≤ 72 hours, is not clinically complicated, and resolves spontaneously or responds to convention medical interventions
- Asymptomatic biochemical laboratory abnormalities resolve to Grade 1 or baseline ≤ 7 days with or without medical interventions

During the DLT assessment window, any other grade of AEs occurred which is assessed to be related to study drug and leads to dose discontinuation or interruption of any study drug (ociperlimab, tislelizumab, or rituximab) for > 7 days will also be considered DLTs after review by the SMC.

Clinically important or persistent AEs that are not part of the DLT criteria (Section 3.2.4) may also be considered a DLT after review by the SMC in consultation with the investigators. Additionally, any clinically significant AEs that occur after the DLT assessment window (eg, late imAE) for a given dose level may be considered regarding decisions of subsequent dose level.

3.2.5. Recommended Phase 2 Dose Confirmation

The combination therapy RP2D will be confirmed from safety, tolerability, and any other relevant and available data (eg, PK and preliminary efficacy data) that is obtained from the Dose Confirmation Stage. Once the combination therapy RP2D is confirmed, it will then be evaluated in the Dose Expansion Stage.

3.3. Details of Dose Expansion

The Dose Expansion Stage of the study will begin once the RP2D has been confirmed from the Dose Confirmation Stage. Approximately 40 patients for Cohort 1 and 20 patients for Cohort 2 will be enrolled in parallel at each RP2D dose level.

Each cohort will be evaluated independently for study endpoints and may be closed due to lack of preliminary antitumor activity according to the Lugano Classification (Cheson et al 2014) or other reasons.

Expansion Cohort 1: Approximately 40 patients will be enrolled at RP2D dose level. One futility interim analysis for ORR is planned to be conducted when approximately 20 patients have been enrolled with a futility boundary of 35% (equivalent to observe ≤ 7 responders). The SMC along with the sponsor will make the decision of proceeding or not. To reflect the natural distribution across PD-L1 expression given a relatively small sample size at interim analysis, the number of eligible patients with PD-L1 expression ≤ 5% on the surface of tumor cells as determined by local laboratory will be capped to ≤ 50% of the first 20 patients enrolled, and the benefit-risk profile may also be evaluated by the SMC and sponsor for these patients. Upon conducting the interim analysis, the enrollment may be paused according to sponsor's decision, provided that the required number of patients for the interim analysis has been reached. After the interim analysis, the number of these patients with PD-L1 expression ≤ 5% on the surface of tumor cells as

determined by local laboratory may be further capped per the SMC's recommendation considering the totality of emerging data.

The interim analysis was conducted in July 2023. During its 21 July 2023 meeting, the SMC reviewed all available data of the 24 patients enrolled in Cohort 1. Because the futility boundary for ORR was not exceeded, the SMC recommended to terminate the enrollment of Cohort 1 immediately.

Expansion Cohort 2: Based on the safety profile and observed preliminary anticancer activity from the Dose Confirmation Stage, the target population is considered to extend to all R/R DLBCL patients. Approximately 20 patients regardless of PD-L1 expression will be enrolled at RP2D dose level.

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 must meet all of the following inclusion criteria to be considered eligible for participation in this study:

1. Signed informed consent form (ICF) and able to comply with study requirements
2. Age ≥ 18 years on the day of signing the ICF
3. Histologically confirmed DLBCL NOS (Not Otherwise Specified), EBV^+ DLBCL NOS, or high-grade B cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology (double/triple-hit lymphoma [DHL/THL]), based on the World Health Organization (WHO) 2016 classification of tumors of hematopoietic and lymphoid tissue
   a. Cohort 1: Patients must have positive tumor PD-L1 IHC testing results as determined by local pathologist
   b. Cohort 2:
      – Dose Confirmation Stage: Patients must have negative tumor PD-L1 IHC testing results as determined by local pathologist.
      – Dose Expansion Stage: All R/R DLBCL patients with confirmed pathology diagnosis regardless of PD-L1 expression on tumor cells.
4. Previously received ≥ 1 line of adequate systemic anti-DLBCL therapy, defined as an anti-CD20 antibody-based chemoimmunotherapy for ≥ 2 consecutive cycles, unless patients had PD before Cycle 2
5. Relapsed or refractory disease before study entry, defined as either:
   a. Recurrent disease after having achieved disease remission (CR or PR) during or at the completion of the latest treatment regimen
   b. Stable disease or PD at the completion of the latest treatment regimen
6. Ineligible for high dose therapy/hematopoietic stem cell transplantation
7. Measurable disease as assessed by computed tomography (CT) or magnetic resonance imaging (MRI) and defined as at least 1 lymph node > 1.5 cm in the longest diameter and/or at least 1 extranodal lesion > 1.0 cm in the longest diameter, and measurable lesion (s) in 2 perpendicular diameters
8. Available for archival tissue or consented to obtain fresh tumor tissue sample through an evaluable core or excisional biopsy.
9. ECOG Performance Status ≤ 2
10. Adequate bone marrow function as indicated by the following laboratory values:

a. Absolute neutrophil count ≥ 1.0 x 10^9/L (≥ 0.75 x 10^9/L for patients with bone marrow involvement by DLBCL), without growth factor support ≥ 7 days before sample collection
b. Platelet count ≥ 75 x 10^9/L (≥ 50 x 10^9/L for patients with bone marrow involvement by DLBCL), without blood transfusion or growth factor support ≥ 7 days before sample collection
c. Hemoglobin ≥ 80 g/L, without blood transfusion or growth factor support ≥ 7 days before sample collection

11. Adequate organ function as indicated by the following laboratory values:
    a. Creatinine clearance ≥ 30 mL/min (as estimated by Cockcroft-Gault equation or as measured by nuclear medicine scan or 24-hour urine collection)
    b. Serum total bilirubin ≤ 2.0 x ULN (unless with documented Gilbert syndrome)
    c. AST and ALT ≤ 2.5 x ULN (unless due to DLBCL)
12. Women of childbearing potential must have a negative urine or serum pregnancy test ≤ 7 days of the first dose of study drug(s) and be willing to use highly effective method of birth control for the duration of the study, and ≥ 120 days after the last dose of ociperlimab or tislelizumab, or ≥ 12 months after the last dose of rituximab, whichever is longer (Appendix 5).
13. Nonsterile men must be willing to use highly effective method of birth control for the duration of the study and for ≥ 120 days after the last dose of ociperlimab or tislelizumab, or ≥ 12 months after the last dose of rituximab, whichever is longer (Appendix 5).
    a. A sterile man is defined as one for whom azoospermia has been previously demonstrated in a semen sample examination as definitive evidence of infertility
    b. Men with known "low sperm counts" (consistent with "subfertility") are not to be considered sterile for purposes of this study

4.2. Exclusion Criteria

Patients who meet any of the following criteria will be excluded from this study:

1. Current or history of central nervous system lymphoma
2. Histologically transformed lymphoma
3. Receipt of the following treatment:
    a. Systemic chemotherapy, targeted small molecule therapy or radiation therapy within 4 weeks (or 5 half-lives, whichever is shorter) before first dose of study drug
    b. Recent treatment with another monoclonal antibody within 4 weeks before first dose of study drug
    c. Investigational treatment within 4 weeks (or 5 half-lives, whichever is shorter) before first dose of study drug
    d. Treatment with autologous stem cell transplantation within 6 months before first dose of study drug
    e. Treatment with allogeneic hematopoietic stem cell transplantation or organ transplantation

f. Treatment with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-TIGIT, anti-CTLA4 or other antibody or drug specifically targeting T cell costimulation or checkpoint pathways

4. Toxicities (as a result of prior antitumor therapy) that have not recovered to baseline, ≤ Grade 1, or stabilized, except for AEs that are not considered a likely safety risk (eg, alopecia, neuropathy, and specific laboratory abnormalities [see Inclusion Criterion #10 and #11 in Section 4.1])

5. Active autoimmune diseases or history of autoimmune diseases that may relapse, with the following exceptions:

   a. Controlled Type 1 diabetes
   b. Hypothyroidism (provided that it is managed with hormone replacement therapy only)
   c. Controlled celiac disease
   d. Skin diseases not requiring systemic treatment (eg, vitiligo, psoriasis, or alopecia)
   e. Any other disease that is not expected to recur in the absence of external triggering factors

6. Any active malignancy ≤ 2 years before the first dose of study drug(s) except for the specific cancer under investigation in this study and any localized or locally recurring cancer that has been treated with curative intent (eg, resected basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix or breast, or localized Gleason score 6 prostate cancer)

7. Any condition that required systemic treatment with either corticosteroids (> 10 mg daily of prednisone or equivalent) or other immunosuppressive medication ≤ 14 days before the first dose of study drug(s), with the following exceptions:

   a. Adrenal replacement steroid (dose ≤ 10 mg daily of prednisone or equivalent)
   b. Topical, ocular, intra-articular, intranasal, or inhalational 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 nonautoimmune condition (eg, delayed-type hypersensitivity reaction caused by contact allergen)

8. History of interstitial lung disease, noninfectious pneumonitis, or uncontrolled lung diseases including but not limited to pulmonary fibrosis, acute lung diseases, or evidence of dyspnea at rest or pulse oximetry < 92% while breathing room air.

9. Severe chronic or active fungal, bacterial and/or viral infection requiring systemic therapy ≤ 14 days prior to the first dose of study drug(s).

10. Serologic status reflecting active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, defined as positive hepatitis B surface antigen (HBsAg) and/or detectable HBV DNA (≥ 20 IU/mL) or HCV RNA (≥ 15 IU/mL).

11. Known history of HIV and human T cell lymphotropic virus infection

12. Any major surgical procedure ≤ 4 weeks before the first dose of study drug(s).

13. Any of the following cardiovascular risk factors:
    a. Acute myocardial infarction ≤ 6 months before screening
    b. Unstable angina ≤ 3 months before screening
    c. Heart failure meeting New York Heart Association Classification III or IV (Appendix 6) ≤ 6 months before the first dose of study drug(s)
    d. Clinically significant arrhythmia (eg, sustained ventricular tachycardia, ventricular fibrillation, or torsade de pointes).
    e. QTcF interval (QT interval corrected for heart rate by Fridericia's formula) > 480 msec
    f. History of Mobitz II second-degree or third-degree heart block without a permanent pacemaker in place
    g. Uncontrolled hypertension as indicated by at least 2 consecutive blood pressure measurements showing systolic blood pressure > 170 mm Hg and diastolic blood pressure > 105 mm Hg at screening
14. Hypersensitivity to ociperlimab, tislelizumab, rituximab, or any of their ingredients
15. History of severe hypersensitivity reactions to other monoclonal antibodies
16. Live vaccine ≤ 4 weeks before the first dose of study drug(s)
    - Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed.
17. Underlying medical conditions or alcohol or drug abuse or dependence that will be unfavorable for the administration of study drug(s), or will affect the explanation of drug toxicity or AEs, or result in insufficient or impaired compliance with study conduct
18. Concurrent participation in another therapeutic clinical study
    - Concurrent participation in observational or noninterventional 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.
19. Women who are pregnant, are breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the prescreening or screening visit through at least 120 days after the last dose of tislelizumab or ociperlimab, or 12 months after the last dose of rituximab, whichever is longer

5. STUDY TREATMENT

5.1. Formulation, Packaging, and Handling

5.1.1. 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 200 mg antibody in 10 mL or 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 condition as 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 (BGB-A1217) Investigator's Brochure for other details regarding ociperlimab.

5.1.2. 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 condition as 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 (BGB-A317) Investigator's Brochure for other details regarding tislelizumab.

5.1.3. Rituximab

Rituximab will be provided by the sponsor, in a single dose vial containing a total of 100 mg antibody in 10 mL or 500 mg antibody in 50 mL of clear solution for intravenous infusion. The labels will include any additional clinical requirements as appropriate. Refer to the Pharmacy Manual for specifics on packaging and label content. The contents of the label will be in accordance with all applicable local regulatory requirements.

Rituximab must be stored in the original package per storage requirements and temperature specified on the label. For more information regarding stability and storage refer to the Pharmacy Manual. Refer to the Rituximab prescribing information 2021 for other details regarding rituximab.

5.2. Dosage, Administration, and Compliance

Study treatment begins on Cycle 1 Day 1. Treatment modifications (eg, dose delay/holds) will be based on specific laboratory and AE criteria, as described in Section 5.4. Guidelines for study treatment modification, delay, or discontinuation as well as management of imAEs or IRRs are provided in Section 9.7 and Appendix 9.

Accurate records of all study drug(s) received, dispensed, returned, and disposed of should be maintained in the site's Drug Inventory Log. Refer to the Pharmacy Manual for details of study drug management, drug preparation, storage, and administration.

5.2.1. Dose Confirmation Stage

Planned dose level(s) for ociperlimab, tislelizumab and rituximab are presented in Table 1.

Table 1: Planned Dose Levels for Ociperlimab, Tislelizumab, and Rituximab

Study drug(s)	Dose
Ociperlimab	900 mg 600 mg (Lower dose levels may be explored.)
Tislelizumab (for Cohort 1 only)	200 mg
Rituximab (for Cohort 2 only)	375 mg/m^2

As shown in Table 1, 200 mg of tislelizumab (for Cohort 1) or 375 mg/m^2 rituximab (for Cohort 2) will be administered first followed by ociperlimab on Day 1 of each 21-day cycle (once every 3 weeks). Ociperlimab, tislelizumab, and rituximab 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. Ociperlimab and tislelizumab or rituximab must be prepared and administered as separate infusions and may not be administered with any other drug. Tislelizumab or rituximab should be administered first followed by ociperlimab.

Table 2 outlines the infusion as well as postinfusion monitoring times for combination of ociperlimab and tislelizumab or rituximab. Monitoring must occur in an area where emergency medical equipment and appropriately trained staff are available. Duration of infusion and postinfusion monitoring can be decreased if tislelizumab or rituximab infusion is well tolerated.

Premedication consisting of acetaminophen and an antihistamine could be administered before each rituximab infusion. Steroids may also be administered before the start of the rituximab infusion according to institutional practice.

Table 2: Administration of Ociperlimab, Tislelizumab, and Rituximab and Monitoring Time

Cycle	Ociperlimab and tislelizumab combination (for Cohort 1)	Ociperlimab and rituximab combination (for Cohort 2)
C1D1 and C2D1	Tislelizumab infusion over 60 minutes Ociperlimab infusion over 60 minutes	Rituximab infusion per local guidance and prescribed information

Cycle	Ociperlimab and tislelizumab combination (for Cohort 1)	Ociperlimab and rituximab combination (for Cohort 2)
	Patient monitoring for ≥ 120 minutes	Ociperlimab infusion over 60 minutes Patient monitoring for ≥ 120 minutes
C3D1[a]	Tislelizumab infusion over 30 minutes Ociperlimab infusion over 60 minutes Patient monitoring for ≥ 60 minutes	Rituximab infusion per local guidance and prescribed information Ociperlimab infusion over 60 minutes Patient monitoring for ≥ 60 minutes
C4D1 onwards[a]	Tislelizumab infusion over 30 minutes Ociperlimab infusion over 30 minutes Patient monitoring for ≥ 60 minutes	Rituximab infusion per local guidance and prescribed information Ociperlimab infusion over 30 minutes Patient monitoring for ≥ 60 minutes

Abbreviations: C, cycle; D, day.
Note: The infusion rate may be decreased or the infusion may be stopped in the event of an infusion-related reaction. See Section 9.7.1 for details.
[a] Subsequent decrease(s) in study drug infusion time and/or postinfusion monitoring time is contingent upon the tolerability of prior study drug administrations. If a cycle is missed, the equivalent number of study drug infusions must be met before a decrease in time can occur.

5.2.2. Dose Expansion Stage

The RP2D of ociperlimab to be used in combination with tislelizumab or rituximab will be confirmed based upon the available clinical data derived from Dose Confirmation Stage as described in Section 3.2.5.

5.3. Incorrect Administration or Overdose

Any incorrect administration of ociperlimab or overdose of tislelizumab (defined as ≥ 600 mg in a 24-hour period) or rituximab (defined as more than 110% of the precise calculated dose) should be noted in the patient's chart and on the appropriate electronic case report form (eCRF). AEs associated with an incorrect administration or overdose of study drug(s) 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 9.6.2. Supportive care measures should be administered as appropriate.

5.4. Dose Delay or Modification

5.4.1. Dose Interruption or Delay for Ociperlimab, Tislelizumab, and Rituximab

In Dose Confirmation Stage, prior to Cycle 1 Day 21, if any toxicity which is assessed to be related to study drug(s) and leads to dose interruption > 7 days of any study drug (ociperlimab, tislelizumab, or rituximab), should be considered as a DLT.

Except Cycle 1 of Dose Confirmation Stage, if a dose delay is required, both study drugs are to be delayed (ie, ociperlimab and tislelizumab or rituximab must both be delayed and if applicable restarted at the same time). As a result, the initiation of the new treatment cycle will be postponed.

In general, dose delays for reasons other than management of AEs is prohibited. A dose delay of ≤ 3 weeks is allowed under the following guidance and at the discretion of the investigator after consultation with the medical monitor or designee. If treatment-related AEs are persistent without any improvement for more than 3 weeks, permanent discontinuation of the study drug should be considered. If the patient recovers from the treatment-related AE after 3 weeks, re-initiation of study drug is permitted only in patients who are deemed to be deriving clinical benefit per the opinion of the investigator following agreement between the investigator and the medical monitor.

If treatment is delayed due to AEs, treatment may resume only after the AEs have returned to baseline or ≤ Grade 1 severity except for alopecia or AEs that, in the opinion of the investigator, are 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.

Two occurrences of dose delays because of treatment-related AEs will be permitted. In the event of a third occurrence of a dose delay due to toxicity, permanent discontinuation of study drug should be considered after consultation with the medical monitor.

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

5.4.2. Dose Modification for Ociperlimab, Tislelizumab, and Rituximab

There will be no dose reductions allowed for tislelizumab and rituximab. No dose reductions for ociperlimab are allowed, except if patients are receiving a dose level of ociperlimab that is determined to be beyond the MTD in Dose Confirmation Stage, the dose level of ociperlimab may be reduced following discussion and agreement with the medical monitor.

6. PRIOR AND CONCOMITANT THERAPY

6.1. Prior Therapy

All prior therapy, dates of administration, best response, and date of progression for DLBCL will be collected at study entry and entered into the eCRF.

Per the study eligibility exclusion criteria (Section 4.2), patients who received prior therapies for DLBCL (including autologous hematopoietic stem cell transplantation within 6 months before the first dose of study drugs and allogeneic hematopoietic stem cell transplantation) or antibody/drug specific targeting T cell costimulation or checkpoint pathways are excluded from study participation.

6.2. Permitted Concomitant Medications/Procedures

The potential for drug-drug interaction between the study drugs (ociperlimab, tislelizumab, or rituximab) and other small molecule drugs is very low because all these are therapeutic monoclonal antibody and are expected to be degraded into amino acids and recycled into other proteins. Thus, it is unlikely to have an effect on drug-metabolizing enzymes or transporters.

Unless noted otherwise, most concomitant medications and therapies deemed necessary and in keeping with local standards of medical care at the discretion of the investigator for supportive care (eg, antiemetics, antidiarrheals, hematopoietic growth factors, red blood cell/platelet transfusions) and in a patient's interest are allowed.

All concomitant medications, including all prescription and over-the-counter drugs, supplements, and intravenous medications and fluids, taken by or administered to the patient within 28 days before the first dose of study drug(s) and 30 days after the last dose of study drug(s) or the initiation of a new anticancer therapy will be recorded.

Tumor lysis syndrome has been infrequently reported in patients with DLBCL. Patients with high tumor burden should be monitored closely and adopt prophylactic measures, including allopurinol, may be instituted per institutional standards.

Patients with hematologic malignancies, particularly patients having received prior lymphodepleting chemotherapy or having prolonged corticosteroid exposure, are predisposed to opportunistic infections because of disease and treatment-related factors. In patients with a high risk for opportunistic infections, including Pneumocystis jirovecii pneumonia (PJP), prophylaxis should be considered as per institutional standards.

Bisphosphonates and RANKL inhibitors are allowed for bone metastases if initiated before enrollment and at a stable dose. Bisphosphonates are permitted during the study for a nonmalignant indication.

Systemic Corticosteroids

Systemic corticosteroids for non-NHL diseases are allowed as follows:

- Systemic corticosteroids administered for the control of imAEs must be tapered gradually (see Appendix 9 and must be administered at nonimmunosuppressive doses (≤ 10 mg/day of prednisone or equivalent) before the next drug administration.

- Patients should not receive treatment with systemic corticosteroid other than intermittently to control or prevent infusion reactions or for short durations (< 2 weeks) to treat non-NHL-related condition(s) (eg, to treat a flare of chronic obstructive pulmonary disease).
- A short course (≤ 7 days) of systemic corticosteroid treatment for control of lymphoma-related symptoms is allowed prior to enrollment provided that it is tapered off within 5 days after initiation of study treatment.
- Chronic systemic corticosteroid use is not permitted, except for adrenal replacement, which requires consultation with the medical monitor.
- To reduce or control symptoms per standard of care and institutional guidelines.

Hepatitis B Treatment

Patients with active hepatitis B, defined as positive HBsAg or positive hepatitis B core antibody (HBcAb) with detectable HBV DNA (≥ 20 IU/mL) are excluded from study. Patients with negative HBsAg, positive HBcAb, and undetectable HBV DNA (< 20 IU/mL) are eligible but must receive at least monthly HBV reactivation monitoring during treatment, and patients should be considered for prophylactic antiviral treatment in consultation with a local HBV expert. Such medications must be documented in the patient's chart and recorded in the eCRF. If a patient is being treated prophylactically with antivirals, HBV DNA monitoring by PCR must be done at least every 3 months. HBV DNA monitoring should continue until the patient starts new antitumor therapy, or for any other reason listed in Section 7.5.2, whichever occurs first.

6.3. Prohibited Concomitant Medications/Procedures

The following medications are prohibited during the study or as otherwise noted:

- Any concurrent antitumor therapy, including radiation therapy, chemotherapy, hormonal therapy, immunotherapy, standard or investigational agents (including Chinese or other country herbal medicine and Chinese or other country patent medicines for the treatment of cancer [regardless of cancer type]), ≤ 14 days (or ≤ 5 half-lives, if applicable, whichever is shorter) before the first dose of study drug(s) and during the study.
- Drugs known to prolong QT/QTc interval should be avoided in the study. See Appendix 10.
- Live vaccines ≤ 28 days before the first dose of study drug(s) and ≤ 60 days following the last dose of study drug(s).
- Immunosuppressive agents (except to treat a drug-mediated AE).
- Patients should not abuse alcohol or other drugs.

  Herbal remedies with immune-stimulating properties (eg, mistletoe extract) or that are known to potentially interfere with liver or other major organ functions (eg, hypericin) ≤ 14 days (or ≤ 5 half-lives, if applicable, whichever is shorter) before the first dose of study drug(s) and during the study. Patients must notify the investigator of all herbal remedies used during the study.

7. STUDY PERIODS, VISITS, OR PROCEDURES

7.1. Screening Period

Screening evaluations will be performed ≤ 28 days before the first dose of study drug(s). A patient who agrees to participate in this study will sign the ICF before undergoing any study-specific screening assessment. Refer to Section 8.1 for instructions regarding screening assessments.

In some conditions (depends on study design and sponsor's decision), patient number may be limited, prescreening evaluations of PD-L1 on the surface of tumor cells status by local laboratory (with sponsor pre-approval, local laboratory collection may be substituted with central laboratory assessments) will be performed for patients who have histologically confirmed DLBCL and show a trend of lack of efficacy in their latest systemic anti-DLBCL treatments.

7.1.1. Informed Consent and Screening Log

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

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. Patient number will be assigned in chronological order starting with the lowest number. Once a patient number has been assigned to a patient, it cannot be reassigned to any other patient. If a patient is allowed to be rescreened, a new patient number will be assigned to the patient after reobtaining informed consent.

7.2. Enrollment

Prior to enrollment, the investigator is responsible for assessing and confirming that each patient meets all inclusion criteria for this study and that none of the exclusion criteria apply. All results from the screening procedure and relevant medical history must be available and reviewed by the investigator before eligibility can be determined. No eligibility waivers will be granted.

Sponsor verification of patient eligibility will be managed by way of source data verification in accordance with International Council for Harmonisation (ICH) E6.

The sponsor's medical monitor will support the investigator and/or site staff by answering any queries or questions relating to protocol eligibility criteria.

Participating women of childbearing potential should be placed on effective birth control as soon as medically reasonable and before initiation of study treatment.

7.3. Treatment Period

Patients enrolled by the sponsor will be treated as described in Section 5.2.

Refer to Section 7.5 and Section 8.3 for additional considerations regarding treatment discontinuation and withdrawal.

7.4. Follow-up Periods

7.4.1. Safety Follow-up Period

Patients who permanently discontinue all study drugs will be asked to return to the clinic for the Safety Follow-up Visit, which is required to be conducted within 30 days (± 7 days) after the last dose of study drugs or before the initiation of new antitumor therapy, whichever occurs first. Additional Safety Follow-up Visits at 60, 90, 120, 180 days after the last dose of study drugs (the visits at 120-day and 180-day are only required for women of childbearing potential) are required (in clinic or over the phone, as needed based on the assessments required). Patients will be contacted by telephone to assess imAEs and relevant concomitant medications (ie, those associated with an imAE or any new anticancer therapy). These contacts should be made at 60 days (± 14 days) and 90 days (± 14 days) after the last dose of study treatment, regardless of whether the patient starts a new anticancer therapy. For women of childbearing potential (see Appendix 5), an additional visit to perform a pregnancy test will occur at approximately 120 days after the last dose of tislelizumab and ociperlimab and 180 days after the last dose of rituximab. If a patient reports a suspected imAE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated.

All AEs, including SAEs, will be collected as described in Section 9.6.

See Appendix 1 for assessments to be performed at the Safety Follow-up Visit.

7.4.2. Efficacy Follow-up Period

Patients who discontinue study drug(s) for reasons other than PD (eg, toxicity) will continue to undergo tumor assessments following the original plan until the patient experiences PD, starts new antitumor therapy, or for any other reason listed in Section 7.5.2, whichever occurs first.

If patients refuse to return for these visits or are unable to do so, every effort should be made to contact the patients by telephone to determine their disease status.

7.4.3. Survival Follow-up

Patients will be followed for survival and to obtain information on subsequent anticancer therapy after discontinuation of study treatment via telephone calls, mail or email, patient medical records, and/or clinic visits approximately every 12 weeks (± 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.

7.4.4. Lost to Follow-up

If attempts to contact the patient by telephone are unsuccessful, additional attempts should be made to obtain protocol-required follow-up information. It may be possible to obtain the

information from other contacts, such as referring physicians or relatives. Attempts of contact should be documented in the patient's source documents. If a patient cannot be contacted despite all attempts, the patient will be considered lost to follow-up, and death information should be obtained through a public record search if local agencies permit.

7.5. Discontinuation From Study Treatment or From the Study

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

Patients have the right to discontinue study treatment at any time for any reason. In addition, the investigator has the right to discontinue a patient from study treatment at any time. Patients who discontinue study treatment for reasons other than PD should be followed for assessments of preliminary antitumor activity (Section 8.3) and safety (Section 8.2), if possible.

The primary reason for discontinuation from study treatment should be documented on the appropriate eCRF. Patients may discontinue study treatment for reasons including but not limited to the following:

- PD
- AE
- Withdrawal of consent
- Pregnancy
- Investigator's decision, including but not limited to:
  - Any medical condition that the investigator or sponsor determines may jeopardize the patient's safety if he or she were to continue the study treatment
  - Use of any concurrent antitumor therapy, including chemotherapy, hormonal therapy, immunotherapy, standard or investigational agents (including Chinese or other country herbal medicine and Chinese or other country patent medicines) for the treatment of cancer [regardless of cancer type])
  - Patient noncompliance
    Study 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 who are consistently noncompliant.

7.5.2. Patient Discontinuation From the 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
- Lost to follow-up
- Study termination by sponsor

7.6. 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. 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 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
- Patients have very limited benefit from treatment (eg, unsatisfactory antitumor activity)

The sponsor will notify each investigator if a decision is made to terminate the study. Should this be necessary, prematurely discontinued patients must be seen for a Safety Follow-up 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.

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

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

At the time of study termination as determined by the sponsor, any patient who is still on treatment and who, in the opinion of the investigator, continues to benefit from study drug(s) will be offered the option of continued access to study drug(s) without the need for further data collection via eCRFs. The study drug(s) will be administered per current assignment until disease progression is assessed by the investigator, any other reasons listed in Section 7.5.1 occur, or the patient has received the maximum of 2 years of study drug(s) after the first dose, whichever occurs first. Refer to Section 7.6.1 regarding the management and monitoring of patients who receive poststudy drug(s) after study termination by the sponsor.

7.6.1. Management and Monitoring for Patients Remaining on Treatment After Study Termination

Safety Assessment, Monitoring, and Reporting

- Safety assessments (eg, laboratory tests, ECGs, hepatitis B and C testing) will be performed at qualified local laboratories per investigator's discretion.
- All AEs should be adequately evaluated and recorded in the clinical source documents; only SAEs will be reported to BeiGene's Global Patient Safety per safety reporting in Section 9.6.2.1.

Tumor and Response Evaluations

- Patients will continue to undergo tumor assessments per investigator's discretion until they begin a subsequent anticancer treatment, experience disease progression, withdraw consent, are lost to follow-up, or die, whichever occurs first.

Pharmacokinetic and Biomarker Testing

- Blood or tissue samples will not be collected for PK, ADA, biomarker, or other exploratory analyses.

Safety Follow-up

- The Safety Follow-up Visit at 30 days after the last dose of study drug(s) will be performed per investigator's discretion.
- Additional Safety Follow-up Visits at 60, 90, 120, and 180 days after the last dose of study drug(s) and Survival Follow-up Visits will not be conducted.

Data Collection and Management

- Data generated after study termination by the sponsor will not be collected in the eCRFs.
- As a part of patient management, the investigator must collect and maintain patient clinical source documents per the requirements of local institutions.

The investigator is encouraged to communicate with the sponsor for any questions regarding patient management and monitoring during treatment with study drug(s). Patient management and monitoring, including tumor and response evaluations, safety assessments, study drug modifications, and follow-up will be generally concordant with the current approved protocol or per the investigator's discretion, with guidance provided above.

8. STUDY ASSESSMENTS

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.

Where applicable, 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.

8.1. Screening Assessments

Screening evaluations will be performed ≤ 28 days before the first dose of study drug(s) (refer to Appendix 1 for details). Patients who agree to participate will sign the ICF before undergoing any study-specific 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 ≤ 28 days before the first dose of study drug(s) may be used for the purposes of screening rather than repeating the standard-of-care tests unless otherwise indicated.

Procedures conducted only during the Screening Visit are described in this section. For the description of assessments that are conducted during screening as well as throughout the study, refer to Safety Assessments (Section 8.2), Tumor and Response Evaluations (Section 8.3), Bone Marrow Examination (Section 8.4), PK and ADA Assessments (Section 8.5) and Biomarkers (Section 8.7) sections.

Rescreening is allowed only once.

8.1.1. Pulmonary Function Tests

Pulmonary function tests may include but are not limited to spirometry and assessment of diffusion capacity, and will be done during the screening period to assist with the determination of suitability for the study.

Tests may be repeated as clinically indicated while on study.

8.2. Safety Assessments

8.2.1. Vital Signs

Vital signs including measurements of body temperature (˚C), pulse rate, blood pressure (systolic and diastolic), and weight will be performed at each study visit. Pulse rate and blood pressure will be measured while the patient is in a seated position after resting for 10 minutes. Height assessment is required only at screening.

8.2.2. Physical Examinations

During the Screening Visit, a complete physical examination will be conducted, including evaluations of 1) head, eyes, ears, nose, and throat; 2) cardiovascular; 3) dermatological; 4) musculoskeletal; 5) respiratory; 6) gastrointestinal; and 7) neurological systems. A complete physical examination also includes an assessment of systems per the standard of care at the study site and as clinically indicated by symptoms. Any abnormality identified during screening will be graded according to NCI-CTCAE Version 5.0 and recorded in the eCRF with appropriate disease/condition terms.

A limited examination of liver, spleen, lymph nodes will be performed at each study visit. New or worsened clinically significant abnormalities are to be recorded as AEs in the eCRF. Refer to Section 9.3 regarding AE definitions and reporting and follow-up requirements.

8.2.3. Ophthalmologic Examination

Because immune checkpoint inhibitors like tislelizumab may be associated with imAEs, an eye examination (including visual acuity test) and optical coherence tomography (or equivalent diagnostic test for retinal examination) will be assessed by an appropriate specialist as clinically indicated (Appendix 1A).

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 appropriate specialist will be made for further management guidance (see Appendix 9).

8.2.4. Eastern Cooperative Oncology Group Performance Status

ECOG Performance Status (Appendix 3) will be assessed during the study.

8.2.5. Laboratory Safety Tests

Local and/or central laboratory assessments of clinical chemistry, hematology, coagulation, and urinalysis will be conducted as outlined in Appendix 2 per the timepoints shown in Appendix 1A.

An investigator may obtain safety laboratory results from the local laboratory as clinically indicated (eg, on the day of a patient's visit before results are available from the central laboratory for dose modifications or AE/SAE monitoring). If required by local regulations, clinical laboratory evaluations performed by a local (instead of a central) laboratory are acceptable.

If clinical chemistry, hematology, and coagulation at screening are not performed ≤ 7 days before study drug administration on Day 1 of Cycle 1, these tests should be repeated and reviewed before study drug administration. After Day 1 of Cycle 1, results are to be reviewed within 72 hours before study drug administration.

For central laboratory assessments, details regarding sample collection and shipment will be provided in a separate laboratory manual.

The following tests will also be conducted in this study at timepoints shown in Appendix 1.

- Serum or urine pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative ≤ 7 days before the first dose of study drug(s). Furthermore, a negative serum or urine pregnancy test must be completed and recorded before administration of study drug(s) at each cycle. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.
- Thyroid function testing (ie, thyroid stimulating hormone, free triiodothyronine [T3], and free thyroxine [T4])
- Hepatitis serology and viral load (refer to Section 8.2.9)

8.2.5.1. Cardiac Enzyme Monitoring

Although immune-mediated myocarditis is a rare complication of immune checkpoint inhibitors, serum creatine kinase and creatine kinase-muscle/brain are monitored in all tislelizumab studies to protect study patients and to quantify the risk of muscle inflammation (see Appendix 1A for the blood collection schedule and Appendix 9 for guidelines for management of suspected immune-related myocarditis, respectively). Serum troponins may be substituted per local guidelines if used consistently throughout the study.

8.2.6. Electrocardiograms

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 and 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, and conversation) before each ECG collection.

The 12-lead ECGs will be performed at screening and when clinically indicated (see Appendix 1A). The ECG at screening must be performed in triplicate.

8.2.7. Echocardiogram/Multiple Gated Acquisition Scan

Echocardiogram/multiple gated acquisition (MUGA) scan assessments will be performed at the Screening Visit unless one has been performed within 28 days before the first dose of study drug, and as clinically indicated during the study (see Appendix 1A).

8.2.8. Adverse Events

AEs will be graded and recorded throughout the study according to NCI-CTCAE Version 5.0. Characterization of toxicities will include severity, duration, and time to onset.

All AEs, including SAEs, will be collected as described in Section 9.6.

8.2.9. Hepatitis B and Hepatitis C Testing

Hepatitis B/C serologic markers and/or viral load will be tested at screening. Hepatitis B and C testing may be performed by a local laboratory if the laboratory is able to perform the test to the required sensitivity (< 20 IU/mL and < 15 IU/mL for HBV and HCV, respectively); otherwise, the results must be confirmed by a central laboratory. The hepatitis B testing will include HBsAg, HBcAb, and hepatitis B surface antibody (HBsAb), as well as HBV DNA by PCR if the patient is negative for HBsAg but positive for HBcAb (regardless of HBsAb status). The hepatitis C testing will include HCV antibody as well as HCV RNA by PCR if the patient is positive for HCV antibody. Patients with positive HBsAg and/or detectable level of HBV DNA or detectable level of HCV RNA are not eligible.

Patients who are HBsAg negative, HBcAb positive, and HBV DNA negative (< 20 IU/mL) at screening must be monitored for HBV DNA by PCR at a monthly frequency. These patients should be considered for prophylactic antiviral treatment in consultation with a local HBV expert. If a patient is being treated prophylactically with antivirals, HBV DNA by PCR must be monitored at least every 3 months.

During monthly monitoring of HBV DNA by PCR, if the value is between 20 IU/mL and 100 IU/mL, then the HBV DNA level should be rechecked within 2 weeks. Study drugs should be stopped, and antiviral therapy should be initiated if the repeated level is between 20 IU/mL and 100 IU/mL. If the HBV DNA by PCR is 100 IU/mL or higher, then study drugs should be stopped, and antiviral therapy should be initiated or continued. Resumption of study drugs in patients whose HBV reactivation resolves should be discussed with and approved by the medical monitor and physicians with expertise in managing hepatitis B.

Patients who are HCV antibody positive and HCV RNA negative (< 15 IU/mL) at screening must be monitored for HCV RNA at a monthly frequency. Patients with HCV RNA of 15 IU/mL or higher should stop study drugs and initiate antiviral therapy. Resumption of study drugs in patients whose HCV reactivation resolves should be discussed with and approved by the medical monitor and physicians with expertise in managing hepatitis C.

HBV DNA and HCV RNA monitoring should continue until the patient starts new antitumor therapy, or for any other reason listed in Section 7.5.2, whichever occurs first.

The medical monitor should be informed of any suspected HBV or HCV reactivation

8.3. Tumor and Response Evaluations

Response will be assessed by the investigator using the Lugano Classification for NHL (see Appendix 8).

Tumor imaging will be performed ≤ 28 days before the first dose of study drug(s). Results of standard-of-care tests or examinations performed before informed consent has been obtained and ≤ 28 days before the first dose of study drug(s) may be used for the purposes of screening rather than repeating the standard-of-care tests. During the study, tumor imaging will be performed every 9 weeks (± 7 days), from Day 1 of Cycle 1, for the first 54 weeks; every 18 weeks (± 7 days) for additional 54 weeks; then every 24 weeks thereafter based on the Lugano Classification (2014) (Cheson et al 2014). For patients who are positive for PET-CT scans at

screening, PET-CT should be repeated at Week 9 (± 7 days), Week 18 (± 7 days), at time when confirming CR or PD, and as clinically indicated.

At screening, all patients must undergo positron-emission scan (PET)-CT scan and CT with contrast of neck, chest, abdomen, and pelvis. Contrast CT will be performed for each subsequent tumor assessment. If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the study, an MRI should be performed but must be used consistently.

PET-CT may be used in lieu of a CT with contrast only if the CT of the PET-CT has been performed with diagnostic quality and contrast is administered. When both PET-CT and CT evaluations are available for the same tumor assessment visit, the results of PET-CT shall prevail.

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).

For immune therapies such as ociperlimab and tislelizumab, pseudoprogression may occur due to immune-cell infiltration and other mechanisms leading to an apparent increase of existing tumor masses or appearance of new tumor lesions. Also, some patients may benefit from additional immune therapies despite evidence of PD. If radiographic PD is suspected by the investigator to reflect pseudoprogression and the clinical condition is stable, patients may continue treatment of study drugs as long as patients meet criteria below and until PD is confirmed by a repeated imaging ≥ 4 weeks later (but not exceeding 12 weeks from the initial documentation of PD).

- Absence of clinical symptoms and signs of PD (including clinically significantly worsening of laboratory values)
- Stable ECOG Performance Status
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, cord compression) that requires urgent alternative medical intervention

Tumor assessment should continue as planned in patients until the patient begins a new antitumor therapy, experiences PD, withdraws consent, is lost to follow-up, dies, or until the study terminates, whichever occurs first. Clinical suspicion of disease progression at any time will require a physical examination and radiological confirmation to be performed promptly, rather than waiting for the next scheduled tumor assessment.

Tumor assessments must be performed on schedule regardless of whether study treatment has been administered or withheld. That is, they should not be adjusted for delays in cycles.

8.4. Bone Marrow Examination

Bone marrow biopsy and aspirate are required to assess bone marrow involvement of patients during the screening period, unless they have been performed within 60 days before the first dose of study drug and there has been no intervening therapy from the time of the biopsy/aspirate until the first dose of study drug. For patients who have evidence of bone marrow disease at screening,

repeated bone marrow biopsy may not be needed if PET-CT shows bone marrow clearance at CR.

8.5. Quantitative Serum Immunoglobulin Assessment

Serum immunoglobulin, including IgG, IgM, and IgA will be quantitatively assessed at screening, together with tumor evaluations during the treatment period (every 9 weeks [± 7 days], from Day 1 of Cycle 1, for the first 54 weeks; every 18weeks [± 7 days] for additional 54 weeks; then every 24 weeks [± 7 days] thereafter [Appendix 1A]), and at the Safety Follow-up Visit.

8.6. Pharmacokinetic Assessment and Antidrug Antibody Testing

Blood samples will be collected for characterizing the PK of ociperlimab and tislelizumab. Serum samples will be assayed for ociperlimab and tislelizumab concentrations using validated immunoassays. Validated screening and confirmatory assays will be employed to detect ADAs at multiple timepoints throughout the study.

Blood sampling for PK and ADA will be collected at the timepoints specified in the Schedule of Assessments (Appendix 1B and Appendix 1C). The actual time and date of each sample collected will be captured in the eCRF and recorded in the database. The samples will be sent to the sponsor or designee for storage and/or analysis.

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

8.7. Biomarkers

Shipping, storage, and handling of blood as well as archival tumor and/or fresh tumor tissue and blood sample for the assessment of biomarkers will be managed through a central laboratory. Refer to the laboratory manual for details of sample handling and the Schedule of Assessments (Appendix 1A) for sample collection timepoints.

The archival or fresh tumor tissues are mandatory for all patients who consent to participate in the study. If no archival samples are available, a fresh tumor biopsy at baseline is required. Also, if the patient can provide eligible archival tumor tissues and is willing to undergo fresh tumor biopsy at screening, a fresh tumor biopsy is strongly recommended. Archival (within 1 year before signing the ICF) and/or fresh tumor tissues (approximately 15 unstained slides) at screening need to be sent to the central laboratory for diagnosis confirmation and biomarker analysis, including expression of PD-L1, TIGIT, CD226, CD155, and CD112, PD-L1/2 gene alteration, EBV status. Tumor microenvironment, immune-related gene expression profile, and gene mutation profile that are related to response or clinical benefit of ociperlimab in combination with tislelizumab or rituximab will also be evaluated. Baseline tissue samples collected during screening will be shipped to a central laboratory for biomarker testing after local regulatory approval. This may occur after the start of study treatment if necessary.

An optional tumor biopsy will be taken from accessible tumor sites at C2D1 and C4D1 to explore tumor biomarkers, including tumor microenvironment and immune-related gene expression profile which may be associated with response and resistance to study drugs. Optional

biopsies will also be obtained for patients treated with study drugs who have confirmed PD during the study from accessible tumor sites to obtain samples to explore tumor microenvironment and gene mutation/expression profiling associated resistance mechanism. 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.

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. Bone marrow biopsy is not acceptable. Tumor biopsy from an inguinal lymph node is only acceptable when a tumor biopsy cannot be obtained from other sites. For fresh biopsy specimens, acceptable samples include core needle biopsies for deep tumor tissue or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.

Blood samples will be collected for all patients at predose of C1D1, C1D2, C1D8, C2D1, and at the time of PD to explore the association of blood-based biomarkers with response, resistance, and prognosis to ociperlimab in combination with tislelizumab or rituximab. Blood-based biomarker analysis includes immune-cell quantification and phenotypes, cytokine profiling, immune-related gene expression profiling, and DNA/ctDNA sequencing.

8.8. 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 treatment administration (Day 1) of each cycle should be performed before study treatment infusion 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 event, 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.

8.9. Unscheduled Visits

Unscheduled visits may be performed at any time at the patient's or the investigator's request and may include vital signs/focused physical examination; ECOG Performance Status; AE review; concomitant medications and procedures review; radiographic assessments; physical examination of 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 assessment as appropriate, and the results of these tests should be entered on the unscheduled visit eCRF.

9. 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.

9.1. Risks Associated With Study Drug

9.1.1. Risks Associated With Ociperlimab and Tislelizumab

Ociperlimab and tislelizumab are investigational agents that are currently in clinical development. The first-in-human Study AdvanTIG-105 evaluating safety, tolerability, and clinical benefit of ociperlimab in combination with tislelizumab in solid tumors is still ongoing. 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 ociperlimab and tislelizumab 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 9.7.3. Ociperlimab-mediated TIGIT inhibition may increase the risk of imAEs. However, no apparent immunotoxicity, or toxicity in general, have 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 affect 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 evaluation and management guidelines for suspected imAEs are provided in Appendix 9.

9.1.2. Risks Associated With Rituximab

Rituximab is a CD20-directed cytolytic antibody, which had been received approval for the treatment of patients with CD20-positive DLBCL and other NHL. The important identified risks of rituximab included IRRs, severe mucocutaneous reactions, HBV reactivation, progressive multifocal leukoencephalopathy, tumor lysis syndrome, infections, cardiovascular adverse reactions, renal toxicity, bowel obstruction and perforation, immunizations, and embryo-fetal toxicity.

Please refer to the Rituximab prescribing information 2021 for details.

9.2. General Plan to Manage Safety Concerns

9.2.1. 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 at risk for study-emergent active autoimmune diseases or with 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 vaccine ≤ 4 weeks before the first dose of study drug(s) are excluded from the study. Patients with contraindications for study drugs and other monoclonal antibodies are also excluded from the study (see Section 4.2 for the full list of exclusion criteria).

9.2.2. Abnormal Liver Function Tests

The finding of an elevated ALT or AST (> 3 x baseline value) in combination with either an elevated total bilirubin (> 2 x ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an AE the occurrence of either of the following:

- Treatment-emergent ALT or AST > 3 x baseline value in combination with total bilirubin > 2 x ULN (of which 35% is direct bilirubin)
- Treatment-emergent ALT or AST > 3 x baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the AE eCRF and reported to the sponsor immediately (ie, ≤ 24 hours after learning of the event).

9.2.3. Safety Monitoring Plan

Safety will be evaluated in this study through the monitoring of all AEs, defined and graded according to NCI-CTCAE Version 5.0.

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 3), 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 infections or autoimmune conditions.

At the start of each cycle, study drug(s) will be administered only after clinical laboratory results have been reviewed. Administration of study drug(s) 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 and tislelizumab in patients for both the Dose Confirmation and Dose Expansion Stages of the study.

Investigators are instructed to report all AEs (includes 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 9.7.

9.3. Adverse Events

9.3.1. 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 drug(s), whether considered related to study drug(s) or not.

Examples of AEs include:

- Worsening of a chronic or intermittent pre-existing condition, including an increase in severity, frequency, duration, and/or has an association with a significantly worse outcome
- Detection or diagnosis of a new condition after study drug(s) administration even though the condition might have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug(s) 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) relative 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 blinded on the copies of the medical records before submission to the sponsor.

9.3.2. Assessment of Severity

The investigator will assess the severity for each AE and SAE reported during the study. AEs and SAEs should be assessed and graded based upon NCI-CTCAE Version 5.0.

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-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 9.6.2.

9.3.3. Assessment of Causality

The investigator is obligated to assess the relationship between the study drug(s) and the occurrence of each AE or SAE using best clinical judgment. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the AE or SAE to the study drug(s) should be considered and investigated. The investigator should consult the Tislelizumab (BGB-A317) Investigator's Brochure, Ociperlimab (BGB-A1217) Investigator's Brochure, and Rituximab prescribing information 2021 in the determination of his/her assessment.

There may be situations when an SAE has occurred, and the investigator has only limited 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 1 of the criteria used when determining regulatory reporting requirements. The investigator may subsequently change his/her opinion of causality considering follow-up information and may amend the SAE report accordingly.

The causality of each AE should be assessed and classified by the investigator as "related" or "not related" based on all information available at the time of reporting. An AE is considered related if there is "a reasonable possibility" that the AE may have been caused by the study drug(s) (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 treatment/study procedure
- Whether an alternative etiology has been identified
- Mechanism of action of the study drug(s)
- Biological plausibility
- An AE should be considered "related" to study drug(s) if any of the following criteria are met; otherwise, the event should be assessed as "not related":
  - 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).

9.3.4. Follow-up of Adverse Events

After the initial AE or SAE report, the investigator is required to proactively follow 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 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 timeframes outlined in Section 9.6.2.

9.3.5. 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 significantly worsen during the study. The definition of clinically significant is left to the judgment 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 treatment 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 5 x ULN associated with cholestasis), only the diagnosis (ie, cholestasis) should be recorded on the AE 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 should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the AE 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.

9.4. 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 was 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 one of the outcomes listed above)

The following are NOT considered to be 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

9.5. Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction is a serious adverse reaction that is both unexpected (ie, not present in the study drug's reference safety information) and meets the definition of a serious adverse drug reaction, the specificity or severity of which is not consistent with those noted in the Tislelizumab (BGB-A317) Investigator's Brochure, Ociperlimab (BGB-A1217) Investigator's Brochure, and Rituximab prescribing information 2021.

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

9.6.1. Adverse Event Recording Period

After informed consent has been signed but before the administration of the study drug(s), only SAEs should be reported.

After the first dose of study drug(s), all AEs and SAEs, regardless of relationship to study drug(s), will be reported until either 30 days after the last dose of study drug(s) or initiation of new antitumor therapy, whichever occurs first. Immune-mediated AEs (serious or nonserious) should be recorded until 90 days after the last dose of ociperlimab and tislelizumab, regardless of whether or not the patient starts a new antitumor 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 according to the details in Table 3. For the follow-up period for AEs, see Section 9.3.4. For the definition of treatment-emergent adverse events (TEAEs), see Section 10.3.2.

Table 3: Guidance for Duration of Recording New or Worsening Adverse Events in Cohort 1 and Cohort 2

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 new antitumor therapy, death, withdrawal of consent, or loss to follow-up, whichever occurs first
Treatment-related SAEs	Signing of informed consent	Patient death, withdrawal of consent, or loss to follow-up, whichever occurs first
Nonserious AEs due to PD	Do not record (see Section 9.6.4)	
All nonserious AEs, except those due to PD	First dose of study drug	Up to 30 days after last dose, initiation of new antitumor 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 antitumor 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.

9.6.2. Reporting Serious Adverse Events

9.6.2.1. 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 4.

Table 4: Timeframes and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

	Timeframe for sending initial/follow-up report[a]	Documentation method	Reporting method
All SAEs before the study termination	≤ 24 hours after first knowledge of the SAE	SAE report	Electronic submission of SAE form to portal[b]

All SAEs after the study termination	≤ 24 hours after first knowledge of the SAE	SAE report	Email or fax SAE form

Abbreviations: AE, adverse event; SAE, serious adverse event.

[a] Report follow-up information that is clinically relevant and pertains 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 electronic data capture system. If the electronic submission is not available for any reason, a paper SAE form should be submitted by email or fax.

9.6.2.2. 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 9.6.2.1. The SAE report will always be completed as thoroughly as possible, including all available details of the event and forwarded to the sponsor or designee within the designated timeframes.

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 9.3.3.

The sponsor will provide contact information for SAE receipt.

9.6.2.3. Regulatory Reporting Requirements for Serious Adverse Events

The investigator will report all SAEs to the sponsor in accordance with the procedures detailed in Section 9.6.2.1. 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 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 suspected unexpected serious adverse reactions (as defined in Section 9.5) will be submitted to all applicable regulatory authorities and investigators for ociperlimab, tislelizumab, and rituximab 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.

9.6.3. 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?

9.6.4. Progressive Disease

Disease progression, which is expected in this study population and is 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 disease progression should not be recorded. However, if there is any uncertainty as to whether a nonserious AE is due to disease progression, it should be recorded as an AE (Section 9.6.2).

9.6.5. Deaths

When a patient dies, if the only information available is death and the cause of death is unknown, then the death is reported as an AE, eg, "death NOS." In all other cases, death is captured as an outcome.

9.6.6. Recording Pregnancies

If a female patient or the partner of a male patient becomes pregnant while receiving study drug(s) or within 120 days after the last dose of ociperlimab and/or tislelizumab, or within 12 months after the last dose of rituximab, 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 following 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 drug(s) should be recorded and reported as an SAE.

9.6.7. 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 (BGB-A1217) Investigator's Brochure
- Tislelizumab (BGB-A317) Investigator's Brochure
- Rituximab prescribing information 2021

9.6.8. Assessing and Recording Immune-Mediated Adverse Events

Since treatment with anti-PD-1 or ociperlimab therapy can cause autoimmune disorders, AEs considered by the investigator to be immune related (see Section 9.7.3) should be classified as imAEs and identified as such in the eCRF AE page. Not all tislelizumab studies include a section in the eCRF AE page where imAEs are clearly identified. Therefore, all studies will rely on the company list of potential imAEs to identify all cases in each study to be further assessed as imAEs by the sponsor, in addition to those imAEs reported by the investigator via the AE CRF page.

Investigators should consult the guidance on diagnostic evaluation and management of imAEs, which are commonly seen with immune checkpoint inhibitors, in Appendix 9.

An extensive list of potential imAEs appears in Table 6. All conditions similar to 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 9.

9.6.9. Recording Infusion-Related Reactions

The symptoms of IRRs 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. Individual signs and symptoms of an infusion reaction should be recorded each as a separate AE in the eCRF and identified as an IRR. Refer to the eCRF completion guidelines for details.

9.7. Management of Adverse Events of Special Interest

As a routine precaution, following completion of study drug(s) administration, patients must be monitored for a period afterward in a setting where emergency medical equipment and staff who are trained to respond to medical emergencies are available.

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

9.7.1. Managing Infusion-Related Reactions

Patients should be closely monitored for IRRs. 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 IRRs.

Treatment modifications for symptoms of IRRs due to study drug(s) are provided in Table 5.

Table 5: Treatment Modifications for Symptoms of Infusion-Related Reactions Due to Study Drug(s)

NCI-CTCAE grade	Treatment modification for ociperlimab, tislelizumab, or rituximab
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. Subsequent infusions should be given after premedication and at the reduced infusion rate.
Grade 2 - moderate Therapy or infusion interruption indicated but 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 once infusion-related reaction has resolved or decreased to Grade 1 in severity. Any worsening is closely monitored. Proper medical management should be instituted as described in the text following this table. Subsequent infusions should be given after premedication and at the reduced infusion rate.
Grade 3 – severe Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae.	Immediately stop the infusion. Proper medical management should be instituted as described in the text following this table. The patient should be withdrawn from study drug treatment.
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 following this table. The patient should be withdrawn from study drug treatment. Hospitalization is recommended.

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

Once the ociperlimab, tislelizumab, or rituximab infusion rate has been decreased by 50% or suspended due to an IRR, it must remain decreased for all subsequent infusions and premedication must be administered. If the patient has a second IRR (≥ Grade 2) on the slower infusion rate, the infusion should be discontinued and the patient should be withdrawn from ociperlimab, tislelizumab, or rituximab treatment.

NCI-CTCAE Grade 1 or 2 infusion reaction: 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 reaction: 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 antihistamines, antipyretics, glucocorticoids, epinephrine, bronchodilators, and oxygen.

9.7.2. Severe Hypersensitivity Reactions and Flu-Like Symptoms

If 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.

In the event of a systemic anaphylactic/anaphylactoid reaction, the infusion must be stopped immediately, and the patient must be discontinued from the study. Systemic anaphylactic/anaphylactoid reactions typically manifest within minutes following administration of the drug/antigen and 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.

The patient will be administered epinephrine injection and dexamethasone infusion if hypersensitivity reaction is observed. The patient should then 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 nonsteroidal anti-inflammatory drugs (ie, 600 mg ibuprofen or 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.

9.7.3. 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 in the eCRF AE page should be checked.

A list of potential imAEs is shown below in Table 6. All conditions similar to those listed should be evaluated in patients receiving tislelizumab or ociperlimab to determine whether they are immune related.

Recommendation for diagnostic evaluation and management of imAEs is based on European Society for Medical Oncology and American Society of Clinical Oncology guidelines (Haanen et al 2017; Brahmer et al 2018) and common immune-mediated toxicities are detailed in Appendix 9. For any AEs not included in Appendix 9, please refer to the American Society of Clinical Oncology Clinical Practice Guideline (Brahmer et al 2018) for further guidance on diagnostic evaluation and management of immune-related toxicities.

Table 6: Examples of 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 9.

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

9.7.4. Management of Immune-mediated AEs in Patients With Pre-Existing Renal Dysfunction

Patients with moderate renal dysfunction (as estimated by Cockcroft-Gault equation or as measured by nuclear medicine scan or 24-hour urine collection) may be enrolled into the study. For patients with baseline renal insufficiency, the following algorithm is proposed for the use of steroid treatment in the management of imAEs:

- If the serum creatinine was normal at baseline, please see Section 9.7.3 and refer to Appendix 9 for the diagnosis and management of patients with abnormal renal laboratory values.
- If the serum creatinine was Grade 1 at baseline and the increase in serum creatinine meets criteria for serum creatinine increase ≥ Grade 2 after starting treatment with study drug(s), refer to Appendix 9 for the diagnosis and management of patients with abnormal renal laboratory values. Check the estimated creatinine clearance using Appendix 7. In the setting of a Grade 2 serum creatinine increase only, study

treatment can continue unless the serum creatinine increases by ≥ 50% from the baseline value.

- If the serum creatinine is Grade 2 at baseline and the increase in serum creatinine meets criteria for serum creatinine increase ≥ Grade 3 after starting treatment with study drug(s), refer to Appendix 9 for the diagnosis and management of patients with abnormal renal laboratory values. In the setting of a Grade 3 serum creatinine increase only, study treatment will be held until serum creatinine improves to baseline and treatment may resume only after discussion with the medical monitor.

10. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

As described in the study objectives, this study is designed to establish the safety and tolerability of ociperlimab in combination with tislelizumab or rituximab and to assess preliminary antitumor activities in patients with R/R DLBCL.

Details of the statistical analyses will be included in a separate statistical analysis plan.

10.1. Statistical Analysis

10.1.1. Analysis Sets

The Safety Analysis Set includes all patients who received any dose of any study drug(s). This will be the analysis set for the safety analyses.

The Efficacy Analysis Set includes all patients who received any dose of any study drug(s), have evaluable disease at baseline, and have ≥ 1 evaluable postbaseline tumor response assessment unless any clinical PD or death occurred before the first postbaseline tumor assessment.

The DLT-Evaluable Analysis Set includes patients who 1) experienced a DLT event or 2) received ≥ 80% each scheduled study drug administration remained on study during the DLT assessment window in the dose confirmation stage.

The PK Analysis Set includes all patients who received any dose of any study drug(s) per the protocol, for whom any quantifiable postdose PK concentrations are available.

The Immunogenicity Analysis Set includes all patients who received any dose of any study drug(s), for whom both baseline ADA and ≥ 1 postbaseline ADA results are available.

10.1.2. Patient Disposition

The number of patients enrolled, treated (by each study drug), and discontinued from study drug(s) and/or the study will be counted. The primary reason for study drug(s) and/or study discontinuation will be summarized according to the categories in the eCRF.

10.1.3. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized descriptively in the Safety Analysis Set. Continuous variables might include age, weight, and body mass index. Categorical variables might include sex, ECOG Performance Status, race, ethnicity, hepatitis B core antibody, and hepatitis C antibody. A listing of demographic and other baseline characteristics will be provided.

10.1.4. Prior and Concomitant Medications

Prior medications will be defined as medications that started before the day of first dose of study drug(s). Concomitant medications will be defined as medications that 1) started before the first dose of study drug(s) and were continuing at the time of the first dose of study drug(s), or 2) started on or after the date of the first dose of study drug(s) and up to 30 days after the patient's last dose or the initiation of a new anticancer therapy. Concomitant medications will be

coded using the World Health Organization Drug Dictionary drug codes. Prior and concomitant medications will be summarized and listed by drug and drug class. A listing of prior and concomitant medications will be provided.

10.2. Efficacy Analyses

Efficacy analyses will be conducted based upon investigators' tumor assessments using the Lugano Classification (2014) (Cheson et al 2014) in the Efficacy Analysis Set, performed by cohort and dose if necessary.

ORR

The primary efficacy endpoint is ORR. ORR is defined as the proportion of patients achieving a best overall response of CR or PR. The point estimate and corresponding two-sided Clopper-Pearson 95% CI for ORR will be presented.

The best overall response is defined as the best response recorded from the date of first dose of study drug(s) to the date of documented PD or new anti-cancer therapy, whichever occurs first. The proportion for each response category (CR, PR, stable disease [SD], and PD) will be presented.

For patients in the Efficacy Analysis Set but with clinical PD or death occurring before the first postbaseline tumor assessment, their best overall response will be considered as PD or Not Assessable, respectively.

CR rate

CR rate will be summarized with the same method as ORR.

DOR

DOR for responders (CR or PR) is defined as the time (months) from the date of the earliest qualifying response (PR or better) to the date of PD, as determined by the investigator, or death for any cause, whichever occurs earlier. The DOR censoring rule will follow the United States Food and Drug Administration Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (US Food and Drug Administration 2018). Kaplan-Meier methodology will be used to estimate the median and other quartiles and 95% CI for DOR. Only responders will be included in this analysis.

PFS

PFS is defined as the time (months) from the date of first dose of study drug(s) to PD, as determined by the investigator, or death of any cause, whichever occurs first. The censoring rules for PFS will follow the DOR censoring rules.

Kaplan-Meier methodology will be used to estimate the median and other quantiles of PFS. Kaplan-Meier curves will be constructed to provide a visual description of the PFS change with time. Two-sided 95% CIs of median and other quartiles, if estimable, will be constructed with a generalized Brookmeyer and Crowley method (Brookmeyer and Crowley 1982) with log-log transformation. PFS rates at selected landmark timepoints (eg, 6-month) will be provided with the corresponding 95% CIs calculated based on the Greenwood's formula (Greenwood 1926) with log-log transformation.

The duration of the follow-up for PFS will be determined by reverse Kaplan-Meier method (Schemper and Smith 1996).

TTR

TTR for responders (CR or PR) is defined as the time (months) from the date of first dose of study drug(s) to the date of the earliest qualifying response (PR or better) as determined by the investigator. TTR will be summarized by sample statistics, such as mean, median, and standard deviation for responders only.

OS

OS is defined as the time (months) from the date of first dose of study drug(s) to death due to any cause. Patients who remain alive before data cutoff date or discontinuation of the study (discontinued study due to reasons other than "Death") will be censored at the time of the last date the patient is known to be alive. OS will be analyzed using the similar method as described for PFS.

All PD-L1-related subgroups analyses will be conducted using the same method as above and based on centrally tested PD-L1 expression level.

10.3. Safety Analyses

Safety analyses will be conducted in the Safety Analysis Set and DLT-Evaluable Analysis Set and by cohort and dose if necessary.

10.3.1. Extent of Exposure

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

The number (percentage) of patients requiring treatment interruption and dose delay will be summarized for each study drug. Reasons for dose modifications will be summarized as well.

Patient data listings will be provided for dosing records and for calculated summary statistics.

10.3.2. Adverse Events

The AE verbatim descriptions (investigator's description from the eCRF) will be coded using MedDRA.

DLTs will be summarized at each dose cohort in dose confirmation stage.

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 following study drug(s) discontinuation or initiation of new antitumor therapy, whichever occurs first. Worsening of any TEAE to Grade 5 beyond 30 days after the last dose of study drugs is also considered a TEAE (if it is prior to the initiation of new anticancer therapy). The TEAE classification also applies to imAEs that are recorded up to 90 days after the last dose of tislelizumab and/or ociperlimab, regardless of whether or not the patient starts a new antitumor therapy. Only AEs that were treatment emergent will be included in summary tables of TEAEs. All AEs, treatment-emergent or otherwise, will be presented in patient data listings.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by System Organ Class and Preferred Term. A patient will be counted only once by the highest severity grade per NCI-CTCAE Version 5.0 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 AEs include those events considered by the investigator to be related to study treatment or with missing assessment of the causal relationship. SAEs, deaths, ≥ Grade 3 TEAEs, imAEs, treatment-related TEAEs, and TEAEs that led to treatment discontinuation, treatment interruption, or dose delay will be summarized.

10.3.3. 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 provided. Laboratory parameters that are graded by NCI-CTCAE Version 5.0 or higher will be summarized by NCI-CTCAE grade.

A data listing of patients with Grade 3 or higher postbaseline toxicity for selected laboratory parameters will be provided. Other analysis such as descriptive summary statistics or changes from baseline by visit for laboratory parameters might be summarized if deemed necessary.

10.3.4. Vital Signs

Descriptive statistics for vital sign parameters (systolic and diastolic blood pressure, pulse rate, and body temperature) and changes from baseline might be presented if deemed necessary.

10.3.5. Electrocardiograms

Actual value and change from baseline for the ECG parameters (such as QT interval, heart rate, and QTcF interval) may be presented by visit if deemed necessary.

10.3.6. Eastern Cooperative Oncology Group (ECOG) Performance Status

A shift table from baseline to worst post-baseline score in ECOG Performance Status may be summarized if deemed necessary.

10.4. Pharmacokinetic Analyses

Serum concentration data and PK parameters (as appropriate) of ociperlimab and tislelizumab for each sampling time will be tabulated and summarized by visit/cycle for each treatment. Descriptive statistics will include means, medians, ranges, and standard deviations, as appropriate.

Additional PK analyses such as population PK analyses may be conducted as appropriate, and the results of such analyses may be reported separately from the clinical study report.

10.5. 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 allow and reported separately from the main clinical study report.

10.6. Other Exploratory Analyses

Exploratory biomarker analyses will be performed in an effort to understand the association of these markers with study drug(s) response, such as efficacy.

10.7. Sample Size Consideration

The study plans to enroll approximately 66 to 80 patients:

- Cohort 1: Approximately 43 to 50 patients
- Cohort 2: Approximately 23 to 30 patients

For Cohort 1, the sample size of approximately 40 patients at RP2D is based on the precision of the estimate of ORR, a consideration that a relatively sufficient number of patients is needed to justify performing further analysis (eg, the subgroup analysis based on cutoff value of tumor PD-L1 expression), and a probability that is high enough to observe certain AEs of interest (eg, rash). With 40 patients, if the observed ORR is 60%, the corresponding Clopper-Pearson 95% CI will be 43.3% to 75.1%. For an AE with a rate of 10%, there is 98.5%probability to observe ≥ 1 event of such an AE among all 40 patients (multiple same AE on one patient will be counted only once). To reflect the natural distribution across PD-L1 expression given a relatively small sample size at interim analysis, the number of eligible patients with PD-L1 expression ≤ 5% on the surface of tumor cells as determined by local laboratory will be capped to ≤ 50% of the first 20 patients enrolled, and the benefit-risk profile may also be evaluated by the SMC and sponsor for these patients. After the interim analysis, the number of these patients with PD-L1 expression ≤ 5% on the surface of tumor cells as determined by local laboratory may be further capped per the SMC's recommendation considering the totality of emerging data. Considering the patients in the Dose Confirmation Stage that are not dosed at RP2D dose level (approximately 3 to 10 patients), approximately 43 to 50 patients in total will be enrolled in Cohort 1.

For Cohort 2, the sample size of approximately 20 patients at RP2D is based on the precision of the estimate of ORR. With 20 patients, if the observed ORR is 60%, the corresponding Clopper-Pearson 95% CI will be 36.1% to 80.9%. Considering the patients in the Dose Confirmation Stage that may not be dosed at RP2D dose level (approximately 3 to 10 patients), approximately 23 to 30 patients in total will be enrolled in Cohort 2.

10.8. Interim Analyses

One futility interim analysis for ORR is planned to be conducted when approximately 20 patients have been enrolled and meet the definition of Efficacy Analysis Set with a non-binding futility boundary of 35% (equivalent to observe ≤ 7 responders) for Cohort 1. If the true ORR is as low as 30%, there is 77% of probability that the futility boundary is met; if the true ORR is otherwise

deemed to be at least 60%, the probability of meeting the boundary is estimated to be ≤ 2%. The final decision will be made by the SMC along with the sponsor.

11. STUDY COMMITTEES

11.1. Safety Monitoring Committee

An 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, efficacy, PK, and exploratory data and make recommendations of RP2D on Dose Confirmation Stage.

The SMC will continue monitoring safety data throughout the study and make the decision along with the sponsor at the interim analysis for Cohort 1. 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.

12. 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.

12.1. Access to Information for Monitoring

In accordance with International Council for Harmonisation 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 study 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 in the eCRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected during these monitoring visits are resolved.

12.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of BeiGene 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 representatives of a regulatory agency or BeiGene access to records, facilities, and personnel for the effective conduct of any inspection or audit.

13. QUALITY ASSURANCE AND QUALITY CONTROL

13.1. Regulatory Authority Approval

The sponsor will 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.

13.2. 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.

13.3. 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.

13.4. Drug Accountability

The investigator or designee (ie, pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug(s). This includes acknowledgment of receipt of each shipment of study drug(s) (quantity and condition), patient drug dispensation records, and returned or destroyed study drug(s). Dispensation records will document quantities received from BeiGene'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 BeiGene requirements specified in the Pharmacy Manual. At appropriate times during the conduct of the study or at the end of the study following final drug inventory reconciliation by the 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 BeiGene's requirements specified in the Pharmacy Manual for disposal, arrangements will be made between the site and BeiGene 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.

14. ETHICS/PROTECTION OF HUMAN PATIENTS

14.1. Ethical Standard

This study will be conducted by the principal investigator and the study center in full conformance with the International Council for Harmonisation 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 patient. The study will also comply with the requirements of the International Council for Harmonisation E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

14.2. 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 IEC/IRB 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.

14.2.1. 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.

14.3. 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.

14.4. Patient and Data Confidentiality

The investigator, institution, sponsor, and site will maintain confidentiality and privacy standards for the collection, storage, transmission, and processing of patients' personal and medical information by following applicable laws and regulations related to the confidentiality, use, and protection of such information, including the ICH Good Clinical Practice Guideline, as implemented locally. Such laws may be more stringent than the requirements in this protocol.

The investigator and site shall code the personal and medical information obtained during the study with a unique patient identification number assigned to each patient enrolled in the study. The investigator must ensure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Unless required to be provided by laws or regulations or specifically requested in exceptional circumstances by the sponsor or its representatives, the investigator and site must ensure that any personal and medical information transmitted to sponsor or its service providers is: 1) required by the protocol, and 2) appropriately de-identified (eg, via redaction and/or coding with the patient identification number) to ensure the following information about patients are NOT shared:

- names or initials (full or partial);
- *full* dates of birth;
- contact information (such as phone numbers or home or email addresses);
- numerical identifiers (eg, hospital or medical record, government, health insurance, or financial account numbers) other than patient identification numbers assigned as part of this study;

- geographic identifiers smaller than a state, province, or local equivalent (such as city, county, zip code, or other equivalent geographic identifiers); or
- information about marital status, family, or household members; employment, sex life, sexual preference, or other sensitive data that is not relevant to the study.

Patient personal and medical information obtained during this study is confidential and may only be disclosed to third parties 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 limited circumstances, such as in connection with insurance purposes or patient support services ancillary to certain study sites (eg, for patient travel or reimbursement), the investigator and site may provide certain of this personal information to the sponsor or its representatives. Such personal information may not be provided as part of the study protocol (eg, as part of the eCRF, on samples or reports submitted to the central lab, on safety reporting forms [except in China], or on product dispensing logs provided to the sponsor, etc.).

Investigator and site must use only the specific forms and clinical trial systems, (eg, the electronic data capture [EDC] system and any secure file transfer platforms [SFTPs]) designated by sponsor for sharing and transfers of personal and medical information.

In the event of a breach of the confidentiality of a patient's personal and medical information, the investigator, site, and sponsor, as appropriate, shall fulfill all mediation steps and reporting obligations under applicable laws. If the sponsor identifies personal or medical information that was not properly de-identified, it may be required to report the disclosure under local applicable 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 where allowed by local law or the patient's signed ICF.

Information generated during this study must be available for inspection upon request by representatives of the United States Food and Drug Administration (US FDA), the China National Medical Products Administration (China NMPA), 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 agrees that all information received from the sponsor, including but not limited to the Investigator's Brochure, this protocol, eCRFs, the investigational drugs, and any other study information, are confidential and 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 or privacy provisions inconsistent with this section is executed, that contract's provisions shall apply to the extent they are inconsistent with this section.

14.5. 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 the clinical investigators and/or disclose those financial interests, as required, to the appropriate health authorities. This is intended to ensure financial interests and arrangements of the clinical investigators with BeiGene 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).

15. DATA HANDLING AND RECORD KEEPING

15.1. Data Collection and Management Responsibilities

15.1.1. 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.

15.1.2. 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 electronic data capture system to attest to its accuracy, authenticity, and completeness.

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

15.1.3. Data Management/Coding

All final patient data, both eCRF and external data (eg, laboratory data), collected according to the protocol will be stored by BeiGene 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 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 with 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, Preferred Term, and primary System Organ Class. Concomitant medications will be coded using the World Health Organization Drug Dictionary. Concomitant diseases/medical history will be coded using MedDRA.

15.2. Study Records Retention

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least 1 of the following 2 categories: 1) investigator's study file and/or 2) 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, screening and enrollment logs, etc.

Following 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 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, 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 BeiGene to store these in sealed containers outside of the site so that they can be returned sealed 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.

Biological samples at the conclusion of this study may be retained as outlined in the agreement with the CRO managing the biological samples, for the shorter of a period of up to 10 years or as allowed by your IRB/IEC.

15.3. 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. The investigator must promptly report any major deviations that might impact patient safety and/or data integrity to the sponsor and to the IRB/IEC, in accordance with established IRB/IEC policies and procedures.

15.4. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency. BeiGene will ensure that the report meets the standards set out in the International Council for Harmonisation 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 Uniform Requirements for Manuscripts or stricter local criteria (International Committee of Medical Journal Editors 2016).

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 sponsor 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. The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this study will be presented in the investigator's clinical study agreement. 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.

15.5. 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 drug(s)
- 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 reason. 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. The sponsor 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 IEC/IRB 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 the return of all unused study drug(s) in accordance with the applicable sponsor procedures for the study.

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

15.6. Information Disclosure and Inventions

All rights, title, and interests in any inventions, know-how, 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 IEC/IRB solely for the evaluation of the study
- Information that is necessary to disclose to provide appropriate medical care to a patient
- Study results may be published as described in Section 15.4

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.

16. REFERENCES

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17. APPENDICES

APPENDIX 1. SCHEDULE OF ASSESSMENTS

Appendix 1A. Schedule of Assessments

Study Phase or Visit	Screening [b]	Treatment (1 Cycle = 21 days)						Safety Follow-up Visit [c]			Long-term Follow-up [d]
Cycle/Period		Cycle 1			Cycle 2		≥ Cycle 3 (Every 1 cycle)				
Day	-28 to -1	1	8	15	1	15	1	+30 days (visit)	+60 days (phone call)	+90 days (phone call)	Every 12 weeks
Window (Days)	-	-	± 1	± 1	± 2		± 3	± 7	± 14	± 14	± 14
Study Treatment											
Ociperlimab [a]		X			X		X				
Cohort 1: Tislelizumab [a]		X			X		X				
Cohort 2: Rituximab [a]		X			X		X				
Procedure											
Informed consent	X										
Eligibility confirmation	X										
Medical and disease history [e]	X										
Demographics/prior treatment history of DLBCL [f]	X										
Biomarker tissue samples [g]	X	To be optionally collected at C2D1, C4D1, and the time of PD									
Biomarker blood samples [h]		To be collected at predose of C1D1, C1D2, C1D8, C2D1, and the time of PD									
Safety Assessments											
Physical examination [i]	X	X			X		X	X			
Vital signs and weight [j]	X	X			X		X	X			
ECOG performance status	X	X			X		X	X			
12-lead ECG [k]	X	As clinically indicated									

Study Phase or Visit	**Screening** [b]	**Treatment (1 Cycle = 21 days)**						**Safety Follow-up Visit** [c]			**Long-term Follow-up** [d]
Cycle/Period		**Cycle 1**			**Cycle 2**		**≥ Cycle 3** (Every 1 cycle)				
Day	**-28 to -1**	**1**	**8**	**15**	**1**	**15**	**1**	**+30 days (visit)**	**+60 days (phone call)**	**+90 days (phone call)**	**Every 12 weeks**
Window (Days)	**-**	**-**	**± 1**	**± 1**	**± 2**		**± 3**	**± 7**	**± 14**	**± 14**	**± 14**
Ophthalmologic examination [l]	As clinically indicated										
Echocardiogram/MUGA [m]	**X**	As clinically indicated									
Adverse event reviews [n]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Concomitant medication Reviews [n]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**			
Laboratory Assessments											
Hematology [o]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**			
Serum chemistry [o]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**			
Coagulation [o]	**X**	As clinically indicated									
Urinalysis [o]	**X**	As clinically indicated									
CK and CK-MB [p]	**X**	**X**			**X**		**X**	**X**			
Thyroid function [q]	**X**				**X**		**X**	**X**			
Pregnancy tests [r]	**X**	**X**			**X**		**X**	**X**			
Quantitative serum immunoglobulins (IgG, IgM, IgA) [s]	**X**	During treatment period, every 9 weeks (± 7 days) from Day 1 of Cycle 1 for the first 54 weeks, every 18 weeks (± 7 days) for additional 54 weeks, then every 24 weeks (± 7 days) thereafter						**X**			
Hepatitis serologies [t]	**X**	Refer to Note t below for details									
Pulmonary function tests [u]	**X**	As clinically indicated									
PK samples [v]	Refer to Appendix 1B and Appendix 1C										
ADA samples [v]	Refer to Appendix 1B and Appendix 1C										

Study Phase or Visit	Screening [b]	Treatment (1 Cycle = 21 days)						Safety Follow-up Visit [c]			Long-term Follow-up [d]
Cycle/Period		Cycle 1			Cycle 2		≥ Cycle 3 (Every 1 cycle)				
Day	-28 to -1	1	8	15	1	15	1	+30 days (visit)	+60 days (phone call)	+90 days (phone call)	Every 12 weeks
Window (Days)	-	-	± 1	± 1	± 2		± 3	± 7	± 14	± 14	± 14
Efficacy Assessments											
Contrast CT (neck, chest, abdomen, and pelvis) [w]	X	From Day 1 of Cycle 1, every 9 weeks (± 7 days) for the first 54 weeks, every 18 weeks (± 7 days) for additional 54 weeks, then every 24 weeks (± 7 days) thereafter									
PET-CT [w]	X	For patients who are positive at screening: Week 9 (± 7 days), Week18 (± 7 days), at time when confirming CR or PD, and clinically indicated									
Bone marrow examination [x]	X	As clinically indicated									
Others											
Survival status [d]											X
Subsequent anticancer therapy [d]											X

Abbreviations: ADA, antidrug antibodies; AE, adverse event; CK, creatine kinase; CK-MB, creatine kinase-muscle/brain; CR, complete response; CT, computed tomography; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; ICF, informed consent form; Ig, immunoglobulin; imAE, immune-mediated AE; MUGA, multiple gated acquisition; MRI, magnetic resonance imaging; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; PD, progressive disease; SAE, serious adverse event; T3, triiodothyronine; T4, thyroxine.

Note: Timepoints containing numbers represent timepoints with special considerations for that respective assessment.

a. Ociperlimab in combination with tislelizumab or rituximab will be given intravenously on Day 1 of each 21-day cycle (once every 3 weeks) (see Section 5.2 for details). Note: Tislelizumab must not be administered concurrently with any other drug.

b. Written informed consent is required before performing any study-specific procedure. Results of standard-of-care tests or examinations performed before informed consent has been obtained and ≤ 28 days before the first dose of study drug(s) may be used for screening assessments rather than repeating such tests unless otherwise indicated. The ICF signature alone does not define the start of the screening period, but the first study-related assessment date is to be used for the date of the Screening Visit.

c. Patients who permanently discontinue study drugs will be asked to return to the clinic for the Safety Follow-up Visit, which is required to be conducted within 30 days (± 7 days) after the last dose of study drugs or before the initiation of new antitumor therapy, whichever occurs first. In addition, telephone contacts with patients will be conducted to assess all imAEs and relevant concomitant medications (ie, associated with an imAE or is a new anticancer therapy) at 60 days (±14 days) and 90 days (±14 days) after the last dose of study treatment, regardless of whether or not the patient starts a new anticancer

therapy. For women of childbearing potential (see Appendix 5), an additional visit to perform a pregnancy test will occur approximately 120 days after the last dose of ociperlimab and tislelizumab, and 180 days after the last dose of rituximab. Visits are performed in the clinic or over the phone, as needed, based on the assessments required.

d. Patients will be followed for survival and to obtain information on subsequent anticancer therapy via telephone calls, mail or email, patient medical records, and/or clinic visits after the last dose of study treatment and approximately every 12 weeks (± 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.
e. Review any medical and disease history any time after obtaining informed consent, including presence or absence of disease-related constitutional symptoms, the date of initial diagnosis, and current disease status, and stage of disease.
f. Includes year of birth (or age), sex, self-reported race, and history of treatment for DLBCL, including prior systemic treatment(s), locoregional treatment(s), and surgical treatment(s).
g. The archival or fresh tumor tissues are mandatory for all patients who consent to participate in the study. If no archival samples are available, a fresh tumor biopsy at baseline is required. Also, if the patient can provide eligible archival tumor tissues and is willing to undergo fresh tumor biopsy at screening, a fresh tumor biopsy is strongly recommended. Archival (within 1 year before signing the ICF) and/or fresh tumor tissues (approximately 15 unstained slides) at screening need to be sent to the central laboratory for diagnosis confirmation and biomarker analysis, including expression of PD-L1, TIGIT, CD226, CD155, and CD112, PD-L1/2 gene alteration, EBV status, tumor microenvironment, immune-related gene expression profile, and gene mutation profile will be evaluated. 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. Bone marrow biopsy is not acceptable. Tumor biopsy from an inguinal lymph node is only acceptable when a tumor biopsy cannot be obtained from other sites. An optional tumor biopsy will be taken from accessible tumor sites at C2D1 and C4D1 to explore tumor biomarkers including tumor microenvironment and immune-related gene expression profile which may be associated with response and resistance to study drugs. Optional biopsies will also be obtained for patients treated with study drugs who have confirmed PD during the study from accessible tumor sites to obtain samples to explore tumor microenvironment and gene mutation/expression profiling associated resistance mechanism. 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.
h. Blood samples will be collected for all patients at predose of C1D1, C1D2, C1D8, C2D1, and at the time of PD to explore the association of blood-based biomarkers with response, resistance, and prognosis to ociperlimab in combination with tislelizumab or rituximab. Blood-based biomarker analysis includes immune-cell quantification and phenotypes, cytokine profiling, immune-related gene expression profiling, and DNA/ctDNA sequencing.
i. Refer to Section 8.2.2 for details regarding physical examination assessment requirements for screening and subsequent timepoints. 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 appropriate specialist will be made for further management guidance.
j. Height assessment is required only at screening. Vital signs including measurements of body temperature (˚C), pulse rate, blood pressure (systolic and diastolic), and weight will be performed at each study visit. Pulse rate and blood pressure will be measured while the patient is in a seated position after resting for 10 minutes. If coinciding with study drug infusions, the patient's vital signs are required to be recorded within 60 minutes before, during, and 30 minutes after the first infusion of study drug(s). For subsequent infusions, vital signs will be collected within 60 minutes before infusion of study drug(s), and if clinically indicated, during and 30 minutes after study drug(s) infusion.
k. The 12-lead ECGs will be performed at screening and when clinically indicated. The ECG at screening must be performed in triplicate. All ECGs are to be obtained before other assessments scheduled at that same time (eg, vital sign measurements and blood draws). The patient should rest in semirecumbent supine position for ≥ 10 minutes in the absence of environmental distractions that may induce changes in heart rate (eg, television, radio, and conversation) before each ECG collection.
l. Ophthalmologic examination includes eye examination (including visual acuity test) and optical coherence tomography (or equivalent diagnostic test for retinal examination); these will be assessed by an appropriate specialist as clinically indicated.

m. An echocardiogram/MUGA is to be performed at screening unless one has been performed within 28 days before the first dose of study drug, and as clinically indicated during the study.
n. The AEs and laboratory abnormalities will be graded per NCI-CTCAE Version 5.0. All AEs will also be evaluated for seriousness. After the ICF has been signed but before the administration of study drug(s), only SAEs should be reported. After the first dose of study drug(s), all AEs and SAEs, regardless of relationship to study drug, will be reported until either 30 days after the last dose of study drug(s) or initiation of new antitumor therapy, whichever occurs first. ImAEs (serious and nonserious) should be reported until 90 days after the last dose of tislelizumab or ociperlimab regardless of whether the patient starts a new antitumor 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. In addition, all concomitant medications taken by or administered to the patient within 28 days before the first dose of study drug(s) and 30 days after the last dose of study drug(s) or the initiation of a new anticancer therapy should be recorded.
o. Local and/or central laboratory assessments of clinical chemistry, hematology, coagulation, and urinalysis will be conducted as outlined in Appendix 2. If clinical chemistry, hematology, and coagulation at screening are not performed ≤ 7 days before study drug(s) administration on Day 1 of Cycle 1, these tests should be repeated and reviewed before study drug administration. After Day 1 of Cycle 1, results are to be reviewed within 72 hours before study drug administration. Hematology and clinical chemistry will be performed on Day 1, Day 8 and Day 15 of the first cycle, on Day 1 and Day 15 of Cycle 2, then on Day 1 on each subsequent cycle. Urinalysis and coagulation tests will be conducted at screening and during the treatment period only if clinically warranted. Refer to Section 9.3.5 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.
p. CK and CK-MB levels will be evaluated at the timepoints specified within the table and when clinically indicated. If CK-MB fractionation is not available, troponin I and/or troponin T should be tested instead. If only 1 of the troponins is assessed per local standards that same test should be evaluated throughout. If significant abnormalities are detected, the affected patients should be evaluated for possible myocarditis/myositis per institutional guidelines, including additional serum CK/CK-MB, serum troponin levels, ECG, etc.
q. Analysis of thyroid function, including free T3, free T4, and thyroid stimulating hormone will be performed by a central laboratory and/or the local study site laboratory.
r. Serum or urine pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative ≤ 7 days before the first dose of study drug(s). A negative urine or serum pregnancy test must be completed and recorded ≤ 72 hours before the administration of study drug(s) at each cycle. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.
s. Serum immunoglobulin, including IgG, IgM, and IgA will be quantitatively assessed at screening, together with tumor evaluations during the treatment period [every 9 weeks (± 7 days), from Day 1 of Cycle 1, for the first 54 weeks; every 18 weeks (± 7 days) for additional 54 weeks; then every 24 weeks (± 7 days) thereafter] and at the Safety Follow-up Visit.
t. Hepatitis serologies will include hepatitis B/C serologic markers and/or viral load at screening. Testing will be performed by a central laboratory and/or the local laboratory (if the local laboratory is able to perform the test to the required sensitivity [< 20 IU/mL and < 15 IU/mL for hepatitis B and C, respectively]). The hepatitis B testing will include HBsAg, HBcAb, and HBsAb, as well as HBV DNA by PCR if the patient is negative for HBsAg but positive for HBcAb (regardless of HBsAb status). The hepatitis C testing will include HCV antibody as well as HCV RNA by PCR if the patient is positive for HCV antibody. Patients who are HBsAg negative, HBcAb positive, and HBV DNA negative (< 20 IU/mL) at screening must be monitored for HBV DNA by PCR at a monthly frequency. If a patient is being treated prophylactically with antivirals, HBV DNA by PCR must be monitored at least every 3 months. Patients who are HCV antibody positive and HCV RNA negative (< 15 IU/mL) at screening must be monitored for HCV RNA at a monthly frequency. HBV DNA and HCV RNA monitoring should continue until the patient starts new antitumor therapy, or for any other reason listed in Section 7.5.2, whichever occurs first. See Section 8.2.9 for more information.
u. Pulmonary function tests may include but are not limited to spirometry and assessment of diffusion capacity, and will be done during the screening period to assist with the determination of suitability for the study.
v. Ociperlimab and tislelizumab PK and ADA: Refer to Appendix 1B and Appendix 1C.

w. Tumor imaging will be performed ≤ 28 days before the first dose of study drug(s). Results of standard-of-care tests or examinations performed before informed consent has been obtained and ≤ 28 days before the first dose of study drug(s) may be used for the purposes of screening rather than repeating the standard-of-care tests. During the study, tumor imaging will be performed every 9 weeks (± 7 days), from Day 1 of Cycle 1, for the first 54 weeks; every 18 weeks (± 7 days) for additional 54 weeks; then every 24 weeks (± 7 days) thereafter based on the Lugano Classification (2014) (Cheson et al 2014). For patients who are positive for PET-CT scans at screening, PET-CT should be repeated at Week 9 (± 7 days), Week 18 (± 7 days), at time when confirming CR or PD, and as clinically indicated. Screening assessments must include both contrast CT and PET-CT scans (with oral/intravenous contrast, unless contraindicated) of the neck, chest, abdomen, and pelvis. Other known or suspected sites of disease must be included in the imaging assessments (brain, etc). Contrast CT will be performed for each subsequent tumor assessment. If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the study, an MRI should be performed but must be used consistently. See Section 8.3 for more information.

x. Bone marrow biopsy and aspirate are required to assess bone marrow involvement of patients during the screening period, unless they have been performed within 60 days before the first dose of study drug and there has been no intervening therapy from the time of the biopsy/aspirate until the first dose of study drug. For patients who have evidence of bone marrow disease at screening, repeated bone marrow biopsy may not be needed if PET-CT shows bone marrow clearance at CR.

Appendix 1B. Dose Confirmation Cohorts 1 and 2: Pharmacokinetic and Immunogenicity Sampling Schedule for Ociperlimab and Tislelizumab

Study week	Study visit	Time	Cohort 1 (Dose Confirmation)		Cohort 2 (Dose Confirmation)	
			PK	ADA	PK	ADA
1	Cycle 1, Day 1	Predose (-60 min to predose)	Ociperlimab PK & Tislelizumab PK	Ociperlimab ADA & Tislelizumab ADA	Ociperlimab PK	Ociperlimab ADA
		Within 30 min after end of infusion	Ociperlimab PK & Tislelizumab PK		Ociperlimab PK	
2	Cycle 1, Day 8 (± 1 day)	At visit	Ociperlimab PK		Ociperlimab PK	
3	Cycle 1, Day 15(± 1 day)	At visit	Ociperlimab PK		Ociperlimab PK	
4	Cycle 2, Day 1	Predose (-60 min to predose)	Ociperlimab PK & Tislelizumab PK	Ociperlimab ADA & Tislelizumab ADA	Ociperlimab PK	Ociperlimab ADA
		Within 30 min after end of infusion	Ociperlimab PK		Ociperlimab PK	
13	Cycle 5, Day 1	Predose (-60 min to predose)	Ociperlimab PK & Tislelizumab PK	Ociperlimab ADA & Tislelizumab ADA	Ociperlimab PK	Ociperlimab ADA
		Within 30 min after end of infusion	Ociperlimab PK & Tislelizumab PK		Ociperlimab PK	
14	Cycle 5, Day 8 (± 1 day)	At visit	Ociperlimab PK		Ociperlimab PK	
15	Cycle 5, Day 15 (± 1 day)	At visit	Ociperlimab PK		Ociperlimab PK	
16	Cycle 6, Day 1	Predose (-60 min to predose)	Ociperlimab PK & Tislelizumab PK	Ociperlimab ADA & Tislelizumab ADA	Ociperlimab PK	Ociperlimab ADA
25	Cycle 9, Day 1	Predose (-60 min to predose)	Ociperlimab PK & Tislelizumab PK	Ociperlimab ADA & Tislelizumab ADA	Ociperlimab PK	Ociperlimab ADA
49	Cycle 17, Day 1	Predose (-60 min to predose)	Ociperlimab PK & Tislelizumab PK	Ociperlimab ADA & Tislelizumab ADA	Ociperlimab PK	Ociperlimab ADA
Safety Follow-up		30 days (± 7 days) after last dose	Ociperlimab PK & Tislelizumab PK	Ociperlimab ADA & Tislelizumab ADA	Ociperlimab PK	Ociperlimab ADA

Abbreviations: ADA, antidrug antibody; h, hour; min, minute; PK, pharmacokinetic.
Note:

Sample collection must be from opposite arm to that used for study drug infusion. If drug was administered via a central venous catheter, sample collection for PK and ADA should be from a different site.
Procedures for collection of blood samples to evaluate ociperlimab and tislelizumab PK are described in the laboratory manual.
If a patient presents with any ≥ Grade 3 imAE, an additional blood PK sample may be taken.
All ADA samples should be collected at the same time as blood collection for predose PK analysis.
These tests are required when it is allowed by local regulations/IRBs/IECs.

Appendix 1C. Dose Expansion Cohorts 1 and 2: Pharmacokinetic and Immunogenicity Sampling Schedule for Ociperlimab and Tislelizumab

Study Week	Study Visit	Time	Cohort 1 (Dose Expansion)		Cohort 2 (Dose Expansion)	
			PK	ADA	PK	ADA
1	Cycle 1, Day 1	Predose (-60 min to predose)	Tislelizumab PK and Ociperlimab PK	Tislelizumab ADA and Ociperlimab ADA	Ociperlimab PK	Ociperlimab ADA
		Within 30 min after end of infusion	Tislelizumab PK and Ociperlimab PK		Ociperlimab PK	
4	Cycle 2, Day 1	Predose (-60 min to predose)	Tislelizumab PK and Ociperlimab PK	Tislelizumab ADA and Ociperlimab ADA	Ociperlimab PK	Ociperlimab ADA
13	Cycle 5, Day 1	Predose (-60 min to predose)	Tislelizumab PK and Ociperlimab PK	Tislelizumab ADA and Ociperlimab ADA	Ociperlimab PK	Ociperlimab ADA
		Within 30 min after end of infusion	Tislelizumab PK and Ociperlimab PK		Ociperlimab PK	
25	Cycle 9, Day 1	Predose (-60 min to predose)	Tislelizumab PK and Ociperlimab PK	Tislelizumab ADA and Ociperlimab ADA	Ociperlimab PK	Ociperlimab ADA
49	Cycle 17, Day 1	Predose (-60 min to predose)	Tislelizumab PK and Ociperlimab PK	Tislelizumab ADA and Ociperlimab ADA	Ociperlimab PK	Ociperlimab ADA
Safety Follow-up		30 days (± 7 days) after last dose	Ociperlimab PK & Tislelizumab PK	Ociperlimab ADA & Tislelizumab ADA	Ociperlimab PK	Ociperlimab ADA

Abbreviations: ADA, antidrug antibody; min, minutes; PK, pharmacokinetic.
Note:
Sample collection must be from opposite arm to that used for study drug infusion. If drug was administered via a central venous catheter, sample collection for PK and ADA should be from a different site.
Procedures for collection of blood samples to evaluate ociperlimab and tislelizumab PK are described in the laboratory manual.
If a patient presents with any ≥ Grade 3 imAE, an additional blood PK sample may be taken.
All ADA samples should be collected at the same time as blood collection for predose PK analysis.
These tests are required when it is allowed by local regulations/IRBs/IECs.

APPENDIX 2. CLINICAL LABORATORY ASSESSMENTS

Clinical chemistry	Hematology	Coagulation	Urinalysis
Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Albumin Total bilirubin Direct bilirubin Blood urea nitrogen or urea Potassium Sodium Total calcium[a] Creatinine Glucose Lactate dehydrogenase Total protein	Red blood cell count Hematocrit Hemoglobin Platelet count White blood cell count Lymphocyte count Neutrophil count	Prothrombin time Partial thromboplastin time or activated partial thromboplastin time International normalized ratio	Glucose Protein Blood

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

APPENDIX 3. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

Grade	Description
0	Fully active, able to carry on all predisease 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 house work, 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. PRE-EXISTING IMMUNE DEFICIENCIES OR AUTOIMMUNE DISEASES

Prospective patients should be carefully questioned to determine whether they have any history of an acquired or congenital immune deficiency or autoimmune disease. Please contact the medical monitor regarding any uncertainty about immune deficiency/autoimmune disease exclusions.

Acute disseminated encephalomyelitis	Addison disease
Ankylosing spondylitis	Antiphospholipid antibody syndrome
Aplastic anemia	Autoimmune hemolytic anemia
Autoimmune hepatitis	Autoimmune hypoparathyroidism
Autoimmune hypophysitis	Autoimmune myocarditis
Autoimmune oophoritis	Autoimmune orchitis
Autoimmune thrombocytopenic purpura	Behcet disease
Bullous pemphigoid	Chronic inflammatory demyelinating polyneuropathy
Chung-Strauss syndrome	Crohn disease
Dermatomyositis	Dysautonomia
Epidermolysis bullosa acquisita	Gestational pemphigoid
Giant cell arteritis	Goodpasture syndrome
Granulomatosis with polyangiitis	Graves disease
Guillain-Barré syndrome	Hashimoto disease
Immunoglobulin A (IgA) neuropathy	Inflammatory bowel disease
Interstitial cystitis	Kawasaki disease
Lambert-Eaton myasthenia syndrome	Lupus erythematosus
Lyme disease (chronic)	Mooren ulcer
Morphea	Multiple sclerosis
Myasthenia gravis	Neuromyotonia
Opsoclonus myoclonus syndrome	Optic neuritis
Ord thyroiditis	Pemphigus
Pernicious anemia	Polyarteritis nodosa
Polyarthritis	Polyglandular autoimmune syndrome
Primary biliary cirrhosis	Psoriasis
Reiter syndrome	Rheumatoid arthritis
Sarcoidosis	Sjögren syndrome
Stiff person syndrome	Takayasu arteritis
Ulcerative colitis	Vogt-Koyanagi-Harada disease

APPENDIX 5. CONTRACEPTION GUIDELINES AND DEFINITIONS OF "WOMEN OF CHILDBEARING POTENTIAL," "NO CHILDBEARING POTENTIAL"

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 (Clinical Trials Facilitation Group 2020). 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, or implantable
    Note: Oral birth control pills are not considered a highly effective form of birth control, and if they are selected, they must be used with a second, barrier method of contraception such as condoms with or without spermicide.
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized male partner
  - Note: This is only considered a highly effective form of birth control when the vasectomized partner is the sole partner of the study participant and there has been a medical assessment confirming surgical success.
  - A sterile man is one for azoospermia has been demonstrated in a semen sample examination as definitive evidence of infertility.
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of exposure associated with the study treatment).
  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 drug(s), 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," and "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 and all alternative medical causes for the lack of spontaneous menses for ≥ 12 months have been ruled out, such as polycystic ovarian syndrome, hyperprolactinemia, etc.

If a follicle-stimulating hormone (FSH) measurement is required to confirm postmenopausal state, concomitant use of hormonal contraception or hormonal replacement therapy should be excluded.

Adapted from Clinical Trials Facilitation Group 2020.

APPENDIX 6. 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 7. COCKCROFT-GAULT FORMULA

FOR SERUM CREATININE CONCENTRATION (SCr) IN MG/DL[a]

Cl_{cr} for males (mL/min) $$\frac{(140\text{-age})(\text{weight}^{b})}{(72)\,(SCr)}$$

CL_{cr} for females (mL/min) $$\frac{(0.85)(140\text{-age})(\text{weight}^{b})}{(72)\,(SCr)}$$

FOR SERUM CREATININE CONCENTRATION (SCr) IN µMOL/L[a]

Cl_{cr} for males (mL/min) $$\frac{(140\text{-age})(\text{weight}^{b})}{(0.81)(SCr)}$$

CL_{cr} for females (mL/min) $$\frac{(0.85)(140\text{-age})(\text{weight}^{b})}{(0.81)(SCr)}$$

a Age in years and weight in kilograms.

b If the subject is obese (>30% over ideal body weight), use ideal body weight in calculation of estimated CL_{cr}.

APPENDIX 8. LUGANO CLASSIFICATION FOR NON-HODGKIN LYMPHOMA

Response and site	PET-CT-based response (patients with PET-avid disease at screening)	CT-based response (patients without PET-avid disease at screening)
Complete	Complete metabolic response	Complete radiologic response (all of the following):
Lymph nodes and extra-lymphatic sites	Score 1, 2, 3* with or without a residual mass on 5-point scale□ It is recognized that in Waldeyer's ring or extra-nodal sites with physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	• Target nodes/nodal masses must regress to ≤ 1.5 cm in longest transverse diameter of a lesion • No extra-lymphatic sites of disease
Non-measured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology, if indeterminate, immunohistochemistry negative
Partial	Partial metabolic response	Partial remission (all of the following):
Lymph nodes and extra-lymphatic sites	Score 4 or 5□ with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	• ≥ 50% decrease in sum of the product of the perpendicular diameters for multiple lesions of up to 6 target measurable nodes and extra-nodal sites • When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value • When no longer visible, 0 × 0 mm • For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Non-measured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable

Response and site	PET-CT-based response (patients with PET-avid disease at screening)	CT-based response (patients without PET-avid disease at screening)
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extra-nodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in sum of the product of the perpendicular diameters for multiple lesions of up to 6 dominant, measurable nodes and extra-nodal sites; no criteria for progressive disease are met
Non-measured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least one of the following cross products of the longest transverse diameter of a lesion and perpendicular diameter progression:
Individual target nodes/nodal masses Extra-nodal lesions	Score 4 or 5 with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma at interim or end of treatment assessment	An individual node/lesion must be abnormal with: • Longest transverse diameter of a lesion > 1.5 cm and • Increase by ≥ 50% from cross product of the longest transverse diameter of a lesion and perpendicular diameter nadir and • An increase in longest transverse diameter of a lesion or shortest axis perpendicular to the longest transverse diameter of a lesion from nadir – 0.5 cm for lesions ≤ 2 cm – 1.0 cm for lesions > 2 cm • In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by ≥ 2 cm from baseline • New or recurrent splenomegaly
Non-measured lesions	None	New or clear progression of pre-existing non-measured lesions

Response and site	PET-CT-based response (patients with PET-avid disease at screening)	CT-based response (patients without PET-avid disease at screening)
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	• Regrowth of previously resolved lesions • A new node > 1.5 cm in any axis • A new extra-nodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma • Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: CT, computed tomography; FDG, [^{18}F] fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography.
Modified from Cheson et al 2014.
*A score 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-finding is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid under treatment). Measured dominant lesions: Up to 6 of the largest dominant nodes, nodal masses, and extra-nodal lesions selected to be clearly measurable in 2 diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal, and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), gastrointestinal involvement, cutaneous lesions, or those noted on palpation. Non-measured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extra-nodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extra-nodal sites (eg, gastrointestinal tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

□PET 5-point scale (Deauville Criteria):
- 1. no uptake above background
- 2. uptake ≤ mediastinum
- 3. uptake > mediastinum but ≤ liver
- 4. uptake moderately > liver
- 5. uptake markedly higher than liver and/or new lesions

X. new areas of uptake unlikely to be related to lymphoma

Note: Temporary withholding of study drug (eg, for drug-related toxicity, surgery, or intercurrent illness) for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. In such circumstances, and if medically appropriate, patients may resume therapy and relevant clinical, laboratory, and/or radiologic assessments should be performed to document whether tumor control can be maintained or whether actual disease progression has occurred.

Isolated increase in lymph nodes and/or splenomegaly during periods of study drug(s) hold will not be considered as progressive disease unless confirmed by a repeat imaging studies ≥ 6 weeks after restarting study drug administration. The response category "indeterminate due to study drug(s)hold" should be selected for such instances. Following the repeated imaging 6 weeks after restarting study drug, response should be in comparison to the imaging at baseline.

APPENDIX 9. IMMUNE-MEDIATED ADVERSE EVENT EVALUATION AND MANAGEMENT

The recommendations below for the diagnosis and management of any immune-mediated AE (imAE) are intended as a 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, disease progression, 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 tislelizumab and the AE?
- How did the patient respond to withdrawal of tislelizumab?
- Did the event recur when tislelizumab was reintroduced?
- Was there a clinical response to corticosteroids?
- Is the event an autoimmune endocrinopathy?
- Is disease progression 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 eCRF should be checked. If further diagnostic evaluations change the assessment, the eCRF should be updated accordingly.

Recommended Diagnostic Tests in the Management of Possible Immune-Mediated Adverse Events	
Immune-mediated Toxicity	**Diagnostic Evaluation Guideline**
Thyroid Disorders	Perform scheduled and repeated 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.

Recommended Diagnostic Tests in the Management of Possible Immune-Mediated Adverse Events	
Immune-mediated Toxicity	**Diagnostic Evaluation Guideline**
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.
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 Grade 3 to 4; every 2 to 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.

Recommended Diagnostic Tests in the Management of Possible Immune-Mediated Adverse Events	
Immune-mediated Toxicity	**Diagnostic Evaluation Guideline**
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 a nephrologist 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, and consider a muscle biopsy.
Myocarditis	Perform ECG, echocardiogram, CK/CK-MB, troponin (I and/or T), and refer to a cardiologist.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; CK, creatine kinase; CK-MB, creatine kinase cardiac isoenzyme; CNS, central nervous system; CRP, C-reactive protein; CT, computed tomography; Dlco, diffusing capacity for carbon monoxide; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; FBC, full blood count; HIV, human immunodeficiency virus; 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 treatment interruption, close monitoring, timely diagnostic work-up, and treatment intervention as appropriate 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 study medical monitor.
- For some Grade 3 toxicities that resolve quickly, rechallenge with study drug may be considered if there is evidence of a clinical response to study treatment, after consultation with the study 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 until ≤ Grade 1 or baseline.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	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 comorbidities, 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 1 or baseline.
Hypophysitis	**1-2** Mild-moderate 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 or 4.	Continue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3-4 Severe or life-threatening symptoms	Refer patient to an endocrinologist for assessment and treatment. Initiate pulse intravenous 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 endocrinologist's advice.	Hold study treatment for patients with headache/visual disturbance due to pituitary inflammation until resolved/improved to ≤ Grade 1 or baseline. 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.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	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 at least 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 (≤ Grade 1 or baseline) on prednisolone ≤ 10 mg/day. Discontinue study treatment if symptoms persist with corticosteroid treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3-4 Severe or life-threatening symptoms: breathless at rest	Admit to a hospital and initiate treatment with intravenous 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	NA	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 ≤ Grade1 or baseline.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3-4 Severe/life-threatening symptoms, Grade 3 or 4 encephalitis, or Grade 3 or 4 Guillain-Barré syndrome	Initiate treatment with oral prednisolone or intravenous 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. Guillain-Barré syndrome: Start intravenous immunoglobulin 0.4 g/kg/day for 5 days or plasmapheresis. Consider corticosteroids (methylprednisolone 2 to 4 mg/kg/day) followed by a slow taper. Monitor for concurrent autonomic dysfunction.	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.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	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 (nonenteric 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 ≤ Grade 1 or baseline.
	3 Severe symptoms: > 6 liquid stools per day over baseline, or if episodic within 1 hour of eating	Initiate intravenous 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 Class 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 ≤ Grade 1 or baseline 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.	Consider holding study treatment and monitor weekly for improvement. If not resolved, interrupt treatment until improved to Grade. 1.
	3 Rash covers > 30% BSA or Grade 2 with substantial symptoms	Avoid skin irritants and sun exposure; topical emollients, oral antihistamines, and high-potency topical corticosteroids recommended. Initiate (methyl)prednisolone 1-2 mg/kg (or equivalent), tapering for a period of ≥ 4 weeks.	Hold study treatment. Re-treat when AE is resolved or improved to mild rash (≤ Grade 1) or baseline or after discussion with the study medical monitor.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	4 Skin sloughing > 30% BSA with associated symptoms (eg, erythema, purpura, epidermal detachment)	Initiate intravenous 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 3 x 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.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	2 ALT or AST 3-5 x ULN	Recheck LFTs every 48-72 hours. Administer prednisolone at a dose of 0.5-2 mg/kg/day for ≥ Grade 2 liver enzyme elevations, with or without concomitant bilirubin elevations. For Grade 2 hepatitis, withhold tislelizumab until the event has resolved or improved to baseline and prednisolone has been tapered to ≤ 10 mg/day over 2-4 weeks.	Hold study treatment; treatment may be resumed when resolved/improved to ≤ Grade 1 or baseline and prednisolone tapered to ≤ 10 mg.
	3 ALT or AST 5-20 x ULN	Immediately start (methyl)prednisolone 1-2 mg/kg/day (or equivalent). Monitor closely. If no improvement after 3 days, consider additional treatment options (mycophenolate mofetil or azathioprine).	If ALT and AST ≤ 10 x ULN: Hold study treatment until improved to baseline grade; reintroduce only after discussion with the medical monitor. If ALT or AST > 10 x ULN: Discontinue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	4 ALT or AST > 20 x ULN	Initiate intravenous methylprednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 6 weeks.	Discontinue study treatment.
	Worsening LFTs despite steroids: If on oral prednisolone, change to pulsed intravenous methylprednisolone. If on intravenous methylprednisolone, add mycophenolate mofetil (MMF) 500 to 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 1.5 x baseline or > ULN to 1.5 x ULN	Repeat creatinine weekly. If symptoms worsen, manage as per criteria below.	Continue study treatment.
	2 Creatinine > 1.5-3 x baseline or > 1.5-3 x 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 ≤ Grade 1 or baseline, restart study drug if tapered to < 10 mg prednisolone.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3 Creatinine > 3 x baseline or > 3-6 x 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 intravenous (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 > 6 x ULN	As per Grade 3, patient should be managed in a hospital where renal replacement therapy is available.	Discontinue study treatment.
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.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	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.	Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1.
Ocular Toxicity	**1** Asymptomatic eye examination/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.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	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 or baseline; reintroduce only after discussion with the study medical monitor.
	4 Blindness (at least 20/200) in the affected eyes	Initiate intravenous (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 intravenous (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 until improved to ≤ Grade 1 or baseline; reintroduce only after discussion with the study medical monitor.
	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.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	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 to worsen, hold study treatment until symptoms improve to baseline or ≤ Grade 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 1 or baseline; 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.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3 Severe pain, limited food and fluid intake, daily living activity limited	Admit to hospital for appropriate management. Initiate intravenous (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when symptoms improve to Grade 2 and taper over at least 4 weeks.	Hold study treatment until improved to ≤ Grade 1 or baseline.
	4 Life-threatening complications or dehydration	Admit to hospital for emergency care. Consider intravenous 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 1 or baseline.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3-4 Severe weakness, limiting self-care	Admit to hospital and initiate oral prednisolone 1 mg/kg. Consider bolus intravenous (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.	For Grade 3: Hold study treatment until improved to ≤ Grade 1 or baseline. Discontinue upon any evidence of myocardial involvement.
Myocarditis [a]	**< 2** Asymptomatic but significantly increased CK-MB or increased troponin OR clinically significant intraventricular conduction delay	Initiate cardiac evaluation under close monitoring with repeat serum testing and including ECG, cardiac echo/MUGA, and/or other interventions per institutional guidelines; consider referral to a cardiologist. If diagnosis of myocarditis is confirmed, treat as Grade 2.	Hold study treatment. If a diagnosis of myocarditis is confirmed and considered immune-mediated, permanently discontinue study treatment in patients with moderate or severe symptoms. Patients with no symptoms or mild symptoms may not restart tislelizumab unless cardiac parameters have returned to ≤ Grade 1 or baseline and after
	2 Symptoms on mild-moderate exertion	Admit to hospital and initiate oral prednisolone or intravenous (methyl)prednisolone at 1-2 mg/kg/day. Consult with a	
	3 Severe symptoms with mild exertion		

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	4 Life-threatening	cardiologist and 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.	discussion with the study medical monitor.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; CHF, congestive heart failure; CK, creatine kinase; CK-MB, creatine kinase cardiac isoenzyme; ECG, electrocardiogram; INR, international normalized ratio; LFT, liver function test; MMF, mycophenolate mofetil; MUGA, multigated acquisition scan; 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.
a. If clinically significant cardiac enzyme abnormalities are detected during laboratory assessment and serial cardiac enzyme assessments pose logistical hardship for the patient, then patient hospitalization should strongly be considered until immune-mediated myocarditis has been ruled out.

APPENDIX 10. DRUGS WITH A KNOWN RISK OF QT PROLONGATION/TORSADES DE POINTES

The text below was obtained from the following sources: Woosley et al 2013 and Flockhart 2007.

Bold font indicates medications or substances that might be relatively commonly used.

- amiodarone
- anagrelide
- arsenic trioxide
- astemizole (off United States [US] market)
- azithromycin
- bepridil (off US market)
- chloroquine
- chlorpromazine
- cilostazol
- ciprofloxacin
- cisapride (off US market)
- citalopram
- clarithromycin
- cocaine
- disopyramide
- dofetilide
- domperidone (not on US market)
- donepezil
- dronedarone
- droperidol
- erythromycin
- escitalopram
- flecainide
- fluconazole
- gatifloxacin (off US market)
- grepafloxacin (not on US market)
- halofantrine (not on US market)
- haloperidol
- ibogaine (not on US market)
- ibutilide
- levofloxacin
- levomepromazine/ methotrimeprazine (not on US market)
- levomethadyl (off US market)
- levosulpiride (not on US market)
- mesoridazine (off US market)
- methadone
- moxifloxacin
- ondansetron
- oxaliplatin
- pentamidine
- pimozide
- probucol (off US market)
- procainamide
- propofol
- quinidine
- roxithromycin (not on US market)
- sevoflurane
- sotalol
- sparfloxacin (off US market)
- sulpiride (not on US market)
- sultopride (non on US market)
- terfenadine (off US market)
- terlipressin (not on US market)
- terodiline (not on US market)
- thioridazine
- vandetanib